

Effects of Febuxostat Therapy on Circulating Adipokine Profiles in Patients with Overweight or Obesity and Asymptomatic Hyperuricemia: A Randomized Controlled Study

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Keywords

Hyperuricemia · Obesity · Febuxostat · Xanthine oxidoreductase · Adipokines

Abstract

Introduction: Elevated levels of serum uric acid (SUA) are strongly associated with several components of the metabolic syndrome, particularly obesity. Previous studies have reported the correlation between SUA levels, xanthine oxidoreductase (XOR) activity, and the imbalanced adipokine levels that are characteristic of obesity. In this study, we explored the effect of febuxostat on circulating adipokine profiles in patients with overweight or obesity and asymptomatic hyperuricemia. **Methods:** This study was a single-center, randomized, and controlled clinical trial that enrolled 130 participants with asymptomatic hyperuricemia and obesity. One hundred seventeen participants were included in the final analysis, with 60 participants in the febuxostat group and 57 in the control group. We compared the circulating adipokine levels at 3 and 6 months, including high molecular weight (HMW) adiponectin, chemerin, omentin, monocyte chemoattractant protein-1, asprosin, fibroblast growth factor 21,

neuregulin-4, leptin, resistin, vaspin, visfatin, adipon, and assessed the correlation between changes in adipokine levels (Δ adipokines) and changes in XOR activity (Δ XOR) after febuxostat treatment. **Results:** The results showed that an increase in HMW adiponectin and omentin levels and a decrease in chemerin and asprosin levels at 3 or 6 months compared to the control group. Additionally, a positive correlation was observed between Δ XOR activity and Δ asprosin. Furthermore, after adjusting for triglyceride (Δ TG) and serum uric acid (Δ SUA) in multiple linear regression analyses, we found that Δ XOR activity was independently correlated with Δ asprosin. **Conclusion:** This study may provide important evidence that febuxostat could alleviate the imbalance in circulating adipokine levels in patients with overweight or obesity and asymptomatic hyperuricemia. Furthermore, we observed a positive correlation between changes in asprosin levels and changes in XOR activity after febuxostat treatment.

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Introduction

Elevated levels of serum uric acid (SUA), the end product of purine metabolism, are strongly associated with several components of the metabolic syndrome, particularly obesity [1, 2]. Hyperuricemia has been identified as an independent predictor of obesity [3]. Xanthine oxidoreductase (XOR) plays a crucial role as the pivotal rate-limiting enzyme responsible for catalyzing the production of uric acid from hypoxanthine and xanthine [4, 5]. This metabolic process also results in the generation of oxygen radicals, the excess of which induces oxidative stress, and subsequent tissue damage [4, 6]. Plasma XOR activity has been demonstrated to be related to insulin resistance, dyslipidemia, and obesity [7–9].

Adipokines, such as adiponectin and leptin, secreted by adipocytes, play a crucial role in maintaining metabolic homeostasis. An imbalance in adipokine secretion has been observed in patients with obesity, with heightened oxidative stress identified as the primary cause of adipokine dysregulation in obesity [10, 11]. SUA levels and XOR activity have been shown to be related with circulating adipokine levels [12, 13]. Hyperuricemia triggers redox-dependent signaling and oxidative stress in adipocytes, leading to a proinflammatory endocrine imbalance in the adipose tissue characterized by an increase in monocyte chemoattractant protein-1 (MCP-1) secretion and a decrease in adiponectin secretion. Furthermore, the inhibition of XOR activity has been found to ameliorate proinflammatory endocrine imbalances in adipose tissue [12]. In addition, clinical studies have shown that plasma XOR activity is significantly correlated with adipokine levels [13].

Febuxostat, a selective and potent XOR inhibitor, effectively inhibits the production of uric acid and the generation of reactive oxygen species [14]. Beyond its primary role in lowering SUA, febuxostat exhibits various beneficial effects, including reducing blood lipids [15], improving insulin resistance [16], and alleviating nonalcoholic fatty liver disease [16, 17]. Given the potent antioxidant stress effect of febuxostat, we hypothesize that it could potentially ameliorate the imbalance of adipokines in patients with overweight or obesity – a topic that has been rarely explored in previous studies. Therefore, we conducted a randomized controlled clinical trial to investigate the effect of febuxostat on circulating adipokine profiles in patients with overweight or obesity and asymptomatic hyperuricemia.

