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

HANS-HENRIK PARVING, ALLAN R. ANDERSEN, EVA HOMMEL, AND ULLA SMIDT

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 151/100 ± 3/2 to 131/87 ± 2/1 mm Hg; diminished albuminuria 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 furosemide (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 between 0900 and 1300 hours. Patients had their normal breakfast and morning insulin before the investigations, which were carried out with the patients resting in the supine position. The investigations were performed two to four times per year in each patient.

The GFR was measured after a single intravenous injection of \(^{51}\)Cr-labeled ethylenediaminetetraacetic acid \((^{51}\)Cr-EDTA) at 0900 hours by studying the plasma disappearance for 4 hours, as described by Brøchner-Mortensen et al. who showed that the mean intraindividual coefficient of variation for GFR with this technique is 4.1%. Results were corrected to 1.73 m\(^2\) 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 analysis (least-square method). Urinary albumin excretion was measured during the 4-hour clearance period by radial immunodiffusion.

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 investigation 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, glucosuria, proteinuria, blood pressure, and body weight were measured and insulin and antihypertensive treatment 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 patients and increased in the untreated group \(p < 0.01\); Figure 1). Albuminuria was reduced in all treated patients, 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) compared 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 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. We confirmed that increase in arterial blood pressure to a hypertensive level is an early feature of diabetic nephropathy in young patients with IDDM. 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 withhold 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. The last is important, since patients with long-term IDDM have a higher blood pressure response to exercise than healthy controls. 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. and Hostetter et al. that intrarenal hypertension is an important factor in the development and progression of diabetic nephropathy, as reviewed by Parving et al. Urinary albumin excretion is normal in effectively treated patients with essential hypertension, but is elevated in insufficiently treated hypertension. Antihypertensive treatment of less than 2 months reduces albuminuria in essential hypertension and in young patients with IDDM with diabetic nephropathy. We found that blood pressure reduction induced by...
ANTIHYPERTENSIVE TREATMENT IN DIABETIC NEPHROPATHY/Parving et al.

FIGURE 4. The average course of GFR in eight untreated (open circles) and eight antihypertensive-treated (closed circles) insulin-dependent diabetic patients with diabetic nephropathy. Vertical bars indicate SEM.

TABLE 2. The Effect of Antihypertensive Treatment on the Course of Blood Pressure, Albuminuria, and GFR in Patients with IDDM with Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Antihypertensive treatment*</th>
<th>Control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation period (mo)</td>
<td>8</td>
</tr>
<tr>
<td>Arterial blood pressure (mm Hg)</td>
<td>59 ± 1</td>
</tr>
<tr>
<td>Albuminuria (µg/min)</td>
<td>729 ± 65</td>
</tr>
<tr>
<td>Rate of decline in GFR (ml/min/mo)</td>
<td>0.37 ± 0.08</td>
</tr>
</tbody>
</table>

*Average of all determinations during the observation period, mean ± SEM indicated.

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.

References

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