PAPERS AND SHORT REPORTS

Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy

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Abstract

Six men aged 26-35 years with proteinuria due to insulin-dependent juvenile-onset diabetes were treated for moderate hypertension (mean blood pressure 162/103 mm Hg) and studied for a mean of 73 months for the effect on the progression of nephropathy. All patients were of normal weight. During a mean control period of 28 months before treatment the mean glomerular filtration rate (three or four measurements) was 86·1 ml/min and mean 24-hour urinary albumin excretion (also three or four measurements) 3·9 g (range 0·5-8·8 g).

During antihypertensive treatment the mean systolic blood pressure fell to 144 mm Hg and mean diastolic pressure to 95 mm Hg. In the control period five patients had shown a mean monthly decline in glomerular filtration rate of 1·23 ml/min; with antihypertensive treatment, however, this decline fell to 0·49 ml/min ($2p = 0·042$). In the remaining patient the glomerular filtration rate was 137 ml/min before treatment and 135 ml/min at the end of the treatment period. In all patients the mean yearly increase in albumin clearance (expressed as a percentage of the glomerular filtration rate) fell from 107% before treatment to 5% during treatment ($2p = 0·0099$).

This small study indicates that antihypertensive treatment slows the decline in renal function in diabetic nephropathy. Clinical trials beginning treatment in the incipient phase of diabetic nephropathy will define the optimal modality of treatment in this large patient population.

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Introduction

Diabetic nephropathy is a major medical problem, yet we still do not know why some patients develop proteinuria and renal failure and others not despite a long history of diabetes.[1 2] Characteristically diabetics without perceptible renal disease have normal blood pressure,[3] whereas patients with nephropathy are hypertensive.[4] Only in the past few years,[5-7] however, has the possible role of high blood pressure in the progression of diabetic nephropathy and other vascular lesions attracted interest. In a previous study I identified high blood pressure as a possible factor in the rapid deterioration of kidney function seen in some patients.[5]

I now report a study in which the rate of progression of nephropathy was measured by serial determination of glomerular filtration rate, renal plasma flow, and urinary albumin excretion before and during long-term antihypertensive treatment in six juvenile-onset diabetics with established nephropathy. The results show that the rate of progression can be impeded, thus postponing renal insufficiency in these patients.

Patients and methods

The study group comprised six men aged 26-35 years (mean 30 ± SD 3 years) with insulin-dependent diabetes of juvenile onset. Mean duration of the disease was 18 ± SD 2 years. The patients were of normal weight (mean 72·0 ± SD 4·1 kg), and their mean height was 174·0 ± SD 9·6 cm. All had persistent proteinuria, ranging from 0·5 to 8·8 g/24 hours (mean 3·9 ± SD 3·4 g/24 hours). Five had stage III retinopathy (proliferative changes), and one had stage I (minor background retinopathy).[8] No patient had electrocardiographic evidence of hypertrophy or strain pattern, and all had a normal cardiothoracic ratio. Mean daily insulin dose was 57·0 ± SD 15·2 IU.

Glomerular filtration rate and renal plasma flow were measured three or four times during 20-31 months before treatment (control period) and 12-18 times during the subsequent 28-86 months (mean 73·0 ± SD 2·8 months) of treatment. In the treatment period tests were performed after the first one and a half and six weeks and then every three to 12 months. A constant-infusion-clearance technique was applied, ^{125}I-iothalamate being used as a filtration marker and ^{131}I-hippuran (uncorrected for renal extraction) for measuring renal plasma flow.[9] Results were corrected to 1·73 m^2 body surface index. The body surface index at the start of the study was used throughout.

During treatment the patients took their antihypertensive drugs as usual and in the morning before the clearance test. Urinary albumin excretion was measured in clearance samples by radioimmunoassay.[10] Progression of nephropathy was expressed as a fall in the glomerular filtration rate and renal plasma flow (ml/min/month) and yearly increase in albumin clearance expressed as a percentage of the glomerular filtration rate. No invasive blood pressure measurements were done.

