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 diabetes[3-6] 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 rats[14] 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 high[28] 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 patients 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 method[29] 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 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 m^2. The ^{125}I-iodothalamate clearance reflected the glomerular filtration rate, and the ^{131}I-hippurate renal extraction measured the effective renal plasma flow. In controls the mean glomerular filtration rate was 118 (8) ml/min/1·73 m^2 (variability 7%) and the effective renal plasma flow 562 (72) ml/min/1·73 m^2 (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 I—*Clinical details of patients in study*

Case No	Sex	Age (years)	Diabetes: Type	Diabetes: Known duration (years)	Body mass index (kg/m^2)	Retinopathy	Total glycosylated haemoglobin (%)	Systolic/diastolic blood pressure	Mean arterial pressure
					Enalaparil 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 II—*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)
Enalapril group (n=10):				
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)
Placebo group (n=10)				
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)

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 $\log_{10}$ 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

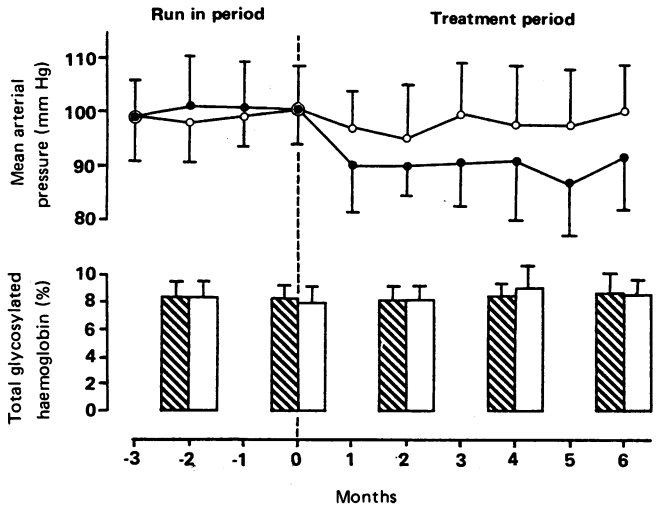

FIG 1—Mean arterial pressure and mean total glycosylated haemoglobin in enalapril group (●, ▨) and placebo group (○, □) during run in and treatment periods. Bars represent SD.

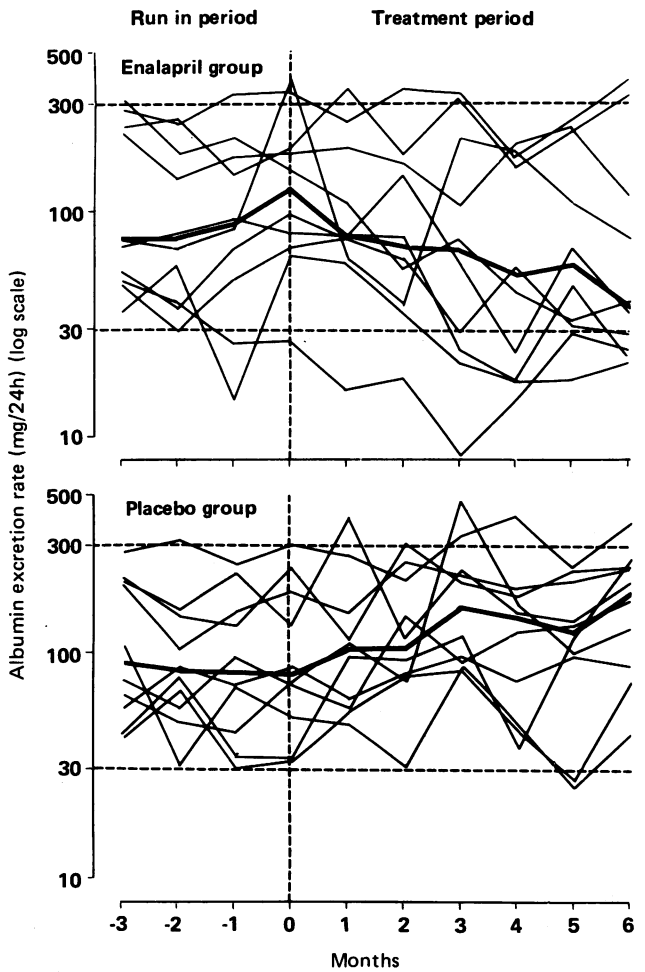

FIG 2—Individual albumin excretion rates in enalapril group (above) and placebo group (below) throughout study. Thick lines indicate median values.

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 ($p<0·005$).

