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ORIGINAL ARTICLE

Effective uric acid-lowering treatment for hypertensive patients with hyperuricemia

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Uric acid (UA) has been associated with hypertension, renal disease and cardiovascular disease. The aim of the present study was to compare the UA-lowering effects of a standard dose of the UA synthesis inhibitor febuxostat to a standard dose of the uricosuric agent benzbromarone, and to investigate the effects of a low-dose combination of both agents in hypertensive patients with hyperuricemia. Twenty hypertensive patients with inadequate UA control were administered febuxostat 40 mg (Feb), benzbromarone 50 mg (Ben) and febuxostat 20 mg and benzbromarone 25 mg (feb/ben) for 3 months each in a randomized modified crossover manner. UA metabolism, blood pressure (BP) and the indices of organ damage were assessed at baseline and the end of each treatment period. No significant changes were observed in BP or estimated glomerular filtration rate (eGFR) after the treatment with each UA-lowering regimen. The change in UA was significantly greater with feb/ben than with Feb. The excretion of UA and clearance of UA were higher with Ben than with Feb and feb/ben. Urinary 8-hydroxydeoxyguanosine and liver-type fatty-acid-binding protein levels were slightly lower with Ben, whereas flow-mediated dilation was slightly higher with feb/ben and Ben. The UA-lowering effects of the low-dose combination of the UA synthesis inhibitor and uricosuric agent were greater than those of the standard dose of each agent alone. The uricosuric agent may be more effective at improving vascular function than the UA synthesis inhibitor. Thus, the appropriate management of hyperuricemia with uricosuric drugs appears to be useful for hypertensive patients with hyperuricemia.
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Keywords: benzbromarone; febuxostat; hyperuricemia; uric acid

INTRODUCTION

Increases in uric acid (UA) levels are known to stimulate the activity of the renin–angiotensin–aldosterone system, promote renal inflammation, enhance endothelial dysfunction and impair renal autoregulation, resulting in glomerular and systemic hypertension, and these UA increases have also been associated with metabolic syndrome, hypertension, renal dysfunction and cardiovascular diseases.[1–4] Hypertensive patients are often complicated with hyperuricemia,[5,6] management recommendations for which are provided in the guidelines of the Japanese Society of Hypertension and the Japanese Society of Gout and Nucleic Acid Metabolism.[7,8]

Most hypertensive patients have been reported to have the decreased UA excretion type of hyperuricemia.[9] However, most hypertensive patients with hyperuricemia are treated with UA synthesis inhibitors, without classification of the type of hyperuricemia.

In the present study, we compared the effects of a standard dose of the UA synthesis inhibitor febuxostat (Feburic) and a standard dose of the uricosuric agent benzbromarone (Urinorm) and investigated the effects of a low-dose combination of both agents on UA levels, blood pressure (BP), kidney and vascular functions, and the indices of oxidative stress and inflammation in hypertensive patients with hyperuricemia.

MATERIALS AND METHODS

Subjects comprised 20 hypertensive patients (2 women and 18 men, mean age 64 ± 12 years) with inadequate UA control (serum UA level >6 mg dl^{-1} despite taking UA-lowering drugs for more than 3 months ($n=11$) or serum UA level $\geqslant 8$ mg dl^{-1} without UA-lowering drugs ($n=9$)) who visited the National Cerebral and Cardiovascular Center. Nineteen subjects were treated with antihypertensive drugs. The study design is shown in Figure 1. Phase I: Febuxostat 40 mg (Feb) or benzbromarone 50 mg (Ben) was randomly administered once daily for 3 months. Phase II: Febuxostat 20 mg and benzbromarone 25 mg (feb/ben) were administered once daily for 3 months. Phase III: Ben or Feb was administered once daily for 3 months in a modified crossover manner. For the patients with the UA level $\geqslant 8$ mg dl^{-1} without UA-lowering drugs, we administered febuxostat from 10 mg and it was increased to 20 mg after 2 weeks and 40 mg after 6 weeks.

Office BP was measured twice with a mercury sphygmomanometer by a doctor while the patients were quietly seated at baseline and at the end of each

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treatment period, and the averaged values were used in analyses. Home BP was measured in the sitting position by patients once in the early morning and evening. The average values of home BP during the last 3 days at baseline and at the end of each period were used in statistical analyses. Ambulatory BP was monitored oscillometrically every 30 min for 25–26 h using an automatic device at baseline and at the end of each period (TM-2431; A&D, Tokyo, Japan). The same recorder was used in each subject to avoid errors due to differences in equipment. After discarding records during the first hour, the average values of 24-h records were used in analyses.

