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ORIGINAL RESEARCH

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/m^2 (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),[1–5] occurs in association with obesity at a high frequency,[6–7] and the reported prevalence of hyperuricemia in Japan is 70%.[8] Hyperuricemia causes the deposition of uric acid crystals in glomeruli, which in turn induces inflammation of the renal parenchyma, thereby leading to renal dysfunction.[9,10] 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.[11] 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.[12]

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 $\geq$ 25 kg/m^2), hypertension (systolic blood pressure [BP] $\geq$ 140 mmHg and/or a diastolic BP $\geq$ 90 mmHg), dyslipidemia (low-density lipoprotein cholesterol [LDL-C] $\geq$ 140 mg/dL, triglyceride [TG] $\geq$ 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 $\geq$ 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

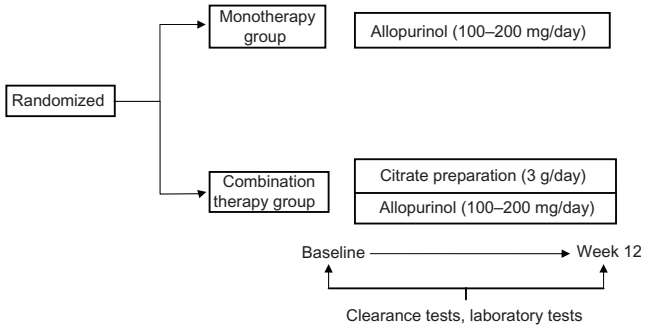

Figure 1. Method used in this study.

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 ± 0.5 to 6.2 ± 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 ± 0.22 to 0.77 ± 0.14 mg/dL and 0.92 ± 0.17 to 0.89 ± 0.17 mg/dL; BUN, 13.2 ± 5.6 to 12.6 ± 3.8 mg/dL and 14.8 ± 4.5 to 14.6 ± 4.4 mg/dL; TG, 165.7 ± 127.2 to 216.9 ± 182.5 mg/dL and 203.8 ± 101.7 to 181.9 ± 89.4 mg/dL; LDL-C, 102.5 ± 23.3 to 104.2 ± 13.6 mg/dL and 125.3 ± 27.6 to 122.0 ± 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 ± 127 to 217 ± 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/m^2)**	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.

