Original Article

Low-Dose Candesartan Cilexetil Prevents Early Kidney Damage in Type 2 Diabetic Patients with Mildly Elevated Blood Pressure

Satoru MURAYAMA, Tsutomu HIRANO, Taro SAKAUE, Kenta OKADA, Reiko IKEJIRI, and Mitsuru ADACHI

To determine the effect of a low-dose angiotensin receptor blocker, candesartan, on early kidney damage associated with diabetes. Fifty-two patients with type 2 diabetes with normo- and microalbuminuria participated in this study. Nineteen patients with high-normal and mildly high blood pressure received low-dose candesartan cilexetil at 4 mg daily (candesartan group), and 33 patients did not receive candesartan (control group). Blood pressure, urinary excretion of albumin, transferrin, and type IV collagen (expressed as urinary creatinine index) and plasma parameters were determined at baseline and at 2, 6, 12 and 18 months after the start of candesartan therapy. Baseline urinary albumin, transferrin, and type IV collagen excretions was similar in the control and candesartan groups. The higher baseline systolic blood pressure was decreased by candesartan treatment to a level similar to that in the control group, such that blood pressure was comparable between the control and candesartan groups during the run-in period. In the control group, urinary albumin excretion was significantly increased at 18 months when compared with baseline, while urinary albumin excretion did not increase in the candesartan group throughout the study. Urinary transferrin excretion was significantly increased at 6, 12, and 18 months when compared with baseline in the control group, while it did not increase in the candesartan group during the study. In both groups, urinary type IV collagen excretion did not change significantly during the study. Hemoglobin A1c, serum urea nitrogen, creatinine, albumin, and lipids were comparable between the two groups throughout the study. In conclusion, low-dose candesartan can prevent early kidney damage in type 2 diabetic patients with mildly higher blood pressure independently of its hypotensive action. (Hypertens Res 2003; 26: 453–458)

Key Words: diabetic nephropathy, candesartan, albumin, transferrin, type IV collagen

Introduction

Diabetic nephropathy is the most serious complication of diabetes mellitus, and is both the principal cause of end-stage renal failure and the strongest predictor of premature death and cardiovascular disease in patients with diabetes. Various studies have shown that increased urinary albumin excretion is a valid predictor of clinical proteinuria and increased morbidity in patients with type 2 diabetes (1–4). A new class of drugs that selectively inhibits the renin-angiotensin system by specifically targeting the angiotensin type 1 receptor has recently been developed for the treatment of hypertension. The Reduction of Endpoints in type 2 diabetes with the Angiotensin Antagonist Losartan study (RENAAL) demonstrated renal benefits of losartan, an angiotensin II receptor blocker (ARB), in patients with type 2 diabetes and nephropathy (5). The renoprotective effects of another ARB, irbesartan, have been documented in patients with type 2 diabetes displaying incipient and chronic overt diabetic nephropathy by

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The Inbesartan Diabetic Nephropathy Trial (IDNT) (6, 7). These studies have shown that the renoprotective effects of ARBs are not dependent on the hypotensive action of these drugs but rather are directly attributable to improvement of hemodynamics by inhibition of angiotensin II. Recently, Suzuki et al. (8) reported that low-dose valsartan (40 mg) reduced urinary albumin excretion in patients with type 2 diabetes without affecting blood pressure (BP). However, their study did not use valsartan alone to treat the subjects, but simultaneously used other antihypertensive drugs, so it is still unclear whether a low-dose ARB alone has renoprotective effects. In fact, Suzuki et al. (9) reported that a small dose of angiotensin-converting enzyme inhibitor did not exert a renoprotective effect independently of its hypotensive action.

