Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy

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Abstract

Objective—To assess whether inhibition of angiotensin converting enzyme protects kidney function in diabetic nephropathy.

Design—Open, randomised follow up study of normotensive insulin dependent diabetics with nephropathy either treated or not with captopril for one year.

Setting—Outpatient diabetic clinic in a tertiary referral centre.

Patients—32 Normotensive patients with insulin dependent diabetes complicated by nephropathy who were randomised either to the treatment group (n=15) or to the control group (n=17).

Interventions—The treatment group was given captopril (25-100 mg/day) for 12 months, the average dose during the second six months of the study being 40 mg daily. Controls were not treated.

Main outcome measures—Albuminuria, arterial blood pressure, and the glomerular filtration rate.

Results—Mean arterial blood pressure fell by 3 (SE 2) mm Hg in the captopril treated group and rose by 6 (1) mm Hg in the controls. In addition, albuminuria declined by 11% in the captopril treated group and rose by 55% in the controls, fractional albumin clearance fell by 17% in the captopril treated group and increased by 66% in the controls, and the glomerular filtration rate declined by 3.1 (2.8) ml/min/1.73 m² with captopril and by 6.4 (3.1) ml/min/1.73 m² in the controls.

Conclusion—Inhibition of angiotensin converting enzyme arrests the progressive rise in albuminuria in normotensive insulin dependent diabetics with nephropathy.

Introduction

The clinical syndrome of diabetic nephropathy is characterised by persistent albuminuria associated with a relentless decline in the glomerular filtration rate and raised arterial blood pressure.¹ Roughly 40% of all insulin dependent and non-insulin dependent diabetics suffer with this complication.^{2,5} Nephropathy is the main cause of the increased morbidity and mortality in patients with insulin dependent disease.^{2,4,6} The excess mortality of insulin dependent diabetics with nephropathy is 80-100 times that of the age and sex matched background population and is due to an enormous excess of deaths from cardiovascular disease (200-400 times that in the age matched population) and end stage renal disease (thousands of times that in the age matched population).^{3,7} The cost of caring for patients with end stage renal disease in the United States currently exceeds \$0.8 billion a year for diabetic nephropathy alone and is rising rapidly.⁸

Effective antihypertensive treatment was the only form of management found to reduce albuminuria and postpone renal insufficiency in diabetic nephro-

pathy.⁹⁻¹⁴ Almost all the patients studied (49/57) satisfied the World Health Organisation's criteria for arterial hypertension (diastolic blood pressure ≥ 95 mm Hg) at the start of antihypertensive treatment, the remaining few patients having borderline hypertension (diastolic blood pressure between 90 and 95 mm Hg). No treatment has been proved to be effective in normotensive insulin dependent diabetics with overt clinical nephropathy (persistent macroalbuminuria >300 mg/24 h). Studies in normotensive rats with streptozocin induced diabetes, however, show that inhibition of angiotensin converting enzyme confers definite long term protection against the development of glomerulopathy.^{15,16} Marre *et al* have shown that long term inhibition of angiotensin converting enzyme in normotensive diabetics with persistent microalbuminuria (30-300 mg/24 h) can delay the development of nephropathy.¹⁷

We report the results of a prospective randomised controlled trial of the effect on kidney function of 12 months of angiotensin converting enzyme inhibition in normotensive patients with insulin dependent diabetes complicated by overt diabetic nephropathy. Captopril was chosen because it is well tolerated and effective in hypertensive diabetic nephropathy.^{12,14,18}

Patients and methods

We examined the records of all insulin dependent diabetics (n=180) with albuminuria >300 mg/24 h (200 μ g/min) visiting the outpatient clinic at Hvidøre Hospital in 1985.⁶ One hundred and seven patients with arterial hypertension ($>160/95$ mm Hg; WHO criteria) were excluded from further investigation. The remaining patients (n=73) were invited to participate if they fulfilled the following criteria: persistent albuminuria (>300 mg/24 h), serum creatinine concentration <120 μ mol/l or a glomerular filtration rate >60 ml/min/1.73 m², average of three or more consecutive blood pressure readings below 150/90 mm Hg, no oedema, not taking other drugs apart from oral contraceptives, age under 50, and onset of diabetes mellitus before the age of 41. Thirty five patients fulfilled these criteria, of whom two men refused the trial and the remaining 33 patients gave fully informed consent (see table I).

