

## CLINICAL RESEARCH

## Effect of captopril on kidney function in insulin-dependent diabetic patients with nephropathy

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### Abstract

The influence of angiotensin II on kidney function in diabetic nephropathy was assessed by studying the effect of 12 weeks' monotherapy with captopril (25-50 mg twice a day) in 16 hypertensive insulin dependent diabetic patients with persistent albuminuria. In an initial one week randomised single blind trial of captopril versus placebo, captopril (for nine patients) reduced arterial blood pressure from 148/94 (SD11/6) to 135/88 (8/7) mm Hg ( $p < 0.05$ ) and albuminuria from 1549 (range 352-2238) to 1170 (297-2198)  $\mu\text{g}/\text{min}$  ( $p < 0.05$ ), while glomerular filtration rate remained stable. No significant changes occurred in seven patients treated with placebo. During the 12 weeks of captopril treatment arterial blood pressure in all patients fell from 147/94 (11/6) to 135/86 (13/7) mm Hg ( $p < 0.01$ ), albuminuria fell from 1589 (range 168-2588) to 1075 (35-2647)  $\mu\text{g}/\text{min}$  ( $p < 0.01$ ), and glomerular filtration rate fell from 99 (SD19) to 93 (25) ml/min/1.73  $\text{m}^2$  ( $p < 0.01$ ). The renin-angiotensin system showed suppressed plasma concentrations of angiotensin II and increased concentrations of angiotensin I and renin.

The study showed that glomerular filtration rate is not dependent on angiotensin II, that captopril reduces albuminuria, probably by lowering glomerular hypertension, and that captopril represents a valuable new drug for treating hypertension in diabetics dependent on insulin with nephropathy.

### Introduction

Several recent studies have shown that the renin-angiotensin system plays a crucial part in regulating glomerular filtration rate when renal perfusion pressure and plasma flow are reduced owing to renal artery stenosis or widespread intrarenal arterial lesions.<sup>1,5</sup> Diabetic glomerulosclerosis is characterised by widespread arteriolar hyalinosis, which may lead to reduced renal plasma flow.<sup>6</sup> These findings suggest that angiotensin II may be important for regulating glomerular filtration rate in diabetic nephropathy. Furthermore, angiotensin II induces proteinuria, mainly by increasing glomerular capillary hydraulic pressure.<sup>7</sup> Recent studies have suggested a link between glomerular hypertension, albuminuria, and the development and progression of diabetic glomerulopathy.<sup>8,9</sup>

To evaluate the influence of angiotensin II on kidney function in diabetic nephropathy we investigated the effect of angiotensin converting enzyme inhibition with captopril on glomerular filtration rate and albuminuria in hypertensive diabetics dependent on insulin and with persistent albuminuria.

### Patients and methods

#### PATIENTS

We examined the records of all insulin dependent diabetics with proteinuria (positive Albustix) visiting the outpatient clinic at Hvidøre Hospital during 1984. All hypertensive patients aged under 50 with persistent albuminuria ( $> 300$  mg/day), a serum creatinine concentration less than 120  $\mu\text{mol}/\text{l}$  (1.36 mg/100 ml), and no oedema who had developed diabetes before the age of 31 years but were receiving no antihypertensive treatment (including diuretics) and were not blind were invited to join the study. Seventeen patients fulfilled these criteria and all gave fully informed consent. The patients were randomly allocated to treatment ( $n=9$ ) or placebo ( $n=8$ ). At the start of the study we had to omit one patient in the placebo group because treatment with thiazide had been started owing to oedema. The remaining 16 patients (table 1) were investigated. The experimental design was approved by the local ethical committee.

