Effect of Antihypertensive Treatment on Progression of Incipient Diabetic Nephropathy

Cramer K. Christensen and Carl Erik Mogensen

SUMMARY The aim of the study was to clarify whether antihypertensive treatment with a selective beta blocker would have an effect on the progression rate of kidney disease in patients with incipient diabetic nephropathy. Six male patients with juvenile-onset diabetes with incipient nephropathy (urinary albumin excretion above 15 µg/min and total protein excretion below 0.5 g/24 hr) were treated with metoprolol (200 mg daily). At the start of the antihypertensive treatment the mean age was 32 years ± 4.2 (SD). The patients were followed a mean 5.4 years ± 3.1 (SD) with repeated measurements of urinary albumin excretion before and during 2.6 years ± 1.0 (SD) of treatment. The blood pressure was depressed by the treatment (systolic blood pressure from 135 mm Hg ± 8.6 to 124 mm Hg ± 6.2, NS; mean blood pressure from 107 mm Hg ± 7.6 to 97 mm Hg ± 3.4, 2p < 0.05; diastolic blood pressure from 93 mm Hg ± 9.1 to 84 mm Hg ± 3.6, 2p < 0.05. Albumin excretion decreased (131.0 µg/min ×/± 2.9 [geometric mean ×/± tolerance factor] to 56.1 µg/min ×/± 3.7, 2p < 0.02). The mean yearly increase in urinary albumin excretion before treatment was 18 ± 17 (mean ± SD). Albumin excretion decreased during treatment: 17% ± 15 per year (mean ± SD, 2p < 0.02). No changes were seen in glomerular filtration rate or renal plasma flow (149 ml/min ± 5.8 vs 144 ml/min ± 11.1, and 516 ml/min ± 31.0 vs 541 ml/min ± 68.5 respectively [n = 5]). No side effects were seen. It is concluded that during antihypertensive treatment using a cardioselective beta blocker, blood pressure decreased and albumin excretion was reduced concomitantly. Glomerular filtration rate was unchanged during treatment. Antihypertensive treatment in the stage of incipient nephropathy may have a more beneficial effect on the progression of the kidney disease than when it is started in the overt stage of nephropathy, where glomerular filtration rate has already begun to decline. (Hypertension 7 [Suppl II]: 11-109-11-113, 1985)

KEY WORDS • blood pressure • microalbuminuria • early nephropathy

The association between high blood pressure (BP) and diabetic nephropathy is now well established from a number of studies. Until the middle of the 1970s it was generally accepted that no treatment could change the course of diabetic nephropathy. Two studies, however, have now shown that by effective antihypertensive treatment the linear fall in glomerular filtration rate (GFR) can be reduced from a mean of about 1 to about 0.5 ml/min/mo, thus probably postponing the uremic stage. These patients had rather advanced diabetic renal disease, GFR being reduced to about 60% of the level prior to nephropathy. Thus effective antihypertensive treatment cannot prevent development of the uremic stage when it is started in the overt stage of nephropathy where BP is in the definitively hypertensive level. Earlier therapy, before a definitively hypertensive level has been reached, might prove more effective in preventing the fall in GFR.

The aim of the present study was to investigate the effect of antihypertensive treatment in incipient diabetic nephropathy characterized by persistently elevated urinary albumin excretion, but still well-preserved or even supranormal kidney function and marginal BP elevation. Urinary albumin excretion rate, renal hemodynamics, and BP were followed before and during treatment in young male patients in a longitudinal study.

Patients and Methods

Six male patients with incipient diabetic nephropathy (IDN) were investigated in a longitudinal study. The disease was defined as urinary albumin excretion (UAE) persistently greater than 15 µg/min and total

From the Second University Clinic of Internal Medicine, Kommunehospitalet Aarhus, Denmark.
This study was supported by the Danish Medical Research Council and the Nordic Insulin Fund.
Address for reprints: Dr. Cramer K. Christensen, Second University Clinic of Internal Medicine, Kommunehospitalet, DK-8000, Aarhus C, Denmark.
A battery of laboratory tests was performed at the start of antihypertensive treatment. These included the measurement of renal vascular resistance (RVR) and mean blood pressure (mBP). Renal vascular resistance (RVR) was calculated as the difference between mBP and diastolic blood pressure (DBP), divided by the renal plasma flow (RPF). Mean blood pressure (mBP) was calculated as the average of all BP measurements during the renal function test. Blood pressure (BP) was measured by a conventional sphygmomanometer technique.