The patients were matched in pairs according to albuminuria, arterial blood pressure, and glomerular filtration rate and assigned at random either to receive captopril (n=16) or not to receive hypotensive treatment (controls; n=17). One woman with persistent microscopic haematuria both before and during the first eight months of treatment with captopril (25-50 mg daily) was excluded because kidney biopsy disclosed mesangioproliferative glomerulonephritis superimposed on diffuse diabetic glomerulosclerosis.

All patients had been insulin dependent from the time of diagnosis and all were receiving at least two

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Br Med J 1989;299:533-6

daily injections of highly purified porcine insulin. All patients took their usual diabetic diet without sodium or protein restriction throughout. Diabetic nephropathy was diagnosed clinically according to established criteria.¹⁰ The study was approved by the local ethical committee.

All investigations in each patient were carried out on the same day between 8 am and 1.30 pm. Patients had their usual breakfast and morning insulin after their plasma volume had been measured (9.30 am). Patients rested supine during the entire investigation, except when urinating. The patients drank 200 ml of tap water per hour during the procedures. The clearance studies were carried out every six months.

Treatment with captopril was aimed primarily at preventing the rise in arterial blood pressure that occurs in diabetic nephropathy and secondarily at reducing the mean arterial blood pressure by 5 mm Hg. Initially all the treated patients received 12.5 mg captopril before breakfast and dinner. This dose was adjusted at the visits to the outpatient clinic (every three months). The highest dose of captopril used was 50 mg twice daily.

TABLE I—Clinical and laboratory data at baseline in normotensive insulin dependent diabetics with nephropathy. Except where stated otherwise, values are means (SD in parentheses)

	Captopril treated group	Controls
No and sex of patients*	5 F, 10 M	4 F, 13 M
Age (years)	32 (8)	30 (8)
Duration of diabetes (years)	20 (8)	20 (8)
No with simplex/proliferative retinopathy	10/5	9/8
Vibratory perception threshold (volts)	15 (8)	21 (16)
Arterial blood pressure (mm Hg)	128/78 (12/8)	127/79 (8/4)
Glomerular filtration rate (ml/min/1.73 m ²)	111 (23)	115 (16)
Albuminuria (μg/min)†	378 (×/÷ 1.3)	471 (×/÷ 1.2)
Fractional urinary albumin clearance (× 10 ⁻³)†	10.8 (×/÷ 1.3)	13.3 (×/÷ 1.2)
Haemoglobin A _{1c} (%)	9.5 (1.6)	8.7 (0.8)
Insulin dose (U/kg/24 h)	0.66 (0.20)	0.64 (0.20)
Energy intake (kJ/24 h)	8756 (1747)	8939 (1349)
Protein intake (g/24 h)	77 (27)	80 (23)
Body mass index (kg/m ²)	22.2 (2.3)	22.9 (1.6)

*A further patient in the captopril treated group (a woman) was excluded because of mesangioproliferative glomerulosclerosis found at biopsy.
†Geometric mean (×/÷ antilog SE).

TABLE II—Changes in arterial blood pressure, glomerular filtration rate, albuminuria, and fractional albumin clearance with and without captopril treatment in normotensive insulin dependent diabetics with nephropathy

	6 Months		12 Months	
	Captopril treated group	Controls	Captopril treated group	Controls
Systolic blood pressure (mm Hg) (mean (SE))	-3.1 (2.5)	2.9 (1.9)	-6.0 (2.8)	6.8 (1.9)**
Diastolic blood pressure (mm Hg) (mean (SE))	-2.3 (2.0)	0.2 (1.2)	-0.9 (2.0)	5.2 (1.5)**
Glomerular filtration rate (ml/min/1.73 m ²) (mean (SE))	-5.9 (3.4)	-4.7 (2.4)	-3.1 (2.8)	-6.4 (3.1)
Albuminuria (mean relative change (95% confidence interval))	0.81 (0.66 to 1.0)	1.34 (0.98 to 1.84)**	0.89 (0.50 to 1.28)	1.55 (1.16 to 2.08)**
Fractional urinary albumin clearance (mean relative change (95% confidence interval))	0.85 (0.68 to 1.0)	1.35 (0.96 to 1.91)*	0.83 (0.50 to 1.39)	1.66 (1.17 to 2.37)*

Captopril treated group v controls: *p<0.05; **p<0.01.

