Original Article

Benidipine Attenuates Glomerular Hypertension and Reduces Albuminuria in Patients with Metabolic Syndrome

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Recent studies have shown that metabolic syndrome is associated with an increased risk for chronic kidney disease. We recently found that the prevalence of sodium-sensitive hypertension in patients with metabolic syndrome was significantly higher than that in patients with essential hypertension but without metabolic syndrome. We therefore assessed the effects of benidipine, a long-acting calcium channel blocker, on the sodium sensitivity of blood pressure and renal hemodynamics in 5 patients with metabolic syndrome. Glomerular hemodynamics were assessed using pressure-natriuresis curves, which were constructed by plotting the urinary excretion of sodium as a function of the mean arterial pressure, which was calculated as the mean of 48 values based on 24-h monitoring, during the intake of low (3 g NaCl daily) and relatively high (10 g NaCl daily) sodium diets. Under the relatively high sodium diet condition, benidipine significantly lowered systolic and diastolic blood pressure. The pressure-natriuresis curve was steeper after the administration of benidipine. Benidipine lowered glomerular capillary hydraulic pressure (P_{GC}) levels (from 54.4 ± 7.5 to 47.0 ± 7.0 mmHg, $p=0.0152$) and reduced both the resistance of the afferent arterioles (from $10,338 \pm 2,618$ to $9,026 \pm 2,627$ dyn-s/cm⁵, $p=0.047$) and the resistance of the efferent arterioles (from $4,649 \pm 2,039$ to $2,419 \pm 2,081$ dyn-s/cm⁵, $p=0.003$). The urinary albumin excretion rate also decreased after the administration of benidipine. These findings indicated that benidipine may be effective for reducing the risk of developing chronic kidney disease in patients with metabolic syndrome. (*Hypertens Res* 2007; 30: 161–165)

Key Words: benidipine, renal hemodynamics, albuminuria, metabolic syndrome

Introduction

It has been postulated that patients diagnosed with metabolic syndrome are also at great risk for developing cardiovascular disease (1, 2). In addition, recent studies have shown that metabolic syndrome is associated with an increased risk for a reduced glomerular filtration rate (GFR) and microalbumin-

uria (3). Recently, in patients with essential hypertension, we found a significantly higher prevalence of sodium-sensitive hypertension in patients with metabolic syndrome than in those without metabolic syndrome (4). On the other hand, experiments with animal models have suggested a link between the sodium sensitivity of blood pressure (BP) and glomerular hypertension (5, 6). We also found that the estimated glomerular capillary pressure (P_{GC}) was elevated in

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patients with sodium-sensitive essential hypertension and primary aldosteronism (7), a typical form of sodium-sensitive hypertension due to secondary causes. In addition, it has been well established that BP becomes sodium sensitive in patients with chronic glomerulonephritis (8), and sodium sensitivity has also been reported to be greater as the GFR declines (9). These findings strongly support the interrelationships among salt sensitivity, glomerular hypertension, renal damage, and microalbuminuria.

Benidipine, a long-acting calcium channel blocker, has been reported to decrease the resistance of efferent as well as afferent arterioles, and has been shown to lower P_{GC} in animal models (10). In addition, in patients with non-diabetic nephropathy, the estimated P_{GC} was reported to decrease after treatment with benidipine (11). We therefore assessed the effects of benidipine on renal hemodynamics in patients with metabolic syndrome in the present study.

Methods

Patients

Five Japanese patients with essential hypertension (4 men and 1 woman), all of whom gave informed consent, were examined in the present study. The administration of any antihypertensive drugs was discontinued at least 2 weeks before the start of the study, and all other medications were maintained at the same dosage throughout the study. Patients were excluded if they had a history of cardiac disease, stroke, hepatic disease, renal disease, or diabetes mellitus. No patient showed any evidence of a detectable secondary cause for hypertension.

