SERUM CYSTATIN C LEVELS IN HYPERTENSIVE TYPE 2 DIABETIC NEPHROPATHY PATIENTS AFTER TREATMENT WITH ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR TEMOCAPRIL

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The purpose of the present study was to determine whether administration of low dose temocapril (2 mg/day), a long-acting non-SH group angiotensin converting enzyme (ACE) inhibitor, might reduce albuminuria and alter glomerular filtration, i.e. serum creatinine (s-Cr), creatinine clearance (CCr) and serum cystatin C, in 11 mildly hypertensive microalbuminuric patients with type 2 diabetic nephropathy. Temocapril was orally administered to these patients at 2mg/day. Duration of administration was 24 months. Before and after 24 months of treatment, blood pressure, fasting plasma glucose (FPG), glycohemoglobin A1c (HbA1c), urinary albumin excretion, s-Cr, CCr and serum cystatin C were evaluated. Levels of urinary albumin excretion after 24 months of treatment were significantly decreased compared with those before treatment (p<0.05). Levels of serum cystatin C and CCr did not exceed the normal range before and after 24 months. However, the levels of serum cystatin C after 24 months of treatment were significantly increased compared with those before treatment (p<0.0005). The levels of CCr after 24 months of treatment were slightly decreased compared with those before treatment, but the difference was not statistically significant. It appears that the reduction of albuminuria after temocapril treatment might be due to that of the glomerular filtration in mildly hypertensive microalbuminuric patients with type 2 diabetic nephropathy. Serum cystatin C was found to be a more sensitive marker for detecting of glomerular filtration than measurement of s-Cr and CCr. (Acta Nephrologica 2002; 16: 62-65)

Key words: albuminuria, serum cystatin C, tepocapril, diabetic nephropathy

INTRODUCTION

Several antihypertensive drugs have been used to prevent the progression of glomerulosclerosis in hypertensive patients with chronic glomerulonephritis, diabetic nephropathy or other renal diseases. One of the most effective drugs is the angiotensin-converting enzyme (ACE) inhibitors which dilate the efferent arterioles in glomeruli and also increase the activities of kinin and vasodilator prostaglandins. These ACE inhibitors and/or angiotensin II AT1 receptor blockers (ARB) may decrease the systemic and glomerular capillary pressure, preserve glomerular function and delay the progression of glomerular injury. Unlike many other ACE inhibitors, temocapril is a long-acting ACE inhibitor that does not contain the sulfhydryl (SH) group in its structure. The pharmacologically active metabolite, temocapril, is excreted in both bile and urine, with the former as the predominant excretory pathway. Thus, temocapril is clinically useful for hypertensive patients with renal dysfunction. Cystatin C is a small non-glycosylated 13 kDa basic protein of the cystatin superfamily of cysteine protease inhibitors, which are produced by all nucleated cells. The stable production rate of cystatin C strongly indicated that the glomerular filtration rate (GFR) is the major determinant of cystatin C levels in sera. Serum cystatin C increases at a faster rate than serum creatinine because its molecular size.

The objectives of the present study were to deter-
mine whether low dose administration of temocapril, a long-acting ACE inhibitor with no SH group, might reduce the levels of urinary albumin excretion and alter glomerular filtration, i.e. increase of serum cystatin C levels, in mildly hypertensive microaluminuric patients with type 2 diabetic nephropathy.

**MATERIALS AND METHODS**

**Patients**

Criteria for patient selection were type 2 diabetic nephropathy, mild hypertension (130-150/70-100 mmHg), microalbuminuria (30 to 300 mg/gCr), normal renal function (serum creatinine <1.0 mg/dl, serum cystatin C <0.86 mg/l), and no drug treatment during the 8 weeks preceding the present study. We enrolled 11 patients who gave their informed consent. Enrolled patients remained on their usual diet (free intake of salt and protein). After baseline measurements of serum and urine samples, a low dose of temocapril (2 mg/day) was administered to all patients for 24 months. Other medications including hypoglycemic agents were prohibited throughout the study.

**Laboratory examinations**

Serum samples were obtained from the patients before and after 24 months of treatment, and were stored at -20.0ºC prior to use. The levels of serum cystatin C were measured using the Dade Behring Cystatin C assay with the automated Dade Behring Nephelometer II (BNII)(software version 2.0). The N Latex Cystatin C kit (Lot No. 29577, Dade Behring Diagnostics, Marburg, Germany) and a fully automated particle-enhanced nephelometric immunoassay were used in this study. The level of cystatin C obtained from 276 healthy controls ranged from 0.50 to 0.86 mg/l (mean±SE; 0.66±0.01 mg/l). Levels of serum creatinine (s-Cr), blood pressure, fasting plasma glucose (FPG), glycohemoglobin A1c (HbA1c) and urinary albumin excretion were examined by routine methods in our hospital. Blood urea nitrogen (BUN), serum uric acid (UA) and creatinine clearance (CCr) were also measured in this study.

**Statistical Analysis**

All results were expressed as mean ± standard error (SE). The group difference was assessed by the paired t test. Differences were considered statistically significant if the p value was less than 0.05.