TABLE III—Laboratory values and protein intake with and without captopril treatment in normotensive insulin dependent diabetics with nephropathy. Values are means (SE in parentheses)

	Start		12 Months	
	Captopril treated group	Controls	Captopril treated group	Controls
Haemoglobin A _{1c} (%)	9.5 (0.4)	8.7 (0.2)	9.0 (0.4)	8.4 (0.4)
Blood glucose (mmol/l)	12.9 (0.9)	12.2 (0.9)	11.9 (0.8)	10.4 (0.7)
Serum albumin (μmol/l)	487 (8)	470 (13)	484 (11)	470 (16)
Serum cholesterol (mmol/l)	6.3 (0.4)	5.4 (0.3)	6.1 (0.4)	5.6 (0.3)
Leucocyte count (× 10 ⁹ /l)	9.4 (0.6)	8.3 (0.8)	9.0 (0.5)	8.4 (0.5)
Plasma volume (l/1.73 m ²)	2.7 (0.05)	2.8 (0.07)	2.7 (0.09)	2.9 (0.08)
Extracellular fluid volume (l/1.73 m ²)	13.7 (0.3)	14.7 (0.3)	14.0 (0.5)	14.6 (0.3)
Urinary sodium excretion (mmol/min)	0.16 (0.02)	0.15 (0.02)	0.23 (0.03)	0.18 (0.02)
Protein intake (g/24 h)	77 (7)	81 (6)	76 (8)	89 (6)

Captopril treated group v controls: all cases NS.

Plasma volume was estimated (at 8.30 am) from the rate of disappearance of intravenously injected human serum albumin labelled with iodine-125 (code MIAK; Institute of Atomic Energy, Kjeller, Norway), as described.¹⁹ The glomerular filtration rate and extracellular fluid volume were measured after a single intravenous injection of 3.7 MBq chromium-51 labelled edetic acid (at 9.30 am) by studying the disappearance in plasma over four hours.^{20,21} Urinary albumin excretion was measured during the four hour clearance period by radioimmunoassay.²² Fractional clearance of albumin was obtained by dividing the clearance of albumin (calculated as UV/P, where U=urine albumin concentration, V=urine flow, P=plasma albumin concentration) by the simultaneously measured glomerular filtration rate.

Blood pressure was measured with a Hawksley random zero device (cuff size 25×12 cm) on the right arm. Two readings were taken at the start, middle, and end of the clearance period. Two readings were also taken when the patients visited the outpatient clinic between 2 and 4 pm. Diastolic blood pressure was recorded at the point of disappearance of the Korotkoff sounds (phase V).

Blood glucose concentration was measured hourly during the four hour clearance period by reflectance meter (Reflomat; Boehringer-Mannheim, Ingelheim, West Germany). Plasma concentrations of renin substrate,²³ active renin,²⁴ angiotensin I,²⁵ and angiotensin II²⁶ were measured in peripheral blood between 10 and 11 am. Recumbent values after one hour's rest are reported. These hormones were measured only after 12 months of investigation because of limited capacity. Leucocyte counts and measurement of serum electrolyte, albumin, and cholesterol concentrations during each investigation were carried out by conventional laboratory techniques. Stable haemoglobin A_{1c} was measured before and at each investigation (normal range 4.1-6.1% of total haemoglobin).²⁷ Urinary sodium excretion during the four hour clearance period was measured with flame photometry.

