Decrease in Glomerular Filtration Rate in Japanese Patients With Type 2 Diabetes Is Linked to Atherosclerosis

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OBJECTIVE — We assessed the effects of atherosclerosis on the glomerular filtration rate (GFR) in patients with type 2 diabetes and who had micro- or normoalbuminuria.

RESEARCH DESIGN AND METHODS — A total of 61 Japanese patients with type 2 diabetes were recruited from inpatients of Osaka City University Hospital. They ranged in age from 40 to 69 years (28 men and 33 women). Each subject collected a 24-h urine sample for quantitative analysis of albumin. Absence of albuminuria was defined as a urinary albumin excretion level of <30 mg/24 h ($n = 36$) and microalbuminuria as a level of 30–300 mg/24 h. The GFR was estimated using ^{99m}Tc diethylenetriamine pentaacetic renogram method. As indexes of atherosclerosis, we measured the intimal-medial thickness (IMT) and distensibility of the carotid artery using high-resolution B-mode ultrasonagraphy and an echo-tracking system. We measured the resistance index (RI) of the renal interlobar arteries by pulsed Doppler sonography.

RESULTS — The clinical characteristics of type 2 diabetic patients with and without microalbuminuria did not differ except for duration of diabetes, which was longer in the patients with microalbuminuria. GFR also did not differ between the patients with and without microalbuminuria. GFR was significantly correlated with the patient's age ($r = -0.256$, $P < 0.05$), carotid IMT ($r = -0.326$, $P < 0.05$), carotid stiffness β ($r = -0.449$, $P < 0.001$), and renal arterial RI ($r = -0.365$, $P < 0.05$). In multiple regression analysis, independent factors associated with GFR were carotid IMT ($R^2 = 0.108$, $P = 0.0102$), carotid stiffness β ($R^2 = 0.208$, $P = 0.0003$), and renal artery RI ($R^2 = 0.130$, $P = 0.0043$).

CONCLUSIONS — The decline in GFR in type 2 diabetic patients in the early stages of nephropathy may be due in part to atherosclerosis.

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Brenner and colleagues (1,2) advocated the concept that glomerular hyperfiltration and/or hypertension are important in the initiation and development of diabetic glomerulopathy. Glomerular hyperfiltration is a well-known feature of patients with type 1 diabetes who are in the early stages of diabetic nephropathy (3). It has been suggested that this functional change can be used to identify patients at risk for clinical nephropathy (4). However, the meaning as well as the occurrence of an elevated glomerular filtration rate (GFR) in patients with type 2 diabetes is controversial. A proportion of these patients develop diabetic nephropathy (5). Some type 2 diabetic patients may present such features as a slow rate of decline in GFR in the presence of proteinuria (5,6). Studies of GFR in patients with type 2 diabetes are few and inconclusive. Some authors have failed to observe an increase in GFR in cross-sectional studies of type 2 diabetic patients (7,8). Results of experimental studies suggest that glomerular hyperfiltration is important in the development of an increase in urinary albumin excretion (UAE) and the glomerular structural changes associated with diabetic nephropathy (1).

The presence of microalbuminuria in type 2 diabetic patients is a predictor of macrovascular disease and mortality, according to results of several independent studies (9–11). Microalbuminuria may predict the development of clinical nephropathy (9,12, 13). It is generally acknowledged that microalbuminuria is not static; it develops in a patient who at one time must have had a normal UAE. In some patients, the microalbuminuria progresses to macroalbuminuria. We previously reported that altered intrarenal hemodynamics are associated with systemic atherosclerosis in type 2 diabetic patients with nephropathy (14). However, little is known about the rate of decline in renal function and its relation to such potential risk factors as hypertension, glycemia, and lipids. When investigating possible risk markers for the development of diabetic renal disease in type 2 diabetic patients, the transition to microalbuminuria but also atherosclerosis in type 2 diabetes during this stage may influence outcome. Our objective is to assess the relationship between the change in the GFR and the intimal-medial thickness (IMT) and the stiffness of the carotid artery, which may reflect a state of generalized vascular damage and arteriosclerotic renal lesions in type 2 diabetic patients who are in an early phase of nephropathy.

RESEARCH DESIGN AND METHODS

Subjects and clinical characteristics

A total of 61 Japanese patients with type 2 diabetes were enrolled. There were 28 men and 33 women, aged 40–69 years, mean 57

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Abbreviations: DTPA, diethylenetriamine pentaacetic; EDV, end-diastolic flow velocity; GFR, glomerular filtration rate; IMT, intimal-medial thickness; PSV, peak systolic flow velocity; RI, resistance index; UAE, urinary albumin excretion.

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

years. We excluded from study patients who were receiving an ACE inhibitor. All had been admitted to Osaka City University Hospital for the treatment of diabetes and to receive education about the disease. None had a clinical history or signs of cerebrovascular disease, peripheral arterial disease, or cardiovascular disease. The presence of cardiovascular disease was evaluated from past history and from a normal response to maximal exercise observed on the electrocardiogram. The diagnosis of type 2 diabetes was verified according to World Health Organization criteria (fasting glucose level >7.8 mmol/l and/or 2-h glucose level >11.1 mmol/l [15]). Patients had to fulfill the following criteria for inclusion in the study: *1*) no episodes of ketoacidosis and no ketonuria; *2*) diagnosis of diabetes made after >30 years of age; *3*) insulin therapy (if any) started after at least 3 years of known disease; and *4*) absence of overt proteinuria. We excluded from the study any patients with known nondiabetic or obstructive kidney disease, microscopic or macroscopic hematuria, abnormal urinary sediment, history of glomerulonephritis or nephroureterolithiasis, or the presence of dilated renal pelvis and atrophied kidney(s) on real-time ultrasonography. During admission, each patient received a special diet (30 kcal · kg^{-1} body weight · day^{-1}) that consisted of 50% carbohydrate, 30% fat, 20% protein, and 10 g of salt per day. The study design was approved by the hospital committee on ethics. Each patient gave informed consent for participation.