Recently, normal-range BP has been classified into three categories: optimal, normal, and high-normal (10). According to the American Diabetes Association (ADA) recommendations for 2002, the BP of diabetic patients should be kept below 130 mmHg in systole (SBP) and 80 mmHg in diastole (DBP) (11), so a high-normal BP in diabetic patients has to be further reduced to the normal or optimal ranges. However, severe hypotension can occur if a full-dose of antihypertensive therapy is given to patients with a mildly raised BP, so administration of a low-dose antihypertensive regimen would be more suitable to achieve better BP control without hypotension. The ADA has recommended angiotensin I converting enzyme inhibitors or ARBs as first-line antihypertensive drugs for diabetics (11). Therefore, the present study was conducted to assess whether low-dose candesartan cilexetil had renoprotective effects in type 2 diabetic subjects with a high-normal BP or mild hypertension.

### Methods

All subjects had type 2 diabetes mellitus according to World Health Organization (WHO) criteria. Normotension and hypertension was defined according to the WHO/International Society of Hypertension (ISH) guidelines (10). Exclusion criteria included hypertensive patients on treatment with antihypertensive drugs, BP > 160/95 mmHg, overt proteinuria or a urinary albumin index > 300 mg/g creatinine (cr), severe chronic or acute illness, and urinary tract infection. Patients were maintained on an isocaloric diet (25–30 kcal/kg ideal body weight) consisting of 17% protein, 23% fat, and 60% carbohydrates under the supervision of dieticians, and their compliance with the diet therapy was monitored. Four patients were managed with dietary intervention alone. A majority of patients were taking sulfonylureas and/or α-glucosidase inhibitors, and 11 were taking insulin (Table 1). The dosages of these drugs were not changed during the study.

Patients were divided into a candesartan group and an untreated control group (Table 1). Subjects with an optimal and normal BP were not given candesartan, and were classified into the control group. We recommended that all subjects with hypertension receive candesartan, but 4 subjects refused any antihypertensive therapy and thus were classified into an untreated control group. We also recommended that subjects with a high normal BP should further reduce their BP to the normal or optimal range. If the subjects agreed with our recommendation, they received candesartan therapy, while subjects who did not choose drug therapy were classified into the control group. The candesartan group comprised 6 diabetic patients with a high-normal BP and 13 with grade 1 hypertension (Table 1). The control group comprised 5 diabetic patients with an optimal BP, 6 with a normal BP, 28 with a high-normal BP, and 4 with grade 1 hypertension (Table 1). Patients received a low-dose of candesartan cilexetil (4 mg once daily) for 18 months, while the control group received no antihypertensive drugs for the duration of the study. Blood pressure, urine tests, and blood tests were done at baseline and at 2, 6, 12, and 18 months afterward. All patients gave their informed consent to participate in the study, and the study was approved by the ethics committee of our department.

Arterial BP was measured in the sitting position after at least 15 min of rest, using a standard sphygmomanometer with an appropriately sized cuff. The measurements were repeated after 2–3 min, and the average of the measurements was used for analysis. Blood samples were collected after an overnight fast. Glycosylated hemoglobin (HbA1c) and serum levels of glucose, urea nitrogen, cr, albumin, and lipids were measured by standard laboratory procedures. A spot urine sample was collected in the morning after at least
30 min of rest. The urinary albumin concentration was measured by the latex turbidimetric immunoassay method using a commercially available kit (LA-System; AIC Co., Tokyo, Japan) (12). The urinary transferrin concentration was measured by the same method using a Superior Microtransferrin kit (Diatrone, Tomakomai, Japan) (13). The urinary type IV collagen was measured by the sandwich enzyme immunoassay method using a kit from Fuji Pharmaceutical Co. (Toyama, Japan) (13). Serum triglyceride and cholesterol levels were measured by enzymatic methods. High-density lipoprotein (HDL) cholesterol was measured after polyanion precipitation of apo B-containing lipoproteins from the plasma.

Results are presented as the means ± SEM. The significance of differences between before and after treatment was evaluated using Wilcoxon’s signed-ranks test, while the unpaired Student’s t-test was used to evaluate the significance of differences between the control group and the candesartan group. Values of $p < 0.05$ were considered to indicate statistical significance.