Study Protocol

After the initial 1- to 2-week hospitalization, during which time BP was stabilized, the patients were subjected to the following study protocol, which lasted another 2 weeks with the patients hospitalized, as previously reported (12–14). The patients were maintained on a low sodium diet containing 3 g of NaCl per day (stage 1) and a relatively high sodium diet containing approximately 10 g of NaCl per day (stage 2) for 1 week each, in a randomized order. After the 2-week study, another 2-week study was carried out with the oral administration of 4 mg of benidipine at 7:00 AM (low sodium diet, stage 3; relatively high sodium diet, stage 4). On the last day of each stage, BP was measured non-invasively with an automatic device every half-hour for a 24-h period (model ES-A531, Terumo, Tokyo, Japan). The mean arterial pressure (MAP) was calculated as the diastolic BP plus one-third of the pulse BP. The urinary sodium excretion rate ($U_{Na}V$) was measured on the last 3 days of each stage. On the last day of stage 2 and stage 4, the effective plasma flow and creatinine clearance were calculated by the standard clearance technique

Table 1. Clinical Characteristics of the Studied Patients

Parameters	
Age (years)	61±2.2
Male/female	4/1
Height (cm)	162.7±8.5
Body weight (kg)	68.8±6.5
Body mass index (kg/m ²)	26.0±1.6
Total cholesterol (mg/dl)	192±29
HDL-cholesterol (mg/dl)	35.8± 6.5
Triglycerides (mg/dl)	125.6±50.0
Fasting glucose (mg/dl)	91.4±7.5
Fasting insulin (μU/ml)	6.3±1.6
Waist circumference (cm)	
Male (<i>n</i> =4)	87.8±1.9
Female (<i>n</i> =1)	91

HDL, high-density lipoprotein.

with para-aminohippurate and endogenous creatinine, respectively. The filtration fraction was calculated as the ratio of creatinine clearance to para-aminohippurate clearance.

A diagnosis of metabolic syndrome was made according to the International Diabetes Foundation definition, as previously reported (4). Specifically, a person who was defined as having metabolic syndrome had to have central obesity, which was defined as a waist circumference of 85 cm or more for Japanese men and 90 cm or more for Japanese women, plus any two of the following four factors: 1) a high serum triglyceride level defined as more than 150 mg/dl, 2) a low high-density lipoprotein (HDL) cholesterol level defined as less than 40 mg/dl in men or less than 50 mg/dl in women, 3) elevated BP defined as an average systolic or diastolic BP of 130/85 mmHg or higher, and 4) an elevated fasting plasma glucose level defined as 100 mg/dl or more.

Glomerular hemodynamics were assessed as reported previously (7, 15). Briefly, pressure-natriuresis curves were constructed by plotting the $U_{Na}V$ as a function of the MAP, which was calculated as the mean of 48 values obtained during a 24-h monitoring period. The difference between the normal sodium diet and the X -intercept of the pressure-natriuresis curve was assumed to be the effective filtration pressure across the glomerular capillary walls. P_{GC} can be represented as the sum of the mean oncotic pressure within the capillaries, the effective filtration pressure, and the hydrostatic pressure in Bowman's space. On the basis of Ohm's law, the resistance of afferent arterioles (R_A) is calculated as the ratio of the equation $(MAP - P_{GC})$ divided by the renal blood flow. The resistance of the efferent arterioles (R_E) is calculated as the difference between the total renal vascular resistance and the R_A . In the present study, we calculated the glomerular hemodynamics during the intake of a relatively high sodium diet, which was considered to be an ordinary level of the sodium intake.

Table 2. Blood Pressure, Pulse Rate and Urinary Excretion of Na

	Stage 1	Stage 2	Stage 3	Stage 4
SBP (mmHg)	121±12	141±10	115±4	128±10**
DBP (mmHg)	77±8	84±5	74±5	78±4*
HR (beats/min)	62±9	60±8	63±7	61±8
U _{Na} V (mmol/day)	27±10	155±38	31±21	172±44

Stage 1: baseline on low sodium diet; Stage 2: baseline on relatively high sodium diet; Stage 3: with benidipine on low sodium diet; Stage 4: with benidipine on relatively high sodium diet. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; U_{Na}V, urinary sodium excretion rate. * $p < 0.05$ and ** $p < 0.01$ vs. stage 2.

Fig. 1. Pressure-natriuresis curves at baseline (○) and with benidipine treatment (●). The sodium sensitivity index significantly decreased from the baseline to the benidipine treatment period (from 0.102 ± 0.060 to 0.055 ± 0.026 , $p = 0.039$).