To determine the level of UAE, 24-h urine collection was performed on 3 consecutive days. The level of urinary albumin was measured in 24-h urine collections by immunoturbidmetry (TIA MicroAlb Kit; Nittobo, Tokyo). The UAE rate was expressed in milligrams per 24 h. The 24-h UAE level for each patient was the mean of three consecutive measurements. Patients were divided into two subgroups according to the level of UAE as follows: no albuminuria, consisting of patients with UAE <30 mg/24 h (n = 25); and microalbuminuria, consisting of patients with a UAE ≥30 mg/24 h and <300 mg/24 h (n = 36).

The diagnosis of hypertension was based on the following: *1*) the administration of antihypertensive agents and/or a history of hypertension; *2*) a systolic blood pressure >160 mmHg; or *3*) a diastolic blood pressure >90 mmHg. Blood pressure was recorded three times after the subject had rested in the supine position for at least 15 min. Blood pressure was determined with a standard mercury sphygmomanometer and cuffs adapted to arm circumference three measurement. The systolic blood pressure was taken as the point of appearance of Korotokof sounds, and the diastolic blood pressure was taken as the point of their disappearance. The average of three measurements was reported.

The patients discontinued taking their usual antihypertensive medication the day before the GFR was evaluated by a ^{99m}Tc diethylenetriamine pentaacetic (^{99m}Tc-DTPA) renogram (albuminuria absent in 12 of 36; microalbuminuria present in 14 of 25).

Information on smoking habits was collected by means of a self-administered patient questionnaire. A lifelong exposure to a smoking habit was estimated from the product of the number of years smoked and the number of tobacco products smoked daily at the time of the study. These data were used in the calculation of cigarette-years.

Blood samples were obtained on the day of the renal investigation. Blood was withdrawn at 0800 after an overnight fast for movement of the serum concentration of glucose, total cholesterol, triglyceride, HDL cholesterol, and HbA_{1c} by means of standard laboratory methods. Patients were considered to be dyslipidemic if they were taking antihyperlipidemic agents, the serum cholesterol level was 5.68 mmol/l, HDL cholesterol was 1.03 mmol/l, or the triglyceride level was >1.69 mmol/l, according to the criteria of the Japan Atherosclerosis Society.

Measurement of GFR by ^{99m}Tc-DTPA renogram

Sequential kidney scintigrams were obtained, and GFR was measured using a gamma camera after the infusion of 10 mCi ^{99m}Tc-DTPA renogram (Shimazu, Kyoto, Japan) (16,17). A 1-min pre-injection count of the administered dose of radioactivity was performed by placing the syringe 30 cm from the center of the parallel-hole medium-energy collimator of a gamma camera that was interfaced with a digital computer. After concluding this part of the study in the patient, we performed a similar 1-min postinjection syringe count. The radionuclide was rapidly administered by intravenous injection. The patient was positioned posteriorly in front of the gamma camera. Results were stored on a 128 × 128 matrix at 15-s intervals. The same-sized matrix was used for the data on the 1-min syringe count. Data acquisition was initiated at the moment of injection. After the 6-min examination was concluded, a composite image of the entire study was created and processed using 50% background subtraction. A light pen was used to outline each kidney with its separate background region as the area of interest. The pre-injection and postinjection static 1-min syringe counts were determined and, by subtraction, the net counts administered were determined. The patient's height and weight were measured at the time of the examination. As the recording with the gamma camera digital computer system was started at the moment of injection, the net radionuclide counts were determined within the kidneys by subtracting the activity in the background region (whose size was normalized to its respective renal area) from the gross renal counts. This calculation was performed at 2–3 min after the arrival of the tracer in the kidneys. We then calculated the percentage of the total renal DTPA renogram.

The formula for calculating the GFR was as follows (16):

$$\text{GFR ml/min} = (\%\ \text{total renal DTPA uptake}) \times 9.75621 - 6.19843$$

The kidneys of each patient were studied by the same operator. The GFR value was corrected per 1.48 m^2 body surface, representing the mean body surface of a Japanese person.

Ultrasonographic measurements of IMT and arterial distensibility

Ultrasonographical B-mode imaging of the carotid artery was performed with a high-resolution real-time ultrasonograph with a 10 MHz in-line Sectascanner (SSD 650 CL; Aloka, Tokyo), as described previously (18–20). At each longitudinal projection, the IMT was taken from the site of the greatest thickness. To assess intra-observer variability, 20 diabetic patients were examined on two different occasions. The coefficient of variation for IMT in these patients was 3.2%.