Blood pressure was determined before and during treatment at the same time as the kidney function tests. Patients were admitted to hospital as inpatients and blood pressure measured by a trained nurse over two or three days three times a day after 20 minutes' rest in the supine position. Diastolic pressure was read as phase V.

All the patients received conventional antihypertensive treatment, initially with propranolol and later with metoprolol 50-100 mg twice daily. Four patients received additional hydralazine 50 mg two to four times daily, which in one was changed to prazosin. Three of these were also given frusemide 40 mg two to four times a day.

Apart from the antihypertensive medication and insulin, one patient was receiving thyroxine 0·15 mg daily for myxoedema and another non-phenacetin analgesics for headache of undetermined cause; the remaining patients received no other drugs.

In all cases the paired *t* test was used for statistical analysis. Rate of progression was calculated by regression analysis.

Results

Blood pressure—Before treatment the mean blood pressure was 162/103 mm Hg. Antihypertensive treatment produced significant falls in systolic and diastolic pressures both initially during treatment and over the whole period (see table).

Renal function—After 10 days of treatment there was a significant fall in albumin excretion, but the glomerular filtration rate, renal plasma flow, and filtration fraction were unchanged. Figures 1 and 2 show the individual values for glomerular filtration rate and renal plasma flow in five patients before and during treatment, and fig 3

Systolic and diastolic blood pressures (mm Hg) before treatment, after 10 days of treatment, and during 28 to 86 months after beginning treatment. (Values are means ± SD)

	Systolic		Diastolic	
Before treatment	162 ± 14	*	103 ± 9	*
After 10 days of treatment	143 ± 7	*	94 ± 7	†
During treatment for 28-86 months (mean 73 months)	144 ± 11		95 ± 8	

*2p < 0·01. †2p ≤ 0·02.