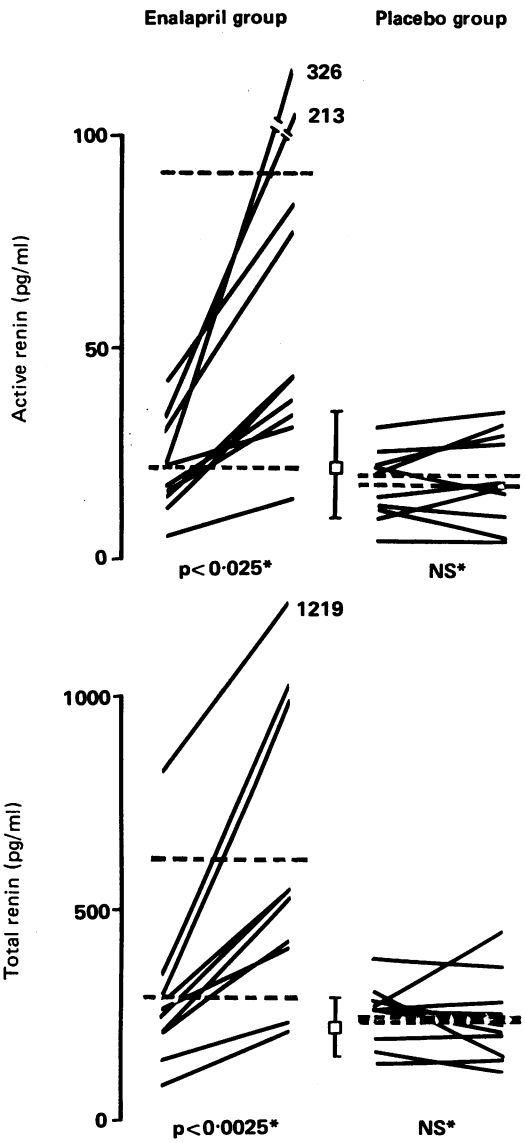

FIG 3—Individual plasma concentrations of active renin (above) and total renin (below) in enalapril group and placebo group before and after six months of treatment. - - - - =Mean values. □=Mean control value. Bars represent 2SD. * Paired *t* test.

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 $2·25\ (1·79)\times10^{-5}$ to $1·25\ (1·40)\times10^{-5}$ ($p<0·05$) but risen significantly in the placebo group from $1·67\ (1·34)\times10^{-5}$ to $2·58\ (1·50)\times10^{-5}$ ($p<0·01$).