Methods

Study Design

This study was a single-center, randomized, and controlled clinical trial approved by the Ethics Committee of Huaian No. 1 People's Hospital (Approval No. KY-P-2018-010-01). All participants signed a written informed consent form. The study was registered in the Chinese Clinical Trial Registry (ChiCTR1800017922) and was monitored by a 3-member quality control team.

Study Participants

Study participants were patients with overweight or obesity and asymptomatic hyperuricemia, recruited between October 2018 and October 2020. Inclusion criteria: (1) Age 18–70 years. (2) Patients with asymptomatic hyperuricemia with SUA ≥ 480 $\mu\text{mol/L}$. (3) Body mass index (BMI) ≥ 25 kg/m^2 . Exclusion criteria: (1) patients with symptoms or history of gouty arthritis. (2) Patients with secondary hyperuricemia. (3) Patients with a history of allergy to febuxostat. (4) Patients who have received or are expected to receive immunosuppressive therapy or glucocorticoid hormone therapy within 6 months prior to the study. (5) Patients who have taken or are unable to discontinue any of the following medications that affect uric acid metabolism within 2 weeks prior to the study: azathioprine, 6-mercaptopurine, aspirin (≥ 325 mg/day) or other salicylic acid, thiazide diuretics, chlorosartan, theophylline, cyclosporine, pyrazinamide, methotrexate sulfonamide. (6) Patients with severe liver dysfunction (aspartate aminotransferase or alanine transaminase ≥ 2 times the upper limit of normal). (7) Patients with severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) or undergoing dialysis. (8) Patients with white blood cell count $< 4 \times 10^9/\text{L}$, platelet count $< 100 \times 10^9/\text{L}$, hemoglobin < 90 g/L, or other hematological disorders. (9) Patients with a history of myocardial infarction, unstable angina, New York Heart Association (NYHA) functional class III or IV heart failure, percutaneous coronary intervention, stroke (ischemic or hemorrhagic) or transient ischemic attack, and other cardiovascular events requiring hospitalization within 3 months prior to the study. (10) Patients with malignant tumors. (11) Patients with a history of alcoholism. (12) Pregnant women, breastfeeding women, women planning to become pregnant during the study period, and women of childbearing potential unwilling to use an effective method of contraception. (13) Patients deemed ineligible for the study by the attending doctor due to other reasons. The flowchart of study participants is shown in Figure 1.

Randomization

Dynamic randomization was performed using the minimization method via a computer program, balanced for sex, age (< 60 , ≥ 60 years), SUA (< 540 , ≥ 540 $\mu\text{mol/L}$), and BMI (< 30 , ≥ 30 kg/m^2).

Treatment Outline

Patients receiving uric acid-lowering therapy underwent a 2-week washout period (from -2 weeks to 0 week). After the washout period, patients were randomized into either the febuxostat group or the control group. All participants in both groups followed a low purine diet. Patients assigned to the febuxostat group received oral febuxostat once daily, starting at a dose of 40 mg/day. The dosage

