Effects of Long-Term Enalapril Treatment on Persistent Microalbuminuria in Well-Controlled Hypertensive and Normotensive NIDDM Patients

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OBJECTIVE — To determine whether long-term treatment with an angiotensin-converting enzyme (ACE) inhibitor has a beneficial effect on the urinary microalbumin excretion and renal function in non-insulin-dependent diabetes mellitus (NIDDM) patients, enalapril (5 mg/day) was administered for 48 months.

RESEARCH DESIGN AND METHODS — Fifty-two patients with NIDDM who had persistent microalbuminuria in the range of 20–300 mg/24 h, serum creatinine <106.1 μM (1.2 mg/dl), supine systolic blood pressure (BP) <150 mmHg, supine diastolic BP <90 mmHg, and HbA_{1c} <10% were divided into four groups. Twenty-six patients with normotension were divided at random into two groups; one group received enalapril (5 mg/day) (NE group), the other did not receive enalapril (NC group). In the same way, 26 other patients who were already well-controlled with nifedipine (30 mg/day) over a long-term period (4–6 years) were divided at random into two groups; one received enalapril (5 mg/day) (HE group), the other did not receive enalapril (HC group).

RESULTS — After 48 months, urinary albumin excretion (UAE) was markedly reduced in group NE from 102.4 ×/÷ 1.3 to 55.5 ×/÷ 1.3 mg/24 h ($P < 0.005$), whereas no significant change occurred in group NC. In the well-controlled hypertensive groups, a significant reduction in UAE occurred in group HE ($P < 0.05$), whereas no significant change occurred in group HC. No changes in creatinine clearance, BP, or blood glucose control were seen during the study.

CONCLUSIONS — Treatment with enalapril for 48 months may have a beneficial effect on the decline of microalbumin excretion in NIDDM patients.

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BP, blood pressure; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; ACE, angiotensin-converting enzyme; UAE, urinary albumin excretion; NAG, *N*-acetyl-β-glucosaminidase.

Hypertension is often associated with the development of diabetic nephropathy in humans (1,2) and in streptozocin-induced diabetic rats (3). In addition, the progression of nephropathy is accompanied by increased blood pressure (BP) (4). Because of the association between high BP and diabetic nephropathy, intensive antihypertensive treatment is considered to be beneficial in slowing and/or preventing the progression of nephropathy in diabetic patients. Interest is currently focused on finding suitable selective therapy from the many different kinds of antihypertensive drugs for patients with insulin-dependent diabetes mellitus (IDDM) (5,6) and non-insulin-dependent diabetes (NIDDM) (7,8).

It has been reported that the improvement of glomerular hyperfiltration is important in preventing the progression of nephropathy in rats and that treatment with angiotensin-converting enzyme (ACE) inhibitors limits the development of proteinuria and glomerular lesions (9). Taguma et al. (10) observed that captopril, an ACE inhibitor, decreased proteinuria in diabetic patients without reducing systemic BP, which suggests that this effect may be the result of a decrease in intrarenal hypertension. Studies by Bauer et al. (11), Kelleher (12), Mathiesen et al. (13), and Hermans et al. (14) suggest that ACE inhibitors have the specific advantages of decreasing proteinuria and slowing the progression of diabetic nephropathy. However, these studies mainly involved IDDM patients and/or short-term observations.

In this study, we investigated whether long-term treatment with an ACE inhibitor prevents diabetic nephropathy in NIDDM patients.

RESEARCH DESIGN AND METHODS

— Fifty-two patients with NIDDM were selected after their informed consent was obtained and the protocols were approved by the regional scientific ethical committee. We evaluated patients who fulfilled the following

Table 1—*Clinical and laboratory data at baseline*

	Normotensive patients		Well-controlled hypertensive patients	
	Control group (NC)	Enalapril-treated group (NE)	Control group (HC)	Enalapril-treated group (HE)
n	12	12	13	11
Age (years)	64.4 ± 2.4	62.4 ± 3.3	65.5 ± 2.6	63.6 ± 2.2
Duration of diabetes (years)	12.8 ± 2.4	13.0 ± 1.9	11.3 ± 1.3	10.8 ± 1.5
Systolic blood pressure (mmHg)	132.0 ± 3.9	134.5 ± 1.9	136.7 ± 4.0	143.0 ± 4.2
Diastolic blood pressure (mmHg)	72.5 ± 3.0	74.5 ± 2.5	72.5 ± 2.8	77.0 ± 2.6
Body weight (kg)	57.1 ± 3.3	58.4 ± 2.8	59.0 ± 2.7	59.0 ± 2.0
BMI (kg/m^2)	22.5 ± 0.9	24.3 ± 0.8	23.8 ± 0.5	23.8 ± 0.8
UAE (mg/24 h)	66.2 ×/÷ 1.3	102.4 ×/÷ 1.3	48.0 ×/÷ 1.2	72.4 ×/÷ 1.2
Creatinine clearance (ml/min)	91.3 ± 8.8	89.6 ± 10.5	90.1 ± 10.7	89.6 ± 8.4
HbA_{1c} (%)	8.1 ± 0.6	8.2 ± 0.4	8.0 ± 0.4	7.8 ± 0.4