At baseline and at the end of each period, fasting blood samples were collected and 24-h urine collection was performed. We measured the excretion of UA (EUA) and clearance of UA (CUA) and assessed UA metabolism on the basis of the guidelines for the management of hyperuricemia and gout.[9] The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula (for men, $194 \times \text{serum Cr levels}^{-1.094} \times \text{age}^{-0.287}$; for women, $194 \times \text{serum Cr levels}^{-1.094} \times \text{age}^{-0.287} \times 0.739$).[10] We assessed salt intake with a 24-h urine collection. This is considered the most reliable and recommended method for evaluating salt intake by the Salt Reduction Committee of the Japanese Society of Hypertension.[11]

Flow-mediated vasodilatation was measured at baseline and at the end of the treatment periods. Flow-mediated vasodilatation, a good indicator of endothelial function, was measured using ultrasonography with an automated edge tracking system (UNEX EF18G, Nagoya, Japan).

Ultrasound examinations by a duplex Doppler apparatus were performed in all patients. Images were obtained (Aplio MX, Toshiba, Tochigi, Japan) at a 2.5-MHz pulsed Doppler frequency and with a 3.5-MHz convex array transducer. With the patient in the supine position, the transducer was placed on the anterior approach. The sample volume of the Doppler beam was placed on the interlobar arteries, visualized by color Doppler and were estimated using the angle correction menu of the apparatus. The angle was less than 60°. The resistive index (RI), which reflects intrarenal vascular resistance, was calculated using the following formula: RI = (peak systolic velocity − end diastolic velocity)/peak systolic velocity. RI was determined at least three times for the bilateral kidneys and was averaged to obtain the mean value of RI for each patient. All Doppler measurements were performed by an investigator who was blinded to the medical status of the patients.

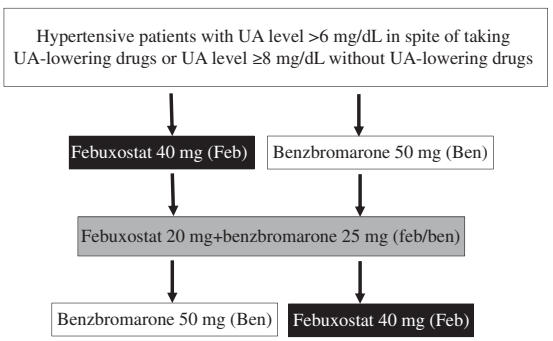

Figure 1 Study design. Phase I: Febuxostat (Feb) 40 mg or benzbromarone (Ben) 50 mg was randomly administered to hypertensive patients with inadequate uric acid control once daily for 3 months. Phase II: Febuxostat 20 mg and benzbromarone 25 mg (feb/ben) were administered. Phase III: Ben 50 mg or Feb 40 mg was administered in a modified crossover manner.

Urinary 8-hydroxydeoxyguanosine as an indicator of oxidative stress, monocyte chemoattractant protein-1 as an indicator of inflammation and liver-type fatty-acid-binding protein as an indicator of tubular dysfunction were also measured at baseline and at the end of the treatment periods.

Other therapies, except for those for hyperuricemia, were continued without any alterations throughout the study protocol. The protocol was explained in detail, and informed consent was obtained from each patient. The study protocol was approved by the Ethics Review Board of the National Cerebral and Cardiovascular Center.

Statistical analysis

Values are presented as the mean ± s.d. Differences in variables were compared by either a paired *t*-test or analysis of variance. A χ^2-test was also utilized where appropriate. The effects of the drugs were ascertained by generalized estimating equations using changes in outcomes as repeat measures with baseline value and randomized group as covariates. *P*-values less than 0.05 were considered significant. All calculations were performed using a standard statistical package (JMP 10; SAS Institute, Cary, NC, USA).

RESULTS

The trend of clinical characteristics, biochemical parameters and the parameters of organ damage and oxidative stress of each group are shown in Table 1. There were no differences in office BP, eGFR, serum UA level, urinary UA/creatinine (UUA/UCr), EUA and CUA at baseline between two groups. However, the evening home BP and ambulatory average BP in Ben were lower than those in Feb. The decreased UA excretion type was assessed by 24-h urine collection and spot urine/creatinine ratio (UUA/UCr less than 0.5) was 95% and 85%, respectively (Figure 2).

