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Effects of Irbesartan on Uric Acid Metabolism in Patients with Treated Essential Hypertension

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Abstract:

Background: Irbesartan has been reported to inhibit renal uric acid reabsorption and thereby decrease serum uric acid (Sur) levels. However, its effect on uric acid metabolism in hypertensive patients has not been reported. **Methods and Results:** We conducted a retrospective observational study that included 40 hypertensive patients to clarify the effects of irbesartan (mean dose 87.5 mg) on blood pressure (BP) and uric acid metabolism [Sur, urinary uric acid (Uur), serum creatinine (Scr), urinary creatinine (Ucr), uric acid clearance (Cur), creatinine clearance (Ccr), urinary uric acid to urinary creatinine ratio (Uur/Ucr), and uric acid clearance to creatinine clearance ratio (Cur/Ccr)] at baseline and after 3 months of treatment. We allocated patients into two groups, patients with Uur/Ucr <0.5 (low Uur/Ucr group) or those with Uur/Ucr ≥0.5 (normal/ high Uur/Ucr group), into other two groups, patients with Cur/Ccr <5.5% (low Cur/Ccr group) or those with Cur/Ccr ≥5.5% (normal/ high Cur/Ccr group). The hypoexcretion group contained low Uur/Ucr group and low Cur/Ccr group, and the normal/ hyperexcretion group contained normal/high Uur/Ucr group and normal/ high Cur/Ccr group. Further, we allocated patients into another two groups, patients with Sur ≥7 mg/dl (hyperuricemic group) or those with Sur <7 mg/dl (normouricemic group). Irbesartan significantly decreased systolic BP without affecting heart rate, and decreased Sur without altering Uur/Ucr or Cur/Ccr. In the hypoexcretion group, irbesartan decreased Sur while increasing Uur/Ucr and Cur/Ccr. In contrast, in the normal/hyperexcretion and hyperuricemic groups, irbesartan decreased Sur without changing Uur/Ucr or Cur/Ccr. In a normouricemic group, patients showed no changes in Sur after treatment with irbesartan. **Conclusions:** Irbesartan improved the secretion of uric acid, and reduced Sur in the hypoexcretion group, but did not influence uric acid excretion in the normal/hyperexcretion group. In hyperuricemic patients, irbesartan did not affect uric acid excretion but may have influenced uric acid production.

Key words:

Irbesartan, Uric acid metabolism, Hypertensive patients, Excretion of uric acid, Angiotensin receptor blocker

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Introduction

Hyperuricemia is frequently associated with the metabolic syndrome[1-3], obesity, and hypertension. Indeed, approximately 25% of hypertensive patients have concomitant hyperuricemia[4,5]. Hyperuricemia may not only be a risk factor for gout and renal failure but may also be a risk factor for cardiovascular events and metabolic syndrome. Thus, controlling serum uric acid (Sur) levels by lifestyle modification or use of antihypertensive drugs is extremely important in hypertensive patients[6]. The Guidelines for the Management of Hyperuricemia and Gout recommend the use of antihypertensive drugs that have favorable effects on uric acid metabolism, such as long-acting calcium channel blockers (CCBs), α-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), such as losartan[6]. CCBs, ACEIs, and α-blockers have been reported to suppress the production of the uric acid precursor hypoxanthine in skeletal muscles[7]. Losartan, specifically, has been reported to decrease Sur by enhancing urinary excretion of uric acid via inhibition of urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9)[8]. As uric acid is reabsorbed into the tubular cells via URAT1 and subsequently transported into the blood by GLUT9, loss-of-function mutations of URAT1 or GLUT9 can induce renal hypouricemia[9,10].

Irbesartan, an ARB with renoprotective effects[11], was reported to decrease Sur in patients with hypertension, diabetes[12], and chronic kidney disease[13]. Experimental studies have shown that irbesartan inhibits both URAT1 and GLUT 9[8]. However, the effect of irbesartan on uric acid metabolism in hypertensive patients with varying levels of urinary uric acid excretion remains unknown.

Methods

Subjects

We originally enrolled 56 hypertensive patients treated with irbesartan, who visited the outpatient clinics of Tottori University Hospital, Nojima Hospital, and Shinsei Hospital or the Nosaka Clinic every month to check whether their blood pressure (BP) was appropriately controlled. Patients with secondary hypertension, uncontrolled diabetes mellitus, serum creatinine (Scr) >2 mg/dL, liver dysfunction, or cancer were excluded. Another 15 patients were excluded because of a lack of data on serum and urinary uric acid and creatinine levels, and one patient was excluded because of intake of both ACEI and irbesartan; thus, we eventually included 40 patients (average age 74 ± 11 years, 27 males) to examine uric acid metabolism before and 3 months after treatment with irbesartan. Out of the 40 patients, 13 had been previously treated with other ARBs (candesartan 8 mg/day, n=3; olmesartan 10 mg/day, n=2; olmesartan 20 mg/day; n=3; telmisartan 20 mg/day, n=1; telmisartan 40 mg/day, n=1; valsartan 80 mg/day, n=3) and were switched to irbesartan without any washout interval to continuously control their BP. In the other patients, irbesartan was the first ARB prescribed. Previously, 17 patients had taken a CCB, four had taken a β-blocker, and six had taken a diuretic. None of them was treated with hyperuricemic drugs, nonsteroidal anti-inflammatory drugs, or fibrates.

