Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria

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Abstract

The effects of a long term reduction in blood pressure on the kidney function of normotensive diabetic patients who had persistent microalbuminuria (30-300 mg albumin/24 hours) were studied in two groups of 10 such patients before and during six months of treatment with either 20 mg enalapril or placebo daily. Treatments were assigned randomly in a double blind fashion. Before treatment both groups had similar clinical characteristics, weight, diet, total glycosylated haemoglobin, median albumin excretion rate (enalapril group 124 mg/24 h, placebo group 81 mg/24 h), and mean arterial pressure (enalapril group 100 (SD 8) mm Hg, placebo group 99 (6) mm Hg). During treatment weight, urinary urea excretion, and total glycosylated haemoglobin remained unchanged. The mean arterial pressure decreased in the enalapril group but not in the placebo group (enalapril group 90 (10) mm Hg, placebo group 98 (8) mm Hg). The median albumin excretion rate also fell in the enalapril group but not in the placebo group (enalapril group 37 mg/24 h, placebo group 183 mg/24 h.) The glomerular filtration rate rose in the enalapril group from 130 (23) ml/min/1.73 m² to 141 (24) ml/min/1.73 m², and total renal resistances and fractional albumin clearance decreased while fractional albumin clearance increased in the placebo group.

These results show that in patients who have diabetes but not hypertension a reduction in blood pressure by inhibition of converting enzyme for six months can reduce persistent microalbuminuria, perhaps by decreasing the intraglomerular pressure.

Introduction

In diabetic patients the long term vital prognosis can be blurred by kidney complications and excessive mortality from cardiovascular disease.^{1,2} The occurrence of microalbuminuria—that is, an albumin excretion rate greater than normal but less than that which gives a positive result with Albustix test strips—is a marker for kidney complications in type I diabetes³⁻⁶ and for both kidney and cardiovascular disease in type II diabetes.⁷

As a high albumin excretion rate in diabetes is of glomerular origin it may be due to either abnormal permeability of the glomerular membrane or increased glomerular perfusion pressure, or both.^{8,9} Diabetic nephropathy occurs after several years of chronic hyperglycaemia,¹⁰⁻¹² which may modify the composition of the glomerular membrane.¹³ But though morphological changes in the glomeruli can be reversed by normal ambient glucose concentrations in rats¹⁴ and humans,¹⁵ the effects of strict metabolic control on the albumin excretion rate in type I diabetes are controversial.¹⁶⁻²⁰

On the other hand, aggressive antihypertensive treatment is an effective way of reducing the decline in the glomerular filtration rate of patients who have established diabetic nephropathy.^{21,22} Microalbuminuria may be accompanied by a slight increase in blood pressure,²³ and preliminary data suggest that early antihypertensive treatment can alter the albumin excretion rate of patients who have incipient diabetic nephropathy.^{24,25}

Experiments on diabetic rats suggest that normal systemic blood pressure and increased glomerular capillary hydraulic pressure are simultaneously reduced by long term inhibition of converting enzyme and that this mechanism may prevent the increase in urinary albumin excretion that would otherwise occur.²⁶ We therefore conducted a six month, randomised, placebo control, double blind study of diabetic patients who had persistent microalbuminuria but were not hypertensive to determine the effects of enalapril, a long acting inhibitor of angiotensin I converting enzyme, on the kidneys. Patients who had long standing diabetes and stable glycaemic control were selected. Enalapril was chosen because it is well tolerated and effective in insulin dependent diabetic subjects who have mild to moderate hypertension.²⁷

Patients and methods

PATIENTS

The participants were selected from the 1500 diabetic patients who attended our clinic regularly. Two comparable groups of 10 patients each were picked using the following criteria: age 20-60; type I or type II diabetes known for at least five years; stable body mass index not exceeding 30 kg/m²; albumin excretion rate 30-300 mg/24 hours in at least two of three monthly measurements; supine blood pressure less than 160/95 mm Hg on three consecutive monthly visits to the outpatient clinic; and no heart, kidney, liver, or systemic disease other than diabetes. The patients were not taking any drugs except for antidiabetic agents and, in the case of two women (cases 1 and 11), progestogen pills as contraceptives (the other women had intrauterine devices). All patients gave their informed consent to participate in the study, which was approved by the ethics committee of the Centre Hospitalo-Universitaire Lariboisière-Saint-Louis, Paris.