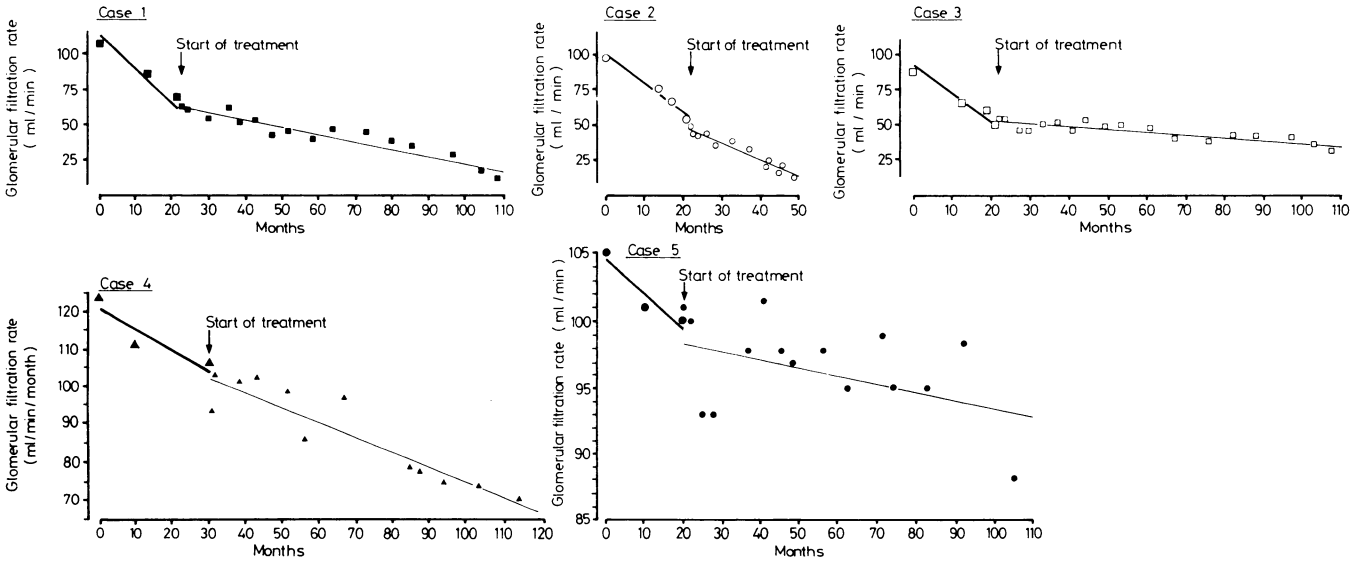

FIG 1—Individual glomerular filtration rates before and during treatment in cases 1 to 5.

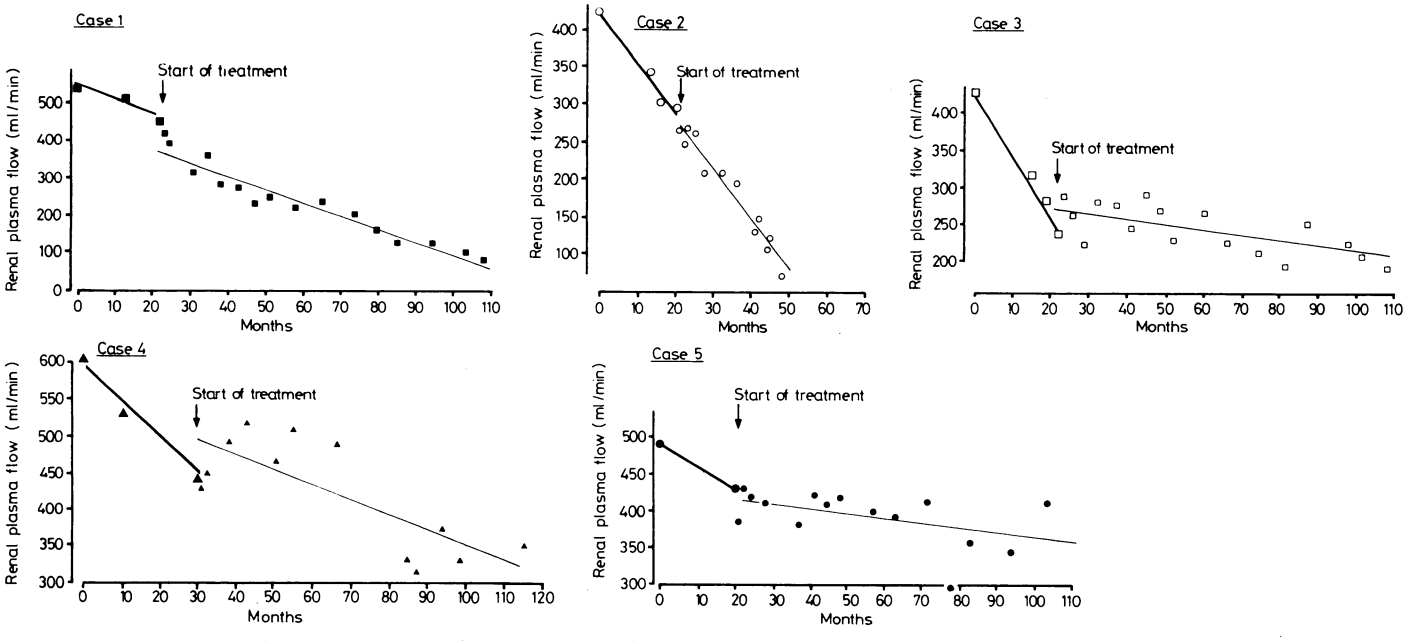

FIG 2—Individual renal plasma flows before and during treatment in cases 1 to 5.