All patients were insulin dependent from the time of diagnosis and all received two daily injections of highly purified porcine insulin (mean dose 0.61 U/kg/day). None of the patients were taking any other drugs. All patients kept their normal diabetic diet without sodium restriction throughout the study. Nephropathy was diagnosed clinically according to previously described criteria.<sup>10</sup>

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TABLE I—Clinical data on insulin dependent diabetic patients with nephropathy

Case No	Sex	Age (years)	Duration of diabetes (years)	Retinopathy	Insulin dose (U/kg/day)	Arterial* blood pressure (mm Hg)	Captopril† treatment (mg)
1	M	43	20	Simplex	0.49	157/92	100
2	M	34	18	Proliferative	0.55	158/100	100
3	M	46	20	Proliferative	0.63	161/81	75
4	M	30	20	Proliferative	0.41	152/102	100
5	M	24	15	Simplex	0.80	147/97	100
6	M	29	15	Proliferative	0.49	159/98	100
7	M	31	27	Proliferative	0.80	140/100	100
8	M	19	13	Simplex	0.96	150/99	100
9	M	19	15	Proliferative	0.84	183/95	100
10	M	34	28	Proliferative	0.62	155/97	50
11	M	26	19	Proliferative	0.75	148/103	100
12	F	25	18	Simplex	0.42	136/99	50
13	M	43	20	Proliferative	0.67	158/108	100
14	F	23	22	Simplex	0.53	150/112	50
15	M	30	17	Simplex	0.50	153/107	75
16	M	46	42	Simplex	0.56	162/97	50
Mean (SD)		31 (9)	20 (7)		0.63 (0.20)	154.99 (11/7)	84 (22)

\*Mean of last three measurements performed in outpatient clinic before start of study.

†Mean dose during 12 weeks' treatment.

## METHODS

All patients were initially studied between January and April 1985; all investigations were carried out on one day, between 0830 and 1500. Patients had their normal breakfast and morning insulin before the investigations, during which the patients were resting supine. The patients stood up only to pass urine. The patients drank 200 ml of tap water per hour during the study.

The study was performed before and after one week's treatment with captopril (cases 1-9) or placebo (cases 10-16) in a single blind design. All patients were reinvestigated after a subsequent 12 weeks of treatment with captopril alone. Each patient underwent a single dose titration starting with 6.25 mg captopril or placebo (1300-1500). Depending on the acute blood pressure response and the glomerular filtration rate, the dose was increased to 12.5-25 mg twice daily. Three days later blood pressure was taken and the dose adjusted to 25-50 mg twice daily. The adjusted dose (84 mg) was kept constant throughout the 12 weeks' trial. The patients were seen in the outpatient clinic four weeks after start of captopril treatment.

Plasma volume was determined (at 0845) from the intravenously injected amount of human serum albumin labelled with iodine-125 (Code MIAK,

Institute of Atomic Energy, Kjeller, Norway) measured by weighing and from the plasma radioactivity sampled after a mixing period of 15 minutes.

Glomerular filtration rate and extracellular fluid volume were measured after a single intravenous injection of 3.7 MBq chromium-51 edetic acid (0900) by studying the plasma disappearance for four hours.<sup>11,12</sup> Blood samples for tracer determinations were drawn before the injection and at 5, 7, 10, 15, 30, 45, 60, 90, 120, 150, 180, 200, 220, and 240 minutes after the <sup>51</sup>Cr edetic acid injection. The mean coefficient of variation between patients for glomerular filtration rate was 2.8%.

Urinary albumin excretion was measured during the four hour clearance period by radioimmunoassay.<sup>13</sup> This assay has a sensitivity of 0.5 mg/l and an interassay coefficient of variation of 9%. Blood pressure was measured with a Hawksley random zero device (cuff 25×12 cm) on the right arm. Blood pressure and heart rate were measured every half hour during each study. Diastolic blood pressure was recorded at the disappearance of the Korotkoff sounds (phase V).

Plasma concentrations of renin substrate,<sup>14</sup> active renin,<sup>15</sup> angiotensin I,<sup>16</sup> angiotensin II,<sup>17</sup> aldosterone,<sup>18</sup> and albumin<sup>19</sup> were measured in peripheral blood between 1000 and 1100. Recumbent values after one hour's rest are shown. Blood glucose was measured hourly during the four hour clearance period by the reflectance meter Reflomat (Boehringer-Mannheim, Ingelheim, West Germany). Plasma electrolytes, leucocytes, and cholesterol were measured during each investigation using conventional laboratory techniques. Stable haemoglobin A<sub>1c</sub> was measured before and after 12 weeks of captopril treatment (normal range 4.1-6.1% of total haemoglobin).<sup>20</sup> Retinopathy was assessed by direct ophthalmoscopy after pupillary dilatation.

