Hypertension in Diabetes as Related to Nephropathy
Early Blood Pressure Changes

Bo Feldt-Rasmussen, Knut Borch-Johnsen, and Elisabeth R. Mathiesen

SUMMARY We measured the blood pressure under standardized conditions in three groups of patients with type I (insulin-dependent) diabetes: group 1, patients with Albustix-negative urine and normal urinary albumin excretion rate below 20 µg/min; group 2, patients with Albustix-negative urine and elevated urinary albumin excretion rate 20 to 200 µg/min; and group 3, patients with Albustix-positive urine at the time of diagnosis of diabetic nephropathy, that is, proteinuria greater than 0.5 g/24 hr on four consecutive visits with an interval of more than 1 month. We also studied blood pressure data at the time of diagnosis of diabetes in patients with type I diabetes who later died with severe nephropathy (n = 84), and in those who survived their disease for more than 40 years (n = 256). Patients subsequently developing diabetic nephropathy could not be identified on the basis of systolic and/or diastolic blood pressure during the first 2 to 10 years of diabetes. Our study also demonstrated that the blood pressure in group 3 (147/93 mm Hg) was significantly higher than that in group 2 (135/86 mm Hg), which again was higher than that in group 1 (128/79 mm Hg). We concluded that arterial hypertension is an early feature in the development of diabetic nephropathy, with blood pressure rising before the presence of clinical proteinuria.

(Hypertension 7 [Suppl II]: II-18-II-20, 1985)

KEY WORDS • type I diabetes • urinary albumin excretion rate • blood pressure

Diabetic nephropathy is the most serious complication of type I (insulin-dependent) diabetes mellitus (IDDM),1 with a grave prognosis after the onset of proteinuria.2-5 It is characterized by glomerular arteriolohyalinosis, glomerulosclerosis, persistent proteinuria, decreasing glomerular filtration rate (GFR), and increasing blood pressure. The etiology of diabetic nephropathy is unknown, and the role of arterial blood pressure in the pathogenesis of clinical nephropathy has been discussed.6-9 Generally, hypertension has been acknowledged to be a late symptom of diabetic nephropathy, but it was recently demonstrated that elevated blood pressure is also present in patients during early stages of nephropathy, that is, normal level of serum creatinine.10 It has also been shown that elevated arterial blood pressure has an enormous impact on the progression of diabetic nephropathy.11,12 The question therefore arises as to whether elevated blood pressure also plays a role in initiating the development of clinical nephropathy. In other words, does blood pressure increase before or after the onset of clinical proteinuria?

Our aim is to add some information to the matter of the time relationship between blood pressure rise and the development of proteinuria. We discuss only patients with IDDM because the clinical course of diabetic nephropathy in type II (non-insulin-dependent) diabetes seems to be different and is probably more benign.13,14

Materials and Methods

Cross-sectional Study

We studied 114 patients with IDDM of onset before age 31 years and with a duration of 5 to 25 years, who were receiving no antihypertensive treatment at the time of blood pressure recordings. Their age range was 18 to 50 years. The patients were randomly selected from our files among those known to belong to one of three groups on the basis of urinary albumin excretion rate (UAE). Patient data are shown in Table 1.

Group 1 (control) consisted of 54 patients with persistently normal UAE. Group 2 (microalbuminuric) was made up of 34 patients with Albustix-negative urine (Albustix; Boehringer, Mannheim, West Germany), but persistently elevated UAE (20–200 µg/min). They had a negative bacterial culture and no history of kidney disease. In group 3 (diabetic ne-
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TABLE 1. Clinical Data in 114 Patients with Type I Diabetes Classified According to Urinary Albumin Excretion Rate

<table>
<thead>
<tr>
<th>Albuminuric level (μg/min)</th>
<th>n</th>
<th>M:F</th>
<th>Age (yr)</th>
<th>Diabetes duration (yr)</th>
<th>Serum creatinine (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (UAE &lt; 20 μg/min)</td>
<td>54</td>
<td>30:24</td>
<td>34±7</td>
<td>16±6</td>
<td>84±10</td>
</tr>
<tr>
<td>Elevated (UAE 20–200 μg/min)</td>
<td>34</td>
<td>22:13</td>
<td>32±9</td>
<td>16±5</td>
<td>85±13</td>
</tr>
<tr>
<td>Diabetic nephropathy (UAE &gt; 200 μg/min)</td>
<td>26</td>
<td>11:15</td>
<td>32±9</td>
<td>19±5*</td>
<td>93±27*</td>
</tr>
</tbody>
</table>

*Significant difference versus groups 1 and 2 (p < 0.05).

phropathy) were 26 patients studied at the time of
diagnosis of diabetic nephropathy, which was defined as (1) urinary protein excretion greater than 0.5 g/24 hr on four consecutive visits to the out-patient clinic and (2) no clinical or laboratory evidence of renal tract infections or kidney diseases other than diabetic glomerulosclerosis.

