Angiotensin I–Converting Enzyme Gene Polymorphism Is Associated With Myocardial Infarction, but Not With Retinopathy or Nephropathy, in NIDDM

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OBJECTIVE — To clarify the relationship between the angiotensin I–converting enzyme (ACE) gene polymorphism and diabetic micro- and macroangiopathy in patients with non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS — We examined 267 NIDDM patients with various stages of diabetic retinopathy, 61 patients with myocardial infarction (MI), and 136 patients without MI. An insertion/deletion polymorphism of the ACE gene was typed by polymerase chain reaction.

RESULTS — Although no association was found between ACE gene polymorphism and diabetic retinopathy or nephropathy, this polymorphism was associated with MI in the patients with NIDDM. Homozygotes for the deletion polymorphism (*DD* genotype) were found more frequently in diabetic patients with MI (31.1%) than in diabetic patients without ischemic heart disease (16.9%), with a relative risk of 2.22 (95% confidence interval 1.11–4.46, $P = 0.024$).

CONCLUSION — These data indicate that ACE gene polymorphism is associated with MI, but not with retinopathy or nephropathy, in patients with NIDDM and suggest that the ACE gene confers susceptibility to diabetic macroangiopathy but not to microangiopathy.

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ACE, angiotensin I–converting enzyme; IDDM, insulin-dependent diabetes mellitus; MI, myocardial infarction; NIDDM, non-insulin-dependent diabetes mellitus.

Diabetic microangiopathy and macroangiopathy are clinically significant complications that affect both quality and length of life in patients with diabetes. The development of vascular complications shows marked interindividual variation (1). Several lines of evidence strongly suggest that genetic factors contribute to the development of diabetic microangiopathies (2). Genetic factors also seem to contribute to myocardial infarction (MI), a macrovascular complication of diabetes, as suggested by the study of familial aggregation (3).

Angiotensin I–converting enzyme (ACE; EC 3.4.15.1) regulates the systemic circulation through angiotensin II formation and kinin metabolism. Serum and cellular ACE levels are genetically determined (4) and are strongly associated with an insertion/deletion polymorphism of the ACE gene. An excess of the *DD* genotype was observed in subjects with MI compared with unaffected subjects in the general population (5). Recently, the association of the ACE gene polymorphism with nephropathy as well as MI was reported in diabetic patients (6,7), suggesting that the polymorphism confers susceptibility to microangiopathy as well as macroangiopathy.

In this study, we typed the alleles of the ACE gene in Japanese diabetic patients with various stages of diabetic retinopathy, nephropathy, and MI to investigate the contribution of this locus to genetic susceptibility to micro- and macroangiopathies.

RESEARCH DESIGN AND METHODS

— Informed consent was obtained from all subjects. For studies on microangiopathy, 267 unrelated patients with non-insulin-dependent diabetes mellitus (NIDDM) were selected from 460 patients attending the Osaka University Hospital and an affiliated hospital so that the mean duration of diabetes was similar in all groups. The association of ACE gene polymorphism with diabetic nephropathy was studied in selected patients ($n = 54$) who had persistent pro-

Table 1—*Distribution of ACE genotypes in subgroups of diabetic retinopathy*

ACE gene polymorphism	Diabetic retinopathy status			
	NDR	SDR	PrePD	PDR
Total				
Allele				
D	32 (35.6)	70 (42.2)	25 (33.8)	73 (35.8)
I	58 (64.4)	96 (57.8)	49 (66.2)	131 (64.2)
Genotype				
DD	6 (13.3)	14 (16.9)	4 (10.8)	15 (14.7)
ID	20 (44.5)	42 (50.6)	17 (46.0)	43 (42.2)
II	19 (42.2)	27 (32.5)	16 (43.2)	44 (43.1)
Duration ≥10 years				
Allele				
D	19 (35.2)	51 (39.8)	22 (37.9)	50 (35.2)
I	35 (64.8)	77 (60.2)	36 (62.1)	92 (64.8)
Genotype				
DD	4 (14.8)	10 (15.6)	4 (13.8)	9 (12.7)
ID	11 (40.8)	31 (48.4)	14 (48.3)	32 (45.1)
II	12 (44.4)	23 (36.0)	11 (37.9)	30 (42.2)

Data are *n* (%). NDR, nondiabetic retinopathy; SDR, simple diabetic retinopathy; PrePDR, preproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2—*Distribution of ACE genotypes and alleles in diabetic patients with MI and diabetic control subjects*

ACE gene polymorphism	Diabetic patients with MI	Control diabetic subjects without ischemic heart disease
n	61	136
Allele		
D	63 (51.6)	105 (38.6)
I	59 (48.4)	167 (61.4)
Genotype		
DD	19 (31.1)	23 (16.9)
ID	25 (41.0)	59 (43.4)
II	17 (27.9)	54 (39.7)