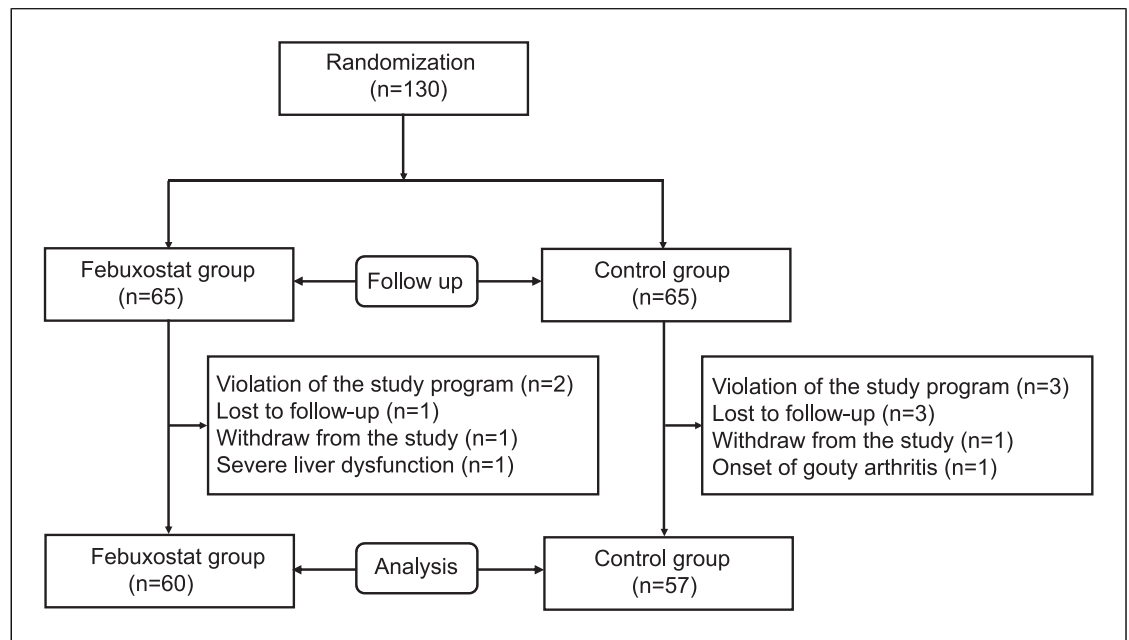


Fig. 1. Flowchart of study participants.

was gradually increased by 20 mg every 2 weeks for individuals with SUA levels above 360 $\mu\text{mol/L}$ (with a maximum dose of 80 mg/day) and was subsequently maintained without further adjustment after 1 month. If SUA levels fell to 120 $\mu\text{mol/L}$ or lower, the dosage was reduced by 20 mg. The total treatment duration was 6 months. The treatment outline is shown in Figure 2. The following medications are contraindicated during the study period: other uric acid-lowering medications (allopurinol, benzbromarone, probenecid, bucolome, and topiroxostat), azathioprine, 6-mercaptopurine, aspirin (≥ 325 mg/day) or other salicylic acid, thiazide diuretics, chlorosartan, theophylline, cyclosporine, pyrazinamide, methotrexate sulfonamide. Background treatment, such as lipid-lowering agents, antihypertensive agents, and glucose-lowering agents, remained unchanged throughout the study, if possible.

Follow-Up and Data Collection

Follow-up visits were performed at 3 and 6 months with a follow-up window of ± 7 days. Renal and liver function tests were performed at each visit to assess safety. Adverse events and concomitant medications were recorded. The following data were collected or measured at each follow-up visit: BMI, triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting blood glucose (FBG), fasting insulin (FINS). Insulin resistance index was assessed by homeostasis model assessment for insulin resistance, calculated as follows: $\text{FINS } (\mu\text{U/mL}) \times \text{FBG } (\text{mmol/L}) / 22.5$.

Measurement of Circulating Adipokines

We measured the following adipokines at baseline, 3 months, and 6 months: high molecular weight (HMW) adiponectin, chemerin, omentin, MCP-1, asprosin, fibroblast growth factor 21

(FGF21), neuregulin-4, leptin, resistin, vaspin, visfatin, adipsin. Peripheral venous blood samples were collected in the morning after a 12-h overnight fast. Serum samples were obtained by centrifugation at 3,000 g for 10 min at 4°C and then transferred to a -80°C freezer. Serum adipokine levels were measured using commercial ELISA kits (online suppl. Table 1; for all online suppl. material, see <https://doi.org/10.1159/000540701>) according to the manufacturer's instructions.