All type I diabetic patients were receiving insulin injections twice daily; the four type II patients were receiving a special diet plus metformin and sulphonylureas. Table I lists the patients' individual characteristics at the start of the trial.

STUDY PROTOCOL

As the variability of the albumin excretion rate is high²⁸ the run in period lasted for three months, during which the inclusion criteria were assessed. At end of the run in period patients were studied for kidney function as described below. The patients were then randomly allocated in pairs to receive either 20 mg enalapril maleate or its matched placebo daily for the next six months (the treatment period). Unmarked formulations were provided by Merck Sharp and Dohme (France), and the randomisation schedule was kept in the hospital pharmacy. The patients were followed up by the same investigator (MM). Neither the investigator nor the patients were aware of the type of treatment each patient was receiving in this double blind study.

The patients took the tablets every morning before breakfast. During both the run in and the treatment periods the systolic, diastolic, and mean arterial pressures, together with the body weight and albumin excretion rate, were measured every month, and the proportion of total glycosylated haemoglobin was measured every two months. At end of the treatment period patients were again investigated for kidney function. In all cases the same antidiabetic treatment as that used before the study was maintained.

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The patients were instructed to follow a constant isocaloric diet (mean (SD) 2075 (255) kcal/day; 50% carbohydrates, 35% lipids, 15% proteins) with no restriction on sodium intake.

CLINICAL DETERMINATIONS

The systolic, diastolic, and mean arterial pressures were measured every three minutes between 9 am and 11 am with an automatic device (Dinamap, Critikon, Florida, United States; cuff size 23-13 cm×13 cm) while the patients were in the supine position. The mean of 10 measurements was recorded: the variation among measurements for single patients was 4%.

The albumin excretion rate was measured in urine collected over the 24 hours before the visit to the clinic. A radioimmunoassay method²⁹ was used (sensitivity 0.1 mg/l; intra-assay and interassay variability 5% and 6%, respectively). The mean (SD) albumin excretion rate of 30 age matched controls was 8.1 (8.0) mg/24 h and the variability was 44%. The course of the albumin excretion rate during treatment was calculated for each patient from the slope of albumin excretion rate by plotting albumin excretion rate values against time.

For determination of kidney function the patients arrived at the hospital having fasted at 7 am. Diuresis at 10-15 ml/min was induced by progressive

renal plasma flow. In controls the mean glomerular filtration rate was 118 (8) ml/min/1.73 m² (variability 7%) and the effective renal plasma flow 562 (72) ml/min/1.73 m² (variability 10%). The mean arterial pressure was recorded automatically every five minutes during clearance. The filtration fraction was calculated by dividing the glomerular filtration rate by the effective renal plasma flow (mean control filtration fraction 0.205 (0.033)), and the total renal resistances were calculated by dividing the mean arterial pressure by the effective renal plasma flow (mean control renal resistance 0.170 (0.024) mm Hg/ml/min). The serum albumin concentrations were measured by laser nephelometry. The fractional albumin clearance was calculated by dividing the urinary albumin clearance by the glomerular filtration rate (mean control fractional albumin clearance 1.17 (0.26)×10⁻⁶). During clearance six consecutive measurements of plasma glucose concentration were performed with a glucose oxidase method and the mean value recorded.

