Dissociation of Microangiopathy and Macroangiopathy in Patients With Type 2 Diabetes

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OBJECTIVE — Although persistent hyperglycemia contributes greatly to the progression of diabetic micro- and macroangiopathy, microangiopathy progresses more rapidly than macroangiopathy in some type 2 diabetic patients, with the opposite being true in others. This study was conducted to identify factors responsible for such dissociation.

RESEARCH DESIGN AND METHODS — Patients with proliferative diabetic retinopathy and a carotid intima-media thickness (IMT) level ≤1.0 mm were classified as the microangiopathy group (MIG); those with an IMT level >1.1 mm and without retinopathy or with background retinopathy were assigned to the macroangiopathy group (MAG). Only middle-aged patients, 50–69 years old, were included in this study. There were 54 patients in the MIG and 68 patients in the MAG.

RESULTS — Patients in the MIG were significantly younger at the onset of diabetes, and those in the MAG had a significantly higher mean ratio of apoprotein (apo) B to apoAI. The percentage of patients with a family history of diabetes was significantly higher in the MIG. Maternal inheritance was common among these patients. Those with obesity, a family history of diabetes, and younger onset of hypertension were more common in the MAG. In the multiple logistic regression analyses, maternal inheritance and early onset of diabetes were independent risk factors for the acceleration of microangiopathy. A personal history of obesity and a family history of hypertension were independently related to the development of macroangiopathy.

CONCLUSIONS — Our results suggest that patients with early onset and maternal inheritance of diabetes may have a high risk for the progression of diabetic microangiopathy, while patients with hyperlipidemia, a history of obesity, and a family history of hypertension seem prone to the development of atherosclerosis.

Diabetes Care 21:1451–1454, 1998

Many epidemiological studies have shown that prolonged duration of diabetes and poor glycemic control are major risk factors for diabetic microangiopathy (1–3). The Diabetes Control and Complications Trial (DCCT) showed that the strict control of glycemia achieved by intensive insulin therapy significantly retards the progression of microangiopathy in patients with type 1 diabetes (4). Recent studies have shown that strict glycemic control is also important in preventing microangiopathy in patients with type 2 diabetes (5,6).

The major risk factors for diabetic macroangiopathy are hypertension, hyperlipidemia, obesity, and insulin resistance. A clustering of these factors increases the risk more than any single factor (7,8). Although microangiopathy is a characteristic complication of diabetes, and glycemic control is known to have a significant impact on its progression, it is not clear whether the strict control of glycemia can inhibit the progression of macroangiopathy (9).

Persistent hyperglycemia is associated with the progression of diabetic angiopathy: both micro- and macroangiopathy are present after vascular damage has advanced to a certain extent in elderly patients with diabetes of long duration. Microangiopathy progresses more rapidly than macroangiopathy in some patients, with the opposite being true in other patients.

Previous studies have not addressed the question of which factors are associated with such dissociation of diabetic angiopathies, although glycemic control and genetic background are possibly involved. To identify those factors, we compared type 2 diabetic patients with known dissociation of the progression of micro- and macroangiopathy, using diabetic retinopathy as an indicator of microangiopathy and the carotid intima-media thickness (IMT) as an indicator of macroangiopathy.

RESEARCH DESIGN AND METHODS

— A total of 545 patients with type 2 diabetes who were seen at our department underwent funduscopy as well as ultrasound measurement of the carotid IMT; these patients were divided into three groups, as shown in Table 1. Patients with proliferative retinopathy and an IMT level ≤1.0 mm were classified as the microangiopathy group (MIG); those with an IMT level >1.1 mm and without retinopathy or with background retinopathy were assigned to the macroangiopathy group (MAG). Because age is a strong risk factor for IMT (10), only middle-aged patients, 50–69 years old, were included in the study. There were 54 patients in the MIG, aged 59.5 ± 7.8 years (mean ± SD), and 68 patients in the MAG, aged 61.3 ± 5.4 years.

The carotid arteries were scanned bilaterally by use of a high-resolution ultra-

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Received for publication 12 January 1998 and accepted in revised form 3 June 1998.

Abbreviations: apo, apoprotein; IMT, intima-media thickness; MAG, macroangiopathy group; MIG, microangiopathy group.