Data are means ± SE. UAE data are geometric means ×/÷ tolerance factor.

criteria: 50–76 years of age, persistent microalbuminuria in the range of 20–300 mg/24 h on 3–4 separate occasions over a 3-month period, serum creatinine <106.1 μM (1.2 mg/dl), supine systolic BP <150 mmHg and diastolic BP <90 mmHg over a long-term period, HbA_{1c} <10% and no history of nondiabetic renal disease. The patients were not taking any drugs apart from oral hypoglycemic agents.

Twenty-six patients with normotension were divided at random into two groups that either received enalapril (5 mg/day) (NE group) or did not receive enalapril (NC group). Similarly, 26 other patients whose BP was already well-controlled with nifedipine (30 mg/day) over a long-term period (4–6 years) were divided at random into two groups that either received enalapril (5 mg/day) (HE group) or did not receive enalapril (HC group). Of the 52 patients who participated in this study, 2 who had poor compliance, 1 who died in a traffic accident, and 1 who moved to another part of the country were excluded from analysis. The clinical and laboratory data of the 48 evaluated patients are given in Table 1. No significant differences between the groups were found using one factor analysis of variance and the Mann-Whitney analysis at the beginning of the study.

All of the patients were seen by the same doctors in the outpatient clinic during the 48-month period. BP was measured in the right arm after 10 minutes of rest in the supine position. At each visit, 24-h urine collections were obtained. Albumin, *N*-acetyl-β-glucosaminidase (NAG), and β_2-microglobulin in the 24-h urine specimens were measured. In addition, creatinine clearance, serum HbA_{1c}, total cholesterol, and triglycerides were determined at each visit (0, 12, 24, 36, and 48 months).

Biochemical analysis

HbA_{1c} was determined by high-performance liquid chromatography (Auto Alc, HA 8121, Kyoto-Daiichi Chemical, Kyoto, Japan). Urinary albumin and β_2-microglobulin were measured by radioimmunoassay (Boehring Werke AG, Marburg, Germany; and Shionogi Pharmaceutical, Kyoto, Japan, respectively). Urinary NAG was measured by the C-peptide response method (Shionogi Pharmaceutical) and serum creatinine was estimated by an enzymatic method (CRE-HA:R2, Kokusai Shiyaku, Kobe, Japan). Serum total cholesterol and triglycerides were measured by an enzymatic method (Dataminer TC-S and TG-S 555, respectively, Kyowa Medics, Tokyo, Japan).

Statistical analysis

Results are shown as means ± SE. (Urinary albumin excretion [UAE] is shown as the geometric mean ×/÷ tolerance factor.) Statistical difference was assessed by the nonparametric manner. Wilcoxon's test was used for paired comparison, and the Mann-Whitney test was used for unpaired comparison.

RESULTS— After 36 months, UAE was persistently lower than that at the baseline in group NE ($P < 0.05$). After 48 months, UAE was markedly reduced in group NE from 102.4 ×/÷ 1.3 to 55.5 ×/÷ 1.3 mg/24 h ($P < 0.005$), whereas the value of UAE in group NC changed from 66.2 ×/÷ 1.3 to 73.3 ×/÷ 1.3 mg/24 h, but the change was not statistically significant (Fig. 1). A significant reduction in UAE, from 72.4 ×/÷ 1.2 to 40.9 ×/÷ 1.3 mg/24 h ($P < 0.05$), was observed after 48 months in group HE, whereas a change of value from 48.0 ×/÷ 1.2 to 62.2 ×/÷ 1.3 mg/24 h was seen in group HC, but this change was also not statistically significant (Fig. 2).

