Effects of Long-term Antihypertensive Treatment on Kidney Function in Diabetic Nephropathy

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SUMMARY The purpose of our prospective study was to evaluate the long-term effect of aggressive antihypertensive treatment on glomerular filtration rate and albuminuria in young female and male patients with insulin-dependent diabetes mellitus with diabetic nephropathy and blood pressure greater than 90 mm Hg. Eight patients received treatment with metoprolol (200-400 mg/day), hydralazine (100-200 mg/day), and furosemide (80-500 mg/day). The untreated control group consisted of eight patients matched for age (mean 32 years), diabetes duration (mean 17 years), and sex (two female and six male patients). All patients except one had diabetic retinopathy. Glomerular filtration rate was measured after a single intravenous injection of $^{51}$Cr-labeled ethylenediaminetetraacetic acid. Urinary albumin concentration was determined with a radial immunodiffusion method. The investigations were performed two to four times per year in each patient. The mean observation period was 59 and 27 months in the treated and untreated groups respectively. Due to a considerable rise in arterial blood pressure, it was considered unethical to prolong the observation in the untreated group. Arterial blood pressure rose from 140/96 ± 4/1 to 150/100 ± 3/2 mm Hg; albuminuria increased from 1517 ± 502 to 1911 ± 120 µg/min; and glomerular filtration rate decreased by a mean of 0.84 ± 0.17 ml/min/mo in the untreated group. Antihypertensive treatment induced blood pressure reduction to 151/100 ± 3/2 to 131/87 ± 2/1 mm Hg; diminished albuminuria to 1467 ± 515 to 729 ± 65 µg/min; and caused a slow rate of decline in GFR, mean 0.37 ± 0.08 ml/min/mo. Our prospective study suggests that prolonged reduction in arterial blood pressure to near normal levels reduces the rate of decline in glomerular filtration rate, and albuminuria in young patients with insulin-dependent diabetes mellitus and diabetic nephropathy. (Hypertension 7 [Suppl II]: 11-114—11-117, 1985)

KEY WORDS • glomerular filtration • albuminuria • insulin-dependent diabetes mellitus • arterial blood pressure

APPROXIMATELY 40 to 50% of all patients with insulin-dependent diabetes mellitus (IDDM) develop persistent proteinuria, decline in glomerular filtration rate (GFR) and elevation of arterial blood pressure, that is, diabetic nephropathy. Renal failure is the leading cause of death (30%) in these patients. On average, death occurs 7 years after the start of persistent proteinuria. Elevated blood pressure accelerates the nephropathy. Recent studies indicate that effective antihypertensive treatment reduces albuminuria and the rate of decline in GFR in these patients. The aim of our prospective study, begun in 1978, was to evaluate the long-term effect of antihypertensive treatment on kidney function and albuminuria in a group of young patients with IDDM with diabetic nephropathy. Previously reported data obtained from an evaluation of the first 30 months of treatment are included and reevaluated after 54 months of treatment.

Patients and Methods
Sixteen patients with IDDM with diabetic nephropathy were investigated (Table 1). All patients were characterized by persistent proteinuria (> 0.5 g/24 hr), serum creatinine less than 150 µmol/L, age less than 45 years, onset of IDDM before age 31 years, and no blindness. All were insulin dependent from the time of diagnosis and all received two daily injections of insulin. None of the patients were taking drugs other than insulin. All 16 patients gave fully informed consent. Diabetic nephropathy was diagnosed clinically according to previously described criteria.

All clinical and laboratory variables were nearly...
identical in the untreated and the treated groups, apart
from a slightly higher systolic blood pressure in the
later-treated group (p < 0.05). Metoprolol (100–400
mg/day), hydralazine (50–200 mg/day), and furose-
mide (80–500 mg/day) were used as antihypertensive
drugs. The goal of treatment was stable reduction in
mean arterial blood pressure (diastolic pulse one-third
of pulse amplitude) of at least 10 mm Hg.

All investigations were made on the same day be-
tween 0900 and 1300 hours. Patients had their normal
breakfast and morning insulin before the investiga-
tions, which were carried out with the patients resting
in the supine position. The investigations were per-
formed two to four times per year in each patient.

