Lowering of Microalbuminuria in Diabetic Patients by a Sympathicoplegic Agent: Novel Approach to Prevent Progression of Diabetic Nephropathy?

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Abstract. There is convincing evidence for a specific BP-independent effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on albuminuria in glomerular disease. Because progression of glomerular disease is not consistently halted by these agents, there is a need to explore potential renoprotective effects of other drugs. Recent animal work documented that nonhypotensive doses of moxonidine, a sympathicoplegic agent, reduce albuminuria and development of glomerulosclerosis in a BP-independent manner. A randomized, crossover design was used to assess the human relevance of the experimental data in 15 normotensive, nonsmoking type 1 diabetic mellitus patients with good glycemic control (age, 37.3 ± 6.6 yr; 9 men/6 women; duration of diabetes, 23.6 ± 5.1 yr) with baseline urinary albumin excretion rates (AER) >20 μg/min in the run-in phase. AER was assessed in overnight timed urine collections. The patients were assigned to a 3-wk placebo and a 3-wk moxonidine (0.2 mg twice a day) period, respectively, in random order. This dose causes modest BP lowering in hypertensive individuals but does not affect BP in normotensive individuals. There was no significant effect on ambulatory BP (mean arterial pressure, 91.8 ± 7.1 mmHg in the third week of placebo and 91.1 ± 8.7 mmHg on moxonidine). There was a significant (P < 0.006) difference of the treatment effects between placebo and moxonidine, respectively, on median AER at the end of the placebo period was 39.8 μg/min (range, 15.9 to 117 μg/min) versus 29.0 μg/min (range, 9.03 to 85.8 μg/min) at the end of the moxonidine period. The data document an antialbuminuric effect of nonhypotensive doses of moxonidine. Diminished sympathetic traffic to the kidney is the most plausible explanation for the finding.

Diabetic nephropathy has become the single most frequent cause of end-stage renal failure in the Western world (1). Pioneering work of Danish authors (2,3) established that microalbuminuria is the earliest clinical sign of nephropathy; at least in type 1 diabetes mellitus, it is an indication of the presence of the characteristic glomerular lesions. There is consensus that diabetic patients with microalbuminuria, even when normotensive, should be given antihypertensive medication, preferably angiotensin-converting enzyme (ACE) inhibitors (4) to reduce the renal risk reflected by increased urinary albumin excretion. This concept is plausible, because it is thought that protein in the urine is a potent “nephrotoxin” (5).

Despite the evidence of a nephroprotective action of ACE inhibitors in diabetic (6) and nondiabetic (7,8) glomerular disease, progressive loss of renal function is still seen in a substantial number of patients, so additional interventions would be most welcome.

In animal studies, hemodynamic and nonhemodynamic actions of angiotensin were shown to contribute to progressive renal damage (9,10). In contrast, a potential role of sympathetic activity on progression has not been well explored. Sympathetic activity is increased in renal disease (11,12). A recent experimental study (13) showed that low doses of moxonidine that failed to affect BP by telemetry significantly reduced albuminuria and interfered with the development of glomerulosclerosis.

To assess the human relevance of such experimental evidence, a prospective, controlled, randomized, crossover comparison between placebo and moxonidine was carried out in normotensive microalbuminuric patients with type 1 diabetes mellitus of long duration and stable good glycemic control. The dose of moxonidine that was selected failed to lower BP in normotensive individuals. The primary end point was the albumin excretion rate in overnight timed urine collections.

**Materials and Methods**

**Patients**

In the clinic of Internal Medicine and Diabetology in Zabrze (Poland), BP and urinary albumin excretion rate were screened in all available type 1 diabetes mellitus patients with diabetes duration >15 years.
yr. Sixty normotensive microalbuminuric (>20 μg/min) patients were approached, and 15 consented to participate in the study. The study had been approved by the Ethics Committee of the Silesian Academy of Medicine. There were nine men and six women, and the duration of diabetes was 16 to 35 yr. All were nonsmokers. Apart from insulin, patients were not taking medication. Further background information is given in Table 1.

**Study Protocol**

During a 1 wk run-in period, patients were adapted to the procedures, i.e., ambulatory BP measurement and collection of nighttime urine. They were then treated in random order for 3 wk with placebo followed by moxonidine (0.2 mg twice a day) or vice versa. Per protocol, measurements of nighttime urine were performed three times each at baseline and during the third week of the respective study periods. During the run-in period and at the end of each study period, we also obtained ambulatory BP measurements. Patients kept log books to document sleeping periods. Nighttime BP was calculated for the hours for which sleeping had been documented. Patients kept records of body temperature (fever episodes did not occur) and physical activity to exclude potential confounders of albuminuria.