Vessel diameter and changes in pulsatile diameter were measured by echo-tracking sonography (21) using a recently developed ultrasound echo-tracking system that can detect the movements of the vessel wall of <10 μm (22,23). We used an electronic echo-tracking instrument that was interfaced with a real-time ultrasound scanner and fitted with a 7.5 MHz linear array transducer (Aloka SSD610; Aloka). In this system, two electronic markers automatically lock to the luminal interface of echoes from the anterior and posterior vessel wall and follow its pulsatile movements. The

Table 1—*Clinical characteristics of 61 patients with type 2 diabetes*

	Type 2 diabetes without microalbuminuria	Type 2 diabetes with microalbuminuria
n	36	25
Sex (M/F)	17/19	11/14
Age (years)	55.6 ± 1.3	57.8 ± 1.4
BMI (kg/m^2)	23.0 ± 0.6	21.8 ± 0.5
Duration (years)	7.8 ± 1.0	13.1 ± 1.9†
Cigarette-years	399 ± 97	471 ± 105
Fasting plasma glucose (mmol/l)	7.53 ± 0.42	7.97 ± 0.38
HbA_{1c} (%)	8.4 ± 1.7	9.0 ± 1.8
Serum creatinine (μmol/l)	58.2 ± 1.9	57.6 ± 2.9
Total cholesterol (mmol/l)	4.94 ± 0.20	4.68 ± 0.15
Triglyceride (mmol/l)	1.29 ± 0.11	1.04 ± 0.08
HDL cholesterol (mmol/l)	1.19 ± 0.06	1.28 ± 0.07
Systolic blood pressure (mmHg)	120.7 ± 3.3	129.3 ± 4.3
Diastolic blood pressure (mmHg)	70.8 ± 2.0	71.8 ± 2.0
UAE (mg/24 h)	15.9 ± 3.1	114.0 ± 13.9†
Carotid IMT (mm)	0.741 ± 0.026	0.838 ± 0.049
Carotid stiffness β	13.9 ± 1.1	13.9 ± 0.9
RI of intrarenal artery	0.695 ± 0.014	0.703 ± 0.013
Retinopathy (PDR/PPDR/SDR/NDR)	2/5/22/7	1/12/3/9*
Therapy (diet/oral hypoglycemic agent/insulin)	10/17/9	0/16/9*

Data are means ± SEM. NDR, nondiabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; SDR, simple diabetic retinopathy. *$P < 0.005$, †$P < 0.0001$ vs. type 2 diabetic patients without microalbuminuria.

markers are shown in real time to indicate the level at which the registration is performed. The smallest movement detected is 10 μm (23).

The distensibility of the arterial wall was calculated as follows:

$$\text{stiffness}(\beta) = \frac{\text{In}(\text{Psyst}/\text{Pdiast})}{(\text{Dsyst} - \text{Ddiast})/\text{Ddiast}}$$

where Psyst and Pdiast are the maximal systolic and end-diastolic blood pressure levels (mmHg), respectively, and Dsyst and Ddiast are the corresponding vessel diameters (mm). Each subject was examined three times at each location. The coefficient of variation for carotid artery stiffness was 3.6% in these patients.

Duplex Doppler sonography of the interlobar artery in the kidneys

After the subject had rested in a supine position for 15 min on the same day of the renal investigation, we performed the ultrasound examination using a duplex Doppler apparatus (Aloka SSD 2000; Aloka), as previously reported by us and others (14,24, 25). Images were obtained with a 5-MHz convex array probe in the real-time/color-coded Doppler and pulsed Doppler modes. The ultrasonic probe was positioned gently on the patient's flank in an oblique projection, and the kidney was visualized as a longitudinal image. The interlobar arteries were visualized in real-time/color-coded Doppler mode images in which the intrarenal arterial and venous flow are depicted in different colors. Sample volumes were obtained so as to position the cursor of the pulsed Doppler mode at the midportion of the interlobar arteries that flow along the renal pyramid. The pulsed Doppler mode was used to obtain quantitative measurements of velocity by placing a cursor along the course of the interlobar arteries. Sample volume was adjusted to a pulse length of 1.0 mm and was estimated using the angle correction menu of the apparatus. The examination was completed in 15 min.

The peak systolic flow velocity (PSV), the end-diastolic flow velocity (EDV), and the time-averaged flow velocity were calculated automatically by the ultrasound apparatus. Flow velocities were determined from signals that were stable for at least five pulse beats. Measurements represented the average of five complete waveforms. The resistance parameter, the resistance index (RI), was determined as follows (24,26): RI = (PSV − EDV)/PSV.

Three different interlobar arteries from each kidney were selected at random and examined, and the mean value from the two kidneys was calculated. The coefficient of variation of the RI in these patients was 3.8%.

Statistical analysis

Data are reported as means ± SEM. Clinical parameters were compared by a one-way analysis of variance with Scheffe's *F* test. Univariate χ^2 analyses were used to evaluate the incidence of retinopathy and therapy in type 2 diabetic patients with versus without microalbuminuria. To evaluate possible association between the carotid IMT, the stiffness β, the intrarenal arterial RI, and GFR, we conducted regression analyses of the risk factors that independently affect GFR. Step-wise multiple regression analyses were performed in each model of a four-model system to assess the combined influence of variables using GFR, age, sex (female = 0, male = 1), known duration of diabetes, BMI, cigarette-years, HbA_{1c}, systolic and diastolic blood pressure, total cholesterol, triglyceride, HDL cholesterol, carotid IMT, stiffness β, and the intrarenal arterial RI. The *F* value was set at 4.0 at each step. All variables that were statistically significant at the 5% level were included in the multiple regression analysis.

RESULTS

Clinical characteristics

The clinical characteristics of each group are shown in Table 1. The two groups were well matched with regard to sex, age, and BMI. There was no significant intergroup difference in the systolic and diastolic blood pressure. Diabetic retinopathy was more common in the type 2 diabetic patients with microalbuminuria than in those with normoalbuminuria, probably because of the longer duration of diabetes in the former ($P < 0.05$). Of the 36 patients without albuminuria, 18 (50%) were treated for dyslipidemia and 12 (33%) were receiving oral antihypertensives. Of 25 microalbuminuric patients, 14 (56%) were being treated for dyslipidemia and 14 (56%) were receiving an oral antihypertensive. A total of 18 (30%) patients were receiving insulin injections, and 33 (54%) were receiving an oral antidiabetic agent. Ten patients (16%) were receiving diet therapy only. The patients had no evidence of macroangiopathy, such as cerebrovascular disease, ischemic heart disease, or arteriosclerosis obliterans.