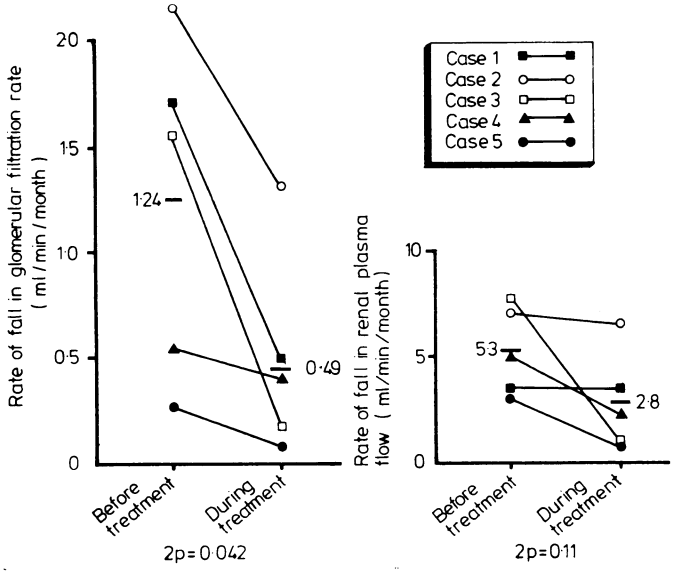

FIG 3—Rates of fall in glomerular filtration rate (top) and renal plasma flow (bottom) in cases 1 to 5 before and during treatment.

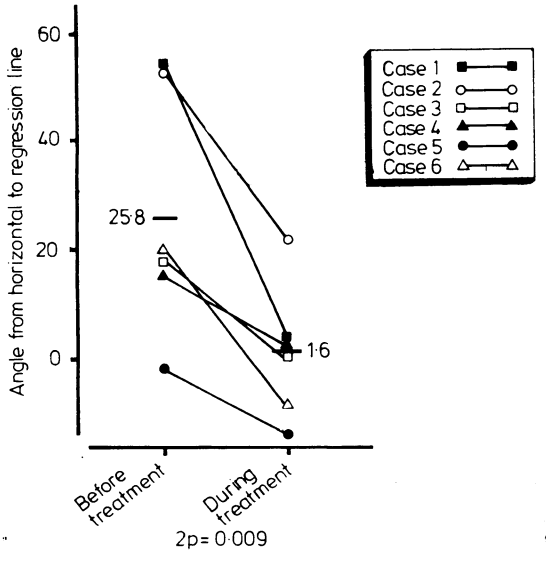

FIG 4—Yearly percentage increases in albumin clearance before and during treatment in all six patients studied. (Values expressed as angle from horizontal to regression line.)

shows the rates of fall in these values. Figure 4 shows the yearly percentage increase in albumin clearance (expressed as the angle from horizontal to regression line) in all six patients. Before antihypertensive treatment the glomerular filtration rate in cases 1 to 5 was falling by a mean of 1·23 ± SD 0·8 ml/min/month; during treatment this was reduced to 0·49 ± 0·5 ml/min/month (2p = 0·042). One patient (case 6) had a high glomerular filtration rate before treatment (137 ml/min) and showed no fall either before or during treatment; at the end of the study his glomerular filtration rate was 135 ml/min. There was also evidence that antihypertensive treatment reduced the decline in renal plasma flow, but the difference was not statistically significant. Progressively smaller extraction of hippuran with worsening renal damage, however, may have given falsely low results late in the study. The yearly percentage increase in albumin clearance in the six patients fell from 107% to 5%—that is, albumin clearance was virtually stabilised (fig 4). Both before and during treatment the decline in glomerular filtration rate correlated significantly with arterial pressures (fig 5). Before treatment the mean coefficients of variance for measurements of glomerular filtration rate and renal plasma flow, which were conducted over three to six periods, were 8·8% and 9·7% respectively; during treatment both values rose to 10·3%, which was slightly higher than in normal people and patients with diabetes of short duration, in whom the coefficient of variance is around 6-8% for both clearance tests.[9]

Fasting blood sugar values—There was no significant change in fasting plasma glucose concentrations and insulin requirements during antihypertensive treatment. The mean fasting plasma glucose value before treatment was 8·6 ± SD 1·8 mmol/l (154·5 ± SD 32·0 mg/100 ml) and during treatment 10·6 ± 2·1 mmol/l (191·0 ± 37·0 mg/100 ml).

