Increased Plasma Endothelin in NIDDM Patients With Retinopathy

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OBJECTIVE — To elucidate the significance of ET in diabetic microvascular disease.

RESEARCH DESIGN AND METHODS — We determined plasma levels of ir-ET-1 in 25 NIDDM patients without hypertension and/or renal dysfunction.

RESULTS — The plasma levels of ir-ET-1 in NIDDM patients with simple (n = 8) and proliferative (n = 8) retinopathy were 0.58 ± 0.04 pM and 0.60 ± 0.04 pM, respectively, which were significantly higher than those in normal, nondiabetic subjects (0.24 ± 0.02 pM [n = 31]) and NIDDM patients without retinopathy (0.30 ± 0.05 pM [n = 9]).

CONCLUSIONS — These results suggest that plasma ET-1 is related to diabetic microvascular disease.

Endothelin (ET) was discovered in porcine aortic endothelial cells and produces a potent, long-lasting vasoconstriction (1). The presence of ir-ET in the circulating blood (2) suggests that ET is involved in the pathophysiology of various cardiovascular diseases. Although Takahashi et al. (3) recently reported elevated plasma levels of ir-ET in patients with diabetes mellitus, the details of the pathophysiological significance of the elevated ET remain to be elucidated. Because retinopathy is often an early manifestation of diabetic microvascular disease, we determined plasma levels of ir-ET-1 in patients with diabetes mellitus and retinopathy.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; ET, ENDOTHELIN; IR-ET-1, IMMUNOREACTIVE ENDOTHELIN-1; ET-1, ENDOTHELIN-1.

RESEARCH DESIGN AND METHODS

— Plasma levels of ir-ET-1 were determined in 25 NIDDM patients (aged 38–69 yr; mean ± SE, 53 ± 2 yr; 13 men, 12 women) and in 31 normal, nondiabetic subjects (51 ± 2 yr; 9 men, 22 women). All diabetic patients were chosen randomly from the clinic population except for their age, which we tried to match with that of normal, nondiabetic subjects. None of the patients had hypertension, evident renal dysfunction—verified by the absence of macroalbuminuria and a normal serum creatinine concentration—or signs of macrovascular disease. The degree of diabetic retinopathy was assessed by ophthalmoscopic examination by diabetic ophthalmologists. Blood samples were collected in chilled tubes containing Na_2-EDTA (4 mM) and 5×10^5 IU/L aprotinin, and the separated plasma was stored at −70°C until assayed. Plasma ir-ET-1 was determined by enzyme immunoassay (2) after extraction with an Amprep C_2 cartridge (Amersham, UK) (4). The results are means ± SE. Statistical analysis was conducted by Student's t test. The differences were considered significant at $P < 0.05$.

RESULTS

— The plasma levels of ir-ET-1 in NIDDM patients were 0.49 ± 0.04 pM (n = 25), which represented significant difference from the values in approximately age-matched normal subjects (0.24 ± 0.02 pM [n = 31]). The NIDDM patients were divided into two groups: those without retinopathy (n = 9) and those with retinopathy (n = 16; simple, n = 8; proliferative, n = 8). No significant difference was noted between the two groups in age (51 ± 3 vs. 54 ± 2 yr), duration of NIDDM (9.6 ± 1.5 vs. 11.1 ± 1.9 yr), blood pressure (127 ± 4/81 ± 2 vs. 126 ± 3/76 ± 2 mmHg), serum creatinine concentration (67.2 ± 3.5 vs. 75.1 ± 5.3 M), or average HbA_{1c} concentration over the preceding year (8.2 ± 0.4 vs. 8.1 ± 0.4%). Plasma levels of ir-ET-1 in patients with retinopa-

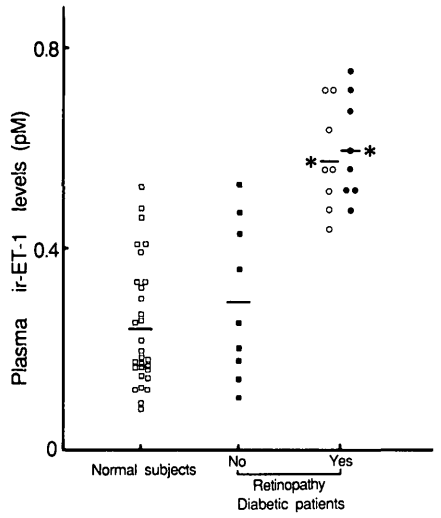

Figure 1—*Plasma levels of ir-ET-1 in diabetic patients. Plasma levels were significantly higher in NIDDM group with simple (○) and proliferative (●) retinopathy than in normal, nondiabetic subjects (□) and in diabetic group without retinopathy (■). Bars represent means. *P < 0.001 vs. values in normal, nondiabetic subjects and NIDDM patients without retinopathy.*

thy (0.59 ± 0.02 pM [n = 16]) were significantly higher (P < 0.001) than those in normal subjects and in NIDDM patients without retinopathy (0.30 ± 0.05 pM [n = 9]). In addition, we observed no significant difference in plasma ir-ET-1 levels between patients with simple retinopathy (0.58 ± 0.04 pM) and proliferative retinopathy (0.60 ± 0.04 pM).

CONCLUSION— In this study, we clearly demonstrated that plasma ir-ET-1 levels are significantly higher in NIDDM patients with diabetic retinopathy than in those without. The details of the mechanism responsible for the increased plasma levels are not known. However, because platelet aggregation often is accelerated in diabetes mellitus, production of ET-1 may be stimulated by the platelet-derived factor(s) (5). In addition, it has been reported recently that plasma levels of ET-1 are increased in patients with atherosclerosis (6). Therefore, the increased plasma ir-ET-1 levels also may be related to the microvascular disease associated with diabetes mellitus. That microaneurysm is accompanied by proliferation of endothelial cells (7) could be morphological evidence to support the stimulated endothelial function.

It is of interest that plasma ir-ET-1 levels are increased even in NIDDM patients with simple retinopathy. This result indicates that an increase in plasma ET-1 is an early phenomenon rather than a result of advanced stage of diabetes mellitus. However, whether the plasma ET-1 participates in the development of diabetic retinopathy is presently unclear.

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