Measurement of Plasma XOR Activity

XOR activity was assessed by liquid chromatography-triple quadrupole mass spectrometry, to detect [$^{13}\text{C}_2$, $^{15}\text{N}_2$]-uric acid production from [$^{13}\text{C}_2$, $^{15}\text{N}_2$]-xanthine, following established procedures [18, 19]. Calibration standard samples of [$^{13}\text{C}_2$, $^{15}\text{N}_2$]-uric acid were measured, and production levels were calculated from the calibration curve. The intra-assay coefficient of variation for plasma XOR activity was 6.5% and the inter-assay coefficient of variation was 9.1%.

Discontinuation Criteria

(1) Patients with gouty attacks. (2) Patients with aspartate aminotransferase or alanine transaminase ≥ 2 times the upper limit of normal. (3) Patients with SUA ≥ 720 $\mu\text{mol/L}$. (4) Patients with estimated glomerular filtration rate declining to less than 30 mL/min/ 1.73 m^2 . (5) Patients requiring prohibited concomitant medications. (6) Patients who have missed more than four consecutive doses of febuxostat. (7) Patients who voluntarily withdraw from the study.

Sample Size

The primary endpoints of the study were the levels of circulating adipokines. According to our previous data and the results of prior studies, we estimated the mean and standard deviation for

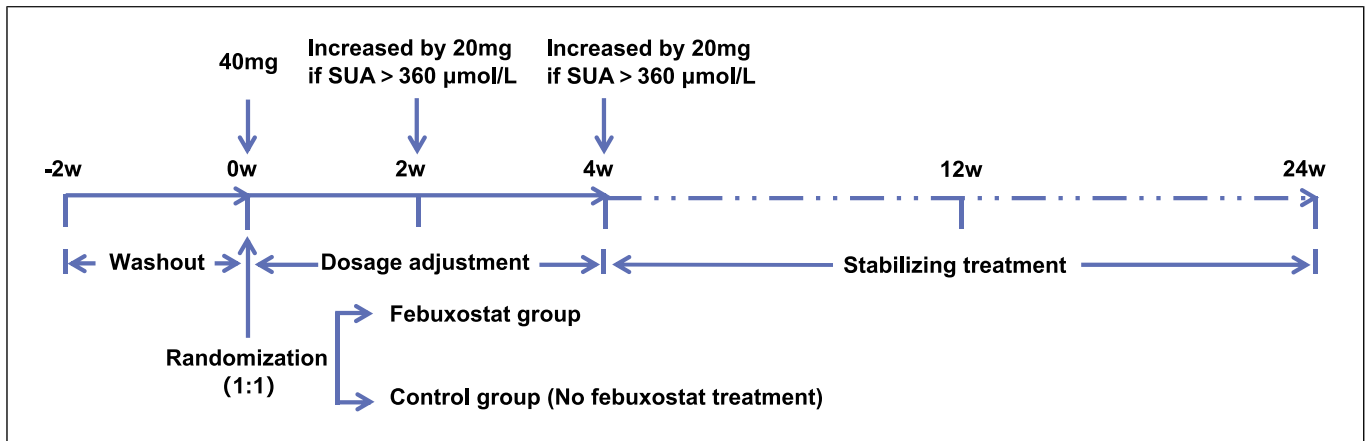


Fig. 2. Treatment outline.

each adipokine in this study. We calculated the sample size using PASS software (version 08.0.8) with $\alpha = 0.05$, $1 - \beta = 80\%$ and an expected dropout rate of 15%. Finally, this study planned to enroll a total of 130 patients and randomly assign them to two groups in a 1:1 ratio.

Statistical Analysis

Statistical analysis was performed using SPSS 24.0 software. The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Continuous variables following a normal distribution were presented as mean $\pm$ standard deviation, and two-tailed t test and one-way analysis of variance were used to compare between groups. Variables with a skewed distribution were described as median (interquartile range), and group comparisons were analyzed with Mann-Whitney U test and Kruskal-Wallis H test. Categorical variables, presented as frequency and percentage, were analyzed using the χ^2 test. The correlation between Δ XOR activity and Δ adipokines was analyzed by Pearson correlation and multiple linear regression. A p value <0.05 was considered statistically significant.