No significant changes were observed in BP, eGFR or renal RI after the administration of the UA-lowering drugs. The change in UA with Feb/Ben was significantly greater than that with Feb and Ben

Table 1 Parameters after the administration of uric acid-lowering drugs

	Febuxostat				*Benzbromarone*			
Uric acid-lowering drug	*Baseline*	*3 M (Feb)*	*6 M (Feb/Ben)*	*9 M (Ben)*	*Baseline*	*3 M (Ben)*	*6 M (Feb/Ben)*	*9 M (Feb)*
eGFR (ml min^{-1} 1.73 m^{-2})	66 ± 26	66 ± 25	66 ± 26	66 ± 27	56 ± 21	55 ± 18	55 ± 22	54 ± 20
Uric acid (mg dl^{-1})	6.9 ± 1.1	4.3 ± 1.1	3.6 ± 0.9	4.3 ± 1.1	7.7 ± 1.5	5.1 ± 1.3	4.5 ± 0.9	5.1 ± 1.0
UUA/UCr	0.35 ± 0.12	0.18 ± 0.08	0.27 ± 0.14	0.45 ± 0.14	0.46 ± 0.34	0.44 ± 0.11	0.30 ± 0.11	0.28 ± 0.18
EUA (mg kg^{-1} h^{-1})	0.26 ± 0.07	0.14 ± 0.12	0.28 ± 0.29	0.34 ± 0.08	0.31 ± 0.12	0.46 ± 0.24	0.22 ± 0.10	0.15 ± 0.07
CUA (ml min^{-1})	4.33 ± 1.35	3.75 ± 3.33	8.68 ± 6.79	9.46 ± 3.93	5.05 ± 2.63	11.07 ± 6.09	5.81 ± 3.10	3.39 ± 1.63
UAE (mg per gCr)	16 ± 23	12 ± 14	11 ± 13	15 ± 23	312 ± 856	249 ± 697	310 ± 859	338 ± 894
Urinary 8-OHdG (ng per mlCr)	12.5 ± 4.0	12.6 ± 4.6	11.3 ± 2.9	11.4 ± 5.0	11.5 ± 5.2	8.3 ± 2.1	11.3 ± 2.4	10.6 ± 1.8
MCP-1 (pg ml^{-1})	287 ± 95	296 ± 59	299 ± 90	305 ± 99	253 ± 70	273 ± 83	271 ± 62	289 ± 69
LFABP (μg per g•Cr)	2.7 ± 1.6	5.1	3.1 ± 1.6	2.9 ± 1.0	12.5 ± 8.1	8.1 ± 3.5	13.3 ± 10.5	11.7 ± 6.6
Flow-mediated dilation (%)	4.5 ± 1.8	4.9 ± 1.9	6.2 ± 2.3	5.3 ± 2.6	4.4 ± 1.9	5.8 ± 3.7	5.2 ± 2.7	4.7 ± 1.7
Renal artery resistive index	0.66 ± 0.06	0.66 ± 0.06	0.67 ± 0.06	0.68 ± 0.06	0.65 ± 0.07	0.65 ± 0.05	0.67 ± 0.05	0.67 ± 0.05

Abbreviations: Ben, Benzbromarone; CUA, clearance of uric acid; eGFR, estimated glomerular filtration rate; EUA, excretion of uric acid; Feb, Febuxostat; LFABP, liver-type fatty-acid-binding protein; MCP-1, monocyte chemoattractant protein-1; UAE, urinary albumin excretion; UUA/UCr: urinary uric acid/creatinine; 8-OHdG, 8-hydroxydeoxyguanosine.
Mean ± s.d.

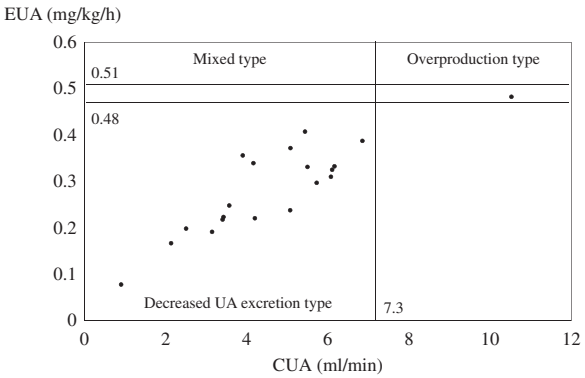

Figure 2 Classification of hyperuricemia in our subjects ($n=20$).