The urinary sodium excretion and plasma potassium concentration were measured with flame photometry. The urinary urea concentration was measured with a urease method. On the day of assessment of kidney function 5 ml blood was drawn, after the patient had been lying for two hours in the supine position, for direct immunometric measurement of active and total renin concentrations.³² The total glycosylated haemoglobin concentration was measured with a Cordis kit (mean control glycosylated haemoglobin 6.1 (0.5)%; intra-assay and interassay variability 4% and 6%, respectively).

TABLE 1—Clinical details of patients in study

Case No	Sex	Diabetes			Body mass index (kg/m ²)	Retinopathy	Total glycosylated haemoglobin (%)	Systolic/diastolic blood pressure	Mean arterial pressure
		Age (years)	Type	Known duration (years)					
Enalapril group									
1	F	23	I	14	22.1	Background	9.8	128/75	91
2	M	60	II	11	26.3	Background	7.4	141/83	104
3	F	33	I	17	21.3	Proliferative	7.9	144/90	107
4	M	43	I	8	21.6	None	8.3	143/89	107
5	M	45	II	12	28.4	Background	8.3	143/89	106
6	M	26	I	15	19.7	Proliferative	9.0	132/81	100
7	M	28	I	14	27.1	None	9.7	128/73	92
8	F	44	I	17	21.9	Background	8.8	125/73	92
9	F	42	I	26	27.7	Background	7.6	142/87	105
10	M	49	I	35	22.6	Proliferative	6.9	144/82	108
Mean (SD)		39.3 (11.6)		16.9 (7.9)	23.9 (3.1)		8.37 (0.91)	137/82 (7/8)	100 (8)
Placebo group									
11	F	30	I	14	22.3	Proliferative	9.5	129/79	98
12	M	52	II	12	29.7	Background	6.7	139/89	105
13	F	30	I	16	22.1	Proliferative	7.0	130/80	100
14	M	45	I	13	26.3	Background	8.6	131/85	101
15	M	50	II	7	24.5	Background	6.7	131/82	99
16	M	21	I	13	21.3	Background	9.5	126/70	87
17	M	30	I	9	22.5	None	9.0	134/81	98
18	F	49	I	36	23.9	Background	7.6	136/88	104
19	F	35	I	20	24.5	Background	8.5	141/89	106
20	M	47	I	40	22.6	Proliferative	8.6	125/71	90
Mean (SD)		38.9 (10.9)		18.0 (11.1)	24.0 (2.5)		8.17 (1.03)	132/81 (5/7)	99 (6)

TABLE 2—Mean (SD) concentrations of plasma glucose during clearance studies and serum potassium and urinary sodium and urea excretion at time of the kidney studies

	Plasma glucose (mmol/l)	Serum potassium (mmol/l)	Urinary sodium (mmol/24h)	Urinary urea (mmol/24h)
<i>Enalapril group (n=10):</i>				
0 months	7.2 (2.1)	4.2 (0.4)	113 (37)	294 (152)
6 months	7.1 (2.3)	4.1 (0.3)	109 (30)	283 (114)
<i>Placebo group (n=10)</i>				
0 months	7.6 (2.4)	4.0 (0.2)	105 (31)	301 (1174)
6 months	7.8 (2.5)	4.1 (0.3)	96 (38)	295 (188)

water loading,³⁰ and patients remained supine when they were not voiding urine. After constant diuresis had been observed for at least one hour, the simultaneous clearances of iodine-125 iodothalamate and iodine-131 hippurate (Amersham Laboratories, Amersham) were calculated from primed infusions at a constant flow rate for two hours.³¹ These clearance values were calculated from six periods of 20 minutes and adjusted for a body surface of 1.73 m². The ¹²⁵I-iodothalamate clearance reflected the glomerular filtration rate, and the ¹³¹I-hippurate renal extraction measured the effective

STATISTICAL ANALYSIS

The values expressed are means (SD), except for the albumin excretion rate, which is shown as median and range values. These albumin excretion rate values were transformed into log₁₀ for calculations because of their skew distribution. For the albumin excretion rate, mean arterial pressure, systolic and diastolic pressures, and total glycosylated haemoglobin a two way, repeated measured analysis of variance was used to assess the effects of time (within subjects) or group (between subjects) during both the run in and the treatment periods.³³ Standard paired and unpaired *t* tests were used for other calculations.