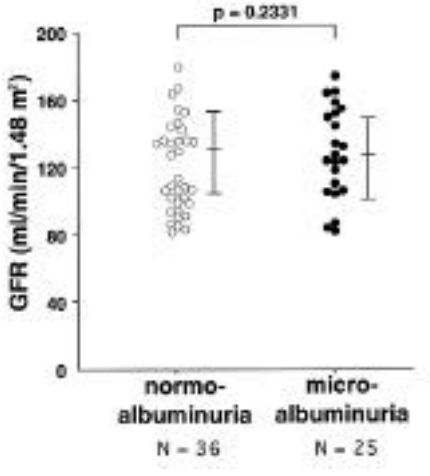

Figure 1—*Comparison of GFR estimated by ^{99m}Tc-DTPA renogram in 61 type 2 diabetic patients with versus without microalbuminuria. ○, Type 2 diabetic patients without microalbuminuria (n = 36); ●, those with microalbuminuria (n = 25).*

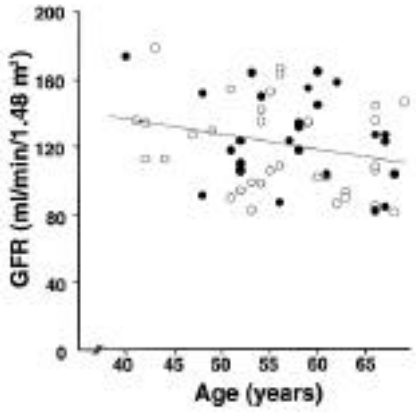

Figure 2—*Relationship between GFR and age in type 2 diabetic patients with versus without microalbuminuria. A statistically significant negative correlation was observed (r = −0.256, P = 0.0461). ○, Type 2 diabetic patients without microalbuminuria (n = 36); ●, those with microalbuminuria (n = 25).*

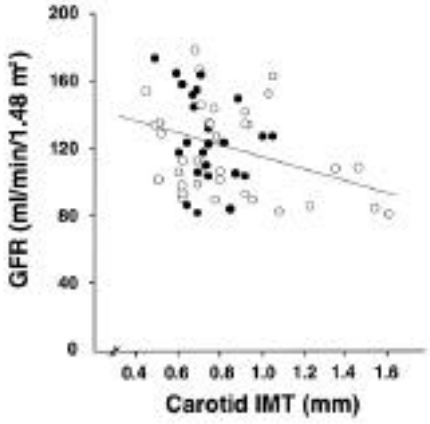

Figure 3—*Relationship between GFR and the IMT of the carotid artery in 61 type 2 diabetic patients with and without microalbuminuria. A highly significant negative correlation was observed (r = −0.326, P = 0.0104). ○, Type 2 diabetic patients without microalbuminuria (n = 36); ●, those with microalbuminuria (n = 25).*

Estimation of GFR

GFR measured by ^{99m}Tc-DTPA renogram is shown in Fig. 1. GFR did not differ significantly between the patients with (127 ± 26 ml · min^{-1} · 1.48 m^{-2}) and without microalbuminuria (119 ± 27 ml · min^{-1} · 1.48 m^{-2}) (P = 0.2331).

Correlations between GFR and clinical parameters

Correlations between GFR and clinical parameters are shown in Table 2. GFR was significantly correlated with older age (r = −0.256, P = 0.0461; Fig. 2), carotid IMT (r = −0.326, P = 0.0104; Fig. 3), carotid stiffness β (r = −0.449, P = 0.0003; Fig. 4), and the renal artery RI (r = −0.365, P = 0.0038; Fig. 5). However, there was no significant correlation between GFR and the duration of type 2 diabetes, HbA_{1c}, BMI, cigarette-years, total cholesterol, triglyceride, HDL cholesterol, or the systolic or diastolic blood pressure (Table 2).

Factors associated with GFR

Table 3 summarizes the results of multiple regression analyses of the possible risk factors that independently affected the GFR in the early stages of diabetic nephropathy. Models I–IV indicated age, sex, BMI, duration of diabetes, cigarette-years, HbA_{1c}, total cholesterol, triglyceride, HDL cholesterol, and systolic or diastolic blood pressure. Age was a risk factor only for the rate of fall in GFR in the type 2 diabetic patients in model I (R^2 = 0.076, P = 0.0326). When the carotid IMT, carotid stiffness β, and renal RI were included as independent variables in models II through IV, respectively, the association between GFR and these variables (except for age) appeared to be significant (model II: R^2 = 0.108, P = 0.0102; model III: R^2 =

Table 2—*Correlations (r) between GFR and various clinical parameters and IMT, the stiffness β of the carotid artery, and the RI of the intrarenal artery*

	r	*P* value
Age (years)	−0.256	0.0461
BMI (kg/m^2)	−0.078	NS
Duration of diabetes (years)	−0.163	NS
Cigarette-years	0.174	NS
HbA_{1c} (%)	0.142	NS
Total cholesterol (mmol/l)	−0.124	NS
Triglyceride (mmol/l)	0.097	NS
HDL cholesterol (mmol/l)	−0.192	NS
Systolic blood pressure (mmHg)	0.103	NS
Diastolic blood pressure (mmHg)	0.115	NS
Carotid IMT (mm)	−0.326	0.0104
Carotid stiffness β	−0.449	0.0003
RI of intrarenal artery	−0.365	0.0038

Significant correlations were observed between GFR and age, IMT, stiffness β, and RI. No significant correlation was observed between GFR and BMI, duration of diabetes, HbA_{1c}, total cholesterol, triglyceride, HDL cholesterol, or systolic or diastolic blood pressure.