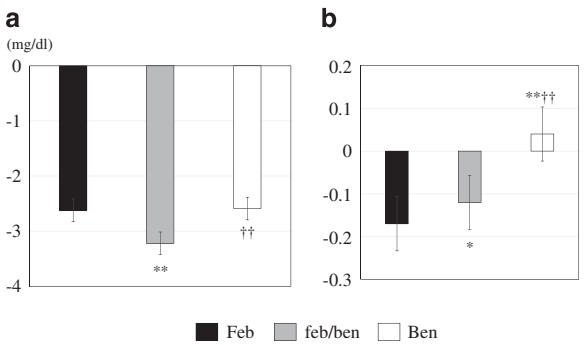

Figure 3 (**a**) Changes in serum uric acid with uric acid-lowering drugs: -2.6 ± 1.8 ($n=20$ in febuxostat (Feb)), -3.2 ± 1.6 ($n=20$ in Feb/Ben), -2.6 ± 1.8 ($n=20$ in benzbromarone (Ben)), $^{**}P<0.01$ *vs.* Feb, $^{\dagger\dagger}P<0.01$ *vs.* Feb/Ben. (**b**) Changes in urinary uric acid/creatinine with uric acid-lowering drugs: -0.17 ± 0.16 ($n=20$ in Feb), -0.12 ± 0.23 ($n=20$ in Feb/Ben), 0.04 ± 0.24 ($n=20$ in Ben), $^{**}P<0.01$, $^{*}P<0.05$ *vs.* Feb, $^{\dagger\dagger}P<0.01$ *vs.* Feb/Ben.

(-3.2 ± 1.6 *vs.* -2.6 ± 1.8, -2.6 ± 1.8, $P<0.01$; Figure 3a). The changes in UUA/UCr with Feb/Ben and Ben were greater than that with Feb (-0.12 ± 0.23, 0.04 ± 0.24 *vs.* -0.17 ± 0.16, $P<0.05$, $P<0.01$, respectively, Figure 3b). The changes in EUA and CUA with Ben were greater than those with Feb and Feb/Ben (EUA; 0.11 ± 0.14 *vs.* -0.14 ± 0.12, -0.03 ± 0.20, $P<0.01$, Figure 4a, CUA; 5.58 ± 3.96 *vs.* -1.13 ± 2.91, 2.55 ± 4.95, $P<0.01$, $P<0.05$, respectively, Figure 4b). The treatment with Ben decreased urinary 8-OHdG (Figure 5a) and liver-type fatty-acid-binding protein (Figure 5b) levels, whereas those with Feb/Ben and Ben slightly increased flow-mediated vasodilatation levels (Figure 5c). No adverse reactions were noted in the present study.

DISCUSSION

In the present study, the UA-lowering effects of the low-dose combination of the UA synthesis inhibitor febuxostat and uricosuric agent benzbromarone were greater than those of the standard dose of each agent alone. No significant difference was observed in UA-lowering effects between the UA synthesis inhibitor and uricosuric agent; however, the latter may be more effective at decreasing oxidative stress and improving vascular function. In addition, there was no difference in renal function between the two drugs.

The prevalence of hyperuricemia has increased slightly and was reported to be 21.5% in Japanese adult men.[12] An increased level of UA has been associated with metabolic syndrome, hypertension, renal dysfunction and cardiovascular diseases.[2–4] Reductions in serum UA

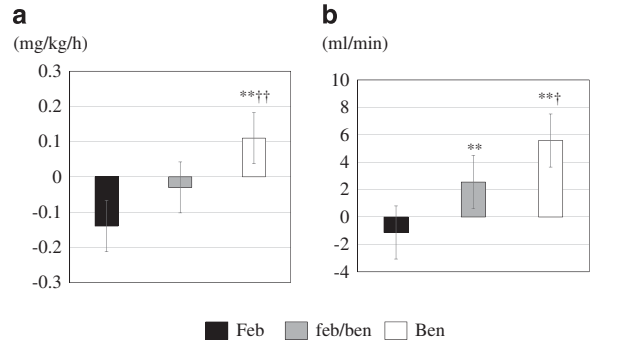

Figure 4 (**a**) Changes in the excretion of uric acid (EUA) with uric acid-lowering drugs: -0.14 ± 0.12 ($n=20$ in febuxostat (Feb)), -0.03 ± 0.20 ($n=20$ in Feb/Ben), 0.11 ± 0.14 ($n=20$ in benzbromarone (Ben)), $^{**}P<0.01$ *vs.* Feb, $^{\dagger\dagger}P<0.01$ *vs.* feb/ben. (**b**) Changes in the clearance of uric acid (CUA) with uric acid-lowering drugs: -1.13 ± 2.91 ($n=20$ in Feb), 2.55 ± 4.95 ($n=20$ in feb/ben), 5.58 ± 3.96 ($n=20$ in Ben), $^{**}P<0.01$ *vs.* Feb, $^{\dagger}P<0.05$ *vs.* Feb/Ben.