Urinary albumin excretion was measured by enzyme-linked immunosorbent assay. Ambulatory BP (Medilog DX, Oxford, UK), blood chemistry, and glycosylated hemoglobin were measured by standard methods.

**Statistical Analyses**

Data are given as median and range or mean ± SD, as appropriate. Group differences were evaluated using t test or Wilcoxon’s test, as appropriate. Statistical analysis of treatment outcome was carried out using the parametric approach to crossover trials according to Senn (14), which permits the evaluation of crossover effects, including potential carryover effects.

**Results**

**Baseline Data**

In the run-in period, by definition, all patients had urinary albumin excretion rates >20 μg/min (Table 1). The nighttime decrease of BP during the run-in phase was <10% in 7 of 15 patients. Body weight, insulin dose, and dietary intake of NaCl and protein (reflected by urea excretion) did not change during the entire study period (for baseline data, see Table 1).

**Urinary Albumin Excretion Rate and BP during the Placebo Period and Moxonidine Period**

To assess a potential effect of moxonidine treatment on albumin excretion rates (AER) versus placebo, we calculated the crossover effect according to Senn (14). It was significant ($t = 3.26; 13$ DF; $P = 0.006$). No evidence of a statistically significant carryover effect was observed ($t = 0.221; 13$ DF; $P = 0.83$).

The individual values of AER at the end of the placebo and moxonidine periods, respectively, are shown in Figure 1. Median AER was 39.8 μg/min (range, 15.9 to 117 μg/min) at the end of the placebo period and 29.0 μg/min (range, 9.03 to 85.8 μg/min) at the end of the moxonidine period. There was no significant difference between the end of the placebo and the end of the moxonidine periods, respectively, for glycosylated hemoglobin (7.66 ± 0.81% versus 7.61 ± 0.83%), total triglycerides (106 ± 40.1 mg/dl versus 94.4 ± 30.7 mg/dl), 24-h urinary sodium excretion (129 ± 21.8 mmol/24 h versus 127 ± 20.8 mmol/24 h), and urea excretion.

**Table 1.** Characteristics of the patients at the end of the run-in period according to the treatment sequence to which they were subsequently assigned

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Placebo/Moxonidine</th>
<th>Moxonidine/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37.3 ± 6.59</td>
<td>37.5 ± 6.39</td>
<td>31.1 ± 7.33</td>
</tr>
<tr>
<td>Duration of diabetes mellitus (yr)</td>
<td>23.4 ± 5.08</td>
<td>25.5 ± 5.52</td>
<td>21.0 ± 3.46</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 ± 2.12</td>
<td>23.3 ± 1.09</td>
<td>24.0 ± 2.98</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.68 ± 0.88</td>
<td>7.68 ± 1.20</td>
<td>7.68 ± 0.37</td>
</tr>
<tr>
<td>Insulin dose (IU/d)</td>
<td>57.3 ± 16.2</td>
<td>52.1 ± 16.8</td>
<td>63.2 ± 14.3</td>
</tr>
<tr>
<td>Insulin dose (IU/kg)</td>
<td>0.87 ± 0.22</td>
<td>0.79 ± 0.25</td>
<td>0.96 ± 0.17</td>
</tr>
<tr>
<td>AER (μg/min)</td>
<td>42.2</td>
<td>39.1</td>
<td>41.9</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.43 ± 0.95</td>
<td>5.71 ± 1.13</td>
<td>5.09 ± 0.64</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.43 ± 0.38</td>
<td>1.49 ± 0.51</td>
<td>1.30 ± 0.34</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.49 ± 0.65</td>
<td>3.67 ± 0.71</td>
<td>3.25 ± 0.55</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.13 ± 0.42</td>
<td>1.19 ± 0.38</td>
<td>1.05 ± 0.48</td>
</tr>
<tr>
<td>Mean daytime BP (mmHg)</td>
<td>95.5 ± 8.70</td>
<td>94.2 ± 8.68</td>
<td>97.0 ± 9.16</td>
</tr>
<tr>
<td>Mean nighttime BP (mmHg)</td>
<td>82.1 ± 9.85</td>
<td>80.2 ± 10.5</td>
<td>84.1 ± 9.28</td>
</tr>
<tr>
<td>24-h urinary Na (mmol/24 h)</td>
<td>128 ± 21.7</td>
<td>118 ± 19.5</td>
<td>138 ± 20.3</td>
</tr>
<tr>
<td>24-h urinary urea (mmol/24 h)</td>
<td>182 ± 156</td>
<td>223 ± 196</td>
<td>135 ± 85.1</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. AER is shown as median and range. BMI, body mass index; HbA1c, glycosylated hemoglobin; AER, albumin excretion rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.*
The creatinine clearance was 103 ± 20.5 ml/min in the placebo period and 104 ± 19.3 ml/min in the moxonidine period.