Results

CONTROL OF BLOOD PRESSURE AND METABOLISM (fig 1)

During the run in period the mean arterial pressure was comparable in the enalapril and placebo groups (100 mm Hg (8) v 99 (6) mm Hg, respectively). Thereafter, during the treatment period, it declined in the enalapril group compared with the placebo group (90 (10) mm Hg v 98 (9) mm Hg respectively); time NS, treatment *p*<0.001, analysis of variance; fig 1. The

FIG 1—Mean arterial pressure and mean total glycosylated haemoglobin in enalapril group (●, ■) and placebo group (○, □) during run in and treatment periods. Bars represent SD.

FIG 2—Individual albumin excretion rates in enalapril group (above) and placebo group (below) throughout study. Thick lines indicate median values.

systolic and diastolic pressures varied similarly from 137/82 (7/8) mm Hg to 124/72 (13/9) mm Hg in the enalapril group and from 132/81 (5/7) mm Hg to 135/78 (11/10) mm Hg in the placebo group.

The total glycosylated haemoglobin was 8.37 (0.91)% in the enalapril group and 8.17 (1.03)% in the placebo group during the run in period, and this remained steady thereafter (fig 1). The mean body weight was unchanged throughout the study; in the enalapril group it ranged from 67 (12) kg to 68 (12) kg and in the placebo group from 70 (14) kg to 70 (14) kg. No side effects of the drug were recorded.

COURSE OF ALBUMIN EXCRETION RATE DURING STUDY (fig 2)

Figure 2 shows the albumin excretion rates for individual patients. During the run in period the variability of the albumin excretion rate for each individual patient ranged from 9% to 101% (mean 36% for enalapril group and 29% for placebo group). The variability and albumin excretion rate were comparable in both groups during the run in period. During treatment the median albumin excretion rate in the enalapril group varied from 124 (range 27-380) mg/24 h to 37 (21-382) mg/24 h six months later and in the placebo group from 81 (32-300) mg/24 h to 183 (43-380) mg/24 h (time NS, treatment $p < 0.01$, analysis of variance). The mean progression of albumin excretion rate was +6.2 mg/24 h/month (95% confidence interval (CI) -12.8 to 25.2) in the placebo group compared with -7.9 mg/24 h/month (95% CI -25.5 to 9.7) in the enalapril group ($p < 0.005$).

FIG 3—Individual plasma concentrations of active renin (above) and total renin (below) in enalapril group and placebo group before and after six months of treatment. — — — = Mean values. □ = Mean control value. Bars represent 2SD. * Paired t test.

KIDNEY FUNCTION AFTER SIX MONTHS OF TREATMENT WITH ENALAPRIL OR PLACEBO (figs 3 and 4)

Both groups had comparable mean plasma glucose and serum potassium concentrations and urinary sodium and urea excretions measured at time zero and six months (table II). In all patients who received enalapril the active and total renin concentrations increased significantly during treatment, whereas no change was observed in patients who received placebo (fig 3). Figure 4 shows the individual glomerular filtration rates, effective renal