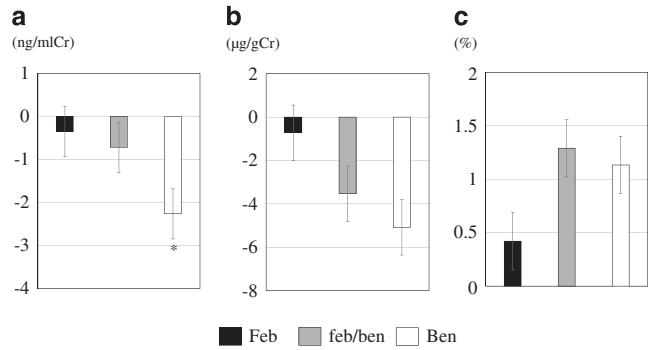

Figure 5 (**a**) Changes in urinary 8-hydroxydeoxyguanosine (8-OHdG) with uric acid-lowering drugs: -0.3 ± 4.9 ($n=19$ in febuxostat (Feb)), -0.7 ± 5.3 ($n=19$ in Feb/Ben) and -2.2 ± 6.4 ($n=18$ in benzbromarone (Ben)); $^{*}P<0.05$ *vs.* Feb. (**b**) Changes in the clearance of liver-type fatty acid-binding protein (LFABP) with uric acid-lowering drugs: -0.7 ± 5.0 ($n=6$ in Feb), -3.5 ± 5.6 ($n=4$ in Feb/Ben), -5.1 ± 6.3 ($n=5$ in Ben). (**c**) Changes in the clearance of flow-mediated dilation (FMD) with uric acid-lowering drugs: 0.4 ± 1.9 ($n=20$ in Feb), 1.3 ± 2.8 ($n=20$ in Feb/Ben) and 1.1 ± 3.3 ($n=20$ in Ben).

levels have been shown to prevent not only glomerulonephrosclerosis and tubulointerstitial fibrosis but also cardiovascular events,[13,14] suggesting that the appropriate treatment of hyperuricemia is important. Although the pharmacologic management of asymptomatic hyperuricemia was not addressed in American College of Rheumatology guidelines for management of gout or EULAR evidence-based recommendations for gout,[15,16] the management of hyperuricemia is recommended in the guidelines of the Japanese Society of Hypertension and the Japanese Society of Gout and Nucleic Acid Metabolism.[7,8] However, its management is often inadequate.

Hyperuricemia has been divided into the following three types: an increase in UA synthesis (the overproduction type), a decrease in urinary UA excretion (the decreased excretion type) and the mixed type, based on the underlying mechanisms. The guidelines for the management of hyperuricemia and gout recommend the classification of hyperuricemia for appropriate treatment.[8] However, classifications using 24-h or 60-min urine collection are not conventional. We previously reported that UUA/UCr determined by spot urine appeared to be useful in clinical practice for classifying hyperuricemia.[17]

When the cutoff value of 0.5 was adopted, the agreement of classification by 24-h and spot urine UUA/UCr was 89.5% in the present study.

Most hypertensive patients have been reported to have the decreased UA excretion type of hyperuricemia.[9] However, most patients with hyperuricemia are treated with UA synthesis inhibitors without being classified. We previously showed that UA metabolism in hypertensive patients with poorly controlled UA who had taken allopurinol, an UA synthesis inhibitor, was improved after changing to benzbromarone.[18] Thus, therapeutic strategies need to be determined after the classification of hyperuricemia.