Retinopathy—There was a slight worsening of retinopathy in three of the patients given laser treatment, whereas two were unchanged. One patient had a large haemorrhage in one eye during treatment. The study, however, did not evaluate the possible beneficial effect on the progression of retinopathy during treatment.[11]

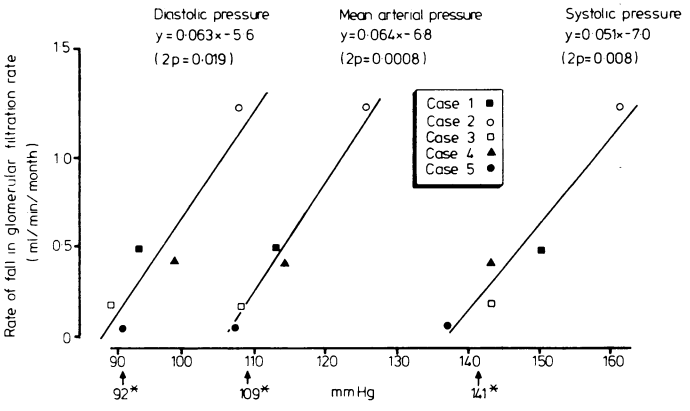

FIG 5—Blood pressures and decline in glomerular filtration rates during treatment cases in 1 to 5.
*Blood pressures during treatment corresponding to decline in glomerular filtration rate of 0·2 ml/min/month.

Discussion

In this small study antihypertensive treatment reduced the decline in the glomerular filtration rate in diabetic nephropathy. Blood pressure was slightly to moderately increased before treatment. During treatment, which lasted up to seven years, the decline in glomerular filtration fell from 1·23 ml/min/month to 0·49 ml/min/month (2p = 0·042), indicating that renal insufficiency was considerably postponed. Larger trials in patients so far followed up for a shorter time have given a closely similar result.[6] In a previous study on the progression of diabetic nephropathy[5] high blood pressure was identified as a possible factor in the rapid progression of renal disease seen in some patients. Failure to confirm this observation in other reports may have been due to differences in the patients studied.[1,12] It was also found that the rate of decline in the glomerular filtration rate could be predicted from repeated measurements of renal function, determinations over a short period correlating well with a decline over years.[5]

This study used a comparatively short pretreatment control period, since we could not justify withholding an effective treatment from patients with moderate hypertension.

Using the monthly rate of decline in the glomerular filtration rate as an index of the progression of nephropathy is a great advantage in evaluating the effect of any therapeutical trial. Such exact measurement is not feasible in diabetic retinopathy, for which many therapeutic trials have been performed. It is therefore surprising that no other attempts have been made to measure and possibly influence the progression of diabetic nephropathy.

High blood pressure is an early phenomenon in the development of diabetic nephropathy[13] and generally does not occur in diabetics without renal disease.[4] The exact relation between high blood pressure and diabetic nephropathy is not clear. It is generally believed that high blood pressure is a result of the nephropathy in diabetic patients; arguably, however, that the

rate of development of renal disorder may be greater in those diabetics who lie in the upper range of blood pressure values before nephropathy is clinically apparent. That was the case in our patient with overt nephropathy.[5]

The present results, however, suggest that it is possible to influence kidney function in diabetic nephropathy by antihypertensive treatment, as we have also shown in patients with essential hypertension.[14 15] In essential hypertension we found a significant fall in urinary albumin excretion during treatment with a beta-blocking agent alone or combined with hydralazine,[15] and therefore a similar scheme of treatment was chosen in the present series of patients with established nephropathy. Also exercise-induced microalbuminuria is corrected by antihypertensive treatment in essential hypertension.[16] Preliminary data suggest the same phenomenon in incipient diabetic nephropathy.[17]