In each hospital, medical records were reviewed for demographic, laboratory, medication, and therapeutic response data before and after treatment with irbesartan. The Institutional Review Board of Tottori University Hospital approved the protocol of this study, and informed consent was obtained from each patient. The privacy of the patients was protected in accordance with the Declaration of Helsinki.

Study design

The 40 enrolled patients were prescribed irbesartan at a daily dose of 50-100 mg (mean dose 87.5 mg). The amount of irbesartan was determined by physicians according to the patient's BP and was then held constant for the entire study period. The daily dose of irbesartan was taken at 7:00 AM, while systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured on the days of examination at 9:00 AM with the patients resting and seated upright. Blood and urinary tests to determine serum urate (Sur), urinary uric acid (Uur), Scr, and urinary creatinine (Ucr) were regularly carried out and analyzed at baseline and after 3 months of treatment. Urate clearance (Cur), creatinine clearance (Ccr), the ratio of urinary uric acid to urinary creatinine (Uur/Ucr), and the ratio of uric acid clearance to creatinine clearance (Cur/Ccr) were determined according to a previously described method[14,15], before and after treatment with irbesartan. To assess changes in uric acid metabolism after treatment, we allocated patients into two groups, patients with Uur/Ucr <0.5 (low Uur/Ucr group, n=20) or those with Uur/Ucr ≥0.5 (normal/high Uur/Ucr group, n=20), into other two groups, patients with Cur/Ccr <5.5% (low Cur/Ccr group, n=15) or those with Cur/Ccr ≥5.5% (normal/ high Cur/Ccr group, n=25). The hypoexcretion group contained low Uur/Ucr group and low Cur/Ccr group, and the normal/ hyperexcretion group contained normal/high Uur/Ucr group and normal/ high Cur/Ccr group[6]. Further, into another two groups, patients with Sur ≥7 mg/dl (hyperuricemic group, n=15) or those with Sur <7 mg/dl (normouricemic group, n=25).

Statistical analysis

Continuous variables are expressed as mean±standard deviation (SD). Differences in continuous variables between the 2 groups were compared using parametric analysis. Categorical variables are expressed as percentages. Categorical variables were compared using Fisher's exact test. A p-value <0.05 indicated statistical significance. All analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Table 1. Baseline characteristics of all cases, hypoexcretion of uric acid group (Uur/Ucr<0.5 or Cur/Ccr<5.5%), normal/hyperexcretion of uric acid group (Uur/Ucr>0.5 or Cur/Ccr>5.5%), hyperuricemia group, and normouricemia group.

	All Cases	Uur/Ucr≥0.5	Uur/Ucr<0.5	p	Cur/Ccr≥5.5	Cur/Ccr<5.5	p	Hyperuricemia group	Normouricemia group	p
N	40	20	20		25	15		15	25	
Age (years)	74±11	75±7	73±13	NS	76±8	72±14	NS	76±10	73±11	NS
Sex (male/female)	27/13	11/9	16/4	NS	15/10	12/3	NS	12/3	15/10	NS
BMI (kg/m^2)	23.5±3.1	24.1±2.9	23.0±3.3	NS	23.7±3.0	23.3±3.3	NS	24.4±3.9	22.8±2.1	NS
SBP (mmHg)	148±15	148±16	147±14	NS	147±14	148±16	NS	146±18	148±12	NS
DBP (mmHg)	77±11	77±11	77±10	NS	77±12	77±8	NS	76±6	77±12	NS
HR (bpm)	69±9	71±10	68±7	NS	70±9	68±7	NS	70±7	69±9	NS
Sur (mg/dL)	6.4±1.6	6.2±1.9	6.6±1.3	NS	5.7±1.6	7.5±0.9	<0.01	8.1±0.7	5.4±1.0	<0.01
Scr (mg/dL)	0.9±0.3	0.8±0.2	1.0±0.3	<0.05	0.8±0.2	0.9±0.3	NS	1.0±0.3	0.8±0.2	<0.05
Uur/Ucr	0.51±0.17	0.64±0.14	0.39±0.08	<0.01	0.58±0.17	0.40±0.11	<0.01	0.47±0.15	0.54±0.18	NS
Cur/Ccr (%)	7.0±3.2	8.5±3.8	5.5±1.3	<0.01	8.4±3.3	4.7±0.5	<0.01	5.3±1.5	8.0±3.5	<0.01
hyperuricemia (%)	15 (37.5)	7 (35.0)	8 (40.0)	NS	4 (16.0)	11 (73.3)	<0.01	15 (100.0)	0 (0.0)	<0.01
diabetes mellitus (%)	3 (7.5)	2 (10.0)	1 (5.0)	NS	2 (8.0)	1 (6.7)	NS	1 (6.7)	2 (8.0)	NS
dyslipidemia (%)	11 (27.5)	7 (35.0)	4 (20.0)	NS	7 (28.0)	4 (26.7)	NS	4 (26.7)	7 (28.0)	NS
CCBs (%)	17 (42.5)	9 (45.0)	8 (40.0)	NS	13 (52.0)	4 (26.7)	NS	5 (33.3)	12 (48.0)	NS
β-blocker (%)	4 (10.0)	1 (5.0)	3 (15.0)	NS	1 (4.0)	3 (20.0)	NS	2 (13.3)	2 (8.0)	NS
diuretics (%)	6 (15.0)	2 (10.0)	4 (20.0)	NS	4 (16.0)	2 (13.3)	NS	4 (26.7)	2 (8.0)	NS
irbesartan dose 50 mg/day (%)	10 (25.0)	3 (15.0)	7 (35.0)	NS	6 (24.0)	4 (26.7)	NS	2 (13.3)	8 (32.0)	NS
irbesartan dose 100 mg/day (%)	30 (75.0)	17 (85.0)	13 (65.0)	NS	19 (76.0)	11 (73.3)	NS	13 (86.7)	17 (68.0)	NS