Data are *n* (%). For alleles, relative risk (95% confidence interval) = 1.70 (1.11–2.61) and $P = 0.016$. For genotype (*DD*/*ID* + *II*), relative risk (95% confidence interval) = 2.22 (1.11–4.46) and $P = 0.024$.

teinuria or who needed hemodialysis. Patients without diabetic nephropathy ($n = 35$) who had had diabetes for at least 10 years and had no proteinuria served as control subjects. For studies on macroangiopathy, 61 male patients with NIDDM who suffered MI and 136 patients with NIDDM with no history of ischemic heart disease or any signs of ischemic change on electrocardiogram were studied. The ACE genotypes were determined according to the method of Rigat et al. (4). Patients subdivided by retinopathy status and ACE genotypes were compared with respect to age, body mass index, known duration of diabetes, HbA_{1c}, and total cholesterol level using analysis of variance. Patients subdivided by MI status were compared with respect to age, body mass index, and total cholesterol level using the unpaired Student's *t* test.

RESULTS

Microangiopathy and ACE gene polymorphism

The clinical data for diabetic patients according to their retinopathy were similar between groups with respect to all variables except for age, therapy, and prevalence of hypertension. There was no association between ACE gene polymorphism and retinopathy in these subjects (Table 1) or in a subsample of 191 diabetic patients whose duration of diabetes was 10 years or more (Table 1). Similarly, no statistically significant differences in clinical and metabolic characteristics were detected in the three groups of patients with different ACE genotypes. The genotype frequencies were not significantly different between the patients with nephropathy and those without (*II* 44% vs. 49%, *ID* 43% vs. 34%, *DD* 13% vs. 17%).

Macroangiopathy and ACE gene polymorphism

ACE gene polymorphism was strongly associated with MI in patients with NIDDM. The *D* allele and *DD* genotype of the ACE polymorphism were significantly more frequent in the MI group than in the control group (Table 2). Since there were significant differences in age (55.5 ± 8.4 vs. 59.8 ± 12.0 years of age, $P < 0.05$, mean ± SD) and prevalence of smoking (82.8% vs. 44.3%, $P < 0.001$) between the MI group and the control group, multiple regression analysis was performed. ACE gene polymorphism was independently associated with MI after controlling for age and smoking ($P < 0.05$).

CONCLUSIONS— Our data demonstrated that ACE gene polymorphism was strongly associated with MI in Japanese patients with NIDDM, whereas this locus was not primarily associated with diabetic retinopathy or nephropathy. This is the first study investigating the associations of ACE gene polymorphism with both micro- and macroangiopathy in diabetes.

The frequency of the *DD* genotype was much higher in diabetic patients with MI than in those without ischemic heart disease, and the association appears to be codominant ($P < 0.05$, Mann-Whitney *U* test). The relationship between MI and genotype was still present after controlling for age and smoking. Thus, as reported in French patients with NIDDM (6), the *D* allele of the ACE gene appears to be an independent risk factor for MI in Japanese patients with NIDDM.

The observed associations in the two studies of different ethnic groups were similar (relative risk 2.22 in Japanese vs. 2.56 in French), suggesting that the contribution of this gene to coronary heart disease in diabetes is universal.

In contrast with the strong association of the deletion polymorphism of the ACE gene with susceptibility to MI, this polymorphism showed little effect, if any, on diabetic retinopathy or nephropathy. The lack of association of the ACE gene polymorphism with retinopathy has recently been reported in French patients with IDDM (7).

The *II* genotype of the ACE gene was previously reported to be less frequent in IDDM patients with nephropathy than in control subjects in the French population (7). In contrast, no association was observed in this study. The reason for the difference between the two studies is not clear, but possible reasons are difference in the definition of diabetic nephropathy, difference in type of diabetes (IDDM vs. NIDDM), and racial difference. Because the results in this study with respect to the nephropathy might be limited because of the small number of subjects studied, further studies are required to investigate whether the ACE gene polymorphism could be associated with diabetic nephropathy in other ethnic groups.

The incidence of both fatal and nonfatal coronary heart disease events is two to three times higher in diabetic patients than in nondiabetic subjects. The ACE gene polymorphism may not account for all of the genetic susceptibility to MI but may be a useful marker for detecting high-risk subjects. Since diabetes itself is associated with an increased risk (about threefold) of coronary heart disease, the subgroup of diabetic patients with the *DD* genotype seems to be much more susceptible to MI. Identifying such a high-risk group seems to be clinically important for the prediction and prevention of MI.

Note added in proof: Tarnow et al. recently reported similar data on the relationship between ACE genotype and microangiopathy in IDDM patients. (Tarnow L, Cambien F, Rossing P, Nielsen FS, Hansen BV, Lecerf L, Poirier O, Danilov S, Parving H-H: Lack of relationship between an insertion/deletion polymorphism in the angiotensin I-converting enzyme gene and diabetic nephropathy and proliferative retinopathy in IDDM patients. *Diabetes* 44:489–494, 1995)

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