plasma flows, total renal resistances, and fractional albumin clearances. In the enalapril group the glomerular filtration rate increased significantly from 130 (23) ml/min/1.73 m² to 141 (24) ml/min/1.73 m² ($p < 0.005$). In the placebo group a non-significant decrease from 133 (26) ml/min/1.73 m² to 127 (25) ml/min/1.73 m² was seen. The initial effective rate plasma flow increased significantly in the enalapril group from 526 (113) ml/min/1.73 m², to 581 (128) ml/min/1.73 m² ($p < 0.05$), but not in the placebo group (597 (124) ml/min/1.73 m² to 602 (15) ml/min/1.73 m²). The mean filtration fraction remained identical in the two groups at times zero and six months (enalapril 0.256 (0.053) to 0.256 (0.064); placebo 0.223 (0.014) to 0.222 (0.027)). The initial total renal resistances declined in the enalapril group from 0.2252 (0.0679) mm Hg/ml/min to 0.1763 (0.0433) mm Hg/ml/min ($p < 0.01$) but not in the placebo group (0.2167 (0.0898) mm Hg/ml/min to 0.2262 (0.1015) mm Hg/ml/min). The initial fractional albumin clearance was greater than the control clearance in both groups. At six months it had

dropped in the enalapril group from $2.25 (1.79) \times 10^{-5}$ to $1.25 (1.40) \times 10^{-5}$ ($p < 0.05$) but risen significantly in the placebo group from $1.67 (1.34) \times 10^{-5}$ to $2.58 (1.50) \times 10^{-5}$ ($p < 0.01$).

Discussion

In this study a significant decrease in the albumin excretion rate was seen over six months in normotensive diabetic patients who had persistent microalbuminuria and whose blood pressure was being reduced by inhibition of converting enzyme. This was shown by measurements of the albumin excretion rate, which were repeated to allow for variation.²⁸ The drop was not caused by improved glycaemic control, as the total proportion of glycosylated haemoglobin remained identical throughout the study in both the enalapril and placebo groups. Neither could it be explained by changes in food intake or protein consumption,^{34,35} as the body weight and urinary urea excretion remained stable. The increases in glomerular filtration rate and effective renal plasma flow seen in the enalapril group were accompanied by a reduction in total renal resistance. The concomitant changes in the renin concentrations of these patients suggest good compliance with treatment and effective inhibition of converting enzyme at the times of measurement. As a reduction in the fractional albumin clearance was seen at these times modifications of renal haemodynamics may have reduced glomerular permeability to albumin.

The aim of this work was not to show that near normoglycaemia has a beneficial effect on the course of albumin excretion rate in diabetic patients. In this respect reports concerning type I diabetes are conflicting and suggest that such control is beneficial^{16,18} or ineffective.^{19,20} As the metabolic condition of the patients studied here was good and stable a reduction in their albumin excretion rate can justifiably be attributed to the connection between albumin excretion rate and variations in blood pressure.

The diabetic patients in this study had initial blood pressures below those defined as signs of mild or moderate hypertension in a general population.³⁶ Christensen and Mogensen *et al* reported that blood pressure was slightly increased in patients with incipient diabetic nephropathy.^{23,37} They also reported a decrease in the albumin excretion rate of six patients treated with metoprolol, a selective β blocker, for a mean period of five years.²⁴ Hommel *et al* reported that the albumin excretion rate of similar patients decreased when their blood pressure was reduced over a short period with clonidine.³⁸ In the present study the patients did not have any hypertension, so no lower limit to blood pressure was set as a selection criterion. Nevertheless, the blood pressure of all the patients receiving enalapril decreased after the run in period. The results obtained with this limited number of patients over six months therefore support the notion that in patients who have diabetes with microalbuminuria a long term reduction in their blood pressure can reverse the course of albumin excretion rate.

In diabetes a high glomerular filtration rate frequently occurs after the onset of the disease³¹ and may also occur in incipient diabetic nephropathy.³⁷ In this study we found initial hyperfiltration in eight of 20 patients (fig 4), a proportion similar to that reported by Feldt-Rasmussen *et al*.²⁰ Clinical and experimental evidence shows that in diabetes chronic hyperfiltration is crucial in generating kidney disease.^{6,9,39} This in turn may increase the resistance of the renal vascular bed during subsequent stages of the disease. The significant increase in glomerular filtration rate found here after six months of treatment with enalapril therefore calls for further reflection.