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, Sur: serum urate, Scr: serum creatinine, Uur/Ucr: urinary urate to urinary creatinine ratio, Cur/Ccr: urate clearance to creatinine clearance ratio, CCBs: calcium channel blockers, ACEIs: angiotensin-converting enzyme inhibitors

Results

Effects of irbesartan on BP and uric acid metabolism in hypertensive patients

The characteristics of the patients at baseline are shown in **Table 1**. Ten patients were prescribed irbesartan 50 mg (25.0%) and 30 patients were prescribed irbesartan 100 mg (75.0%), such that the mean dose of irbesartan was 87.5 mg.

Irbesartan treatment significantly decreased SBP (from 148±15 to 131±16 mmHg, p<0.001) without affecting DBP (from 77±10 to 73±13 mmHg, p=0.786) and HR (from 69±8 to 69±12 bpm, p=0.744) (**Figure 1A, B**).

The effect of irbesartan on uric acid metabolism is illustrated in **Figure 1C-E**. During treatment with Irbesartan, Sur decreased significantly and Uur tended to decrease, whereas Scr remained unchanged. No statistically significant differences in Uur/Ucr or Cur/Ccr between baseline values and those measured after treatment were found.

We also divided the 40 patients into those who were taking diuretics (n=6) and those who were not (n=34), and used uric acid data to assess the effect of diuretics on uric acid metabolism (**Figure 2**). Sur decreased regardless of the presence of diuretics, whereas Scr, Uur/Ucr and Cur/Ccr remained constant in all cases.

We also divided the patients into those who were switched from other ARBs to irbesartan (switch group) (n=13) and those taking irbesartan as their first ARB (first group) (n=27). Systolic BP decreased in both groups (switch group: before vs. after=148±19 vs. 138±18 mmHg, p<0.05, first group: before vs. after=147±12 vs. 127±14 mmHg, p<0.001). Diastolic BP decreased only in the first group (switch group: before vs. after=74±8 vs. 76±11 mmHg, p=0.564; first group: before vs. after=79±12 vs. 71±15 mmHg, p<0.05). There was no change in HR in any of the 40 patients (data not shown).

Changes in uric acid metabolism in the first and switch groups are illustrated in **Figure 3**. Irbesartan decreased Sur, but did not affect Scr, Uur/Ucr or Cur/Ccr. In the switch group, Sur tended to decrease regardless of the type and dose of previous ARBs (candesartan, olmesartan, telmisartan, and valsartan) (**Supplemental Table 1**). Irbesartan decreased Uur only in the first group, and there was a significant difference between the first group and the switch group after taking irbesartan.

Effects of irbesartan on uric acid metabolism in patients with uric acid hypoexcretion or normal/hyperexcretion

It has been reported that the ability of azelnidipine to lower Sur differs depending on the uric acid excretion type or Sur levels[16]. Thus, we divided patients into two groups, a hypoexcretion group (low Uur/Ucr group and low Cur/Ccr group) and a normal/hyperexcretion group (normal/high Uur/Ucr group and normal/high Cur/Ccr group). There were no significant differences in age, sex, BMI, or proportion of people taking irbesartan 50 mg/d and 100 mg/d between the groups. In the hypoexcretion group, Sur significantly de-