Urinary albumin excretion was determined by radioimmunoassay and expressed as micrograms per minute. Beta2-microglobulin was also measured by radioimmunoassay (Pharmacia Kit, Phadebas, Sweden) and expressed as micrograms as micrograms per minute. At least three urine samples were collected, using 20-minute periods, after drinking water for at least 1.5 hours (200 ml every 20 minutes both before and during the test).

The GFR and renal plasma flow (RPF) were measured by a constant infusion technique. 9 [123I]iodohippuran were used as test substances, measured by a radioimmunoassay (Pharmacia Kit, Phadebas, Sweden) and expressed as micrograms per minute.8 Betaj-microglobulin was also measured by radioimmunoassay (Pharmacia Kit, Phadebas, Sweden) and expressed as micrograms per minute.4-5 The mean age was 32 years ± 4.2 (SD) and the mean duration of diabetes was 18 years ± 1.2 (SD). Further clinical data are shown in Table 1. For comparison, 18 male healthy controls, age 28.6 ± 4.8, weight 71.8 kg ± 7.4 (mean ± SD), were also investigated. In addition to IDN, the inclusion criteria for start of antihypertensive treatment were age below 40 years, no other clinically evident cardiovascular or neurological complications, and no evidence of being unable to feel hypoglycemia. Furthermore, prior to treatment the patients should have been followed for more than 1.5 years with a minimum of three UAE measurements before the start of antihypertensive treatment. We used a cardioselective beta blocker, metoprolol (100 mg two times a day). The patients were examined in the outpatient clinic either in supine or sitting position. The examination was always performed in the morning, insulin and breakfast being given afterward.

Urinary albumin excretion was determined by radioimmunoassay and expressed as micrograms per minute. Beta2-microglobulin was also measured by radioimmunoassay (Pharmacia Kit, Phadebas, Sweden) and expressed as micrograms per minute. At least three urine samples were collected, using 20-minute periods, after drinking water for at least 1.5 hours (200 ml every 20 minutes both before and during the test).

### Statistics

Standard parametric statistics were used. Urinary albumin and urinary beta2-microglobulin excretion were calculated after log transformation since protein excretion seems to be distributed normally after log transformation. Because of log transformation, urinary albumin and beta2-microglobulin excretion were expressed as geometric mean ×/± tolerance factor instead of mean ± SD.

### Results

#### Blood Pressure Levels

During the 6 months before start of antihypertensive treatment, the following BP levels were found: systolic blood pressure (SBP), 135 mm Hg ± 8.6 (mean ± SD); range 127–151 mm Hg; mBP, 107 mm Hg ± 7.6 (range 96–115 mm Hg); and DBP, 93 mm Hg ± 9.1 (range 80–103 mm Hg). During the first 6 months of antihypertensive treatment with metoprolol, SBP, mBP, and DBP decreased significantly to 127 mm Hg ± 4.7 (range 120–134 mm Hg), 96 mm Hg ± 5.7 (range 90–104 mm Hg), and 88 mm Hg ± 8.9 (range 71–93 mm Hg) respectively. No further decrease was seen during the rest of the study (Table 2). The values for the whole treatment period were SBP, 125 mm Hg ± 4.6; mBP, 97 mm Hg ± 3.1; and DBP, 83 mm Hg ± 6.0 (significant fall in all cases, 2p < 0.01).

#### Urinary Albumin and Beta2-microglobulin Excretion

During antihypertensive treatment a significant decrease in albumin excretion from 131.0 μg/min ×/± 2.9 to 56.1 μg/min ×/± 0.3 (geometric mean ×/± tolerance factor) (2p < 0.02) was noted (Table 2). The mean yearly percentage change in albumin excretion reverted from an increase of 18 ± 17 (mean ± SD) in the pretreatment period to a decrease of 17 ± 15 during the treatment period (2p < 0.01; Table 3).

Beta2-microglobulin excretion did not change during treatment and levels were within the normal range.