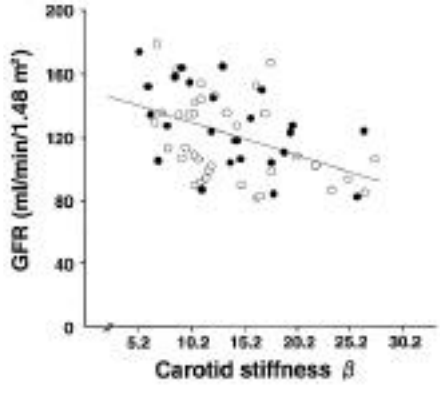

Figure 4—*Relationship between GFR and the stiffness β of carotid artery was shown in 61 type 2 diabetic patients with and without microalbuminuria. A highly significant negative correlation was observed (r = −0.449, P = 0.0003). ○, Type 2 diabetic patients without microalbuminuria (n = 36); ●, those with microalbuminuria (n = 25).*

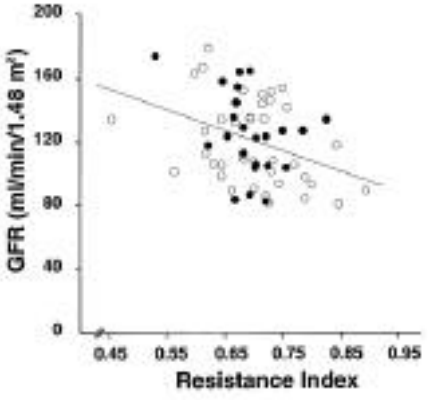

Figure 5—*Relationship between GFR and the RI of the interlobar artery was shown in 61 type 2 diabetic patients with and without microalbuminuria. A highly significant negative correlation was shown (r = −0.365, P = 0.0038). ○, Type 2 diabetic patients without microalbuminuria (n = 36); ●, those with microalbuminuria (n = 25).*

0.208, $P = 0.0003$; model IV: $R^2 = 0.130$, $P = 0.0043$).

IMT, stiffness β of the carotid artery, and RI in patients with and without microalbuminuria

Patients with versus without microalbuminuria showed no significant differences between the IMT and stiffness β of the carotid artery and RI of the intrarenal artery (Table 1, Fig. 6).

CONCLUSIONS

The development of diabetic nephropathy has been associated with elevated blood pressure (27), poor control of glycemia, dyslipidemia, prolonged duration of diabetes (5,28), and smoking habit (29). The present cross-sectional study evaluated the relation of potential risk factors to the decline in kidney function and the effects of atherosclerosis in the carotid artery on GFR in patients with type 2 diabetes during the transition from normal albumin excretion to microalbuminuria.

To examine the possible contribution of advanced arteriosclerosis to GFR, we studied the relationship between GFR and age, IMT, stiffness β of the carotid artery, and the RI of the interlobar renal artery. A significant negative correlation was found between GFR and age, IMT, stiffness β of the carotid artery, and the RI. Aging is known to be associated with profound anatomic and functional changes in organs, such as the kidney. Damsgaard and Mogensen (7) discussed the effects of age on GFR. GFR normally shows a decrease with age, especially after 40 years (30). Advanced arteriosclerosis is related to aging (18,19,31,32). Diabetes is a strong risk factor for arteriosclerosis (18,19,33), with a prolonged duration of diabetes presenting as is a significant risk factor for the progression of arteriosclerosis (31,34). Kogawa et al. (19) found that the carotid IMT in diabetic patients significantly exceeded that in age-matched control subjects; the carotid IMT showed an increase with age in both diabetic and control subjects. Type 2 diabetic patients exhibit abnormally stiff arteries; the decrease in elasticity is independent of arterial wall thickness (35). We recently reported that in patients with type 2 diabetes, abnormalities in intrarenal hemodynamics, as measured by duplex Doppler sonography, are significantly influenced by a decrease in glomerular function, advanced age, and a prolonged duration of diabetes. Abnormalities in intrarenal hemodynamics may be related to arteriosclerosis as assessed by the IMT of the carotid and femoral arteries (14).

We performed multiple regression analysis to determine the combined impact on GFR of such clinical variables as age, sex, BMI, cigarette-years, duration of diabetes, HbA_{1c}, total cholesterol, triglyceride, HDL cholesterol, blood pressure, and the values for the IMT and stiffness β of the carotid artery and the RI. The analysis revealed that in model I, age contributed independently to GFR in type 2 diabetic patients with or without microalbuminuria. However, in models II through IV, the carotid IMT, stiffness β, and the RI, not age, were independent risk factors for GFR. Additionally, in model II, including the carotid IMT, these variables jointly accounted for 10.8% of the variation in GFR. In model III, including carotid stiffness β, these variables jointly explained 20.8% of the variation in GFR. In model IV, including the RI values, these variables jointly explained 13.0% of the variation in GFR. Results suggest that the reduction in GFR observed in type 2 diabetic patients with or without microalbuminuria may be associated with systemic atherosclerosis.

