Alkalizer Administration Improves Renal Function in Hyperuricemia Associated with Obesity

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Abstract: We evaluated the combination effect of the alkalizer citrate with the xanthine oxidase inhibitor allopurinol on renal function and uric acid in patients with hyperuricemia associated with obesity and/or metabolic syndrome (MetS), who were extracted from among the subjects enrolled in a prospective randomized controlled study aimed at assessing the efficacy of such a combination for improving renal function. We also conducted a post hoc analysis to examine influences on lipid profiles. Patients who consented to participate in the study were randomly allocated to receive either allopurinol alone (monotherapy) or in combination with a citrate preparation (combination therapy). The analysis population consisted of 31 obese patients with a body mass index greater than 25 kg/m² (monotherapy, 15 patients; combination therapy, 16 patients). The creatinine clearance rate (Ccr), serum uric acid levels, and lipid profiles were measured before and at 12 weeks after the start of treatment. In the combination therapy group, Ccr increased significantly and serum uric acid levels decreased significantly in obese patients, while Ccr tended to increase and serum uric acid levels decreased, though not significantly, in patients with MetS-related clinical parameters. Overall, blood triglyceride levels tended to improve in the combination therapy group as compared with the monotherapy group.

Keywords: Obesity, hyperuricemia, renal function, citrate, alkalizer

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Introduction
Hyperuricemia, a risk factor for metabolic syndrome (MetS), occurs in association with obesity at a high frequency, and the reported prevalence of hyperuricemia in Japan is 70%. Hyperuricemia causes the deposition of uric acid crystals in glomeruli, which in turn induces inflammation of the renal parenchyma, thereby leading to renal dysfunction. Uric acid deposition in the renal tubule lumen, which is caused by immunological glomerular damage and impaired urinary flow, decreases the glomerular filtration rate, and thereby promotes renal dysfunction in hyperuricemic patients. We previously conducted a prospective randomized controlled study to evaluate the combination effect of the alkalizer citrate with the xanthine oxidase inhibitor allopurinol on renal function in hyperuricemic patients. In that study, an additional use of a citrate preparation with allopurinol was found to reduce circulating uric acid and improve the glomerular filtration rate. Furthermore, the creatinine clearance rate (Ccr) was unaltered in both the allopurinol monotherapy (MT) and the combination therapy (CT) group in general, whereas it was significantly increased in a subset of the CT group with decreased renal function.

The present study was designed to evaluate the effects of combining a xanthine oxidase inhibitor and a citrate preparation on renal function, uric acid, and lipid profiles in patients with obesity and/or features of MetS.

Materials and Methods
Patient enrollment
This study was approved by the Yokohama Rosai Hospital Ethics Committee. All enrolled patients, who had serum uric acid levels of 7.0 mg/dL or higher and had been diagnosed with hyperuricemia, provided written informed consent prior to participation in the study.

These patients were randomly allocated to receive either allopurinol alone (MT group) or in combination with citrate (CT group). The alkalizer citrate preparation was composed of Na citrate, K citrate, and citric acid in a ratio of 2:2:1. Allopurinol (100–200 mg/day) was administered alone, or in combination with the citrate preparation (3 g/day), for 12 weeks. Patients who were administered uricosuric drugs were excluded. Doses of concomitant drugs used at the time of enrollment were not altered for the duration of the treatment period.

MetS was diagnosed based on the following criteria: obesity (defined as a body mass index ≥ 25 kg/m²), hypertension (systolic blood pressure [BP] ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg), dyslipidemia (low-density lipoprotein cholesterol [LDL-C] ≥ 140 mg/dL, triglyceride [TG] ≥ 150 mg/dL, or high-density lipoprotein cholesterol [HDL-C] < 40 mg/dL), and glucose tolerance abnormality (75-g glucose tolerance test at 2-hr ≥ 200).

Of the 56 patients who completed the treatment (MT group 30, CT group 26), 31 obese patients (MT group 15, CT group 16) were analyzed. This study was performed at the Yokohama Rosai Hospital and was approved by the Institutional Ethics Committee.

Laboratory tests
Figure 1 shows the test methods. Ccr was measured by the 60-min method. Patients ate low purine diets for 3 days before the start of the test, fasted on the day of the test, and voided at 30 minutes after drinking 500 mL of water. Then, urine was collected during a period of 60 minutes and a blood sample was obtained at the mid-point of urine collection. Before and at 12 weeks after the start of treatment, values were determined for Ccr, uric acid clearance (Cua), the Cua/Ccr ratio, serum uric acid, urinary uric acid, urine pH, serum creatinine, blood urea nitrogen (BUN), urine volume, urinary osmotic pressure, specific gravity of urine, BP, serum potassium concentration, and blood TG levels.

Statistical analysis
Each value indicates the mean ± standard deviation. For statistical analysis, Student’s t-test, Fisher’s exact
test, and the Wilcoxon test were used for comparisons between groups, and 1-way analysis of variance (ANOVA) for between-group comparisons. In 2-tailed tests, the significance level was set at $P < 0.05$. If the $P$-value was between 0.05 and 0.1, the value was considered to show a significant tendency though failing to reach statistical significance. For between-group comparisons, analysis of covariance (ANCOVA) was used to adjust the value before treatment and allopurinol administration prior to the test. The statistical analysis software used was SAS9.1 (SAS Institute Japan Ltd.).