Results

Baseline Clinical Characteristics

This study randomly included 65 patients in the febuxostat group and 65 patients in the control group. Ultimately, a total of 60 patients in the febuxostat group and 57 patients in the control group completed the follow-up visits (Fig. 1). The median age was 56.22 ± 8.02 years in the febuxostat group and 55.18 ± 8.57 years in the control group. 54 (90.0%) patients in the febuxostat group and 53 (93.0%) in the control group were male. Baseline clinical characteristics of the control and febuxostat groups are shown in Table 1.

Clinical Follow-Up Data

Both groups followed a low purine diet. The febuxostat group started febuxostat treatment at 40 mg/day and gradually increased the dose according to SUA levels, with no change in the maintenance dose after 1 month (Fig. 2). The mean febuxostat dose per day at the end-point was 48.4 mg. Figure 3 shows the percentage of patients with SUA levels below 420 µmol/L and 360 µmol/L at 3 and 6 months of follow-up.

Clinical follow-up data for the two groups are presented in Table 2. The results showed that TG levels were lower in the febuxostat group compared to the control group at 6 months. Additionally, patients in the febuxostat group exhibited decreased TG levels at 6 months of treatment compared to baseline levels.

Changes in Adipokine Profiles

We examined the serum levels of several adipokines at baseline, 3 months, and 6 months (Table 3). The results showed an increase in HMW adiponectin and omentin and a decrease in chemerin and asprosin at 3 or 6 months compared to the control group. We also compared serum levels of adipokine profiles before and after treatment in the febuxostat group. The results showed an increase in HMW adiponectin and omentin and a decrease in chemerin and asprosin at 3 or 6 months after treatment compared to baseline.

Relationship between Δ XOR Activity and Δ Adipokines

As febuxostat is a potent XOR inhibitor, we assessed XOR activity in both groups. As expected, XOR activity was significantly lower in the febuxostat group compared to the control group at 3 and 6 months. In addition, XOR activity exhibited a significant decrease after febuxostat

Table 1. Baseline clinical characteristics in the study participants

Variables	Febuxostat group (n = 60)	Control group (n = 57)	p value
Age, years	56.22±8.02	55.18±8.57	0.498
Male, n (%)	54 (90.0)	53 (93.0)	0.564
Smoking, n (%)	8 (13.3)	10 (17.5)	0.528
Drinking, n (%)	34 (56.7)	31 (54.4)	0.804
Hypertension, n (%)	9 (15.0)	8 (14.0)	0.882
Diabetes mellitus, n (%)	6 (10.0)	7 (12.3)	0.695
Hyperlipidemia, n (%)	16 (26.7)	15 (26.3)	0.966
SBP, mm Hg	118 (109.25–131.75)	120 (114–128)	0.534
DBP, mm Hg	69.5 (64–73.5)	68 (62–72.75)	0.138
BMI, kg/m ²	26.69±1.12	26.28±1.34	0.375
SUA, μ mol/L	521.03±26.08	516.30±39.60	0.444
TG, mmol/L	2.14 (1.71–3.18)	2.50 (1.90–3.33)	0.233
TC, mmol/L	4.95±0.79	4.69±0.99	0.113
LDL-C, mmol/L	2.90±0.75	2.99±0.84	0.526
HDL-C, mmol/L	1.19±0.31	1.21±0.28	0.670
HOMA-IR	2.69 (2.36–3.73)	2.98 (2.43–3.57)	0.967

Values are listed as frequency (percentage), mean $\pm$ standard deviation (SD), or median (interquartile range). SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; SUA, serum uric acid; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance.