Statistical Analysis

The results are expressed as the mean±SD. The significance of differences in the parameters between the groups was determined by Student's *t*-test for non-paired samples. A *p* value of <0.05 was considered to indicate statistical significance.

Results

The mean age of the studied patients with metabolic syndrome was 61 ± 2.2 (Table 1). All 5 studied patients had central obesity and hypertension. Among the 5 patients, 4 had high serum triglyceride levels, 4 had low HDL cholesterol levels, and one had elevated fasting plasma glucose concentrations.

The average BP and heart rate values are shown in Table 2. The low sodium diet was not associated with any differences in the BP levels of stage 1 and stage 3. However, when the subjects were on a relatively high sodium diet, benidipine sig-

nificantly lowered systolic and diastolic BP from stage 2 to stage 4. The heart rates were the same in patients with all stages of disease. The U_{Na}V was measured in patients on low (stages 1 and 3) and high (stages 2 and 4) sodium diets. The changes in the U_{Na}V level in those on a low to a relatively high sodium diet were the same during the baseline and benidipine treatment periods.

Since the sodium sensitivity index significantly decreased after benidipine treatment, the pressure-natriuresis curve was steeper after the administration of benidipine (Fig. 1). Changes in the parameters in renal hemodynamics before and after treatment with benidipine are shown in Table 3. The creatinine clearance, renal plasma flow, and filtration fraction did not change after the administration of benidipine. However, benidipine lowered the P_{GC} and reduced both R_A and R_E . The albumin excretion rate (AER) also decreased after treatment with benidipine.

Discussion

Metabolic syndrome is a constellation of physical and laboratory abnormalities including central obesity, dyslipidemia, hyperglycemia, and hypertension. The syndrome has recently emerged as a critically important risk factor for cardiovascular disease (1, 2). On the other hand, it has been postulated that people with metabolic syndrome also have an increased risk for developing chronic kidney disease (CKD). In a report from the Third National Health and Nutrition Examination Survey (NHANES III), metabolic syndrome was found to significantly increase the risk of CKD (3). We recently found a relationship between metabolic syndrome and the sodium sensitivity of BP (4). Based on Bartter's original definition (5), 4 of 5 patients (80%) in the present study were diagnosed with sodium-sensitive hypertension. On the other hand, we previously found the prevalence of sodium-sensitive hypertension in patients without metabolic syndrome to be 36% (13). Therefore, the relationship between metabolic syndrome and the sodium sensitivity of BP was once again confirmed. Increased sensitivity of the BP to sodium has been reported to be associated with elevated P_{GC} (5, 7). In addition, it is also well established that the BP becomes sodium sensitive in advanced chronic renal disease, and sodium sensitivity has also been reported to become greater as the GFR decreases

Table 3. Changes in the Renal Hemodynamics by Benidipine

	Baseline	<i>p</i>	Benidipine
GFR (ml/min/1.73 m ²)	110±31	0.32	131±26
RPF (ml/min/1.73 m ²)	395±89	0.22	451±152
FF	0.29±0.11	0.74	0.31±0.81
<i>P</i> _{GC} (mmHg)	54.4±7.5	0.0152	47.0±7.0
<i>R</i> _A (dyn·s/cm ⁵)	10,338±2,618	0.047	9,026±2,627
<i>R</i> _E (dyn·s/cm ⁵)	4,649±2,039	0.003	2,419±2,081
AER (μg/min)	25.5±11.3	0.03	16.3±6.3

GFR, glomerular filtration rate estimated by creatinine clearance; RPF, renal plasma flow; FF, filtration fraction; *P*_{GC}, glomerular capillary pressure; *R*_A, resistance of afferent arterioles; *R*_E, resistance of efferent arterioles; AER, albumin excretion rate.

(9). Furthermore, the urinary AER has been reported to be greater in patients with a sodium-sensitive type of essential hypertension than in those with a non-sodium-sensitive type of essential hypertension (16). These findings indicate that, in patients with metabolic syndrome, the *P*_{GC} is elevated and this elevation in *P*_{GC} may contribute to the development of CKD. In fact, whereas in the non-sodium sensitive essential hypertension patients, the *P*_{GC} value was 47±1 mmHg (15), the *P*_{GC} value increased to 54.4±7.5 mmHg in our patients with metabolic syndrome.