Table 3—*Risk factors affecting GFR in patients with type 2 diabetes*

	Model I		Model II		Model III		Model IV	
	β	*F* value	β	*F* value	β	*F* value	β	*F* value
Age (years)	−0.276	4.791	−0.152	1.346	−0.050	0.145	−0.121	0.865
Sex (M/F)	0.077	0.338	0.097	0.545	0.055	0.170	0.061	0.215
BMI (kg/m²)	−0.060	0.203	−0.035	0.070	−0.055	0.171	−0.110	0.715
Duration of diabetes (years)	−0.117	0.792	−0.154	1.382	−0.174	1.785	−0.052	0.156
Cigarette-years	0.162	1.541	0.217	2.813	0.211	2.652	0.097	0.549
HbA_{1c} (%)	0.119	0.821	0.099	0.579	0.092	0.494	0.181	1.975
Total cholesterol (mmol/l)	−0.139	1.128	−0.043	0.103	−0.218	2.838	−0.054	0.171
Triglyceride (mmol/l)	0.086	0.425	0.168	1.665	0.074	0.317	0.031	0.057
HDL cholesterol (mmol/l)	−0.168	1.653	−0.218	2.840	−0.240	3.496	−0.106	0.659
Systolic blood pressure (mmHg)	0.174	1.784	0.097	0.540	0.232	3.230	0.160	1.523
Diastolic blood pressure (mmHg)	0.105	0.637	0.061	0.211	0.071	0.291	0.033	0.062
Carotid IMT (mm)	—	—	−0.329	7.044	—	—	—	—
Carotid stiffness β	—	—	—	—	−0.456	15.189	—	—
RI of intrarenal artery	—	—	—	—	—	—	−0.360	8.810
R^2	0.076 ($P = 0.0326$)		0.108 ($P = 0.0102$)		0.208 ($P = 0.0003$)		0.130 ($P = 0.0043$)	

$n = 61$. Significant predictors of GFR in type 2 diabetes were explored among such parameters as age, sex (female = 0, male = 1), BMI, duration of diabetes, HbA_{1c}, total cholesterol, triglyceride, HDL cholesterol, systolic blood pressure, and diastolic blood pressure. *F* value was set at 4.0 at each step. β is the standard regression coefficient. R^2 is the multiple coefficient of determination.

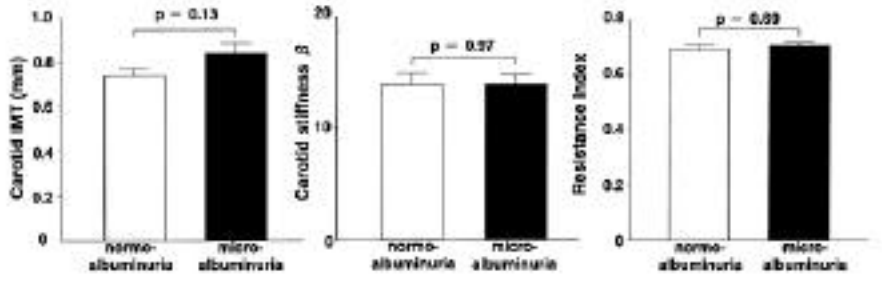

Figure 6—*Comparison of IMT, the stiffness β of the carotid artery, and the RI of the interlobar artery in 61 type 2 diabetic patients with versus without microalbuminuria. The values for IMT, stiffness β, and the RI were higher but not significant between the two groups.*

Although the size of the carotid arteries differs from that of the interlobar renal arteries, the extent and severity of arteriosclerosis of the medium-sized arteries (such as the carotid) and of the small arteries (such as the coronary and renal arteries) were found in autopsy studies to be correlated (36,37). A close association of arteriosclerosis among arteries of different sizes has been demonstrated (32–34,36,37), showing the systemic nature of arteriosclerosis and its relationship to hypertension, age, and diabetes. However, as shown in the Malmoe study (36), arteriosclerosis varies among arteries of differing sizes. Thus, the significant correlations between the carotid IMT and stiffness β and a reduced GFR provide indirect evidence of the contribution of advanced intrarenal arteriosclerosis to the decrease in GFR.

Long-term prospective studies have determined that microalbuminuria, which is considered to be a microvascular complication of type 1 diabetes, is a powerful predictor for the development of diabetic nephropathy and retinopathy in such patients (4,38). Microalbuminuria is associated with pronounced glomerular structural damage (39) as well as with more advanced microvascular and macrovascular damage elsewhere in the body. Studies in patients with type 2 diabetes have demonstrated an association between microalbuminuria and cardiovascular events (40,41). No reports have evaluated asymptomatic atherosclerosis in type 2 diabetic patients with and without microalbuminuria. Results of the present study indicate that the values for IMT, stiffness β of the carotid artery, and the RI were higher but not significantly so in type 2 diabetic patients with microalbuminuria as compared with those without this complication. In addition, there was no difference in age, control of glycemia, or blood pressure between the patients with and without microalbuminuria, and none evidenced macrovascular disease.