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

Table 1—*Diabetic retinopathy and carotid IMT in 545 type 2 diabetic patients*

Retinopathy classification	IMT ≤ 1.0 mm	1.0 mm < IMT < 1.1 mm	IMT > 1.1 mm
NDR, BDR	151 (28)	5 (1)	87 (16)
PDR	114 (21)	6 (1)	182 (33)

Data are *n* (%). BDR, background diabetic retinopathy; NDR, no existence of diabetic retinopathy; PDR, proliferative diabetic retinopathy.

sonographic system (EUB-565; Hitachi Medico, Tokyo) with a 7.5-mHz linear transducer as reported previously (10). Scanning was performed at three different longitudinal projections (anterior-oblique, lateral, and posterior-oblique), and all images were photographed. A micrometer was used to measure IMT of the carotid artery at the site of greatest thickness and at two other points, 1 cm upstream and 1 cm downstream from the site of greatest thickness. The average thickness at these three points was computed for each carotid artery, and the highest value was considered the IMT. All measurements were performed by one trained physician. Second studies of 10 subjects were performed, 1–2 weeks after the first study, to estimate reproducibility. The coefficient of variance of IMT was 2.5%.

The severity of diabetic retinopathy was determined by an ophthalmologist, and each patient was classified as having no diabetic retinopathy, background diabetic retinopathy, or proliferative diabetic retinopathy (11).

Blood samples were drawn after overnight fasting. HbA_{1c} was measured by high-performance liquid chromatography; serum total cholesterol, triglyceride, and HDL cholesterol levels were determined by enzymatic methods (Eiken Kagaku, Tochigi, Japan), and apoproteins (apo) were determined by immunoturbidimetry (Sanwa Kagaku, Nagoya, Japan).

Patients were considered to have diabetic neuropathy if they had relevant symptoms, a positive R-R interval, or a positive result on Schellong's test (12).

The background factors investigated included a family history of diabetes and hypertension, early onset of hypertension (<40 years), and a history of obesity (BMI ≥27 kg/m²).

Data are expressed as means ± SD. The unpaired *t* test was used to examine the significance of differences in mean values between two groups, and a χ^2 test (the Mantel-Haenszel test) was used to examine differences in frequency.

Multiple logistic regression analyses were used to evaluate risk factors for discriminating between micro- and macroangiopathy. The SPSS medical package was employed in data analysis (version 6.1, SPSS, Chicago). A level of $P < 0.05$ was accepted as statistically significant.

RESULTS — The groups did not differ significantly with respect to mean duration of diabetes (~14 years), BMI (~23 kg/m²), HbA_{1c} (~8.9%), blood pressure (~143/~79 mmHg), serum total cholesterol (~5.3 mmol/l), triglycerides (~1.6 mmol/l), HDL cholesterol (~1.26 mmol/l), and the prevalence of subjects receiving treatment for hypertension and hyperlipidemia. The incidence of diabetic neuropathy and nephropathy and of insulin therapy was significantly higher in the group with diabetic microangiopathy (Table 2). These patients were significantly younger at the onset of diabetes, although they did not have a longer duration of diabetes. The group with macroangiopathy had a significantly higher mean apoB-to-apoAI ratio than the group with microangiopathy.

The percentage of patients with a family history of diabetes (77.8 vs. 41.2%, $P < 0.0005$) was significantly higher in the MIG (31.5 vs. 76.8%, $P < 0.0005$), whereas patients with a history of obesity and a family history of hypertension were more common in the MAG (20.3 vs. 52.9%, $P < 0.0005$). The prevalence of subjects who were younger at onset of hypertension did not differ between the two groups.

Among patients with a family history of diabetes, maternal inheritance occurred in 31 of 54 patients in the MIG, and paternal inheritance occurred in 13 of 68 patients in the MAG. There was no sex-related difference in the pattern of inheritance in either group. No patient had symptoms suggesting the presence of mitochondrial myopathy, encephalopathy, lactic acidosis, or stroke-like episodes (MELAS) (13,14).

Multiple logistic regression analyses were applied to identify factors that would distinguish the two groups. Independent variables for microangiopathy were maternal inheritance of diabetes, insulin therapy, neuropathy, nephropathy, age at onset of diabetes, and duration of diabetes; those for macroangiopathy were paternal inheritance of diabetes, a family history of hypertension, early onset of hypertension, obesity, smoking, and the apoB-to-apoAI ratio. Maternal inheritance and early onset of diabetes were independent risk factors for microangiopathy (odds ratios were 2.13, $P < 0.005$, and 1.73, $P < 0.05$, respectively). A history of obesity and a family history of hypertension were independently related to the development of macroangiopathy (odds ratios were 3.74, $P < 0.05$, and 1.60, $P < 0.05$, respectively).