In rat models, benidipine has been reported to reduce the resistance of efferent arterioles as well as afferent arterioles, while also lowering *P*_{GC} levels. (10). In addition, in patients with non-diabetic nephropathy, Morikawa *et al.* reported that benidipine lowered *P*_{GC} by decreasing the resistance of efferent arterioles (11); here, we used the same methods to estimate glomerular hemodynamics, and we found a decrease in the resistance of both the efferent and afferent arterioles and in the *P*_{GC} level with benidipine treatment. In addition, AER, a marker of glomerular hypertension (16), also significantly decreased after benidipine treatment. These results indicate that benidipine reduced AER by lowering the elevated *P*_{GC} levels in patients with metabolic syndrome.

In the present study, benidipine did not produce a reduction in the GFR, but it did reduce *P*_{GC}. In patients with non-diabetic nephropathy, Morikawa *et al.* also reported that benidipine reduced *P*_{GC} levels without reducing the GFR (11). Our group and that of Morikawa *et al.* (11) estimated the GFR using a standard clearance technique with endogenous creatinine. Creatinine clearance may not be a sufficiently sensitive test for the detection of changes in *P*_{GC}.

There are several limitations to this study. The study sample was rather small. Estimations of glomerular hemodynamics were based on Gomez's equations (17) under the assumption that the gross filtration coefficient of the glomerular capillaries was normal (15). Since the pressure-natriuresis curves were constructed by MAP, the sodium-sensitivity index could have been affected by changes in systemic BP, and not changes in the renal perfusion pressure. In addition, the mechanism responsible for the vasodilatory effects of benidipine on the efferent arterioles has not yet been precisely

elucidated. Voltage-dependent calcium channels, particularly L-type channels, have been demonstrated to be predominant on afferent arterioles, and conventional types of calcium antagonists (such as nifedipine, verapamil, and diltiazem) have been reported to induce increases in the GFR *via* afferent arteriolar dilation (18, 19). Recently, novel calcium-channel blockers, which exert an inhibitory effect on L/N-type or L/T-type calcium channels, were reported to induce both afferent and efferent arteriolar dilation (20). These novel drugs may reduce the GFR *via* efferent arteriolar dilation. Although some calcium-channel blockers have been reported to dilate the efferent arterioles by blocking certain subtypes of calcium channels found on the efferent arterioles (20), it is not yet known whether or not benidipine blocks the calcium channels on efferent arterioles. However, in a diabetic animal model, benidipine has been reported to preserve the tetrahydrobiopterin level (21), which was found to be a cofactor of nitric oxide (NO) synthesis. NO was reported to inhibit both L-type and T-type calcium channel activity (22). In addition, calcium-channel blockers can reduce oxidative stress (23, 24). Furthermore, NO has been shown to be an important modulator of the renal excretory response to changes in arterial pressure. An experimental model has been used to demonstrate that verapamil partially normalizes the pressure-natriuresis relationship, which was blunted by the inhibition of NO synthesis (25). Therefore, the enhanced synthesis of NO and/or the reduction in oxidative stress in the kidney due to the administration of benidipine may therefore influence glomerular hemodynamics and pressure natriuresis.

In conclusion, benidipine lowered the *P*_{GC} levels and reduced the AER in patients with metabolic syndrome. Benidipine may be effective at reducing the risk of developing CKD in patients with metabolic syndrome.

References

1. Isomaa B, Almgren P, Tuomi T, *et al*: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; **24**: 683–689.
2. Kahn R, Buse J, Ferrannini E, Stern M: The metabolic syndrome: time for a critical appraisal: joint statement from the