**Results**

Table 1 shows patient background characteristics. Co-existing diseases included hypertension (58%), dyslipidemia (71%), and glucose tolerance abnormalities (29%) at the time of the study. There were no significant differences in background factors between the MT and CT groups.

After treatment, urine pH significantly increased from $5.7 \pm 0.5$ to $6.2 \pm 0.4$ in the CT group ($P = 0.0295$), whereas there was no significant difference in pH level in the MT group. In addition, some parameters changed in both the MT and the CT group (Ccr, $0.82 \pm 0.22$ to $0.77 \pm 0.14$ mg/dL and $0.92 \pm 0.17$ to $0.89 \pm 0.17$ mg/dL; BUN, $13.2 \pm 5.6$ to $12.6 \pm 3.8$ mg/dL and $14.8 \pm 4.5$ to $14.6 \pm 4.4$ mg/dL; TG, $165.7 \pm 127.2$ to $216.9 \pm 182.5$ mg/dL and $203.8 \pm 101.7$ to $181.9 \pm 89.4$ mg/dL; LDL-C, $102.5 \pm 23.3$ to $104.2 \pm 13.6$ mg/dL and $125.3 \pm 27.6$ to $122.0 \pm 33.6$ mg/dL, respectively), although these differences did not reach statistical significance.

Figure 2 shows the effects of MT and CT on Ccr. In the entire patient population, Ccr rose significantly after the start of treatment in the CT group ($P = 0.0378$). In patients with co-existing obesity and hypertension, Ccr tended to rise after the start of treatment in the CT group, with a significant difference between the MT and CT groups in variation after the start of treatment ($P = 0.0452$). In patients with co-existing obesity and dyslipidemia, a tendency for Ccr to rise after the start of treatment was detected in the CT group.

Table 2 shows the effects of MT and CT on serum uric acid levels. Serum uric acid levels decreased significantly after the start of treatment in the entire patient population ($P = 0.0002$); according to co-existing disease, a significant decrease in uric acid levels was also observed in those with obesity and hypertension ($P = 0.0199$), those with obesity and dyslipidemia ($P = 0.0001$), and those with obesity, hypertension, and dyslipidemia ($P = 0.0163$). In patients with obesity and glucose tolerance abnormalities, no significant differences were detected between values before and after the start of treatment.

Blood TG levels tended to rise in the MT group (from $166 \pm 127$ to $217 \pm 182$ mg/dL; $P = 0.0961$),

**Table 1. Patient background characteristics.**

| Characteristics                  | Total     | MT group | CT group |
|----------------------------------|-----------|----------|----------|
| All (obesity + hyperuricemia)*    | 31        | 15       | 16       |
| Male:female*                     | 25:6      | 12:3     | 13:3     |
| Age*                             | 53.9 ± 15.6| 52.2 ± 18.0| 55.5 ± 13.4|
| BMI (kg/m²)**                    | 29.9 ± 4.1| 29.8 ± 4.4| 30.0 ± 3.9|
| Ccr (mL/min)**                   | 97.4 ± 31.8| 108.1 ± 34.3| 87.4 ± 26.6|
| Serum uric acid (mg/dL)**        | 7.6 ± 1.3 | 7.2 ± 1.4 | 7.9 ± 1.1 |
| Creatinine (mg/dL)**             | 0.87 ± 0.20 | 0.82 ± 0.22 | 0.92 ± 0.17 |
| BUN (mg/dL)**                    | 14.0 ± 5.1 | 13.2 ± 5.6 | 14.8 ± 4.5 |
| TG (mg/dL)**                     | 185.4 ± 114.4 | 165.7 ± 127.2 | 203.8 ± 101.7 |
| LDL-C (mg/dL)**                  | 114.7 ± 27.7 | 102.5 ± 23.3 | 125.3 ± 27.6 |

*With MetS parameters*  
| + hypertension + dyslipidemia | 12 | 4 | 8 |
| + hypertension                | 18 | 9 | 9 |
| + dyslipidemia                | 22 | 7 | 15 |
| + glucose tolerance abnormalities | 9 | 4 | 5 |

**Notes:** *Numbers indicate number of subjects; **values indicate means ± standard deviations of the parameters indicated.

**Abbreviations:** BMI, body mass index; Ccr, creatinine clearance rate; BUN, blood urea nitrogen; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; MT, monotherapy; CT, combination therapy.
but did not vary markedly in the CT group (from $204 \pm 102$ to $182 \pm 89.4$ mg/dL; $P = 0.3233$). There was a tendency for a difference between the MT and CT groups ($P = 0.0815$).

**Discussion**

Obesity is involved in the onset and progression of diabetic nephropathy, hypertensive nephropathy, and chronic kidney disease (CKD) due to glomerulosclerosis, and is closely associated with hyperuricemia. Since hyperuricemia, like obesity, is a factor exacerbating renal impairment, it is necessary to prevent the progression of renal impairment by treating hyperuricemia co-existing with obesity.