We could not evaluate whether effects on nephropathy of the present treatment, which included beta-blockers, were due solely to reduction in blood pressure, since beta-blockers have several other vascular and metabolic effects.[18 19] From the results, however, a reduction in the rate of fall in the glomerular filtration rate correlated with a reduction in blood pressure. We find that propranolol has a considerable disadvantage in diabetic patients—namely, an increased tendency to hypoglycaemic unawareness. Once we had changed to metoprolol (a cardioselective beta-blocker) hypoglycaemic unawareness was not a problem for the patients during many months of treatment. The value of cardioselective beta-blockers for diabetics has been questioned by others.

We could not arrest the progression of nephropathy in our patients, who had established nephropathy and a mean glomerular filtration rate of only 86 ml/min, or about 60% of that found in long-term non-proteinuric diabetics.[20] Hence the next step is to clarify whether intervention at an earlier stage would be more effective—for example, before the fall in glomerular filtration rate is evident. Such studies are in progress.[17] Finally, the safety of cardioselective beta-blockers in diabetes has now been established.[21]

Besides the effect on systemic blood pressure, possibly modified glomerular haemodynamics, by blocking local receptors, play a part. Hostetter *et al*, from experimental studies on Munich Wistar rats,[22 23] recently postulated glomerular hypertension as an important pathogenetic factor in diabetic nephropathy.

I thank Merete Møller and Bodil Willumsen for skilful technical work, and the staff of the department of nuclear medicine and clinical chemistry for much valuable help.

The study was supported by grants from Hjerteforeningen and Statens Laegevidenskabelige Forskningsråd, Denmark.

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(*Accepted 8 July 1982*)

The herb SANICLE is by many called Butterwort. Ordinary Sanicle sends forth many great round leaves, standing upon long brownish stalks, every one somewhat deeply cut or divided into five or six parts, and some of these also cut in somewhat like the leaf of crow's-foot, or dove's-foot, and finely dented about the edges, smooth, and of a dark shining colour, and somewhat reddish about the brims; from among which arise up small, round green stalks, without any joint or leaf thereon, saving at the top, where it branches forth into flowers, having a leaf divided into three or four parts at that joint with the flowers, which are small and white, starting out of small round greenish yellow heads, many standing together in a tuft, in which afterwards are the seeds contained, which are small round burs, somewhat like the leaves of clevers, and stick in the same manner upon any thing that they touch. The root is composed of many blackish strings or fibres, set together at a little long head, which abides with green leaves all the Winter, and perishes not.

It is found in many shadowy woods, and other places of this land. It flowers in June, and the seed is ripe shortly after.

This is one of Venus's herbs, to cure the wounds or mischiefs Mars inflicts upon the body of man. It heals green wounds speedily, or any ulcers, imposthumes, or bleedings inward, also tumours in any part of the body; for the decoction or powder in drink taken, and the juice used outwardly, dissipates the humours: and there is not found any herb that can give such present help either to man or beast, when the disease falleth upon the lungs or throat, and to heal up putrid malignant ulcers in the mouth, throat, and privities, by gargling or washing with the decoction of the leaves and roots made in water, and a little honey put thereto. It helps to stay women's courses, and all other fluxes of blood, either by the mouth, urine, or stool, and lasks of the belly; the ulcerations of the kidneys also, and the pains in the bowels, and gonorrhea, being boiled in wine or water, and drank. The same also is no less powerful to help any ruptures or burstings, used both inwardly and outwardly: And briefly, it is as effectual in binding, restraining, consolidating, heating, drying and healing, as comfrey. bugle, self-heal, or any other of the vulnerary herbs whatsoever, (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)