#### Kidney Function

As shown in Table 2, no changes were seen during treatment either in GFR or RPF. The GFR was at a supranormal level, whereas RPF was within normal range. No significant changes occurred in renal vascular resistance or in filtration fraction, although the former had a tendency to fall.

#### Metabolic Control and Body Weight

Plasma glucose values did not change during treatment (see Table 2); nor did body weight (81.2 ± 9.7 before and 80.4 ± 10.7 at the end of the study). Also, prior to treatment no change in plasma glucose values was found.

### Discussion

According to two studies on patients with overt diabetic nephropathy,1,2 effective antihypertensive treatment can reduce the linear rate of decline in GFR from about 1 to about 0.5 ml/min/mo, and thus if the effect persists, postpone end-stage renal failure. Unfortunately, in spite of well-controlled BP, the rate of decline cannot be completely impeded when treatment is started in this rather late stage of nephropathy. Therefore it was of interest to study whether much
TABLE 2. Blood Pressure, Kidney Function, and Blood Glucose Level Before and During (2.6 yr ± 1.0) Antihypertensive Treatment with Selective Beta Blockers in Six Patients with Incipient Diabetic Nephropathy

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 18)</th>
<th>Before</th>
<th>Number of measurements</th>
<th>During</th>
<th>Number of measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>First 6 months</td>
<td>Last 6 months</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>115±9.8</td>
<td>135±8.6Δ</td>
<td>2.5±0.8</td>
<td>127±4.7*</td>
<td>4.0±1.7</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>87±7.8</td>
<td>107±7.6Δ</td>
<td>2.5±0.8</td>
<td>98±5.7†</td>
<td>4.0±1.7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73±8.0</td>
<td>93±9.1Δ</td>
<td>2.5±0.8</td>
<td>88±8.9†</td>
<td>4.0±1.7</td>
</tr>
<tr>
<td>Albumin excretion rate (μg/min)</td>
<td>4.3×/±1.3</td>
<td>131.0×/±2.9Δ</td>
<td>2.5±0.8</td>
<td>103.6×/±2.1</td>
<td>4.0±1.7</td>
</tr>
<tr>
<td>Beta2-microglobulin excretion rate (μg/min)</td>
<td>0.050×/±1.8</td>
<td>0.062×/±2.6</td>
<td>2.5±0.8</td>
<td>0.060×/±1.5</td>
<td>4.0±1.7</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min/1.73 m²)</td>
<td>123±11.8</td>
<td>149±5.8Δ</td>
<td>1</td>
<td>142±13.5</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Renal plasma flow (ml/min/1.73 m²) (n = 5)</td>
<td>546±55.4</td>
<td>516±31.0</td>
<td>1</td>
<td>515±66.6</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Renal vascular resistance (mm Hg/ml/min) (n = 5)</td>
<td>0.162±0.022</td>
<td>0.202±0.034Δ</td>
<td>1</td>
<td>0.199±0.035</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Filtration fraction (n = 5)</td>
<td>0.227±0.020</td>
<td>0.290±0.019Δ</td>
<td>1</td>
<td>0.278±0.032</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>123±11.8</td>
<td>149±5.8Δ</td>
<td>1</td>
<td>142±13.5</td>
<td>1.8±0.8</td>
</tr>
</tbody>
</table>

Mean of one or more numbers of measurements, 6 months before, during the first 6 months, and during the last 6 months of treatment. Values are given in mean ± SD except for albumin and beta2-microglobulin, which are expressed as geometric mean ×/± tolerance factor because of the log transformation. Δ refers to significant elevation in comparison to nondiabetic controls.

Significant decrease (two-tailed probability) compared to pretreatment levels: *2p < 0.05; †2p < 0.01; ‡2p < 0.02.