CONCLUSIONS — Major risk factors for the progression of microangiopathy include poor glycemic control, a prolonged history of diabetes, and hypertension (3,15,16). Those for macroangiopathy are aging, obesity, abnormal lipid metabolism, hypertension, and smoking (9,17). Although some risk factors are associated with the pro-

Table 2—*Clinical characteristics of subjects*

Characteristics	Microangiopathy	Macroangiopathy	*P*
n (M/W)	54 (30/24)	68 (40/28)	NS
Retinopathy classification	PDR	NDR, SDR	
IMT (mm)	<1.0	>1.1	
Age (years)	59.5 ± 7.8	61.3 ± 5.4	NS
Age at onset of type 2 diabetes (years)	44.8 ± 10.6	48.9 ± 9.1	<0.05
apoB/apoAI	0.88 ± 0.38	1.04 ± 0.43	<0.05
Neuropathy prevalence (%)	62.5	35.5	<0.05
Macroalbuminuria prevalence (%)	37.0	19.1	<0.05
Insulin treatment (%)	44.4	20.6	<0.005

Data are means ± SD. NDR, no existence of diabetic retinopathy; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.

gression of both micro- and macroangiopathy, microangiopathy does not always progress simultaneously with macroangiopathy, and one type of diabetic angiopathy often worsens more rapidly than the other.

We used diabetic retinopathy as an index of microangiopathy and the carotid IMT as a measure of macroangiopathy. Retinopathy was selected as an indicator of microangiopathy because the clinical features of diabetic neuropathy are diverse and difficult to evaluate. In addition, diabetic nephropathy is the least common microangiopathy, and patients with advanced diabetic nephropathy often develop macroangiopathy because of the long duration of diabetes. Because advanced diabetic macroangiopathy often coexists with advanced microangiopathy, we selected carotid IMT as an index of early macroangiopathy. The IMT for normal subjects is reported to be <1.1 mm (18) or 1.0 mm (19); therefore, the criterion of IMT for microangiopathy was set at ≤1.0 mm, and that for macroangiopathy was set at >1.1 mm. Visona et al. (20) reported that the IMT value was greater in the patients with diabetic microangiopathy than in those without diabetic microangiopathy.

Of the more than 500 type 2 diabetic patients in whom we examined IMT and diabetic retinopathy, 28% of patients did not demonstrate both diabetic retinopathy and atherosclerosis, and 34% of patients did demonstrate both conditions, indicating that the degree of progression of the micro- and macroangiopathy was linked in more than half the patients with type 2 diabetes. Based on the findings that progressed diabetic retinopathy alone was seen in 17% of patients and that carotid atherosclerosis alone was detected in 21%, we assume that dissociation of micro- and macroangiopathy may occur in ~30–40% of middle-aged Japanese type 2 diabetic patients with a mean diabetes duration of 14 years.

The maternal inheritance of diabetes and early onset of type 2 diabetes were independent risk factors for a predominance of microangiopathy. Although long duration of diabetes was considered to be a major risk factor for microangiopathy in previous studies (15,16), it is also linked to macroangiopathy. Thus, long duration of diabetes is not considered to be a significant risk factor for the progression of retinopathy alone. Patients with early onset of diabetes that has a maternal inheritance pattern may have a high risk for the progression of diabetic microangiopathy.

Among the type 2 diabetic patients in whom macroangiopathy predominated, 20 had a family history of diabetes, and in 13 of these patients, the diabetes had a paternal inheritance pattern. A history of obesity and a family history of hypertension were significantly more common in this group. Multiple logistic regression analyses showed that a history of obesity and a family history of hypertension were independent risk factors for the early progression of macroangiopathy. Thus, insulin resistance was associated with obesity, and a genetic susceptibility of hypertension, rather than hyperglycemia itself, appeared to precipitate the earlier progression of macroangiopathy.

The genetic contribution to the development of type 2 diabetes is well known (21,22), and genetic involvement in diabetic angiopathy has also been reported (23–26). In the present study, maternal inheritance was predominant in the MIG, and paternal inheritance tended to predominate in the group with macroangiopathy, suggesting a relationship between diabetic angiopathy and parental history. Although not investigated in this study, mitochondrial gene abnormalities were recently reported to be associated with type 2 diabetes (14,27). It may be important to study the relationship between microangiopathy and mitochondrial gene mutations in patients with type 2 diabetes that has a maternal inheritance pattern.

A few reports have suggested an association of macroangiopathy with genetic factors. ACE polymorphism (28), which may be associated with hypertension, was found to be related to the presence of myocardial infarction, but not to the presence of microangiopathy (29,30), in type 2 diabetic patients. Results of the present study also suggest that a family history of hypertension is a risk factor for macroangiopathy, but not microangiopathy.

In conclusion, our results suggest that patients with early onset of diabetes that has a maternal inheritance pattern may have a high risk for the progression of diabetic microangiopathy, whereas patients with hyperlipidemia, a history of obesity, and a family history of hypertension seem prone to the development of atherosclerosis. Further studies that include larger numbers of patients than this study, and parameters such as hemostatic factors, are necessary to investigate whether our observations might contribute to the management of diabetic vascular complications.

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