GFR did not differ significantly between the patients with and without normoalbuminuria. A large variation in GFR values was seen in the patients with and without microalbuminuria. Hyperfiltration is the first abnormality in renal function to be detected in patients with type 1 and type 2 diabetes, especially those with type 1. A positive correlation between the initial hyperfiltration and the subsequent increase in albuminuria and the development of clinical nephropathy has been described in patients with type 1 but not in those with type 2 diabetes (42). In the present study, we found no evidence of hyperfiltration in type 2 diabetic patients with versus those without microalbuminuria. It would be necessary to study at follow-up those type 2 diabetic patients with an elevated GFR and normoalbuminuria. Several studies have shown that hyperfiltration predicts the progression to microalbuminuria and overt renal disease, although such hyperfiltration may also be secondary to the poor control of glycemia (43). Because metabolic control, which is one cause of hyperfiltration, did not differ between the diabetic patients with and without microalbuminuria in the present study, we may not expect to find any significant difference in GFR. Schmitz et al. (44) reported a lack of glomerular hyperfiltration and renal hypertrophy in Caucasian patients with type 2 diabetes but without albuminuria. This finding is challenged by results of other studies that demonstrated an elevated GFR in Native Americans, black Americans, and Polynesians who had uncomplicated type 2 diabetes. Vora et al. (45) clearly demonstrated an elevated GFR with effective renal plasma flow (expressed to 1.73 m^2) in 76 newly diagnosed, nonproteinuric, normotensive Caucasian patients with type 2 diabetes. Vedel et al. (46) also demonstrated an elevated GFR by means of ^{51}Cr-EDTA. However, Gragnoli et al. (17) reported a normal GFR using ^{99m}Tc-DTPA scintigraphy in normo- and microalbuminuric Caucasian patients with type 2 diabetes. The mean HbA_{1c} was below 7%. This finding is consistent with our results. The discrepancies between the present results and those earlier studies may be attributable to differences in metabolic control and/or to racial differences. Histopathologically, nephropathy in type 2 diabetes is considered to differ from that in type 1 diabetes and to be more heterogeneous (47). It is possible that the pathogenesis of renal disease may differ in type 1 and type 2 diabetic patients. We found no significant difference in GFR, IMT, the stiffness β of the carotid artery, or the RI value in type 2 diabetic patients with or without microalbuminuria. However, the incidence of retinopathy in the type 2 diabetic patients with microalbuminuria was higher than in those without microalbuminuria. The duration of diabetes was longer in the patients with than in those without microalbuminuria. This finding supports the association between the incidence of retinopathy and albuminuria in patients with type 2 diabetes. This finding is also consistent with the data in the Diabetes Control and Complications Trial (48). Any association between the histological stage of nephropathy and the stage of retinopathy was not evaluated, as renal biopsies were not performed.

In conclusion, the results of our cross-sectional study indicate that a decrease in GFR is associated with the presence of atherosclerosis in patients with type 2 diabetes. There were no significant differences in carotid IMT, stiffness β, or intrarenal arterial resistance in diabetic patients with microalbuminuria versus normal albumin excretion.

References

1. Hostetter TH, Rennke HG, Brenner BM: The case for intrarenal hypertension in the initiation and progression of diabetic and glomerulopathies. *Am J Med*72:375–380, 1982
2. Anderson S, Brenner BM: Pathogenesis of diabetic glomerulopathy: hemodynamic considerations. *Diabetes Metab Rev*4:163–177, 1988
3. Mogensen CE: Glomerular filtration rate and renal plasma flow in long-term juvenile diabetics without proteinuria. *Br Med J* 2:257–259, 1972
4. Mogensen CE, Christensen CK: Predicting

diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 311:89–93, 1984
5. Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT: The kidney in maturity onset diabetes mellitus: a clinical study of 510 patients. *Kidney Int* 21:730–738, 1982
6. Friedman R, Gross JL: Evolution of glomerular filtration rate in proteinuric NIDDM patients. *Diabetes Care* 14:355–359, 1991
7. Damsgaard EM, Mogensen CE: Microalbuminuria in elderly hyperglycaemic patients and controls. *Diabet Med* 3:430–435, 1986
8. Schmitz A, Hansen HH, Christiensen T: Kidney function in newly diagnosed type 2 (non-insulin dependent) diabetic patients before and during treatment. *Diabetologia* 32:434–439, 1989
9. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. *N Engl J Med* 310: 356–360, 1984
10. Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G: Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes* 41:736–741, 1992
11. Gall MA, Borch-Johnsen KB, Hougaard P, Nielsen FS, Parving HH: Albuminuria and poor glycemic control predict mortality in NIDDM. *Diabetes* 44:1303–1309, 1995
12. Alzaid AA: Microalbuminuria in patients with NIDDM: an overview. *Diabetes Care* 19:79–89, 1996
13. Chan JCN, Cheung CK, Cheung MYF, Swaminathan R, Critchley JAJH, Cockram CS: Abnormal albuminuria as a predictor of mortality and renal impairment in Chinese patients with NIDDM. *Diabetes Care* 7: 1013–1016, 1995
14. Ishimura E, Nishizawa Y, Kawagishi T, Okuno Y, Kogawa K, Fukumoto S, Maekawa K, Hosoi M, Inaba M, Emoto M, Morii H: Intrarenal hemodynamic abnormalities in diabetic nephropathy measured by duplex Doppler sonography. *Kidney Int* 51:1920–1927, 1997
15. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group* Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
16. Gates FG: Glomerular filtration rate: estimation from fractional renal accumulation of 99mTcDTPA (stannous). *Am J Roentgenol* 138:565–570, 1982
17. Gragnoli G, Signorini AM, Tanganelli I, Fondelli C, Borgogni P, Borgogni L, Vattimo A, Ferrari F, Guercia M: Prevalence of glomerular hyperfiltration and nephromegaly in normo- and microalbuminuric type 2 diabetic patients. *Nephron* 65:206–211, 1993
18. Hosoi M, Nishizawa Y, Kogawa K, Kawagishi T, Konishi T, Maekawa K, Emoto M, Fukumoto S, Shioi A, Shoji T, Inaba M, Okuno Y, Morii H: Angiotensin converting enzyme gene polymorphism is associated with carotid arterial wall thickness in non-insulin-dependent diabetic patients. *Circulation* 94:704–707, 1996
19. Kogawa K, Nishizawa Y, Hosoi M, Kawagishi T, Maekawa K, Shoji T, Okuno Y, Morii H: Effect of polymorphism of apolipoprotein E and angiotensin-converting enzyme genes on arterial wall thickness. *Diabetes* 46:682–687, 1997
20. Kawagishi T, Nishizawa Y, Konishi T, Kawasaki K, Emoto M, Shoji T, Tabata T, Inoue T, Morii H: High-resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. *Kidney Int* 48:820–826, 1995
21. Hokansson DE, Mozersky DJ, Sumner DJ, Strandness DE Jr: A phase-locked echo-tracking system for recording arterial diameter changes in vivo. *J Appl Physiol* 32:728–733, 1972
22. Lindstrom K, Gennser G, Sindberg Eriksson P, Bentin M, Dahl P: An improved echo-tracker for studies on pulse-waves in the fetal aorta. In *Fetal Physiological Measurements* Rolfe P, Ed. London, Butterworths, 1987, p. 217–226
23. Benthin M, Dahl P, Ruzicka R, Lindstrom K: Calculation of pulse wave velocity using cross-correlation effects of reflexes in the arterial tree. *Ultrasound Med Biol* 17:461–469, 1991
24. Platt JF: Duplex Doppler evaluation of native kidney dysfunction: obstructive and nonobstructive disease. *Am J Roentgenol* 158:1035–1042, 1992
25. Platt JF, Ellis JH, Rubin JM, Dipietro MA, Sedman AB: Intrarenal arterial Doppler sonography in patients with nonobstructive renal disease: correlation of resistive index with biopsy findings. *Am J Roentgenol* 154:1223–1227, 1990
26. Kawagishi T, Nishizawa Y, Emoto M, Konishi T, Mohawk K, Hagiwara S, Okuno Y, Inada H, Isshiki G, Morii H: Impaired retinal artery blood flow in IDDM patients before clinical manifestation of diabetic retinopathy. *Diabetes Care* 18:1544–1549, 1995
27. Nielsen S, Rehling M, Schmitz A, 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
28. Anderson AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T: Diabetic nephropathy in type 1 (insulin-dependent) diabetes: an epidemiological study. *Diabetologia* 25:496–501, 1983
29. Chase HP, Garg SK, Marshall G, Berg CL, Harris S, Jackson WE, Hamman RE: Cigarette smoking increases the risk of albuminuria among subjects with type 1 diabetes. *J Am Med Assoc* 256:614–617, 1991
30. Gross JL, Friedman R, Azevedo MJ, Silveiro S, Pecis M: Effect of age and sex on glomerular filtration rate measured by 51Cr-EDTA. *Brazilian J Med Biol Res* 25:129–134, 1992
31. Kawamori R, Hougaku H, Yamasaki T, Maeda H, Matsushima H, Handa N, Nishizawa H, Matsumoto M, Nao K, Kamada T: Prevalence of carotid atherosclerosis in diabetic patients. *Diabetes Care* 15: 1290–1294, 1992
32. Michel JB, Salzmann JL, Safar M: Stuctural modifications of the arterial wall in hypertension. In *Diseases of the Arterial Wall*. Camilleri JP, Berry CL, Fiessinger JN, Bariety J, Eds. Berlin, Springer-Verlag, 1989, p. 91–96
33. Gaziano JM: Epidemiology of risk-factor reduction. In *Vascular Medicine: A Textbook of Vascular Biology and Diseases* 2nd ed. Loscalzo J, Creager MA, Dzau VJ, Eds. Boston, MA, Little, Brown, 1996, p. 569–586
34. Ito H, Harano Y, Suzuki M, Hattori Y, Taleuchi M, Inada H, Inoue J, Kawamori R, Murase T, Ouchi Y, Umeda F, Nawata H, Orimo H: Risk factor analysis for macrovascular complication in non-obese NIDDM patients: multiclinical study for diabetic macroangiopathy (MSDN). *Diabetes* 45 (Suppl. 3):S19–S23, 1996
35. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR: Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the ARIC study. *Circulation* 91:1432–1443, 1995
36. Sternby N: Atherosclerosis in a defined population: an autopsy survey in Malmoe, Sweden. *Acta Pathol Microbiol Scand* 194 (Suppl.):111–118, 1968
37. Sternby N: Atherosclerosis of peripheral arteries: an autopsy survey in Malmoe, Sweden. *Acta Pathol Microbiol Scand* 194 (Suppl.):98–110, 1968
38. Mogensen CE: Microalbuminuria as a predictor of clinical diabetic nephropathy in insulin-dependent diabetics. *Kidney Int* 31:673–689, 1989
39. Osterby R: Microalbuminuria in diabetes mellitus: is there a structural basis? (Editorial). *Nephrol Dial Transplant* 10:12–14, 1995
40. Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, den Ottolander GJ: Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. *Lancet* 340:319–323, 1992
41. Klein R, Klein BE, Moss SEM: Prevalence of microalbuminuria in older-onset diabetes. *Diabetes Care* 16:1325–1330, 1993
42. Mogensen CE: Early glomerular hyperfiltration in insulin-dependent diabetics and late nephropathy. *Scand J Clin Lab Invest* 46:201–206, 1986
43. Mogensen CE: Glomerular hyperfiltration in human diabetes. *Diabetes Care* 17:770–

775, 1994
44. Schmitz A, Gundersen HJG, Osterby R: Glomerular morphology by light microscopy in non-insulin-dependent diabetes mellitus: lack of glomerular hypertrophy. *Diabetes* 37:38–43, 1988
45. Vora J, Dolben J, Williams J, Peters JR, Owens DR: Renal hemodynamics in newly presenting non-insulin-dependent diabetic patients (NIDDMs): changes over two years after diagnosis (Abstract). *Diabet Med* 10 (Suppl. 1):S25, 1993
46. Vedel P, Obel J, Nielsen FS, Bang LE, Svendsen TL, Pedersen OB, Parving HH: Glomerular hyperfiltration in microalbuminuric NIDDM patients. *Diabetologia* 39: 1584–1589, 1996
47. Gambara V, Mecca G, Remuzzi G, Bertani T: Heterologous nature of renal lesions in type II diabetes. *J Am Soc Nephrol* 3:1458–1466, 1993
48. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993