As seen in Figs. 1 and 2 and Table 2, arterial BP, HbA_{1c}, body weight, and renal function (creatinine clearance) were measured as usual in the clinical setting and remained constant in all of the groups throughout the 4 years. No significant

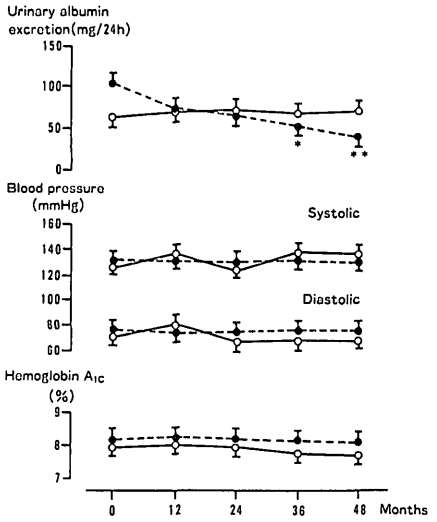

Figure 1—*Time course of UAE (mg/24 h), BP, and HbA_{1c} over 48 months in normotensive NIDDM patients. Control group (NC) (○——○), n = 12; enalapril-treated group (NE) (●----●), n = 12. Data are means ± SE (UAE as geometric mean ×/÷ tolerance factor).*

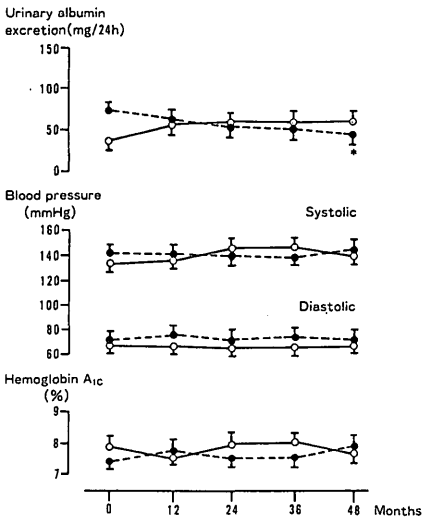

Figure 2—*Time course of UAE (mg/24 h), BP, and HbA_{1c} over 48 months in well-controlled hypertensive NIDDM patients. Control group (HC) (○——○), n = 13; enalapril-treated group (HE) (●----●), n = 11. Data are means ± SE (UAE as geometric mean ×/÷ tolerance factor).*

changes were noted in creatinine clearance, serum total cholesterol and triglycerides, and urinary NAG and β_2-microglobulin in any of the groups.

No side effects of enalapril or nifedipine were reported during the study period.

CONCLUSIONS— The clinical diagnosis of diabetic nephropathy is generally made either through a decline in renal function or through the appearance of persistent proteinuria, although nephropathy is histologically defined by the observation of glomerular lesion changes. In the early phase of diabetic nephropathy, however, a decrease in renal function does not appear (5). Therefore, persistent microalbuminuria is an important sign of early diabetic nephropathy.

Parving et al. (15) suggested that the development and progression of nephropathy in NIDDM patients appear to be closely related to elevated BP, as was observed in IDDM patients. It is well documented that proteinuria decreases in diabetic patients treated with antihypertensive agents, such as antidiuretics, calcium antagonists, and β-blockers (5–7). Many studies indicate that the maintenance of a well-controlled hypertensive state with antihypertensive drugs is important in NIDDM patients because it may decrease albuminuria and delay the progression of nephropathy (5–7,15). In our study of NIDDM patients with persistent microalbuminuria, the ACE inhibitor enalapril reduced UAE in both normotensive patients and well-controlled hypertensive patients who were given nifedipine for a long time before the study, whereas UAE was not lowered in the control groups (Figs. 1 and 2). Recently, among antihypertensive drugs, ACE inhibitors such as captopril and enalapril have been specifically investigated in diabetes because of their possible selective benefits on renal function in addition to their antihypertensive action (11,12). Björck et al. (16) reported that captopril decreased the elevated glomerular filtration rate of hypertensive IDDM patients who had nephropathy and that no correlation between reductions in BP and the renal effect of captopril was observed. They also found that proteinuria in hypertensive IDDM patients was reduced more effectively by enalapril than by metoprolol, a β_1-selective blocker, despite the similar antihypertensive effect of the two drugs (16). In studies of normotensive IDDM patients for 1 year (17,18) and normotensive NIDDM patients for 6 months (19), enalapril decreased UAE. However, Baba et al. (20) reported that they did not find any difference in renal effects between hypertensive NIDDM patients with microalbuminuria who were treated with enalapril and those who were treated with nifedipine. Epstein (21) reported that calcium antagonists diminish proteinuria and that their antiproteinuric effects may be equal in efficacy to ACE inhibitors. Some reasons for the conflicting reports of the effect of ACE inhibitors on renal function in diabetes may be that many of the previous studies were short-term and/or with IDDM patients; and that both normotensive patients and well-controlled hypertensive patients treated with a different kind of antihypertensive drug must be investigated and must be accompanied by control groups that do not receive ACE inhibitors. In addition to a lack of change in arterial BP and glomerular filtration in our patients, the concerns mentioned above were addressed in this study. Therefore, the significant reduction in UAE induced by long-term enalapril in this study cannot be attributed to a decrease in BP.