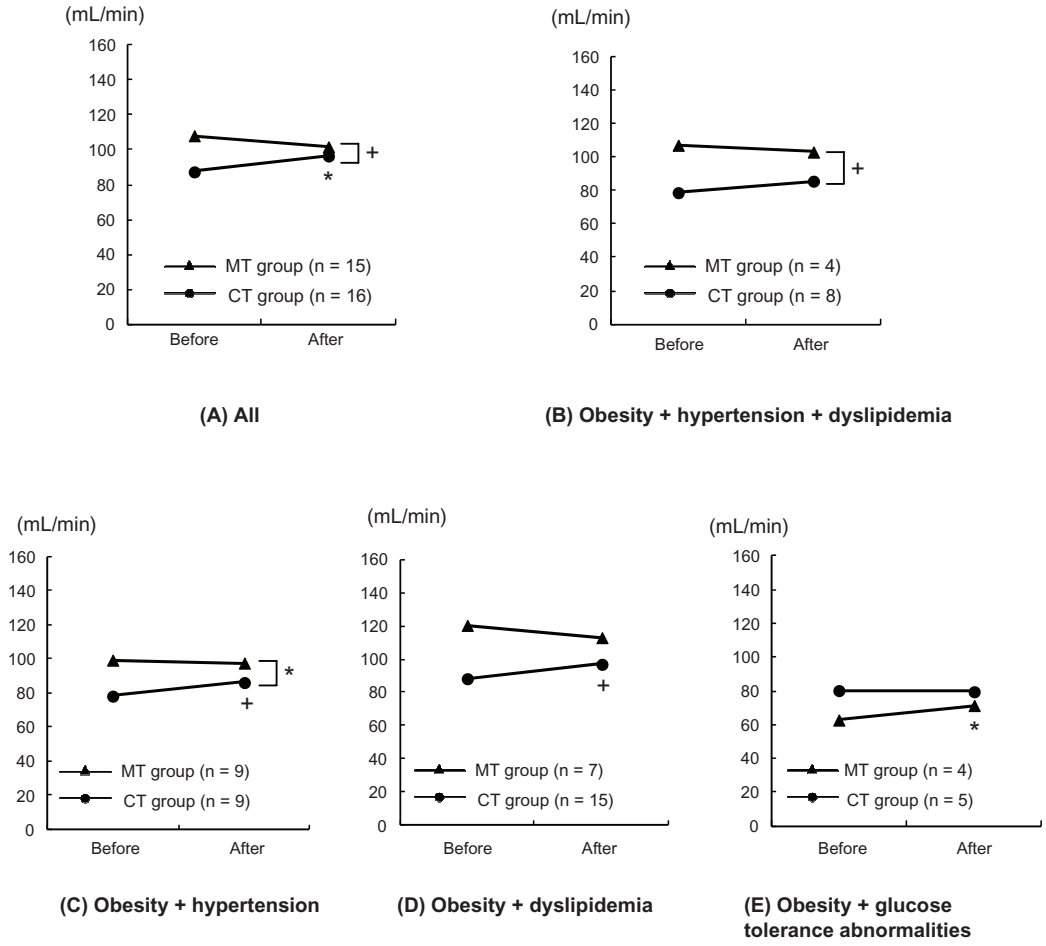

Figure 2. Changes in urinary creatinine clearance rate after versus before treatment in monotherapy and combination therapy groups.
Notes: $^{+}P \geq 0.05$ to $P < 0.1$, $^{*}P < 0.05$: Changes in the urinary creatinine clearance rate after versus before treatment are shown for groups A, B, C, D, and 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.

but did not vary markedly in the CT group (from 204 ± 102 to 182 ± 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,[13,14] and is closely associated with hyperuricemia.[15–17] Since hyperuricemia, like obesity, is a factor exacerbating renal impairment,[9–11] 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,[18] slow the progression of CKD,[19] and improve renal impairment in patients with hypertensive nephrosis.[20] 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.[21] 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,[21] 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,[22,23] prevent CKD progression,[24] and improve renal function in polycystic kidney disease.[25] Increased urinary citrate excretion

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 abnormalities	MT group	7.8 ± 1.3	7.0 ± 0.7	*P* = 0.1337	*P* = 0.5019
	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.

due to an alkalizer and lysis of uric acid accumulated in the kidney via urinary alkalization[26,27] have been suggested to contribute to the improvement of renal function.

Recently, low urine pH has come to be considered a predictor of MetS,[28] as shown by reports on inverse correlations between urine pH and insulin resistance as well as CKD risk factors,[29–32] lower urine pH associated with a decrease in HDL-C,[33] and the rising prevalence of MetS with the lowering of urine pH in the 21-year period spanning 1985 through 2005.[34] 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.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

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References

1. Sui X, Church TS, Meriwether RA, et al. Uric acid and the development of metabolic syndrome in women and men. *Metabolism*. 2008;57:845–52.
2. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am J Med*. 2007;120:442–7.