The GFR was measured after a single intravenous
injection of 51Cr-labeled ethylenediaminetetraacetic
acid (51Cr-EDTA) at 0900 hours by studying the plas-
ma disappearance for 4 hours, as described by
Brøchner-Mortensen et al.8 who showed that the mean
intraindividual coefficient of variation for GFR with
this technique is 4.1%. Results were corrected to 1.73
m² body surface area, using the area at the initiation of
the study throughout. The rate of decline in GFR
(ml/min/mo) was calculated by linear regression anal-
ysis (least-square method). Urinary albumin excretion
was measured during the 4-hour clearance period by
radial immunodiffusion.9

Blood pressure was measured with a standard clinical
sphygmomanometer, Erkameter, Berlin, West
Germany (cuff 25 x 12 cm) on the right arm with the
subject in the supine position for at least 10 minutes.
Blood pressure was measured twice during each inves-
tigation and visit to the outpatient clinic. Diastolic
blood pressure was recorded at the disappearance of
Korotkoff sounds (phase 5). The patients visited the
clinic every 2 to 4 months during the investigation
period. At each visit, postprandial blood glucose, glu-
cosuria, proteinuria, blood pressure, and body weight
were measured and insulin and antihypertensive treat-
ment was adjusted.

In all cases the paired and unpaired t test was used
for statistical analysis. Mean values are given with
standard error of mean (SEM).

Results

Arterial blood pressure decreased in all treated pa-
tients and increased in the untreated group (p < 0.01;
Figure 1). Albuminuria was reduced in all treated pa-
tients, while enhanced albuminuria was found in the
untreated group (p < 0.01; Figure 2). The rate of
decline in GFR was less in the treated group (mean
0.37 ml/min/mo, range 0.10–0.77 ml/min/mo) com-
pared with the untreated group (mean 0.84 ml/min/mo,
range 0.36–1.46 ml/min/mo, p < 0.05; Figure 3). The
average course of GFR compiled from all patients in
the two groups is shown in Figure 4. The effect of
antihypertensive treatment on arterial blood pressure, albuminuria, and GFR is shown in Table 2. Mean postprandial blood glucose was nearly identical in the two groups.

Discussion

Our prospective study demonstrated that long-term effective antihypertensive treatment reduces albuminuria and the decline in GFR in young male and female patients with IDDM with diabetic nephropathy. We confirmed and extended Mogensen's 3 original observation in six male patients. Previously, we demonstrated that short-term aggressive antihypertensive therapy diminished albuminuria and the decline in kidney function in diabetic nephropathy.7 We confirmed that increase in arterial blood pressure to a hypertensive level is an early feature of diabetic nephropathy.8 Arterial blood pressure thus seems to have a complex relation with diabetic nephropathy; nephropathy raises blood pressure and blood pressure accelerates the course of nephropathy.

Due to the considerable rise in blood pressure in the untreated group, it was considered unethical to prolong

the observation period and thus withholding effective antihypertensive therapy from patients with light to moderate arterial hypertension.

Our main reasons for selecting metoprolol were its effectiveness, safety, and pronounced effect on arterial blood pressure during physical exertion.3,13 The last is important, since patients with long-term IDDM have a higher blood pressure response to exercise than healthy controls.14 Although metoprolol and other beta blockers can mask some clinical signs of hypoglycemia, only one patient experienced a hypoglycemic attack requiring treatment with intravenous glucose during the 5-year treatment period. Apart from this, no important side effects were observed, and all eight patients are still receiving metoprolol.

Several studies in animals and humans with diabetes mellitus support the hypothesis of Steffes et al.13 and Hostetter et al.15 that intrarenal hypertension is an important factor in the development and progression of diabetic nephropathy, as reviewed by Parving et al.17 Urinary albumin excretion is normal in effectively treated patients with essential hypertension, but is elevated in insufficiently treated hypertension.18 Antihypertensive treatment of less than 2 months reduces albuminuria in essential hypertension and in young patients with IDDM with diabetic nephropathy.19,20 We found that blood pressure reduction induced by
intravenous injection of clonidine immediately diminishes albuminuria in these patients. The simplest explanation of our findings may therefore be the correct one: a reduction of glomerular capillary pressure induced by the antihypertensive treatment.
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