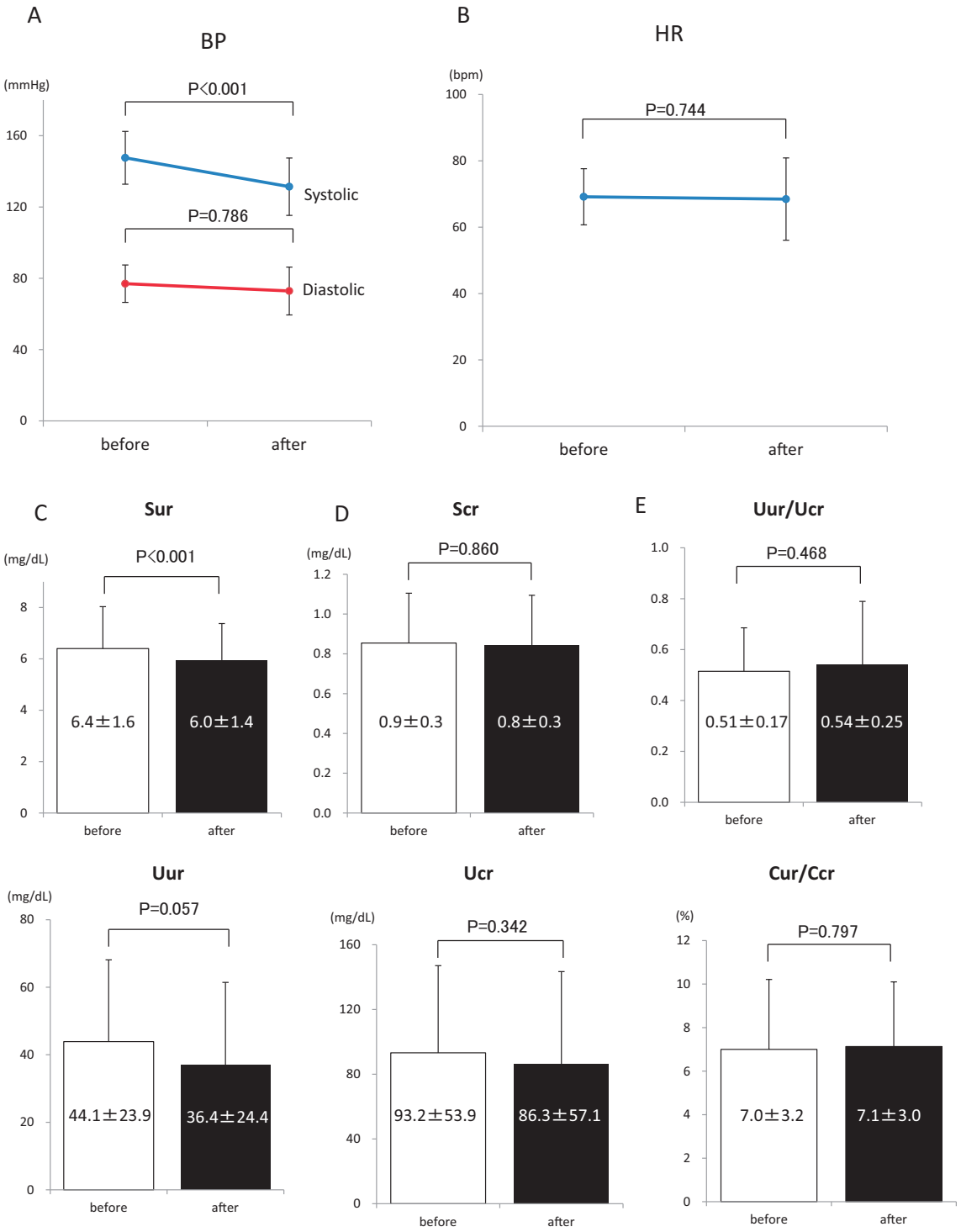

Figure 1. Effects of irbesartan on uric acid metabolism in treated hypertensive patients
before: in the absence of irbesartan, after: in the presence of irbesartan
A: Effects of irbesartan on BP
B: Effects of irbesartan on HR
C: Upper; Effects of irbesartan on Sur, lower; Effects of irbesartan on Uur
D: Upper; Effects of irbesartan on Scr, lower; Effects of irbesartan on Ucr
E: Upper; Effects of irbesartan on Uur/Ucr, lower; Effects of irbesartan on Cur/Ccr
BP: blood pressure, HR: heart rate, Sur: serum uric acid, Uur: urinary uric acid, Scr: serum creatinine, Ucr: urinary creatinine, Uur/Ucr: urinary uric acid to urinary creatinine ratio, Cur/Ccr: urate clearance to creatinine clearance ratio
Irbesartan decreased systolic BP without change of HR.
Irbesartan significantly decreased Sur without changes in either Scr, Uur/Ucr, Uur or Cur/Ccr.