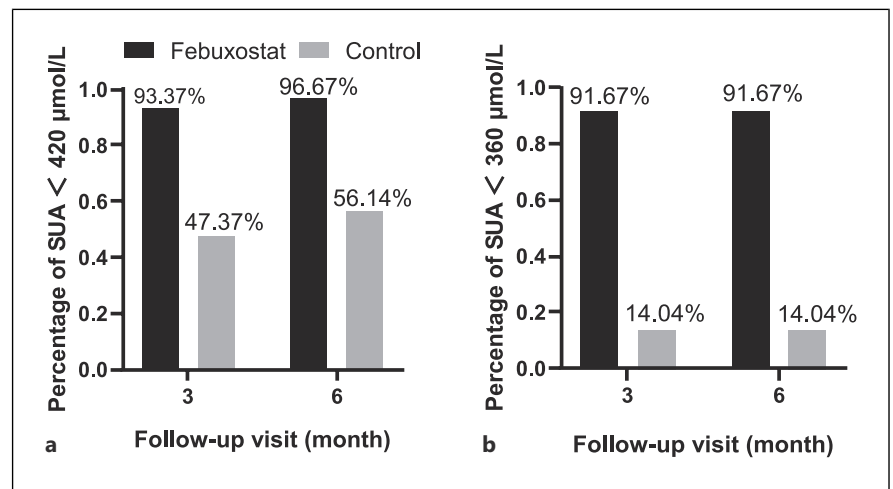


Fig. 3. Percentage of patients with SUA levels below 420 μ mol/L (a) and 360 μ mol/L (b) at 3 and 6 months of follow-up.

treatment compared to baseline (Fig. 4). We calculated the values for the changes in adipokine levels (Δ adipokines) and changes in XOR activity (Δ XOR activity) at 6 months compared to baseline in the febuxostat group by subtracting the baseline values from the 6-month values.

Subsequently, we assessed the correlation between Δ XOR activity and Δ adipokines. The results showed a positive correlation between Δ XOR activity and Δ asprosin (Fig. 5). We further adjusted for Δ TG and Δ SUA for multiple linear regression analysis (no multicollinearity

Table 2. Comparison of clinical characteristics at follow-up visits between febuxostat and control groups

Variables	Febuxostat group (n = 60)	Control group (n = 57)	p value
BMI, kg/m ²			
Baseline	26.69±1.12	26.28±1.34	0.375
3 months	26.54±1.25	26.30±1.44	0.345
6 months	26.34±1.24	26.12±1.43	0.379
p value	0.276	0.377	
SUA, µmol/L			
Baseline	521.03±26.08	516.30±39.60	0.444
3 months	291.70±69.86 ^{a,b}	423.23±56.17 ^a	<0.001
6 months	273.55±76.33 ^{a,b}	413.95±55.00 ^a	<0.001
p value	<0.001	<0.001	
TG, mmol/L			
Baseline	2.14 (1.71–3.18)	2.50 (1.90–3.33)	0.233
3 months	2.05 (1.62–2.73)	2.31 (1.87–3.10)	0.084
6 months	1.71(1.54–2.18) ^{a,b}	2.38 (1.75–3.12)	0.001
p value	0.012	0.712	
TC, mmol/L			
Baseline	4.95±0.79	4.69±0.99	0.113
3 months	4.79±0.85	4.59±1.00	0.240
6 months	4.75±0.97	4.48±1.07	0.149
p value	0.409	0.554	
LDL-C, mmol/L			
Baseline	2.90±0.75	2.99±0.84	0.526
3 months	2.94±0.80	2.92±0.70	0.819
6 months	2.73±0.59	2.93±0.75	0.105
p value	0.224	0.822	
HDL-C, mmol/L			
Baseline	1.19±0.31	1.21±0.28	0.670
3 months	1.22±0.30	1.23±0.25	0.801
6 months	1.23±0.28	1.33±0.30	0.069
p value	0.744	0.065	
HOMA-IR			
Baseline	2.69 (2.36–3.73)	2.98 (2.43–3.57)	0.967
3 months	2.69 (2.33–3.78)	3.05 (2.43–4.00)	0.649
6 months	2.54 (2.05–3.51)	2.94 (2.22–3.87)	0.101
p value	0.161	0.866	

Values are listed as frequency (percentage), mean ± SD, or median (interquartile range). BMI, body mass index; SUA, serum uric acid; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; SD, standard deviation. ^ap value <0.05 compared to baseline in the same group. ^bp value <0.05 compared to control group.

between variables) and found that Δ XOR activity was independently correlated with Δ asprosin ($F = 3.594$, $p = 0.019$, adjusted $R^2 = 0.117$, Table 4).