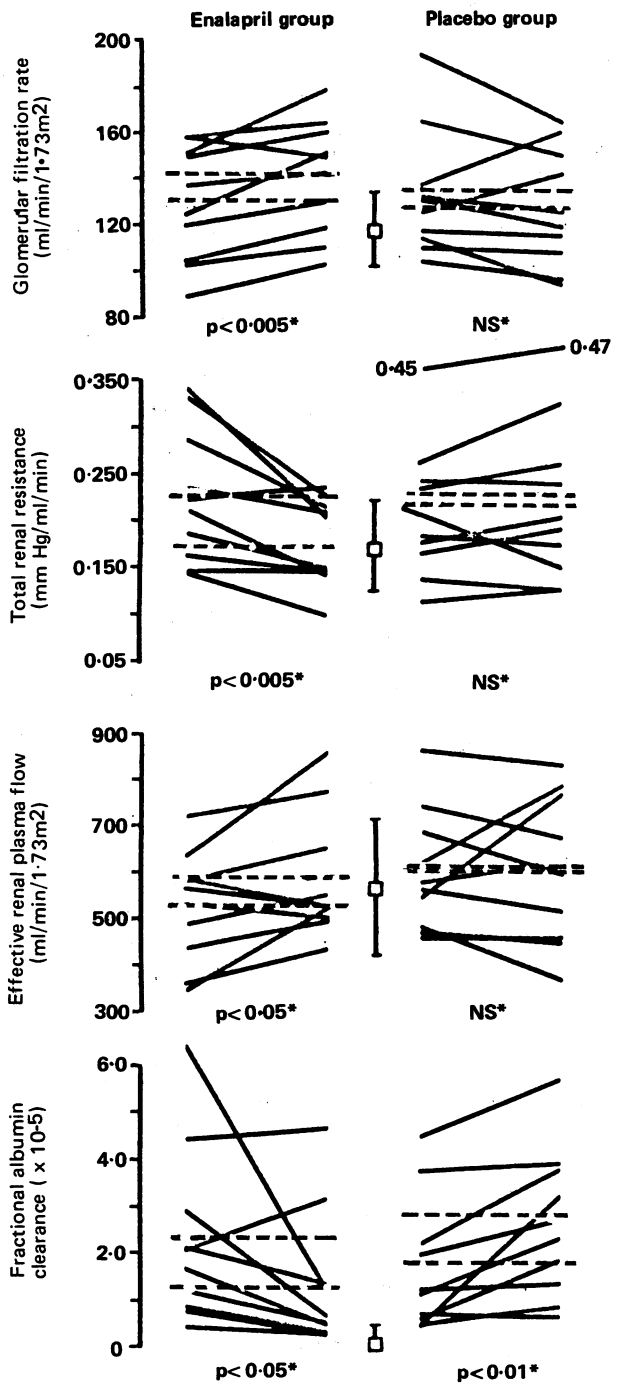

FIG 4—Individual values for glomerular filtration rate (above), total renal resistance (above middle), effective renal plasma flow (below middle), and fractional albumin clearance (below) in enalapril group and placebo group before and after six months of treatment. - - - - =Mean values. □=Mean control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

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 disease[31] 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

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 proportionately[43] 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 nephropathy[47] 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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References