## STATISTICAL ANALYSIS

Wilcoxon's non-parametric test for unpaired and paired comparison was used for statistical analysis. Mean values are given with the standard deviation; as urinary albumin excretion is not normally distributed median and range are used.

## Results

Captopril treatment (25-50 mg twice daily) for one week reduced arterial blood pressure from 148/94 (11/6) to 135/88 (8/7) mm Hg ( $p<0.05$ ), albuminuria diminished from 1549 (352-2238) to 1170 (297-2198) µg/min ( $p<0.05$ ), and glomerular filtration rate remained stable (97 (19) before and 96 (20) ml/min/1.73 m<sup>2</sup> during treatment) (table II). No significant changes occurred in arterial blood pressure, glomerular filtration rate, and

TABLE II—Arterial blood pressure, glomerular filtration rate, and albuminuria before and after one and 12 weeks' monotherapy with captopril in 16 insulin dependent diabetic patients with nephropathy

Case No	Arterial blood pressure (mm Hg) (SD)			Glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )			Albuminuria (µg/min)		
	Baseline	After 1st week captopril v placebo	After 12 weeks' captopril	Baseline	After 1st week captopril v placebo	After 12 weeks' captopril	Baseline	After 1st week captopril v placebo	After 12 weeks' captopril
<i>Patients who received captopril in first week</i>									
1	147/88 (8/9)	137/88 (4/4)	149/91 (7/6)	85	88	80	1101	844	1141
2	129/86 (8/5)	120/84 (5/4)	120/76 (10/8)	70	71	59	1549	1170	694
3	158/92 (8/4)	141/83 (3/3)	153/90 (4/7)	82	77	75	2238	2198	1328
4	164/94 (7/7)	137/86 (4/3)	146/91 (8/4)	93	93	88	1677	1165	1121
5	134/96 (7/5)	140/98 (3/9)	126/86 (3/4)	104	101	99	745	302	315
6	155/94 (6/5)	144/91 (5/6)	139/93 (4/6)	115	122	119	352	297	195
7	151/104 (5/4)	134/100 (5/3)	132/91 (6/4)	104	92	99	1864	1900	1663
8	141/92 (4/4)	123/87 (7/5)	129/84 (5/3)	134	133	151	1489	1396	1055
9	153/100 (5/3)	142/79 (6/10)	151/86 (5/3)	89	86	85	2021	1914	2647
Mean (SD) (n=9)	148/94 (11/6)	135/88 (8/7) $p<0.05$		97 (19)	96 (20) NS		1549* (range 352-2238)	1170 (range 297-2198)* $p<0.05$	
<i>Patients who received placebo in first week</i>									
10	133/90 (7/2)	139/93 (4/2)	126/85 (3/3)	80	85	79	1628	1934	1092
11	129/93 (4/5)	134/93 (4/4)	122/79 (1/5)	124	124	108	275	293	167
12	152/98 (3/9)	136/96 (5/1)	129/82 (7/4)	134	136	127	626	604	720
13	161/102 (5/3)	151/95 (4/4)	147/96 (8/7)	91	91	81	2097	2288	1156
14	154/100 (11/2)	147/94 (9/6)	109/72 (6/6)	81	74	52	2588	2178	483
15	141/88 (4/3)	137/89 (3/4)	138/87 (4/1)	96	94	94	168	96	34.7
16	156/85 (7/2)	149/88 (6/2)	138/83 (4/4)	94	84	93	2946	3665	2351
Mean (SD) (n=7)	147/94 (12/6)	142/92 (12/3) $p<0.01$		100(21)	98 (23) $p<0.01$		1628* (range 168-2588)	1934* (range 96-3665) $p<0.01$	
Mean (SD) (n=16)	147/94 (11/6)	$p<0.01$	135/86 (13/7)	99 (19)	$p<0.01$	93 (25)	1589* (range 168-2588)	1075* (range 34.7-2647) $p<0.01$	

\*Median value and range.

albuminuria in the seven patients treated with placebo (table II). Plasma concentrations of renin substrate, active renin, angiotensin I and II, and plasma aldosterone concentration were all within the normal range before captopril treatment (table III). The renin-angiotensin system showed suppressed plasma concentration of angiotensin II, increased concentrations of angiotensin I and renin, and a clearly raised ratio between angiotensin I and II (3.3 before, 12.1 after captopril) ( $p < 0.01$ ), indicating inhibition of converting enzyme activity. Blood glucose concentration was 11.2 (3) mmol/l (201.8 (54) mg/100 ml) before and 11.0 (4) mmol/l (198.2 (72.1) mg/100 ml) after captopril treatment for one week. Table IV compares the changes in measured variables during one week's treatment with captopril or placebo.