**RESULTS**

Results of this study are summarized in Table 1, and Fig. 1 and 2. There were no significant changes in the levels of FPG, HbA1c, BUN, s-Cr and UA before and after 24 months of the treatment (Table 1). The levels of urinary albumin excretion after 24 months of temocapril treatment (29.3±7.3 mg/g • Cr) were significantly lower than those before treatment (104.5±27.5 mg/g • Cr) (p<0.05). Systolic and diastolic blood pressures significantly decreased after 24 months of treatment (p<0.05, p<0.001, respectively). The levels of serum creatin C after 24 months of temocapril treatment (0.82±0.04 mg/l) were significantly increased compared with those before treatment (0.69±0.04 mg/l) (p<0.0005). However, the levels of serum cystatin C before and after 24 months of temocapril treatment remained within normal limits (276 healthy controls ranged from 0.50 to 0.86 mg/l ;mean±SE; 0.66±0.01 mg/l) (Fig. 1). The levels of CCr after 24 months of temocapril treatment (95.2±4.49 ml/min) were slightly decreased compared with those before treatment (107.0±3.92 ml/min), but the difference was not statistically significant (Fig. 2).

**DISCUSSION**

It is well known that ACE inhibitors show renoprotective effects in patients with IgA nephropathy and diabetic nephropathy with or without systemic hypertension. Recently, the authors determined the potential beneficial effects of the ACE inhibitor temocapril on the chronic puromycin aminonucleoside nephropathy (PAN) model. Our data confirmed that temocapril reduced massive proteinuria and renal insufficiency for up to 4 weeks after PAN injection. The pharmacologically active metabolite of temocapril is excreted in both bile and urine, with the former as the predominant excretory pathway. Thus, temocapril is clinically useful for hypertensive patients with renal dysfunction.

There have been several reports in recent years suggesting that cystatin C in sera correlates with the glomerular filtration rate (GFR). Newman et al. reported that serum cystatin C has been shown to be in all likelihood a more sensitive marker of early deterioration of GFR than serum creatinine (s-Cr). The measurement of creatinine clearance (CCr) is not so easy in outpatient clinics. The authors reported that the measurement of serum cystatin C may predict the prognostic stages of patients with IgA nephropathy and diabetic nephropathy prior to renal biopsy. In this study, the levels of urinary albumin excretion after 24 months of temocapril treatment were significantly decreased compared with those before treatment. Systolic and diastolic blood pressures also decreased after 24 months of the treatment. The serum cystatin C levels after 24 months of temocapril treatment were significantly higher than those before treatment. The levels of CCr after 24
months of temocapril treatment were slightly decreased compared with those before treatment. Thus, the increase of serum cystatin C levels might be due to the decrease of glomerular filtration rate (GFR). Although the levels of serum cystatin C and CCr before and after 24 months of temocapril treatment remained within normal limits, serial measurement of serum cystatin C is important to evaluate the renal dysfunction during such treatment. No significant changes in the levels of BUN and s-Cr before and after 24 months of treatment were observed in this study. Lifestyles and hypoglycemic treatment were not changed throughout this study. Thus, the levels of FPG and HbA1c did not significantly differ before and after 24 months of the treatment. It appears that treatment with temocapril might decrease the intraglomerular capillary pressure and then decrease

### Table 1. Laboratory data of mildly hypertensive type 2 diabetic patients before and after 24 months of temocapril treatment

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (y)</th>
<th>Gender</th>
<th>FBS (mg/dl)</th>
<th>HbA1c (%)</th>
<th>BUN (mg/dl)</th>
<th>S-Cr (mg/dl)</th>
<th>UA (mg/dl)</th>
<th>U-Alb (mg/g • Cr)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>Cystatin C (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
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<tr>
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<td>156</td>
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<td>158</td>
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<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>94</td>
<td>127</td>
<td>6.5</td>
<td>6.4</td>
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<td>188</td>
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<td>14</td>
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<td>6</td>
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<tr>
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<td>0.6</td>
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</table>

**Mean** 147 126 7.2 6.8 13.9 14.6 0.8 0.8 5.6 5.4 104.5 29.3* 139.8 135.6* 86.0 82.4** 0.69 0.82***

**SE** 10.0 9.7 0.3 0.3 1.0 0.8 0.04 0.04 0.4 0.4 27.5 7.3 1.6 1.8 2.7 2.5 0.04 0.04

**p<0.05 vs before treatment, **p<0.001 vs before treatment, ***p<0.0005 vs before treatment

Data expressed as means ± SE. SE, Astandard error of the means; M, male, F, female; FBS, fasting blood sugar; S-Cr, serum creatinine U-Alb, Albuminuria; SBP, systolic blood pressure; DBP, Adiastolic blood pressure

Fig. 1. Levels of serum creatinine (s-Cr) and cystatin C before and after 24 months of temocapril treatment

Fig. 2. Levels of creatinine clearance (CCr) before and after 24 months of temocapril treatment

### N.S. ; not significant
the urinary albumin excretion in hypertensive mildly albuminuric patients with type 2 diabetic nephropathy. Serum cystatin C is considered to be an early prognostic marker rather, which is somewhat better than BUN, s-Cr and CCr, in patients with type 2 diabetic nephropathy.

REFERENCES