### Table 2. Metabolic Parameters with and without Candesartan Treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2-month</th>
<th>6-month</th>
<th>12-month</th>
<th>18-month</th>
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<tbody>
<tr>
<td><strong>Candesartan group</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobin A1c (%)</td>
<td>7.2 ± 0.3</td>
<td>7.2 ± 0.3</td>
<td>7.3 ± 0.3</td>
<td>7.2 ± 0.3</td>
<td>7.3 ± 0.3</td>
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<tr>
<td>Glucose (mg/dl)</td>
<td>139 ± 3</td>
<td>151 ± 10</td>
<td>171 ± 15</td>
<td>167 ± 12</td>
<td>149 ± 12</td>
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<tr>
<td>S-urea nitrogen (mg/dl)</td>
<td>16 ± 1</td>
<td>16 ± 1</td>
<td>16 ± 1</td>
<td>16 ± 1</td>
<td>16 ± 1</td>
</tr>
<tr>
<td>S-creatinine (mg/dl)</td>
<td>0.7 ± 0.0</td>
<td>0.6 ± 0.0</td>
<td>0.7 ± 0.0</td>
<td>0.7 ± 0.0</td>
<td>0.7 ± 0.0</td>
</tr>
<tr>
<td>S-albumin (g/dl)</td>
<td>4.1 ± 0.0</td>
<td>4.1 ± 0.0</td>
<td>4.1 ± 0.0</td>
<td>4.1 ± 0.0</td>
<td>4.1 ± 0.0</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>170 ± 35</td>
<td>165 ± 34</td>
<td>138 ± 22</td>
<td>162 ± 30</td>
<td>151 ± 28</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>206 ± 8</td>
<td>195 ± 6</td>
<td>195 ± 5</td>
<td>205 ± 7</td>
<td>203 ± 9</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>55 ± 3</td>
<td>55 ± 1</td>
<td>53 ± 3</td>
<td>55 ± 3</td>
<td>57 ± 4</td>
</tr>
<tr>
<td><strong>Control group (without candesartan)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>6.7 ± 0.2</td>
<td>6.7 ± 0.2</td>
<td>6.9 ± 0.2</td>
<td>6.8 ± 0.2</td>
<td>6.7 ± 0.2</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>142 ± 8</td>
<td>151 ± 10</td>
<td>152 ± 10</td>
<td>147 ± 8</td>
<td>146 ± 9</td>
</tr>
<tr>
<td>S-urea nitrogen (mg/dl)</td>
<td>15 ± 1</td>
<td>14 ± 0</td>
<td>15 ± 1</td>
<td>15 ± 1</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>S-creatinine (mg/dl)</td>
<td>0.7 ± 0.0</td>
<td>0.7 ± 0.0</td>
<td>0.7 ± 0.0</td>
<td>0.7 ± 0.0</td>
<td>0.7 ± 0.0</td>
</tr>
<tr>
<td>S-albumin (g/dl)</td>
<td>4.2 ± 0.0</td>
<td>4.1 ± 0.0</td>
<td>4.2 ± 0.0</td>
<td>4.2 ± 0.0</td>
<td>4.2 ± 0.0</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>142 ± 24</td>
<td>129 ± 16</td>
<td>124 ± 13</td>
<td>140 ± 20</td>
<td>156 ± 30</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>194 ± 7</td>
<td>189 ± 6</td>
<td>195 ± 5</td>
<td>197 ± 5</td>
<td>196 ± 7</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>54 ± 3</td>
<td>54 ± 3</td>
<td>53 ± 4</td>
<td>53 ± 3</td>
<td>53 ± 3</td>
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</tbody>
</table>

Data represent mean ± SEM. S, serum; HDL, high-density lipoprotein.