TABLE III—Mean (SD) plasma concentrations of renin substrate, active renin, angiotensin I and II, and aldosterone and urinary sodium excretion before and after one and 12 weeks' monotherapy with captopril in 16 insulin dependent diabetic patients with nephropathy

	Renin substrate ( $\mu$ mol angiotensin I/l)	Active renin (mU/l)	Angiotensin I (pmol/l)	Angiotensin II (pmol/l)	Angiotensin I/ angiotensin II	Aldosterone (pmol/l)	Urinary sodium excretion (mmol/min)
Cases 1 to 9							
Before	1.2 (0.2)	52 (23)	21 (8)	7.5 (3.5)	3.3 (1.7)	68 (37)	0.19 (0.1)
1 week (captopril)	1.1 (0.2)	103 (70*)	70 (65†)	5.0 (2.9†)	12.1 (5.7†)	59 (26)	0.19 (0.1)
Cases 10 to 16							
Before	1.2 (0.3)	29 (12)	24 (9)	4.8 (4.9)	6.9 (3.4)	72 (42)	0.20 (0.1)
1 week (placebo)	1.2 (0.2)	29 (12)	28 (12)	8.1 (2.7)	3.5 (0.7)	76 (68)	0.18 (0.1)
Cases 1 to 16							
Before	1.2 (0.2)	42 (22)	22 (8)	6.4 (4.2)	4.8 (3.0)	70 (38)	0.19 (0.1)
12 weeks (captopril)	1.2 (0.2)	92 (52†)	82 (70†)	7.1 (3.7)	12.6 (8.3†)	64 (45)	0.16 (0.1)
Normal range	0.25-2.1	6-60	6-34	3-30	1-3	60-440	

\* $p < 0.05$ . † $p < 0.01$ .

TABLE IV—Mean (SD) changes in arterial blood pressure, glomerular filtration rate, albuminuria, plasma concentrations of renin substrate, active renin, angiotensin I and II, and aldosterone during one week's treatment with captopril or placebo in 16 insulin dependent diabetic patients with nephropathy

	Cases 1 to 9 (captopril)	Cases 10 to 16 (placebo)	p Value
Systolic blood pressure (mm Hg)	-12.7 (8.9)	-4.7 (7.9)	<0.05
Diastolic blood pressure (mm Hg)	-5.6 (6.7)	-1.1 (4.1)	NS
Glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	-1.4 (5)	-1.7 (5)	NS
Albuminuria ( $\mu$ g/min)	-205 (198)	104 (352)	<0.05
Renin substrate ( $\mu$ mol angiotensin I/l)	0.12 (0.2)	0 (0)	NS
Active renin (mU/l)	51 (77)	-0.1 (16)	<0.01
Angiotensin I (pmol/l)	50 (63)	5 (15)	<0.01
Angiotensin II (pmol/l)	-2.5 (4.5)	3 (4.2)	<0.05
Angiotensin I/angiotensin II	9.9 (7)	3.2 (3.1)	<0.01
Aldosterone (pmol/l)	-9.3 (44)	-0.3 (87)	NS