Discussion

Adipokines secreted by adipose tissue have been identified as either anti-inflammatory (e.g., adiponectin, adiposin, and omentin) or proinflammatory (e.g., MCP-1, resistin, chemerin, and visfatin) [20]. The imbalance of

adipokines contributes to the metabolic dysfunction associated with obesity. Restoring this balance emerges as a potential approach for treating obesity and its complications [11, 20]. To explore ways to alleviate the imbalance of adipokine levels, we investigated the effect of febuxostat on circulating adipokine profiles in patients with overweight or obesity and asymptomatic hyperuricemia. Our study revealed that febuxostat significantly improved certain imbalances in circulating adipokine levels in patients with overweight or obesity and asymptomatic hyperuricemia. Importantly, we also observed a positive correlation

Table 3. Comparison of circulating adipokine profiles at follow-up visits between febuxostat and control groups

Variables	Febuxostat group (n = 60)	Control group (n = 57)	p value
Adiponectin, µg/mL			
Baseline	8.83±3.70	9.60±4.41	0.308
3 months	10.12±3.19 ^a	8.58±2.62	0.005
6 months	10.98±3.63 ^{a,b}	9.74±3.17	0.050
p value	0.004	0.156	
Leptin, pg/mL			
Baseline	26.35±4.28	24.97±6.13	0.161
3 months	27.04±6.03	26.06±6.16	0.387
6 months	25.31±4.55	26.69±5.84	0.154
p value	0.165	0.311	
Resistin, ng/mL			
Baseline	16.38±3.67	16.08±3.94	0.665
3 months	17.08±3.58	16.18±3.85	0.193
6 months	16.81±3.64	16.60±3.71	0.902
p value	0.573	0.743	
Chemerin, ng/mL			
Baseline	328.5 (306.5–355.5)	319 (289–348)	0.152
3 months	309 (266.5–342) ^b	325 (297–351)	0.109
6 months	305.5 (254.5–325) ^{a,b}	318 (394–337)	0.028
p value	<0.001	0.498	
Omentin, ng/mL			
Baseline	2.26 (1.96–3.06)	2.24 (1.96–2.87)	0.723
3 months	2.47 (2.05–3.25)	2.20 (1.93–3.26)	0.268
6 months	3.05 (2.22–3.93) ^{a,b}	2.44 (2.16–3.05)	0.032
p value	0.025	0.414	
MCP-1, ng/L			
Baseline	144.63±24.00	148.85±24.90	0.352
3 months	148.05±23.97	152.74±23.90	0.291
6 months	150.67±26.50	149.99±28.48	0.895
p value	0.412	0.712	
Vaspin, ng/mL			
Baseline	0.91±0.30	0.94±0.34	0.547
3 months	0.94±0.27	0.93±0.32	0.902
6 months	0.93±0.35	0.92±0.33	0.941
p value	0.817	0.939	
Visfatin, ng/mL			
Baseline	44.34±16.77	48.79±29.04	0.308
3 months	40.91±15.28	44.44±16.81	0.236
6 months	42.10±15.11	42.13±15.09	0.994
p value	0.482	0.238	
Asprosin, ng/mL			
Baseline	24.40±5.76	23.72±6.04	0.535
3 months	23.12±5.04	23.48±3.68	0.669
6 months	21.83±4.82 ^{a,b}	23.29±4.59	0.013
p value	0.028	0.849	
Adipsin, µg/mL			
Baseline	6.24 (4.10–7.60)	5.27 (4.06–6.96)	0.221
3 months	5.43 (3.78–6.72) ^a	4.06 (3.16–6.08)	0.048
6 months	5.31 (3.91–7.63)	4.87 (3.50–6.54)	0.475
p value	0.304	0.070	

Table 3 (continued)

Variables	Febuxostat group (n = 60)	Control group (n = 57)	p value
Neuregulin-4, ng/mL			
Baseline	4.01±1.51	3.68±1.37	0.219
3 months	3.74±1.49	3.73±1.38	0.982
6 months	3.70±1.36	4.14±1.59	0.112
p value	0.459	0.182	
FGF21, pg/mL			
Baseline	314.20±64.14	306.23±54.03	0.470
3 months	299.07±42.31	311.35±48.48	0.139
6 months	299.55±45.14	309.42±54.65	0.288
p value	0.190	0.813	

Values are listed as frequency (percentage), mean ± SD, or median (interquartile range). MCP-1, monocyte chemotactic protein-1; FGF21, fibroblast growth factor 21; SD, standard deviation. ^ap value <0.05 compared to control group. ^bp value <0.05 compared to baseline in the same group.