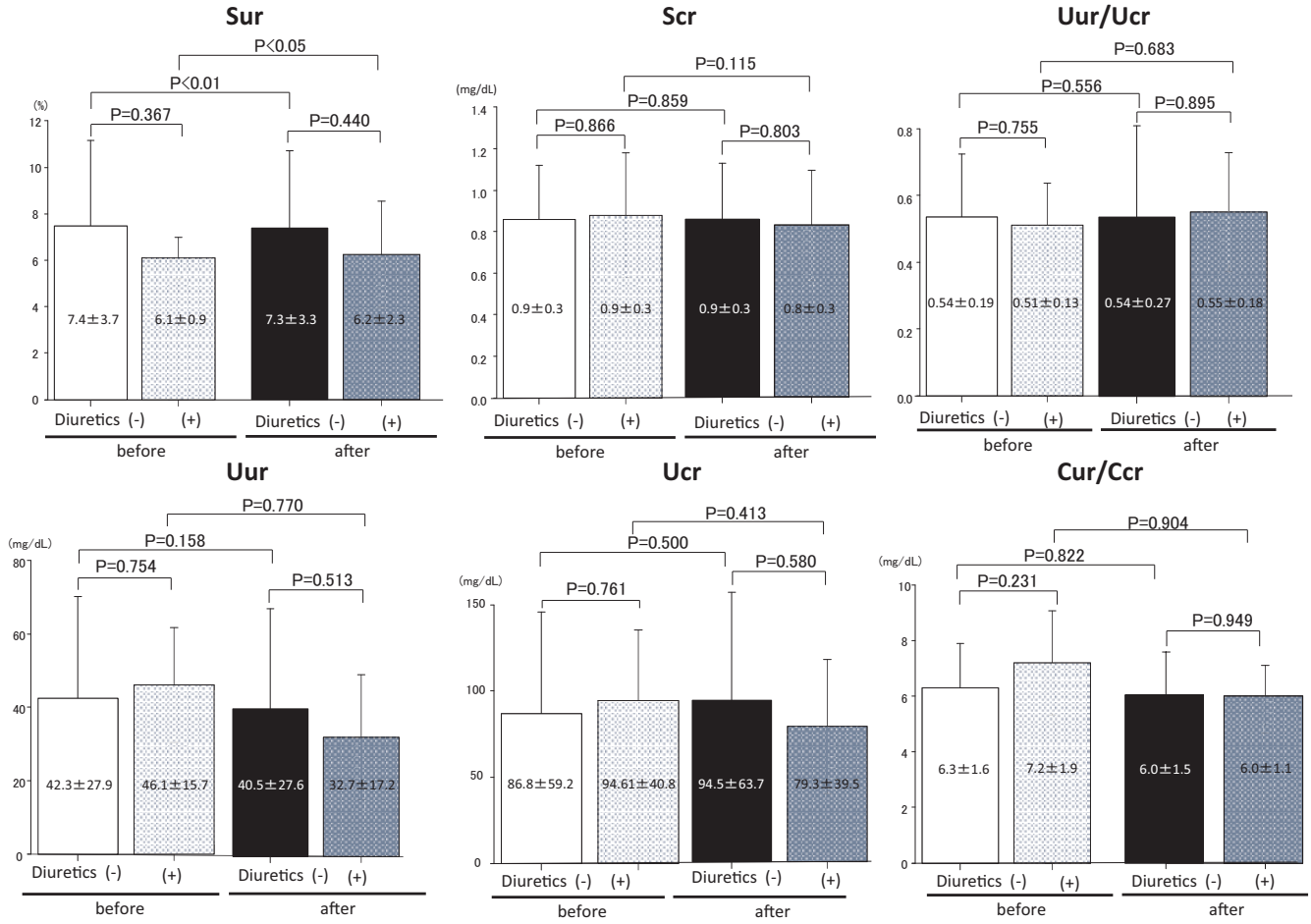

Figure 2. Effects of irbesartan on uric acid metabolism in patients who are or are not taking diuretics
Before: in the absence of irbesartan, after: in the presence of irbesartan.
Sur: serum uric acid, Uur: urinary uric acid, Scr: serum creatinine, Ucr: urinary creatinine, Uur/Ucr: urinary uric acid to urinary creatinine ratio, Cur/Ccr: urate clearance to creatinine clearance ratio
Irbesartan decreased Sur both in patients who took and who did not take diuretics, but did not affect Scr, Uur/Ucr, Uur, or Cur/Ccr in either group.

creased, and the Uur/Ucr and Cur/Ccr ratios increased (**Figure 4A**). In contrast, in the normal/hyperexcretion group, Sur decreased, but there were no significant differences in either Uur/Ucr or Ccr/Ccr between pre- and post-treatment values (**Figure 4B**).

Effects of irbesartan on uric acid metabolism in patients with or without hyperuricemia

Next, we divided patients into two different groupings, namely, a hyperuricemic group and a normouricemic group. As shown in **Table 1**, there were no differences in age, sex, BMI, or proportion of people taking irbesartan 50 mg/d and 100 mg/d between the groups. Scr was higher in the hyperuricemic group than in the normouricemic group (**Table 1**). Irbesartan significantly decreased Sur only in the hyperuricemic group without changing the Uur/Ucr or Cur/Ccr ratios. In contrast, in the normouricemic group, none of these three parameters changed during treatment with irbesartan (**Figure 5**).

Discussion

The present study showed that irbesartan decreased Sur in treated essential hypertensive patients. However, the effect of irbesartan differed depending on the uric acid excretion type or Sur levels.

The levels of Sur are known to be regulated by the renal urinary excretion of uric acid and its production in the liver and muscles. Uric acid is reabsorbed into the tubular cells via URAT1 and subsequently transported to the blood by GLUT9. These two transporters play important roles in uric acid metabolism.

Hyperuricemia is associated with the metabolic syndrome[1-3], hypertension, renal failure, and cardiovascular events. Thus, it is extremely important to control Sur in hypertensive patients. It has been reported that in hypertensive patients, activation of the renin-angiotensin system (RAS), insulin resistance, and sympathetic nervous system increases reabsorption of uric acid via stimulation of URAT1 in the renal proximal tubular cells, thereby reducing its urinary excretion[17-19]. In contrast, we previously reported that myo-