Although the UA-lowering effects of a combined low dose of allopurinol and benzbromarone were previously shown to be inconsistent,[19,20] we revealed that the UA-lowering effects of the low-dose combination of febuxostat and benzbromarone were greater than those of the standard dose of each agent alone. Xanthine oxidase (XO) is an enzyme responsible for the production of UA. XO is one of the major enzymatic sources of reactive oxygen species. Activation of vascular XO represents an early mechanism that contributes to increased radical formation and endothelial dysfunction in the atherosclerotic disease process. UA synthesis inhibitors inhibit the XO system and decrease oxidative stress generated during the production of UA. On the other hand, uricosuric agents do not inhibit the XO pathway; however, it was shown to improve inflammatory markers and insulin resistance. Thus, combination therapy of these two drugs seems to clarify the organ-protective effects through the different mechanisms and may have been due to the different sites of action and synergistic effects. In fact, the changes in UA were comparable between febuxostat and benzbromarone, even though the level of EUA with febuxostat decreased and that with benzbromarone increased, as shown in Figure 4a. Approximately 90% of our subjects were classified as decreased excretion types by 24-h urine collection and spot urine; however, almost all our subjects may be the mixed type.

Benzbromarone appeared to be more effective at improving vascular function than febuxostat in the present study. UA is incorporated into vascular cells by the UA transporter (URAT)-1, expressed on vascular endothelial cells or vascular smooth muscle cells and induces inflammatory pathways with the activation of p38 mitogen-activated protein kinases, nuclear factor-κB and activator protein-1, and UA increased the expression of cyclooxygenase-2 and monocyte chemoattractant protein-1.[21] UA synthesis inhibitors are known to be effective at improving endothelial function because they block XO-associated oxidants,[22–24] whereas benzbromarone has been shown to decrease reactive oxygen species production induced by angiotensin II or UA in vascular endothelial cells by functioning as both a URAT1 inhibitor and radical scavenger.[25–27] As oxidative stress is one of the key factors in the pathophysiology of cardiovascular diseases, it may be appropriate to administer UA-lowering therapy that includes an uricosuric agent to hypertensive patients with hyperuricemia.

Hyperuricemia has been associated with increased renal vascular resistance, and UA-lowering drugs were found to prevent arteriopathy.[28,29] However, in the present study, no significant changes were observed in renal RI, eGFR or urinary albumin excretion following the administration of UA-lowering drugs. The reason for these results currently remains unclear; however, renal parameters in the study subjects had not yet severely deteriorated, and the treatment period was not as long in our study.

Although BPs in the present study were assessed at the office, home and with 24-h ambulatory monitoring, no significant changes were observed at any BP level after the administration of UA-lowering drugs. The mechanism underlying reductions in BP by UA-lowering drugs involves decreases in systemic vascular resistance and plasma renin activity.[30,31] BP levels at baseline were not very high in the present study because most subjects were being treated with antihypertensive drugs. Therefore, UA-lowering therapy may exert antihypertensive effects if these levels are markedly elevated in study subjects.

Our study had several limitations. The sample size was small, and this study was conducted in one institution. Therefore, the results obtained may not be representative of the current status of Japanese hypertensive patients with hyperuricemia. If the number of subjects was sufficiently large, we may have observed significant changes and differences in vascular function, the parameters of oxidative stress and inflammation after the treatments with the three UA-lowering strategies. Further large-scale studies are needed to confirm the results of the present study. Moreover, the duration of the treatment may have been too short. A wash-out period was also not provided in the present study. However, the effects of each drug were assessed after 3 months. This 3-month period was considered sufficient to have offset the effects of previously administered drugs. In addition, most subjects were treated with antihypertensive drugs. Although diuretics and specific Angiotensin II Receptor Blockers occasionally affect the serum level of UA, they did not influence its metabolism after UA-lowering therapy. Four of our subjects had taken lipid-lowering drugs. There were no significant differences in endothelial vascular function and oxidative stress in consideration of cardiovascular therapies, such as Angiotensin II Receptor Blockers or lipid-lowering drugs. Furthermore, there are many indicators of endothelial function and oxidative stress. However, flow-mediated vasodilatation and 8-hydroxydeoxyguanosine were assessed in the present study, which were reported as good indicators. In addition, we only used febuxostat and benzbromarone; therefore, our results may not be extended to all UA synthesis inhibitors and uricosuric agents. We also did not evaluate dietary or exercise habits, which may modify the effects of UA-lowering drugs. However, no significant changes were observed in body weight after UA-lowering therapy.

In conclusion, most hypertensive patients with hyperuricemia had the decreased UA excretion type. The UA-lowering effects of the low-dose combination of the UA synthesis inhibitor febuxostat and uricosuric agent benzbromarone was greater than those of the standard dose of either drug alone. The uricosuric drug may be more effective at improving vascular function than the UA production inhibitor. Thus, the appropriate management of hyperuricemia, including uricosuric drugs, may be useful for hypertensive patients with hyperuricemia. Further long-term observations about cardiovascular events seems to be necessary.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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