TABLE 3. Increase in Urinary Albumin Excretion Rate Before and During Antihypertensive Treatment with Selective Beta Blockers in Six Patients with Incipient Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>IUAE %/yr (anti-log α -1100)</th>
<th>Followed (yr)</th>
<th>n</th>
<th>IUAE %/yr (anti-log α -1100)</th>
<th>Followed (yr)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>y = -0.023x + 1.45</td>
<td>8</td>
<td>8.00 - 5</td>
<td>y = -0.184x + 1.58</td>
<td>12</td>
<td>3.75 - 34</td>
</tr>
<tr>
<td>2</td>
<td>y = 0.152x + 2.20</td>
<td>3</td>
<td>1.65 42</td>
<td>y = -0.144x + 2.19</td>
<td>10</td>
<td>3.30 - 28</td>
</tr>
<tr>
<td>3</td>
<td>y = 0.106x + 1.52</td>
<td>9</td>
<td>6.33 28</td>
<td>y = -0.092x + 1.87</td>
<td>8</td>
<td>3.25 - 19</td>
</tr>
<tr>
<td>4</td>
<td>y = 0.014x + 2.27</td>
<td>7</td>
<td>5.90 3</td>
<td>y = 0.019x + 2.25</td>
<td>11</td>
<td>1.75 4</td>
</tr>
<tr>
<td>5</td>
<td>y = 0.086x + 2.14</td>
<td>5</td>
<td>1.75 22</td>
<td>y = -0.004x + 2.16</td>
<td>8</td>
<td>1.58 - 1</td>
</tr>
<tr>
<td>6</td>
<td>y = 0.073x + 1.46</td>
<td>11</td>
<td>8.75 18</td>
<td>y = -0.120x + 2.14</td>
<td>10</td>
<td>1.83 - 24</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>7.2 5.40 18</td>
<td></td>
<td></td>
<td>9.8 2.58 - 17</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td>2.9 3.05 17</td>
<td></td>
<td></td>
<td>1.6 0.96 15</td>
</tr>
<tr>
<td>2p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>
earlier intervention with antihypertensive treatment would have a beneficial effect on the progression of kidney disease. The major variables used to measure the progression in the overt stage of nephropathy are UAE and in particular GFR. As GFR may be normal or even supranormal in IDN, however, if it has not started to decline, this value may not be used in this very early phase of renal disease. Albumin excretion can be used as a test value when progression in IDN has to be evaluated. In addition, UAE appears to be a strong predictor for overt diabetic nephropathy. Elevated BP and supranormal GFR also seem to be risk factors.

The present study showed that slightly elevated BP in patients with incipient nephropathy can be normalized during treatment with metoprolol, and this decrease was associated with a significant fall in UAE (Tables 2 and 3; Figure 1). The fall in UAE while BP is

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Individual curves for urinary albumin excretion before and during antihypertensive treatment. The dotted line and arrow indicate the start of treatment.}
\end{figure}
lowered was reported in earlier studies in overt diabetic nephropathy and in essential hypertension. It is not known exactly when the GFR starts to decline; however, from measurements in a limited number of diabetics, in those with incipient diabetic nephropathy GFR is stable early but seems to start to decline in the late part of this phase. No change in GFR or RPF was seen during 2.6 years of antihypertensive treatment in the present study. Thus antihypertensive treatment together with standard diabetes treatment may prove to offer some protection against overt nephropathy, but additional therapy, such as supercontrol of blood glucose, may be of importance.

Metoprolol was well tolerated and the patients had no notable side effects. Masking of the symptoms of hypoglycemia was not a problem for the patients during the study period, which agrees with results of earlier studies in which cardioselective beta blockers were given to diabetic patients. From experimental studies on Munich Wistar rats, the important hypothesis has been put forward that glomerular hypertension is a major pathogenetic factor in diabetic nephropathy. Antihypertensive treatment may also lower intraglomerular pressure, as the decline in UAE suggests, but it is possible that structural lesions can regress during treatment. In conclusion, antihypertensive treatment decreased the BP in patients with incipient diabetic nephropathy and this was associated with a decrease in albumin excretion; GFR was stable for a mean of 2.6 years of treatment. Starting therapy in this early stage of diabetic nephropathy may prove to have a more pronounced long-term beneficial effect on the progression of kidney disease than initiating it in the overt stage of diabetic nephropathy.

Acknowledgment
Merete Møller provided skilful technical assistance.

References
Effect of antihypertensive treatment on progression of incipient diabetic nephropathy.
C K Christensen and C E Mogensen

_Hypertension_. 1985;7:II109
doi: 10.1161/01.HYP.7.6_Pt_2.II109
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/7/6_Pt_2/II109

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/