- American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005; **28**: 2289–2304.
3. Chen J, Muntner P, Hamm LL, et al: The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 2004; **140**: 167–174.
4. Uzu T, Kimura G, Yamauchi A, et al: Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. *J Hypertens* 2006; **24**: 1647–1632.
5. Kimura G, Frem G J, Brenner BM: Renal mechanism of salt sensitivity in hypertension. *Curr Opin Nephrol Hypertens* 1994; **3**: 1–12.
6. Uzu T: Circadian rhythm of blood pressure and cardiovascular risk in sodium sensitive hypertension. *Clin Exp Nephrol* 1999; **3**: 229–236.
7. Kimura G, Uzu T, Nakamura S, Inenaga T, Fujii T: High sodium sensitivity and glomerular hypertension/hyperfiltration in primary aldosteronism. *J Hypertens* 1996; **14**: 1463–1468.
8. Konishi Y, Okada N, Okamura M, et al: Sodium sensitivity of blood pressure appearing before hypertension and related to histological damage in immunoglobulin a nephropathy. *Hypertension* 2001; **38**: 81–85.
9. Koomans HA, Roos JC, Boer P, Geyskes GG, Mees EJ: Salt sensitivity of blood pressure in chronic renal failure. Evidence for renal control of body fluid distribution in man. *Hypertension* 1982; **4**: 190–197.
10. Kimura K: Effects of benidipine hydrochloride on renal arterioles. *Ther Res* 1994; **15**: 411–414.
11. Morikawa T, Okumura M, Konishi Y, Okada N, Imanishi M: Effects of benidipine on glomerular hemodynamics and proteinuria in patients with nondiabetic nephropathy. *Hypertens Res* 2002; **25**: 571–576.
12. Uzu T, Kazembe FS, Ishikawa K, Nakamura S, Inenaga T, Kimura G: High sodium sensitivity implicates nocturnal hypertension in essential hypertension. *Hypertension* 1996; **28**: 139–142.
13. Uzu T, Ishikawa K, Fujii T, Nakamura S, Inenaga T, Kimura G: Sodium restriction shifts circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation* 1997; **96**: 1859–1862.
14. Fujii T, Uzu T, Nishimura M, et al: Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertension. *Am J Kidney Dis* 1999; **33**: 29–35.
15. Kimura G, Imanishi M, Sanai T, et al: Intrarenal hemodynamics in patients with essential hypertension. *Circ Res* 1991; **69**: 421–428.
16. Bigazzi R, Bianchi S, Baldari D, Sgherri G, Baldari G, Campese VM: Microalbuminuria in salt-sensitive patients. A marker for renal and cardiovascular risk factors. *Hypertension* 1994; **23**: 195–199.
17. Gomez DM: Evaluation of renal resistance with special reference to changes in essential hypertension. *J Clin Invest* 1951; **30**: 1143–1155.
18. Carmines PK, Navar LG: Disparate effects of Ca channel blockers on afferent and efferent arteriolar responses to ANG II. *Am J Physiol* 1989; **256**: F1015–F1020.
19. Fleming JT, Parekh N, Steinhausen M: Calcium antagonists preferentially dilate preglomerular vessels of hydronephrotic kidney. *Am J Physiol* 1987; **253**: F1157–F1163.
20. Richard S: Vascular effects of calcium channel antagonists: new evidence. *Drugs* 2005; **65**: S1–S10.
21. Okumura M, Masada M, Yoshida Y, et al: Decrease in tetrahydrobiopterin as a possible cause of nephropathy in type II diabetic rats. *Kidney Int* 2006; **70**: 401–406.
22. Feng MG, Navar LG: Nitric oxide synthase inhibition activates L- and T-type Ca^{2+} channels in afferent and efferent arterioles. *Am J Physiol Renal Physiol* 2006; **290**: F873–F879.
23. Hirooka Y, Kimura Y, Nozoe M, Sagawa Y, Ito K, Sunagawa K: Amlodipine-induced reduction of oxidative stress in the brain is associated with sympatho-inhibitory effects in stroke-prone spontaneously hypertensive rats. *Hypertens Res* 2006; **29**: 49–56.
24. Yasunari K, Maeda K, Nakamura M, Watanabe T, Yoshikawa J: Benidipine, a long-acting calcium channel blocker, inhibits oxidative stress in polymorphonuclear cells in patients with essential hypertension. *Hypertens Res* 2005; **28**: 107–112.
25. Fortepiani LA, Rodrigo E, Ortiz MC, et al: Pressure natriuresis in nitric oxide-deficient hypertensive rats: effect of antihypertensive treatments. *J Am Soc Nephrol* 1999; **10**: 21–27.