The insulin dose remained unchanged (0.87 ± 0.23 IU/kg per 24 h versus 0.87 ± 0.23 IU/kg per 24 h).

Table 2 shows that at the end of the two treatment periods, there was no significant difference in nighttime systolic or diastolic BP and 24-h systolic or diastolic BP, respectively.

**Discussion**

The main finding of this study is that despite there being no significant change in nighttime or 24-h BP, a low dose of moxonidine caused a highly significant decrease in urinary albumin excretion rate in normotensive, microalbuminuric type 1 diabetes mellitus patients.

The study was not designed to evaluate maximal reduction of albuminuria by moxonidine but was designed as proof of the principle that a low dose of the sympathicoplegic agent that is devoid of the confounding effects of BP lowering effectively reduced albuminuria. This strategy explains the relatively modest antialbuminuric effect of moxonidine in the present study.

A number of potential confounding factors that may have an impact on urinary albumin excretion, e.g., dietary intake of protein and sodium or glycemic control, were controlled and kept constant. The dose of moxonidine chosen has been shown to lower BP in hypertensive patients (15,16) but not in normotensive individuals (17). This was confirmed by ambulatory BP measurements, but even with this method, minor BP changes obviously cannot be excluded.

The study participants were selected on the basis of timed overnight albumin excretion rates in the screening and run-in periods. During the study, the AER of two participants was within the normal range (< 20 µg/min), presumably reflecting regression to the mean.

We emphasize that the change in albuminuria cannot be explained by potential changes in GFR, because there was no significant difference of endogenous creatinine clearance between the placebo and moxonidine treatment periods.

The most plausible interpretation of the above results is that moxonidine, which is known to reduce central sympathetic activity (18), reduced efferent sympathetic nerve traffic to the kidney. We admit, though, that there are imidazoline receptors in the kidney (19) and that intra-arterial administration of moxonidine modifies renal function (20). Consequently, direct renal effects, although unlikely, cannot be excluded with certainty.

Increased sympathetic activity has been demonstrated not only in patients with renal disease (11,12) but also in diverse experimental models of renal damage (21,22). It is thought that in damaged kidneys, chemoreceptors and baroreceptors are activated and send stimulatory afferent signals into the central nervous system. In agreement with this concept, deafferentation by dorsal root section (21) reduces BP in rats with renal failure. The observation of increased activation of the hypothalamic centers (22), as documented by Campese et al. (21,22), is also in agreement with this concept. This hypothesis, however, does not exclude complementary mechanisms of sympathetic stimulation, e.g., via increased leptin concentrations (23). Recent studies suggest that

**Table 2. Ambulatory BP measurements during periods studied**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Moxonidine</th>
</tr>
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<tbody>
<tr>
<td>24 h</td>
<td></td>
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<tr>
<td>systolic BP (mmHg)</td>
<td>125.0 ± 12.9</td>
<td>127.0 ± 12.7</td>
</tr>
<tr>
<td>diastolic BP (mmHg)</td>
<td>75.7 ± 5.8</td>
<td>75.1 ± 8.0</td>
</tr>
<tr>
<td>Nighttime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic BP (mmHg)</td>
<td>118.0 ± 15.5</td>
<td>117.0 ± 19.3</td>
</tr>
<tr>
<td>diastolic BP (mmHg)</td>
<td>67.4 ± 6.3</td>
<td>64.9 ± 9.6</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. There were no significant changes between periods studied.*
hyperinsulinemia activates sympathetic function (24) and specifically increases sympathetic activity during sleep as recently shown in nephropathic diabetes mellitus patients with nocturnal hypertension (25).

The effect of moxonidine on urinary albumin, an accepted surrogate marker of glomerular damage, is tantalizing. In view of interaction between the renin angiotensin system and the sympathetic system (12), it is possible that reduction of sympathetic drive lowers the activity of the (intrarenal) renin system. Whether renin-independent effects are involved is unknown but are of interest in view of the obvious therapeutic consequences.

In any case, the present investigation clearly identifies the sympathetic nerve system as a promising new therapeutic target in the management of diabetic nephropathy.

Acknowledgments

Moxonidine and matching placebo tablets were supplied by Lilly Deutschland GmbH.

References


Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org