All patients collected urine over at least one 24 hour period every six months for measurement of urea excretion. These collections were used for calculating protein intake from the urinary urea nitrogen and an

estimated non-urea nitrogen excretion of 31 mg/kg/day.²⁸ Given a constant nitrogen balance, nitrogen intake equals urinary urea nitrogen excretion and non-urea nitrogen excretion; protein intake (g/day)=nitrogen×6.25.²⁹

All patients visited the clinic every three months during the study. At each visit the postprandial blood glucose concentration was measured along with glucosuria, blood pressure, and body weight and the insulin and captopril doses were adjusted. Ophthalmoscopy was carried out on dilated pupils at least every 6-12 months.

Statistical analysis—Results are expressed as means and standard error (SE), means and standard deviation

TABLE IV—Plasma concentrations of renin substrate, active renin, and angiotensins I and II after 12 months' treatment with or without captopril in normotensive insulin dependent diabetics with nephropathy. Values are means (SE in parentheses)

	Renin substrate (μmol angiotensin I/l; normal 0.25-2.1)	Active renin (mU/l; normal 6-60)	Angiotensin I (pmol/l; normal 6-34)	Angiotensin II (pmol/l; normal 3-30)	Angiotensin I/ Angiotensin II (normal 1-3)
Captopril treated group	1.3 (0.1)	122 (26)	176 (56)	2.7 (0.4)	61 (18)
Controls	1.4 (0.1)	50 (6)	38 (14)	5.1 (0.6)	8 (2)
p Value*	NS	<0.05	<0.01	<0.01	<0.01

*Captopril treated group v controls.

Average course of mean arterial blood pressure, glomerular filtration rate, albuminuria, and fractional urinary albumin clearance in normotensive insulin dependent diabetics with nephropathy. Fifteen patients received captopril (●) and 17 served as untreated controls (○). Bars are SE. * $p < 0.05$ (Captopril treated group v controls)

(SD) being used for descriptive information. Urinary albumin excretion and fractional albumin clearance were logarithmically transformed before analysis because of their positively skewed distribution; the geometric mean ($\times/\div$ antilog SE) is indicated. We estimated the relative change in albuminuria and fractional albumin clearance by calculating the ratio between the geometric means. Table II gives the 95% confidence intervals for the mean relative changes. Paired and unpaired Student's *t* tests were used and a *p* value < 0.05 (two tailed) considered significant. All calculations were made with commercially available program Statgraphic (STSC, Rockville, Maryland, USA).

Results

The two groups were well matched (table I). Treated patients received an average of 28 (SD 16) and 40 (SD 20) mg captopril daily at six and 12 months respectively.

Arterial blood pressure, albuminuria, and fractional albumin clearance were significantly lower in the captopril treated group than in the untreated controls ($p < 0.05$; figure; table II). The rates of decline in the glomerular filtration rate at 12 months were not significantly different between the two groups (3.1 (SE 2.8) v 6.4 (3.1) ml/min/1.73 m²) (figure; table II).

Table II compares the changes in blood pressure, glomerular filtration rate, and urinary albumin excretion after six months and one year in the treated and control groups. Albuminuria and fractional albumin clearance were on average reduced by 11% and 17% at 12 months in the captopril treated group, whereas in the controls these values were increased by 55% and 66% respectively (table II; $p < 0.05$). The figure shows a significant rise in mean arterial blood pressure, albuminuria, and fractional albumin clearance in the control group ($p < 0.01$) and a non-significant reduction in these values in the captopril treated group. Arterial hypertension—that is, a sustained diastolic blood pressure ≥ 95 mm Hg—did not occur in any untreated patient during the 12 months of observation.

Three men (one in the captopril treated group) had a sudden onset of asymptomatic microscopic haematuria and albuminuria in the nephrotic range (> 2400 $\mu\text{g}/\text{min}$). Kidney biopsies showed diffuse diabetic glomerulosclerosis without superimposed non-diabetic renal disease in all three cases.

Metabolic control, serum albumin and cholesterol concentrations, and leucocyte counts showed no significant changes during the study (table III). Plasma and extracellular fluid volume, urinary sodium excretion, and protein intake remained about the same in both groups (table III).

The renin-angiotensin system showed a suppressed plasma concentration of angiotensin II, increased concentrations of angiotensin I and renin, and a clearly raised ratio between angiotensins I and II in patients receiving captopril as compared with controls (61 (SE 18) v 8 (2); $p < 0.01$), indicating inhibition of converting enzyme activity (table IV).