Blood pressure in groups 1 and 2 was measured on two separate occasions on the right arm with subjects in the supine position for at least 10 minutes. The diastolic pressure was taken at Korotkoff sound phase 5. Blood pressure in group 3 was obtained from patient records at the time of diagnosis of diabetic nephropathy (±2 yr).

Longitudinal Study

All patients with IDDM diagnosed prior to 1943, aged 0 to 30 years at time of diagnosis, and hospitalized at least once during the first 10 years of disease were divided into two groups: in group 1 were patients surviving more than 40 years (n = 256) and in group 2 were patients dying from diabetic nephropathy within the first 30 years of IDDM (n = 84).

Estimations of mean systolic and diastolic blood pressures within the first 2 to 10 years of IDDM were made from the hospital records. All resting, supine blood pressures measured during the third to tenth day of hospitalization were used.

Albustix sensitivity is 200 to 300 mg/L. The UAE rate was measured from 24-hour urine collections using an immunodiffusion method. Serum creatinine was measured by a reaction rate method that eliminates pseudocreatinines (upper reference limit 120 μmol/L for men and 100 μmol/L for women).

Results

Cross-sectional Study

Figure 1 shows the arterial blood pressure in each patient. Those with diabetic nephropathy had elevated blood pressure (147/93 ± 21/11 mm Hg, mean ± SD) compared with 135/86 ± 14/7 mm Hg in patients without diabetic nephropathy, but with elevated UAE (p < 0.01). The latter blood pressure (group 2) again was elevated compared with 128/79 ± 13/6 mm Hg in patients with normal UAE (p < 0.01).

Diastolic blood pressure higher than 94 mm Hg was found in 12 of the 26 patients with diabetic nephropathy and in 6 of 34 patients with elevated UAE, com-
pared to none in the normoalbuminuric group ($\chi^2 = 28.2, df = 2; p < 0.0001$).

### Longitudinal Study

The arterial blood pressure within the first 10 years of diagnosis of IDDM is shown in Table 2. There was no difference in the initial blood pressures between patients surviving 40 years or more and those dying from diabetic nephropathy.

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Surviving &gt; 40 yr ($n = 256$)</th>
<th>Dying from diabetic nephropathy ($n = 84$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic (mm Hg)</td>
<td>117 (±14)</td>
<td>114 (±15)</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>70 (±11)</td>
<td>69 (±12)</td>
</tr>
</tbody>
</table>

*119 female and 137 male patients.†36 female and 48 male patients.

**Discussion**

Our study demonstrated that patients with type I diabetes who will subsequently have diabetic nephropathy cannot be identified during the first years of disease on the basis of systolic and/or diastolic blood pressure. This is in accordance with the previous findings of Deckert and Poulsen. We also noted a high frequency of significantly elevated blood pressure in persons with juvenile-onset type I diabetes at the time of diagnosis of diabetic nephropathy when the serum creatinine was still normal. This confirms the findings of Parving et al., who found a similar blood pressure of 146/96 mm Hg in type I diabetic patients with persistent proteinuria and normal serum creatinine.

Our study further elucidated that blood pressure is also significantly elevated in patients with UAE ranging from 20 to 200 μg/min. This group of patients had no classic clinical signs of renal disease, that is, their urine was Albustix-negative and serum creatinine was very similar to that of normoalbuminuric patients (85 vs 84 μmol/L). Furthermore, their blood pressures would frequently be considered normal, diastolic reading being below 95 mm Hg in 28 of the 34 patients. It is an open question whether these apparently normal but elevated blood pressures should be treated. Early and aggressive antihypertensive treatment does reduce the rate of decline in kidney function when diabetic nephropathy has developed. Further studies concerning the pathogenesis of diabetic nephropathy are needed.

In conclusion, we found that arterial hypertension is an early feature in the development of diabetic nephropathy with blood pressure rising before the presence of clinical proteinuria. Blood pressures of patients who later develop diabetic nephropathy are indistinguishable from those who do not. The blood pressure rise therefore is very closely connected in time to the events initiating diabetic nephropathy.

### References

Hypertension in diabetes as related to nephropathy. Early blood pressure changes.
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Hypertension. 1985;7:II18
doi: 10.1161/01.HYP.7.6_Pt_2.II18

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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