Treatment of the whole group of patients with captopril (25-50 mg twice daily) for 12 weeks induced the following changes in the 16 patients: mean arterial blood pressure decreased from 147/94 (11/6) to 135/86 (13/7) mm Hg ( $p < 0.01$ ), mean albuminuria from 1589 (range 168-2588) to 1075 (range 35-2647)  $\mu$ g/min ( $p < 0.01$ ), and mean glomerular filtration rate from 99 (20) to 93 (25) ml/min/1.73 m<sup>2</sup> ( $p < 0.01$ ) (table II). The reduction in relative glomerular filtration rate was more than 10% in four patients (cases 2, 11, 13, and 14). Both plasma and extracellular fluid volume diminished during treatment with captopril from 3081 (433) to 2985 (554) ml (NS) and 16 196 (2588) to 15 136 (2885) ml ( $p < 0.01$ ), respectively. Plasma albumin concentration remained stable, 477 (60) before and 483 (50)  $\mu$ mol/l during treatment. A 23 year old woman (case 14) had the largest drop in mean arterial blood pressure (24 mm Hg) and glomerular filtration rate (29 ml/min/1.73 m<sup>2</sup>) during captopril treatment. Her renin-angiotensin system was normal, and radioisotope renography showed normal bilateral kidney function, excluding the possibility of renal artery stenosis.

Table III shows inhibition of the angiotensin converting enzyme activity, as indicated by the clearly raised ratio between angiotensin I and II. Urinary sodium excretion measured during the four hour clearance showed a slight, insignificant reduction during captopril treatment. Blood glucose concentration, measured hourly during the four hour clearance period, was lower after 12 weeks of captopril treatment, mean 8.9 (4) mmol/l, than before treatment, mean 11.8 (3) mmol/l ( $p < 0.02$ ). The long term metabolic control, however, remained stable as indicated by haemoglobin A<sub>1c</sub> (mean

8.9 (2)% before and 9.2 (1)% during captopril treatment). The insulin dose remained constant during the study, at 0.63 (0.2) U/kg/day before and 0.62 (0.2) U/kg/day at 12 weeks. Serum concentrations of potassium, sodium, and cholesterol showed no significant changes during captopril treatment: 3.9 (0.3) to 3.9 (0.4) mmol(mEq)/l, 136 (2) to 137 (2) mmol(mEq)/l, and 6.1 (1.0) mmol/l (235.5 (38.6) mg/100 ml) to 6.3 (0.6) mmol/l (243.2 (23.2) mg/100 ml), respectively.

None of the 16 patients experienced rash, taste disturbance, headache, fatigue, depression, orthostatic symptoms, or sexual dysfunction. Neutropenia was not observed. All but two patients had reduced albuminuria. All 16 patients are still receiving captopril, either alone or in combination with a diuretic drug.

## Discussion

Our short term study was conducted to see if the glomerular filtration rate is dependent on angiotensin II concentrations in diabetic nephropathy. Our results show that this is not the case in mild hypertensive insulin-dependent diabetics with early nephropathy (glomerular filtration rate  $> 70$  ml/min/1.73 m<sup>2</sup>), as angiotensin converting enzyme inhibition for one week did not affect glomerular filtration rate despite a mean reduction in blood pressure of 8 mm Hg. Our finding of a significant decrease in albuminuria may be explained by diminished glomerular capillary hydraulic pressure induced by the angiotensin converting enzyme inhibition.<sup>21 22</sup> Consequently, a diminished glomerular filtration rate would be expected, unless some of the remaining determinants of glomerular filtration rate—that is, renal plasma flow and glomerular ultrafiltration coefficient, are changed in the opposite direction. Enhanced renal plasma flow has been shown during angiotensin converting enzyme inhibition in essential hypertension, despite the reduction in blood pressure.<sup>23 24</sup> Intravenous infusion of a suppressor dose of angiotensin II in the rat causes profound changes in all three major determinants of filtration rate—increased glomerular capillary hydraulic pressure, diminished glomerular plasma flow, and reduced glomerular ultrafiltration coefficient—resulting in a slight reduction in glomerular filtration rate.<sup>25 26</sup> Angiotensin converting enzyme inhibition in this animal model has the opposite effects.<sup>26</sup>