3. Ebrahimpour P, Fakhrzadeh H, Heshmat R, et al. Serum uric acid levels and risk of metabolic syndrome in healthy adults. *Endocr Pract*. 2008;14: 298–304.
4. Matsuura F, Yamashita S, Nakamura T, et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. *Metabolism*. 1998;47:929–33.
5. Tamba S, Nishizawa H, Funahashi T, et al. Relationship between the serum uric acid level, visceral fat accumulation and serum adiponectin concentration in Japanese men. *Intern Med*. 2008;47:1175–80.
6. Ogura T, Matsuura K, Matsumoto Y, et al. Recent trends of hyperuricemia and obesity in Japanese male adolescents, 1991 through 2002. *Metabolism*. 2004;53(4):448–53.
7. Tokunaga K, Matsuzawa Y, Kotani K, et al. Ideal body weight estimated from the body mass index with the lowest morbidity. *Int J Obes*. 1991;15:1–5.
8. Matsuura F, Yamashita S, Nakamura T, et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. *Metabolism*. 1998;47:929–33.
9. Obermayr RP, Temml C, Gutjahr G, et al. Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol*. 2008;19:2407–13.
10. Domrongkitchaiporn S, Sritara P, Kitiyakara C, et al. Risk factors for development of decreased kidney function in a southeast Asian population: a 12-year cohort study. *J Am Soc Nephrol*. 2005;16:791–9.
11. Gibson T, Highton J, Potter C, et al. Renal impairment and gout. *Ann Rheum Dis*. 1980;39:417–23.
12. Saito J, Matsuzawa Y, Ito H, et al. The alkalizer citrate reduces serum uric Acid levels and improves renal function in hyperuricemic patients treated with the xanthine oxidase inhibitor allopurinol. *Endocr Res*. 2010;35: 145–54.
13. Kopple JD. Obesity and chronic kidney disease. *J Ren Nutr*. 2010;20: 29–30.
14. Hsu CY, McCulloch CE, Iribarren C, et al. Body mass index and risk for end-stage renal disease. *Ann Intern Med*. 2006;144:21–8.
15. Meshkani R, Zargari M, Larijani B. The relationship between uric acid and metabolic syndrome in normal glucose tolerance and normal fasting glucose subjects. *Acta Diabetol*. 2011;48:79–88.
16. Lim JH, Kim YK, Kim YS, et al. Relationship between serum uric Acid levels, metabolic syndrome, and arterial stiffness in Koreans. *Korean Circ J*. 2010;40:314–20.
17. Ichida K. Hyperuricemia and metabolic syndrome. *Nihon Yakurigaku Zasshi*. 2010;136:321–4.
18. Brito-Ashurst, Varagunam M, Raftery MJ, et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol*. 2009;20:2075–84.
19. Souma T, Abe M, Moriguchi T, et al. Luminal alkalinization attenuates proteinuria-induced oxidative damage in proximal tubular cells. *J Am Soc Nephrol*. 2011;22:635–48.
20. Phisitkul S, Khanna A, Simoni J, et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. 2010;77:617–23.
21. Yamasaki S, Kanda T, Shinohara Y, et al. Role of visceral adiposity and aciduria in animal protein + low-potassium-induced obese rats. *Journal of Metabolic Syndrome*. 2007;4:44–52.
22. Byer K, Khan SR. Citrate provides protection against oxalate and calcium oxalate crystal induced oxidative damage to renal epithelium. *J Urol*. 2005; 173:640–6.
23. Tungsanga K, Sriboonlue P, Futrakul P, et al. Renal tubular cell damage and oxidative stress in renal stone patients and the effect of potassium citrate treatment. *Urol Res*. 2005;33:65–9.
24. Gadola L, Noboa O, Márquez MN, et al. Calcium citrate ameliorates the progression of chronic renal injury. *Kidney Int*. 2004;65:1224–30.
25. Tanner GA. Potassium citrate/citric acid intake improves renal function in rats with polycystic kidney disease. *J Am Soc Nephrol*. 1998;9:1242–8.
26. Hess B. Acid-base metabolism: implications for kidney stones formation. *Urol Res*. 2006;34:134–8.
27. Hirayama A, Uehara S, Honjo K, et al. Clinical effect of Uralyt-U for hyperuricemia associated with hypertension. *Jpn J Med Pharm Sci*. 1991;25: 201–6.
28. Hara S, Tsuji H, Ohmoto Y, Amakawa K, et al. High serum uric acid level and low urine pH as predictors of metabolic syndrome: a retrospective cohort study in a Japanese urban population. *Metabolism*. 2012;61(2):281–8
29. Maalouf NM, Cameron MA, Moe OW, et al. Low urine pH: a novel feature of the metabolic syndrome. *Clin J Am Soc Nephrol*. 2007;2:883–8.
30. Abate N, Chandalia M, Cabo-Chan AV Jr, et al. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int*. 2004;65:386–92.
31. Takahashi S, Inokuchi T, Kobayashi T, et al. Relationship between insulin resistance and low urinary pH in patients with gout, and effects of PPARalpha agonists on urine pH. *Horm Metab Res*. 2007;39:511–4.
32. Hara S, Tsuji H, Ubara Y, et al. Significance of hyperuricemia and low urine pH as a risk factor for CKD in general health check population on cohort study during five years. *American Society of Nephrology*. 2007:SA-PO907.
33. Otsuki M, Kitamura T, Goya K, et al. Association of urine acidification with visceral obesity and the metabolic syndrome. *Endocr J*. 2011;58:363–7.
34. Tsuji H, Miyakawa M, Arimoto S, et al. The relationship of uric acid and urinary pH to metabolic syndrome and its defining factors. *Japan Society of Ningen Dock*. 2007;22:383–8.