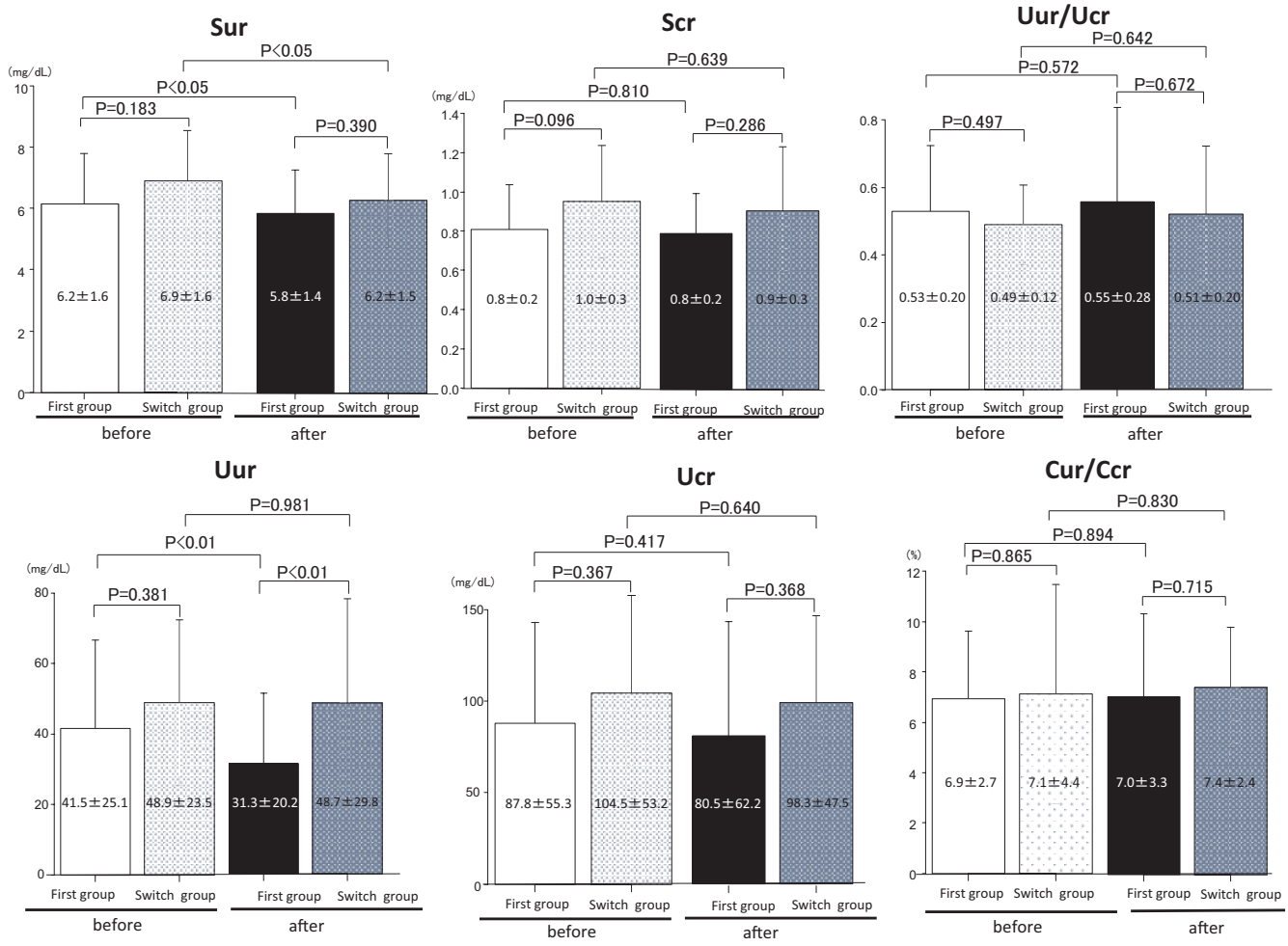

Figure 3. Effects of irbesartan on uric acid metabolism in the first group and the switch group
Before: in the absence of irbesartan, after: in the presence of irbesartan.
Sur: serum uric acid, Uur: urinary uric acid, Scr: serum creatinine, Ucr: urinary creatinine, Uur/Ucr: urinary uric acid to urinary creatinine ratio, Cur/Ccr: urate clearance to creatinine clearance ratio, ARB angiotensin receptor blocker
Irbesartan decreased Sur in both the group of patients where irbesartan was their first angiotensin receptor blocker prescribed (first group) and in the group of patients who were switched from another ARB (switch group), but did not affect Scr, Uur/Ucr, or Cur/Ucr in either group.

genic hyperuricemia was caused by excessive degradation of the uric acid precursor hypoxanthine in skeletal muscles of hypertensive patients[7].

Losartan, one of the ARBs, has been reported to decrease Sur in hypertensive patients via inhibition of URAT1[20], and several reports have shown that this property of losartan was abolished in hypertensive patients who carried a loss-of-function mutation in the URAT1 gene[21].

Irbesartan has been reported to reduce Sur by inhibiting the uptake of uric acid by both URAT1 and GLUT9[8,12]. The inhibition of URAT1 by irbesartan exceeded those of losartan *in vitro*. A large clinical study indicated that the uric acid-lowering effect of irbesartan was less than that of losartan in hypertensive patients with hyperuricemia[22]. These previous studies indicated that the effect of irbesartan on uric acid metabolism in hypertensive patients is still unclear.

In the present study, we showed that irbesartan significantly decreased Sur in hypertensive patients regardless of the presence of diuretics or previous use of other ARBs. The most prominent finding was that the action of irbesartan on uric acid metabolism differed in the hypoexcretion group and the normal/hyperexcretion group. In the hypoexcretion group, irbesartan decreased Sur, whereas it increased Uur/Ucr and Cur/Ccr, indicating that irbesartan enhanced the urinary excretion of uric acid accompanied by a reduction in Sur. This may be attributed to the inhibitory action of irbesartan on URAT1 and GLUT9. In contrast, in the normal/hyperexcretion group, irbesartan reduced Sur without altering Uur/Ucr and Cur/Ccr, indicating that irbesartan reduced Sur without affecting uric acid excretion. Although its underlying mechanism remains unclear, irbesartan may influence the production of uric acid. Previous studies have shown that irbesartan enhanced the production of nitric oxide[23], which might attenuate myogenic hyperuricemia[7].

Next, we showed that irbesartan significantly decreased Sur only in hyperuricemic patients without affecting Uur/Ucr or Cur/Ccr, suggesting that irbesartan may influence the production of uric acid accompanied by reduction of Sur[7].