Mean arterial blood pressure fell from 112 to 102 mm Hg during the 12 weeks of captopril treatment. Three out of 16 patients had no reduction in blood pressure. We might have expected an even greater failure rate as our study showed that the renin-angiotensin-aldosterone system is already suppressed in untreated insulin dependent diabetics with early nephropathy. It is well established that this system is suppressed in advanced diabetic nephropathy, probably owing to retention of sodium and fluid.<sup>27</sup> We have suggested the use of the molar ratio between the plasma concentrations of angiotensin I (the precursor decapeptide) and angiotensin II (the effector octapeptide) as a logical index of angiotensin converting enzyme inhibition.<sup>28</sup> As shown in table III, this index documents effective angiotensin converting enzyme inhibition in our patients treated with captopril. Angiotensin II plasma concentrations do

not, however, decrease significantly from the initial, quite low values; this is not very surprising in view of the known blank value, caused by immunoreactive peptides other than true angiotensin II octapeptide.<sup>29</sup> The plasma concentration of aldosterone was low and remained unchanged in our study and extracellular fluid volume diminished. This volume depletion may well contribute to the observed hypotensive effect of captopril. It should be emphasised that sodium intake was unchanged and restriction not applied in our study. Urinary sodium excretion showed no significant changes.

Monotherapy with low dose captopril for 12 weeks induced changes in glomerular filtration rate of the same order of magnitude as previously shown for other antihypertensive drugs.<sup>10</sup> This suggests an effect of blood pressure reduction per se on glomerular filtration rate. Four out of 16 patients had a drop in glomerular filtration rate of more than 10% of the pretreatment values. Impaired autoregulation of glomerular filtration rate is probably the major causative factor.<sup>30</sup> Despite the reduction in glomerular filtration rate at the start of effective antihypertensive treatment, long term observations clearly indicate that careful blood pressure control slows the progression of diabetic nephropathy.<sup>10, 31</sup>

Our finding of diminished albuminuria (32%) can be explained neither by the slight decrease in glomerular filtration rate (6%) nor by improved metabolic control.<sup>32, 33</sup> Lowering of glomerular capillary hydraulic pressure may, as recently suggested, be the crucial factor.<sup>34</sup> Micropuncture studies in hypertensive and diabetic rats have shown that angiotensin converting enzyme inhibition reduces the intraglomerular hypertension and albuminuria.<sup>21, 22</sup> The reduction in glomerular hypertension during angiotensin converting enzyme inhibition is a result of lower systemic arterial blood pressure and of a diminished efferent arteriolar resistance. Moreover, arterial hypertension induces an appreciable rise in glomerular capillary hydraulic pressure in streptozotocin diabetic spontaneous hypertensive rats (52.6 versus 43.8 mm Hg in non-diabetic rats).<sup>35</sup> This finding provides a possible explanation for the damaging effect of hypertension in diabetes and for the beneficial effect of aggressive antihypertensive treatment on kidney function in established diabetic nephropathy.<sup>10, 31</sup>

Angiotensin converting enzyme inhibitors have been regarded as rather toxic drugs. This misleading picture of toxicity has emerged because in early studies too high a dose of captopril was used and without adequate dose reduction in renal failure.<sup>36</sup> Subsequently, it was shown that even in patients with normal kidney function many of the side effects of captopril were dose related and could be avoided by using less than 150 mg daily with little or no loss of efficacy.<sup>37, 38</sup> Most commonly used antihypertensive drugs—for example,  $\beta$  blockers and diuretics—reduce glucose tolerance in normal and diabetic people.<sup>39, 40</sup> Furthermore,  $\beta$  blockers can mask some clinical signs of hypoglycaemia and prolong the blood glucose recovery after a hypoglycaemic attack. These problems are not present during angiotensin converting enzyme inhibition, which may actually enhance insulin sensitivity.<sup>37, 41</sup>

In conclusion, the results of our study show that glomerular filtration rate is not dependent on angiotensin II concentrations in diabetic nephropathy, that albuminuria is pressure dependent to a large extent, and that captopril represents a valuable new drug for treating hypertensive type I diabetic patients with nephropathy.

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## 100 YEARS AGO

The intense heat which has prevailed here during several days this week has been felt with increased force in Paris, where, we are informed, a large number of cases of sunstroke have occurred among the recruits taking part in the autumn manoeuvres, and four deaths are said to have taken place. In the north of France, where the thermometer has stood in the shade at 104° Fahr., the troops have suffered very severely. From the official returns, it appears that on Wednesday, at Lille, six soldiers of the regular army had died from sunstroke, and that twenty-three, suffering from the same cause, were in the military hospital. Instructions have been issued to the commandant of army corps to suspend evolutions during the great heat of the day. (*British Medical Journal* 1886;ii:466.)