### Fig. 1. Systolic and diastolic blood pressure (SBP and DBP) during the study in type 2 diabetics with or without low-dose candesartan (4 mg/day) therapy. Data represent the means ± SEM. * $p < 0.05$ vs. control group, ** $p < 0.001$ vs. baseline.
Results

The baseline clinical characteristics of the 19 patients in the candesartan group and the 33 patients in the control group are shown in Table 1. There were no significant differences of gender, age, body mass index (BMI), HbA1c, or antidiabetic therapy between the two groups. SBP was significantly higher in the candesartan group than in the control group, but DBP was similar between the groups. In the majority of subjects from both groups, urinary albumin excretion was classified as normoalbuminuria (<30 mg/g Cr), while the remainder had microalbuminuria (<110 mg/g Cr). At baseline, two-thirds of the candesartan group had mild hypertension and one-third had a high-normal BP according to WHO/ISH criteria (10).

Table 2 shows the changes of HbA1c and serum levels of glucose, urea nitrogen, Cr, albumin, and lipids between the control and candesartan groups throughout the study. There were no significant differences of these parameters between the two groups. These parameters also did not alter significantly during the study in either the control or the candesartan group.

Figure 1 demonstrates the changes of SBP and DBP between the control and candesartan groups throughout the study. The SBP was significantly decreased by treatment with candesartan for 2 months and the reduction persisted throughout the study. In contrast, SBP and DBP were not altered in the control group during the study. Thus, the SBP and DBP levels were comparable between the candesartan and control groups at least for 16 months. Figure 2 demonstrates the changes of urinary albumin excretion in the control and candesartan groups during the study. Urinary albumin excretion did not change significantly in the candesartan group.
group during the study, but it was significantly increased after 18 months compared with baseline in the control group. There were no significant differences in urinary albumin excretion between the control and candesartan groups at any of the measurement time points.

Figure 3 demonstrates the changes of urinary transferrin excretion between the control and candesartan groups. Urinary transferrin excretion did not change during the study in the candesartan group, while it was significantly increased at 6 and 12 months in the control group and further elevated at 18 months when compared with the baseline value. There was no significant difference of the urinary transferrin excretion between the control and candesartan groups at any of the measurement time points.

Figure 4 shows the changes of urinary type IV collagen excretion. Urinary type IV collagen excretion was not significantly altered in either the candesartan or control group, or between these groups at any of the time points.

Discussion

The RENAAL (5) and the IDNT (6) are two recently reported trials that were conducted in patients with advanced stages of diabetic nephropathy. Two other studies, the Irbesartan Microalbuminuria Study (IRMA)-2 (7) and the Microalbuminuria Reduction with Valsartan (MARVAL) study (14) were conducted in patients with type 2 diabetes and microalbuminuria. All of these studies have revealed that ARBs have a significant ability to suppress the progression of diabetic nephropathy from early stage to end stage. In addition, these studies have suggested that the renoprotective effect is partly independent of a hypotensive effect.

We wished to determine whether low-dose ARB therapy could suppress the progression of early kidney damage associated with type 2 diabetes. Although low-dose candesartan did not reduce urinary albumin excretion, it completely suppressed the increase of albumin excretion that was observed in the control group without candesartan treatment. Our study is the first to demonstrate that a low-dose of an ARB alone can prevent the progression of early kidney damage in type 2 diabetics. Suzuki et al. (8) reported that 6 months of low-dose valsartan (40 mg/day) therapy could significantly decrease urinary albumin excretion in patients who had incipient and overt diabetic nephropathy without affecting BP. However, because the standard dose of valsartan (80 mg) has an effect comparable to that of 5 mg of amlodipin (13), we doubt that 40 mg valsartan has no effect on the BP. It is likely that most of their diabetic patients were hypertensive and were already being treated with other antihypertensive drugs, which may have masked the mild hypotensive effect of a low-dose valsartan therapy. Low-dose candesartan did lower the SBP, but our experimental design enabled us to assess the direct renoprotective effect of this drug, because the initial BP in the candesartan group was higher than that of the control group and the BP values became comparable after treatment with candesartan. A low-dose antihypertensive regimen is preferred for patients with mild hypertension, since it is associated with fewer side effects due to hypotension. Of course, because a full dose of ARB is expected to have a stronger renoprotective effect than a small dose of ARB, the indication of a small dose of ARB should be limited.