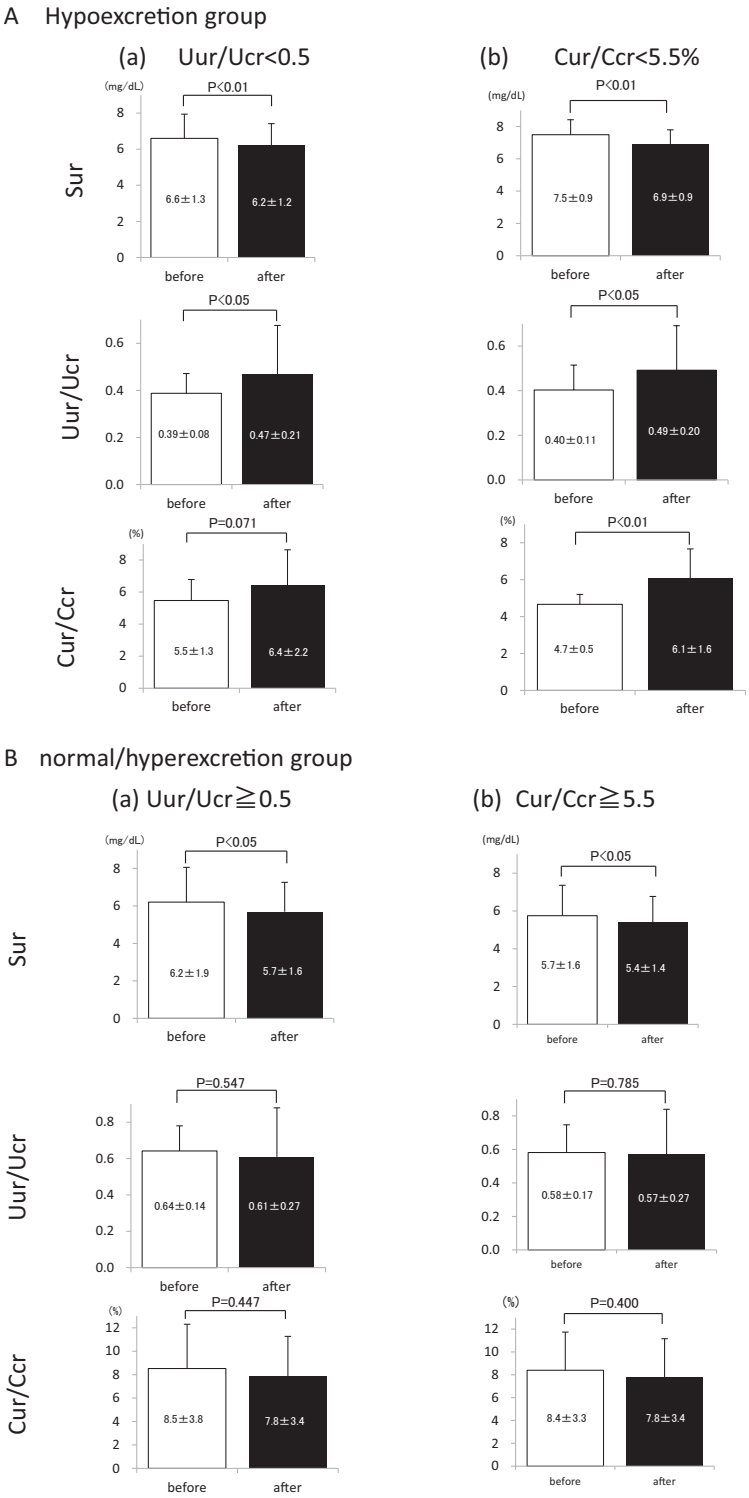

Figure 4. Effects of irbesartan on uric acid metabolism in the hypoexcretion and normal/hyperexcretion groups

Before: in the absence of irbesartan, after: in the presence of irbesartan.

A: Hypoexcretion group (a) low Uur/Ucr group (Uur/Ucr<0.5), (b) low Cur/Ccr group (Cur/Ccr<5.5%)

B: normal/hyperexcretion group (a) normal/high Uur/Ucr group (Uur/Ucr≥0.5), (b) normal/high Uur/Ucr group (Cur/Ccr≥5.5%)

Sur: serum uric acid, Uur/Ucr: urinary uric acid to urinary creatinine ratio, Cur/Ccr: urate clearance to creatinine clearance ratio

In the hypoexcretion group, irbesartan significantly decreased Sur, increased Uur/Ucr and showed a tendency to increase Cur/Ccr. In contrast, in the normal/hyperexcretion group, Sur was significantly decreased with no change in Uur/Ucr and Ccr/Ccr after treatment with irbesaratan.