Alkalizers reportedly lessen oxidative injury of proximal renal tubules, slow the progression of CKD, and improve renal impairment in patients with hypertensive nephrosis. It has also been reported that, in an obesity model with low urine pH, visceral fat weight correlated with urinary cortisol excretion, and that an alkalizer reduced urinary cortisol excretion. Regarding the effect of combining citrate with other treatments on blood TG levels, reductions of which were detected in the present study, urine alkalization has also been reported to suppress increases in visceral fat, warranting further study of this effect. The mechanism by which an alkalizer improves the glomerular filtration rate involves suppression of uric acid crystallization in the renal tubular lumen. An alkalizer has been shown to provide protection against the injury to renal epithelial cells which occurs via crystallization of oxalic acid and calcium oxalate in the renal tubular lumen in patients with renal calculi, prevent CKD progression, and improve renal function in polycystic kidney disease. Increased urinary citrate excretion

**Figure 2.** Changes in urinary creatinine clearance rate after versus before treatment in monotherapy and combination therapy groups. Notes: $P \leq 0.05$ to $P < 0.1$, $P < 0.05$: Changes in the urinary creatinine clearance rate after versus before treatment are shown for groups A, B, C, D, and E, as indicated; Intergroup comparisons of the parameters were adjusted with baseline values of each parameter and with prior use of allopurinol using ANCOVA. Abbreviations: MT, monotherapy; CT, combination therapy.
due to an alkalizer and lysis of uric acid accumulated in the kidney via urinary alkalization have been suggested to contribute to the improvement of renal function.

Recently, low urine pH has come to be considered a predictor of MetS, as shown by reports on inverse correlations between urine pH and insulin resistance as well as CKD risk factors, lower urine pH associated with a decrease in HDL-C, and the rising prevalence of MetS with the lowering of urine pH in the 21-year period spanning 1985 through 2005. As new knowledge is emerging concerning the potential of alkalizers and the significance of urine pH measurement, large-scale interventional studies are awaited to determine the efficacy of alkalizers for MetS-related clinical parameters.

In conclusion, the present study clearly demonstrated that the use of citrate combined with allopurinol raised Ccr, and decreased serum uric acid levels. Furthermore, allopurinol and citrate combination treatment might be useful for improving blood TG profiles in obese patients with hyperuricemia.

Author Contributions
Conceived and designed the experiments: JS, TN. Wrote the first draft of the manuscript: JS. Contributed to the writing of the manuscript: TK. Agree with manuscript results and conclusions: JS, TN, YM, HI, MO, TK. Jointly developed the structure and arguments for the paper: JS, TN, YM, HI, MO, TK. Made critical revisions and approved final version: JS, TN, YM, HI, MO, TK. All authors reviewed and approved of the final manuscript.

Table 2. Changes in serum uric acid (mg/dL) after versus before treatment.

| Parameters                        | Group     | Before treatment | After treatment | P values* | P values for group comparison after treatment** |
|-----------------------------------|-----------|------------------|-----------------|-----------|-----------------------------------------------|
| All                               | MT group  | 7.2 ± 1.4        | 6.6 ± 0.7       | P = 0.0644 | P = 0.4813                                     |
|                                   | CT group  | 7.9 ± 1.1        | 6.4 ± 1.0       | P = 0.0002 |                                               |
| Obesity + hypertension + dyslipidemia | MT group  | 7.2 ± 0.6        | 6.1 ± 0.8       | P = 0.0950 | P = 0.6182                                     |
|                                   | CT group  | 8.2 ± 1.4        | 6.5 ± 1.1       | P = 0.0163 |                                               |
| Obesity + hypertension            | MT group  | 7.5 ± 1.5        | 6.6 ± 0.8       | P = 0.0925 | P = 0.9801                                     |
|                                   | CT group  | 8.0 ± 1.4        | 6.6 ± 1.0       | P = 0.0199 |                                               |
| Obesity + dyslipidemia            | MT group  | 7.1 ± 1.1        | 6.3 ± 0.8       | P = 0.0576 | P = 0.9849                                     |
|                                   | CT group  | 8.0 ± 1.1        | 6.4 ± 1.0       | P = 0.0001 |                                               |
| Obesity + glucose tolerance       | MT group  | 7.8 ± 1.3        | 7.0 ± 0.7       | P = 0.1337 | P = 0.5019                                     |
| abnormalities                     | CT group  | 8.4 ± 1.5        | 6.5 ± 1.1       | P = 0.0527 |                                               |

Notes: Each value indicates means ± standard deviations. (MT Group: n = 15; CT Group: n = 16). *P values obtained by comparing values measured before and after treatment; **P values obtained by comparing values of MT and CT groups. Intergroup comparisons of the parameters were adjusted with baseline values of each parameter and with prior, use of allopurinol using ANCOVA.

Abbreviations: MT, monotherapy; CT, combination therapy.

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Competing Interests
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