According to the recommendation of the ADA2002 (11), the BP in diabetic patients should be lower than 130/80 mmHg to prevent microangiopathy and macroangiopathy. Therefore, we believe that the administration of low-dose ARB therapy is not over-medication for diabetic patients, even if their BP is within the high-normal range. The mechanism by which a low-dose of candesartan protects against an increase of albumin excretion irrespective of an effect on BP remains unknown, but this beneficial effect is probably due to suppression of an increase in glomerular capillary pressure associated with diabetes by inhibiting the action of angiotensin II (16). In the present study, glycemic control and serum lipid levels were comparable between the control and candesartan groups, and no significant changes were observed in either group during the study. Thus, the renoprotective effect of candesartan was not due to amelioration of hyperglycemia or hyperlipidemia.

A number of studies have suggested that an elevated urinary transferrin excretion is a more sensitive indicator for early kidney damage than elevated albumin excretion (13, 17, 18). In the present study, urinary transferrin excretion was suppressed by candesartan treatment, whereas it was increased in the absence of candesartan treatment. An increase of urinary transferrin excretion in the control group was observed 6 months after the start of the study, when urinary albumin excretion still remained at the baseline level, suggesting that transferrin is a more sensitive marker of early kidney damage than albumin. Thus, the effect on urinary transferrin may provide additional evidence that low-dose candesartan can suppress the progression of early kidney damage associated with diabetes. Urinary albumin and transferrin excretion were not lower in the candesartan group than in the control group, but this may be attributable to the somewhat higher baseline values in the candesartan group. A longer study period and a larger number of patients would be required to obtain significant differences of urinary albumin and transferrin excretion between the control and candesartan groups. We examined whether the increment of transferrin or albumin in the control group was due to the control subjects’ initial BP, but did not find a significant relationship between the kidney injury and the BP. This also suggests that a longer study period is required to clarify the effect of BP on kidney damage.

Increased albumin or transferrin excretion would be derived from abnormalities of hemodynamics and/or permeability, whereas mesangial matrix expansion in diabetic nephropathy gives rise to a reduction in glomerular filtration surface and a decrease in renal function. Several studies have suggested that the overproduction of extracellular matrix
proteins underlying glomerulosclerosis in diabetes is associated with the increased excretion of type IV collagen in the urine (14, 19). In some cases an increase of urinary type IV collagen excretion precedes an increase of urinary albumin excretion (20). Therefore, we measured type IV collagen in the urine as a possible sensitive marker of early kidney damage. The baseline value in our diabetic patients was about 6.0 µg/g cr, which was higher than that reported in nondiabetic controls (3.44 ± 0.11 µg/g cr, mean ± SEM) (21). Unlike albumin and transferrin, urinary type IV collagen excretion was not increased in the control group during the study. Our observation period might have been too short to observe a change of urinary type IV collagen excretion reflecting morphological change of the glomeruli. Long-term study will be required to examine whether the suppressive effect of candesartan on hemodynamic and/or permeability abnormalities can prevent the progression of glomerulosclerosis.

In conclusion, the present study demonstrated that low-dose candesartan (4 mg/day) therapy prevents an increase of urinary excretion of albumin and transferrin excretion in diabetic patients with normoalbuminuria and microalbuminuria independently of any hypotensive effect. Low-dose candesartan may be beneficial for diabetics with a mildly raised BP in order to prevent the early-stage diabetic nephropathy without causing profound hypotension.

References