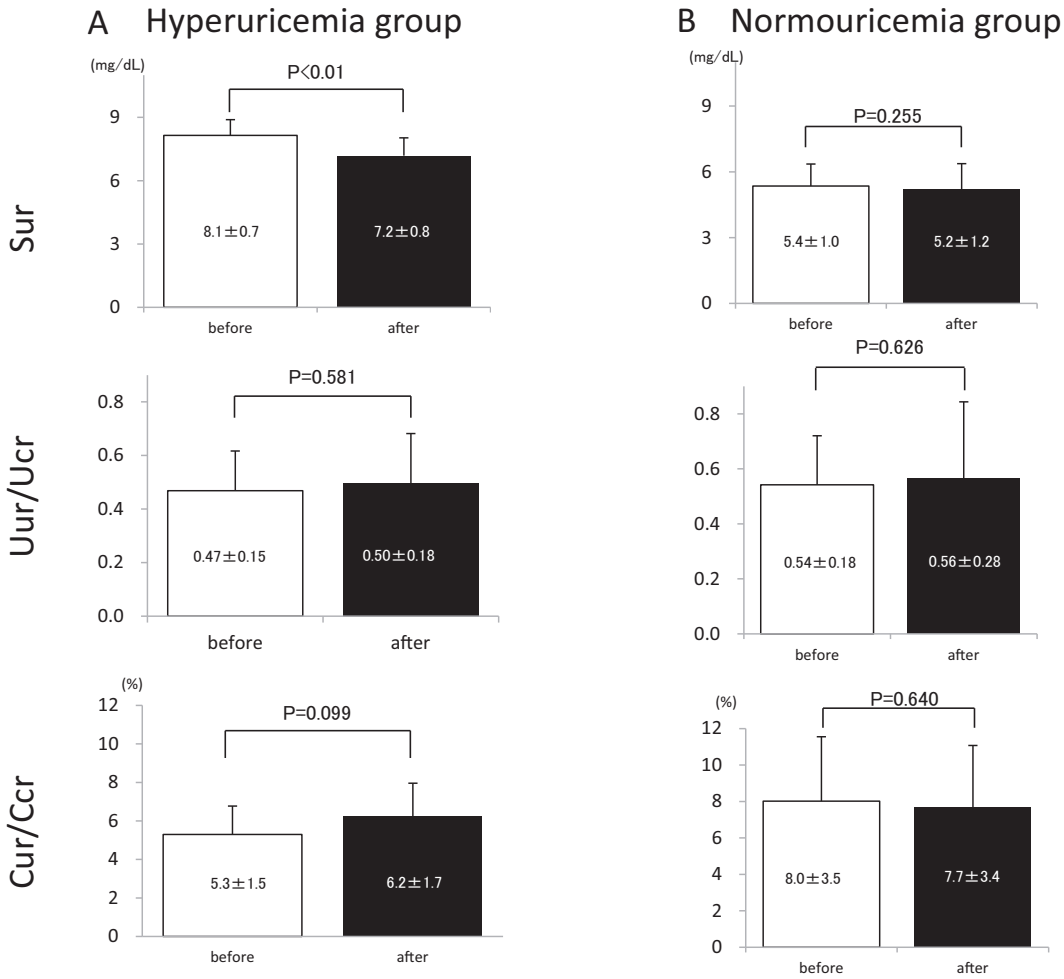

Figure 5. Effects of irbesartan on uric acid metabolism in hyperuricemia and normouricemia groups
before: in the absence of irbesartan, after: in the presence of irbesartan.
A: Hyperuricemia group
B: Normouricemia group
Sur: serum uric acid, Uur/Ucr: urinary uric acid to urinary creatinine ratio, Cur/Ccr: urate clearance to creatinine clearance ratio
Irbesartan significantly decreased Sur in the hyperuricemia group with no changes in either Uur/Ucr or Cur/Ccr. In contrast, there was no change in Sur, Uur/Ucr, and Cur/Ccr in the normouricemia group before and after treatment with irbesartan.

In contrast, there was no change in Sur, Uur/Ucr or Cur/Ccr in normouricemic patients treated with irbesartan. Nakamura et al. recently reported that irbesartan decreased Sur in hypertensive patients with diabetes and Sur above 5.9 mg/dL, whereas it did not influence Sur levels in patients with Sur ≤ 5.9 mg/dL[12]. These results indicate that the effects of irbesartan on uric acid metabolism differ depending on the level of Sur present. We excluded patients with Scr >2 mg/dL, and the mean Scr was 0.8-1.0 mg/dL in both hyperuricemic and normouricemic groups, which suggests that kidney function has little effects on uric acid metabolism in the two groups. In this study, there were no significant differences in BMI or dyslipidemia between hyperuricemic and normouricemic patients, although hyperuricemia often occurs in patients with the metabolic syndrome. The reason for this remains unknown; however, our patients were over 70 years old, on average, which may have influenced prevalence of obesity and dyslipidemia in the cohort.

This study had several limitations. First, the study should ideally have been randomized with pre-selection, an equal distribution of all groups, and with all patients treated with irbesartan at the recommended dose; however, our study was a retrospective evaluation of a small number of patients and the evaluation occurred during a short period. Due to these reasons, we could not perform a multivariate analysis, and we could not see a difference in effects according to the dose of irbesartan. Second, we did not include a control group; therefore, the results of the drug's effects on BP and uric acid metabolism could not exclude the possibility of the regression to the mean. Third, patients did not have dietary restrictions; thus, there was a possibility that dietary factors affected uric acid metabolism. Fourth, the mean dose of irbesartan (87.5 mg) used in this study was below the recommended dose (150 mg) because irbesartan was used as con-

comitant medicine together with other hypotensive drugs. Thus, the effects of irbesartan observed in this study might have been underestimated. In addition, some patients were prescribed other drugs prior to the administration of irbesartan; this may have changed the effects of irbesartan on uric acid metabolism. For example, CCBs are known to affect uric acid metabolism, and 17 patients in the present study were treated with CCBs prior to the administration of irbesartan, suggesting that the effects of CCBs on uric acid metabolism could be minimal.

Thus, the mechanisms by which irbesartan reduces Sur, independent of urinary uric acid excretion, remain to be elucidated in future studies.

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Conflicts of Interest

Dr. I. Hisatome reported receiving lecturer's fee from Sanwa Kagaku Kenkyusho Co. Ltd, Feizer Co. Ltd. and Fuji Yakuhin Co. Ltd., and research grants from Teijin Pharma, Fuji Yakuhin Co. Ltd, Sanwa Kagaku Kenkyusho Co. Ltd., Shionogi & Co. Ltd, and Dainippon Sumitomo Pharmaco Co.

Miyazaki S, Sugihara S and Sakuragi T contributed equally to this study.

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