No severe side effects occurred, and after the study all 15 patients in the treatment group continued with captopril. In two patients a diuretic was added to control blood pressure.

Discussion

An important, novel observation in this prospective, randomised controlled trial was that captopril can arrest the progressive rise in albuminuria over one year in normotensive insulin dependent diabetics with clinically overt nephropathy. Marre *et al* have shown that enalapril (20 mg/day) for one year induces a progressive reduction in albuminuria in normotensive diabetics with persistent microalbuminuria¹⁷—that is, incipient nephropathy.

The beneficial effect noted in our study was not caused by a reduction in the glomerular filtration rate or in serum albumin concentration, as fractional albumin clearance declined in proportion to the decline in absolute albumin excretion. Improved metabolic control was also ruled out as a cause of the difference in albuminuria, as haemoglobin A_{1c} and blood glucose concentrations during the renal clearance studies remained about the same in both groups. Furthermore, improved metabolic control achieved by continuous subcutaneous insulin infusion does not arrest or reverse the progressive rise in albuminuria in patients with overt diabetic nephropathy.³⁰ Protein restriction was not applied, and the protein intake remained practically unchanged during the study.

The difference in albuminuria between the two groups may be explained by differences in glomerular capillary hydraulic pressure induced by the angiotensin converting enzyme inhibitor.¹⁵ The predominant action of angiotensin II is confined to the efferent arteriole, thereby inducing a rise in glomerular capillary hydraulic pressure.³¹ Conversely, angiotensin converting enzyme inhibition diminishes glomerular capillary pressure in animals^{15, 32} and probably also in

man, as reflected by a drop in filtration fraction.^{14,33,34} The present and previous results suggest that albuminuria is dependent on glomerular hydraulic pressure.^{12,13,35,36} This is supported by micropuncture studies in rats¹⁵ and by the finding of a close correlation between the reduction in filtration fraction and the decrease in albuminuria during short term treatment with captopril in normotensive insulin dependent diabetics with nephropathy.³³

Systemic and glomerular hypertension enhance albuminuria and the development of diabetic glomerulopathy and accelerate the decline in the glomerular filtration rate in diabetic nephropathy.^{15,16,37,42} Glomerular hypertension has been found even in normotensive rats with streptozotocin induced diabetes treated with insulin.^{43,44} Conversely, hypotensive treatment with enalapril or a low protein diet, both of which cause a reduction in glomerular capillary hydraulic pressure, diminishes albuminuria and mitigates the haemodynamically induced glomerular lesions in diabetic animals.^{14,40}

Studies suggest that high glomerular capillary hydraulic pressure is most damaging to enlarged glomeruli where an increased capillary diameter is expected to result in greater tension transmitted to the peripheral capillary wall (Laplace's law).⁴⁵ Enlarged hyperfiltering glomeruli are typically found from the onset of insulin dependent diabetes,⁴⁶ while a wide range of glomerular lesions, ranging from occluded to enlarged glomeruli, is found in patients who have diabetic glomerulosclerosis.⁴⁷ These findings provide a likely explanation for the damaging effect of systemic or glomerular hypertension in diabetes and for the beneficial effect of hypotensive treatment on albuminuria in diabetic nephropathy.

Recent data in rats suggest that angiotensin converting inhibitors suppress the growth of glomerular and mesangial cells in vivo and in vitro by means of mechanisms independent of glomerular haemodynamics.⁴⁸ If confirmed this effect may be a factor in the ability of these drugs to reduce subsequent glomerular sclerosis.

In conclusion, the finding that angiotensin converting enzyme inhibition with captopril can arrest the progressive rise in albuminuria in normotensive insulin dependent diabetics with nephropathy is encouraging but should be interpreted with caution. The crucial question, requiring longer term follow up, has not been answered—namely, Can the progression (that is, the rate of decline in the glomerular filtration rate) be reduced or even prevented in normotensive diabetic nephropathy by captopril or other hypotensive regimens? Though captopril was effective and well tolerated, the safety of longer term inhibition of angiotensin converting enzyme remains to be established.

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(Accepted 14 June 1989)