In this study, it must be emphasized that, in the early phase of diabetic nephropathy, long-term treatment with enalapril reduced UAE without altering BP in normotensive NIDDM patients and well-controlled hypertensive NIDDM patients given nifedipine for a long time before the study.

Several studies have shown that tight blood glucose control (22) and a low-protein diet (23,24) are effective in reducing the albuminuria of IDDM patients. In our study, HbA_{1c}, total cholesterol, triglycerides, and body weight remained nearly identical in all of the

Table 2—*Changes in baseline clinical and laboratory data after 48 months*

	Normotensive patients				Well-controlled hypertensive patients			
	Control group (NC)		Enalapril-treated group (NE)		Control group (HC)		Enalapril-treated group (HE)	
	0 months	48 months	0 months	48 months	0 months	48 months	0 months	48 months
n	12		12		13		11	
Body weight (kg)	57.1 ± 3.3	57.1 ± 3.3	58.4 ± 2.8	57.8 ± 2.7	59.0 ± 2.7	57.6 ± 2.5	59.0 ± 2.0	58.0 ± 2.0
BMI (kg/m^2)	22.5 ± 0.9	22.5 ± 0.9	24.3 ± 0.8	24.2 ± 0.8	23.8 ± 0.5	23.2 ± 0.5	23.8 ± 0.8	23.8 ± 0.7
HbA_{1c} (%)	8.1 ± 0.6	7.6 ± 0.6	8.2 ± 0.4	8.1 ± 0.4	8.0 ± 0.4	8.0 ± 0.6	7.8 ± 0.4	8.0 ± 0.6
Creatinine clearance (ml/min)	91.3 ± 8.8	88.5 ± 9.2	89.6 ± 10.5	94.1 ± 13.4	90.1 ± 10.7	87.2 ± 8.4	89.6 ± 8.4	94.2 ± 8.1
Serum total cholesterol (mM)	4.84 ± 0.24	4.93 ± 0.29	5.53 ± 0.41	5.46 ± 0.41	4.94 ± 0.43	4.89 ± 0.32	5.74 ± 0.43	5.59 ± 0.33
Serum triglycerides (mM)	1.54 ± 0.30	1.59 ± 0.24	1.83 ± 0.39	1.85 ± 0.29	1.26 ± 0.22	1.19 ± 0.15	1.75 ± 0.41	1.77 ± 0.22
Urinary NAG (U/L)	5.7 ± 1.0	5.0 ± 0.8	4.0 ± 0.7	4.1 ± 0.9	3.4 ± 0.8	3.6 ± 0.4	5.4 ± 1.6	4.2 ± 0.6
Urinary β_2-microglobulin (nM)	15.4 ± 5.7	18.5 ± 6.1	12.3 ± 3.0	10.8 ± 3.0	14.8 ± 5.6	21.1 ± 6.9	36.5 ± 24.5	31.6 ± 16.2

Data are means ± SE.

groups during the 4-year treatment period. Thus, these factors also appear to have no effect on declining UAE. Recent reports have indicated that inhibition of vascular angiotensin formation may be related to the antiproteinuric effects of ACE inhibitors. It has been confirmed that ACE inhibition in patients with established diabetic glomerulopathy diminished glomerular permeability to proteins by enhancing barrier size selectivity (25) and that enalapril inhibited both systemic and local ACE activities (26). Moreover, the release of vascular angiotensin stimulated by prenaline is inhibited by β-adrenoceptor blockers (27,28). In addition, when the antihypertensive effect is linked to the inhibition of angiotensin release or synthesis, a decrease in albuminuria is observed in hypertensive diabetic patients (29). Another study also has shown that ACE inhibitors reduce UAE in normotensive NIDDM patients without producing any changes in systemic BP or renal hemodynamics (20).

Although this study used limited numbers of patients, the significant differences of the effects in enalapril groups might be observed in a more short-term period (12 months or 24 months). The study of increasing numbers must be conducted in the future.

In conclusion, the results of this long-term prospective study suggest that an ACE inhibitor, enalapril, can reduce urinary microalbumin excretion in both normotensive and well-controlled hypertensive NIDDM patients without altering BP or blood glucose control.

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