Hollenberg *et al* reported increases in the glomerular filtration rate when teprotide, an angiotensin I converting enzyme inhibitor, was given over a short period to patients who had essential hypertension.⁴⁰ The increases in glomerular filtration rate and effective renal plasma flow that we observed in patients given enalapril in this study can be attributed to the opening up of additional glomeruli and capillary loops, with a subsequent reduction in renal resistance.⁴¹ The filtration fraction, however, did not decrease in patients given enalapril in this study, despite angiotensin II acting predominantly on the efferent arteriole.⁴² This may be

FIG 4—Individual values for glomerular filtration rate (above), total renal resistance (above middle), effective renal plasma flow (below middle), and fractional albumin clearance (below) in enalapril group and placebo group before and after six months of treatment. — — — = Mean values. □ = Mean control values. Bars represent 2SD. * Paired *t* test.

due to the method not being precise enough to measure minimal variations in humans. It is also possible that the afferent and efferent arteriolar resistances were reduced proportionately⁴³ or that the glomerular ultrafiltration coefficient increased during inhibition of converting enzyme.²⁶

Our results agree with those of Zatz *et al*, who observed that in normotensive rats who had experimental diabetes reducing the blood pressure with enalapril restricted the intraglomerular pressure and consequently reduced albuminuria but did not alter hyperfiltration.²⁶ The reduction in fractional albumin clearance found here after six months of treatment with enalapril suggests that the renal haemodynamic changes discussed above decreased the glomerular permeability to albumin. The concomitant reduction of albumin excretion rate and increase in glomerular filtration rate support the idea that in diabetes the intraglomerular capillary pressure may be more important than hyperfiltration in modifying permeability to albumin.

Nevertheless, the relative importance of the decrease in systemic blood pressure and of the reduction in intraglomerular pressure cannot be analysed separately in our study. Other studies of inhibition of converting enzyme in humans have dealt with hypertensive patients who had diabetic nephropathy; thus Taguma *et al* reported that in patients with advanced diabetic nephropathy severe proteinuria can be reduced by captopril without affecting the blood pressure and suggested that this drug might also reduce intrarenal hypertension.⁴⁴ Björck *et al* mentioned increased renal plasma flow and unchanged glomerular filtration rate in similar patients.⁴⁵ Hommel *et al* reported that in insulin dependent diabetic patients with overt nephropathy albuminuria declined with a reduction in blood pressure after 12 weeks of captopril treatment.⁴⁶ A slight but significant decrease in the glomerular filtration rate was also seen during the same period. An explanation for this apparent discrepancy between Hommel's study and ours could be that autoregulation of the glomerular filtration rate is impaired in overt diabetic nephropathy⁴⁷ but not in incipient nephropathy.³⁸

The finding that inhibition of converting enzyme can reduce microalbuminuria in diabetic patients even in the absence of hypertension is promising but should be interpreted with caution. Firstly, the treatment with enalapril lasted for only six months, and longer studies are needed to confirm the beneficial effects of combining inhibition of converting enzyme with antidiabetic treatment in diabetes accompanied by microalbuminuria. Secondly, the potential long term side effects of inhibition of converting enzyme are not yet known. Thirdly, it is not clear whether the reduction in albumin excretion rate seen in this study was due to a reduction in systemic blood pressure independent of the antihypertensive agent used or to specific changes in intraglomerular pressure caused by inhibition of converting enzyme inhibition. Fourthly, the reduction of microalbuminuria can be only an index of the mechanical consequences of the reduction in blood pressure or glomerular pressure, or both, and we do not have any evidence of a proportional reduction in the glomerular lesions. Lastly, the reduction in blood pressure must not prevent studies to find the best possible control of blood glucose: recent data suggest that in insulin dependent diabetes two years of strict glycaemic control can slow down the course of nephropathy.⁴⁸

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