1 Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in type 1 (insulin-dependent) diabetes: an epidemiological study. *Diabetologia* 1983;2:496-501.
2 Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979;2:120-6.
3 Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982;ii:1430-2.
4 Parving HH, Oxenboll B, Svendsen PAA, Sandhal Christiansen J, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy: longitudinal study of urinary albumin excretion. *Acta Endocrinol (Copenh)* 1982;**100**:550-5.
5 Mathiesen ER, Oxenboll B, Johansen K, Svendsen PAA, Deckert T. Incipient nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia* 1984;**26**:406-10.
6 Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 1984;**311**:89-93.
7 Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984;**310**:356-60.
8 Viberti GC, Mackintosh D, Keen H. Determinants of the penetration of proteins through the glomerular barrier in insulin-dependent diabetes mellitus. *Diabetes* 1983;**32**(suppl 2):92-5.
9 Hostetter TH. Diabetic nephropathy. *N Engl J Med* 1985;**312**:642-4.
10 Pirart J. Diabète et complications dégénératives. Présentation d'une étude prospective portant sur 4400 cas observés entre 1947 et 1973. *Diabete Metab* 1977;**3**:97-107.
11 Pirart J. Diabète et complications dégénératives. Présentation d'une étude prospective portant sur 4400 cas observés entre 1947 et 1973. *Diabete Metab* 1977;**3**:173-82.
12 Pirart J. Diabète et complications dégénératives. Présentation d'une étude prospective portant sur 4400 cas observés entre 1947 et 1973. *Diabete Metab* 1977;**3**:245-56.
13 Spiro RG. Search for a biochemical basis of diabetic microangiopathy. *Diabetologia* 1976;**12**:1-14.
14 Mauer SM, Steffes MW, Sutherland DER, Najarian JS, Michael AF, Brown DM. Studies of the rate of regression of the glomerular lesion in diabetic rats treated with pancreatic islet transplantation. *Diabetes* 1975;**24**:280-5.
15 Abouna GM, Al-Adnani MS, Kremer GD, Kumar SA, Daddah SK, Kusma G. Reversal of diabetic nephropathy in human cadaveric kidneys after transplantation in non-diabetic recipients. *Lancet* 1983;ii:1274-6.
16 Viberti GC, Pickup JC, Jarrett RJ, Keen H. Effect of control of blood glucose on urinary excretion of albumin and beta-2-microglobulin in insulin dependent diabetes. *N Engl J Med* 1979;**300**:638-41.
17 Viberti GC, Bilous RW, Mackintosh D, Bending JJ, Keen H. Long-term correction of hyperglycaemia in progression of renal failure in insulin dependent diabetes. *Br Med J* 1983;**286**:598-602.
18 Kroc collaborative study group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria: a preliminary multicenter trial. *N Engl J Med* 1984;**311**:365-77.
19 Beck-Nielsen H, Richelsen B, Mogensen CE, *et al*. Effect of insulin pump treatment for one year on renal function and retinal morphology in patients with IDDM. *Diabetes Care* 1985;**8**:385-9.
20 Feldt-Rasmussen B, Mathiesen ER, Hegedus L, Deckert T. Kidney function during 12 months of strict metabolic control in insulin-dependent diabetic patients with incipient nephropathy. *N Engl J Med* 1986;**314**:665-70.
21 Parving HH, Andersen AR, Smidt UM, Svendsen PAA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1983;ii:1175-9.
22 Mogensen CE. Long term antihypertensive treatment inhibiting progression of diabetic nephropathy. *Br Med J* 1982;**285**:685-8.
23 Christensen CK. Abnormal albuminuria and blood pressure rise in incipient diabetic nephropathy induced by exercise. *Kidney Int* 1984;**25**:819-23.
24 Christensen CK, Mogensen CE. Effect of antihypertensive treatment on progression of incipient diabetic nephropathy. *Hypertension* 1985;**7**:9-13.
25 Friedman PJ, Dunn PJ, Jury DR. Metoprolol and albumin excretion in diabetes. *Lancet* 1986;ii:43.
26 Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 1986;**77**:1925-30.
27 Passa P, Leblanc H, Marre M. Effects of enalapril in insulin-dependent diabetic subjects with mild to moderate uncomplicated hypertension. *Diabetes Care* 1987;**10**:200-4.
28 Feldt-Rasmussen B, Mathiesen ER. Variability of urinary albumin excretion in incipient diabetic nephropathy. *Diabetic Nephropathy* 1984;**3**:101-3.
29 Christensen CK, Orskov C. Rapid screening PEG radioimmunoassay for quantification of pathological albuminuria. *Diabetic Nephropathy* 1984;**3**:92-4.
30 Viberti GC, Mogensen CE, Keen H, Jacobsen FK, Jarrett RJ, Christensen CK. Urinary excretion of albumin in normal man. The effect of water loading. *Scand J Clin Lab Invest* 1982;**42**:147-51.
31 Mogensen CE. Glomerular filtration rate and renal plasma flow in short-term and long-term juvenile diabetes mellitus. *Scand J Clin Lab Invest* 1971;**28**:91-100.
32 Ménard J, Guyenne T, Corvol P, Pau B, Simon B, Roncucci R. Direct immunometric assay of active renin in human plasma. *J Hypertension* 1985;**3**(suppl 3):275-8.
33 Winer BJ. *Statistical analysis in experimental design*. 2nd ed. New York: McGraw-Hill, 1971.
34 Vasquez B, Glock EV, Savage PJ, *et al*. Sustained reduction of proteinuria in type 2 (non-insulin-dependent) diabetes following diet induced reduction of hyperglycaemia. *Diabetologia* 1984;**26**:127-33.
35 Brenner B, Meyer TW, Hostetter T. Dietary protein intake and the progressive nature of kidney disease. *N Engl J Med* 1982;**307**:652-9.
36 Joint National Committee on detection, evaluation and treatment of high blood pressure. The 1984 report of the joint national committee on detection, evaluation and treatment of high blood pressure. *Arch Intern Med* 1984;**144**:1045-7.
37 Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient nephropathy. *Diabetes* 1983;**32**(suppl 2):64-78.
38 Hommel E, Mathiesen E, Edsberg B, Bahnsen M, Parving HH. Acute reduction of arterial blood pressure reduces albumin excretion in type 1 (insulin-dependent) diabetic patients with incipient nephropathy. *Diabetologia* 1986;**29**:211-5.
39 Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 1982;72:375-80.
40 Hollenberg NK, Swartz SL, Passan DR, Williams GH. Increased glomerular filtration rate after converting-enzyme inhibition in essential hypertension. *N Engl J Med* 1979;**301**:9-12.
41 Ichikawa I, Brenner BM. Glomerular actions of angiotensin II. *Am J Med* 1984;**76**:43-9.
42 Hall JE, Guyton AC, Jackson TE, Coleman TG, Lohmeier TE, Tripoddo NC. Control of glomerular filtration rate by renin-angiotensin system. *Am J Physiol* 1977;**233**:F366-72.
43 Navar LG, Rosivall L. Contribution of the renin-angiotensin system to the control of intrarenal hemodynamics. *Kidney Int* 1984;**25**:857-68.
44 Taguma Y, Kilamoto Y, Futaki G, *et al*. Effect of captopril on heavy proteinuria in azotemic diabetics. *N Engl J Med* 1985;**313**:1617-20.
45 Björck S, Nyberg G, Mulec H, Granerus G, Herlitz H, Aurell M. Beneficial effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. *Br Med J* 1986;**293**:471-4.
46 Hommel E, Parving HH, Mathiesen E, Edsberg B, Nielsen MD, Giese J. Effect of captopril on kidney function in insulin dependent diabetic patients with nephropathy. *Br Med J* 1986;**293**:467-70.
47 Parving HH, Kastrup H, Smidt UM, Andersen AR, Feldt-Rasmussen B, Sandahl-Christiansen J. Impaired autoregulation of glomerular filtration rate in type 1 (insulin-dependent) diabetic patients with nephropathy. *Diabetologia* 1984;**27**:547-52.
48 Feldt-Rasmussen B, Mathiesen ER, Deckert T. Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. *Lancet* 1986;ii:1300-4.

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