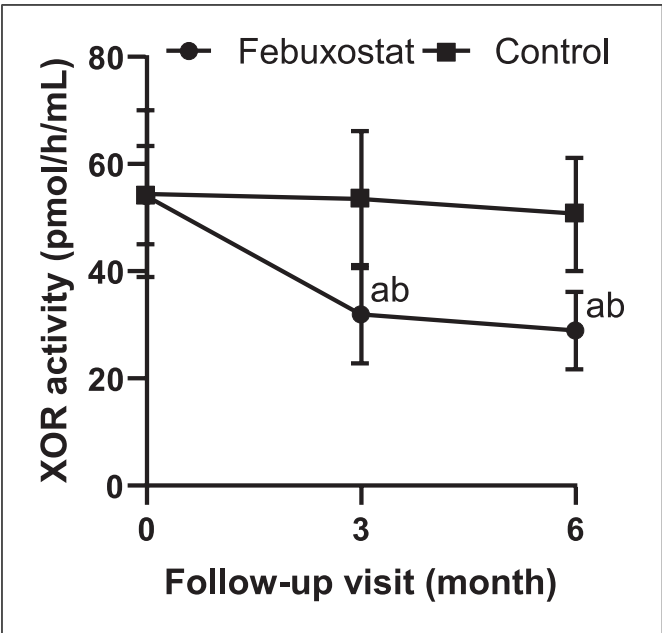


Fig. 4. XOR activity in febuxostat and control groups. ^ap value <0.05 compared to baseline in the same group. ^bp value <0.05 compared to control group.

between changes in asprosin levels and changes in XOR activity, which has not been reported previously.

Hyperuricemia has been identified as a mediator of the proinflammatory endocrine imbalance in adipose tissue in the murine model of the metabolic syndrome [12]. Clinical studies have unveiled a negative correlation between SUA levels and circulating adiponectin [21–23]. Notably, an independent association was observed between plasma

XOR activity and adiponectin levels in young participants [7]. Additionally, plasma XOR activity showed a negative correlation with adiponectin levels and a positive correlation with levels of fatty acid binding protein-4 (FABP4) and FGF21 in normal subjects [13]. Several intervention studies have examined the impact of XOR inhibitors on adiponectin levels in humans [24–27]. Nishizawa et al. [25] reported a significant increase in adiponectin levels among hyperuricemic patients following a 6-month treatment with febuxostat. However, Beddhu et al. [26] did not observe a notable impact of febuxostat on adiponectin in asymptomatic hyperuricemic patients with diabetic nephropathy, with SUA levels ≥ 327 $\mu\text{mol/L}$ in men and ≥ 274 $\mu\text{mol/L}$ in women. In comparison, we included patients with SUA ≥ 480 $\mu\text{mol/L}$ and BMI ≥ 25 kg/m^2 and we found a different result. In this study, we observed that febuxostat significantly elevated circulating HMW adiponectin levels. Furthermore, the relationship between febuxostat and other adipokines has not been investigated in previous studies.

It has been demonstrated that circulating levels of adiponectin and omentin are lower, while chemerin and asprosin are higher in metabolic diseases such as obesity, type 2 diabetes mellitus, and hyperuricemia [10, 28–31]. In this study, we found that febuxostat effectively improved the imbalance of circulating adipokine levels, elevating levels of HMW adiponectin and omentin and lowering levels of chemerin and asprosin. More important, we also confirmed the positive correlation between the reduction in circulating asprosin levels and the inhibitory effect of febuxostat on XOR activity.

Asprosin is a recently identified adipokine released in response to fasting [32]. It has been reported to be pathologically elevated in circulating levels in humans

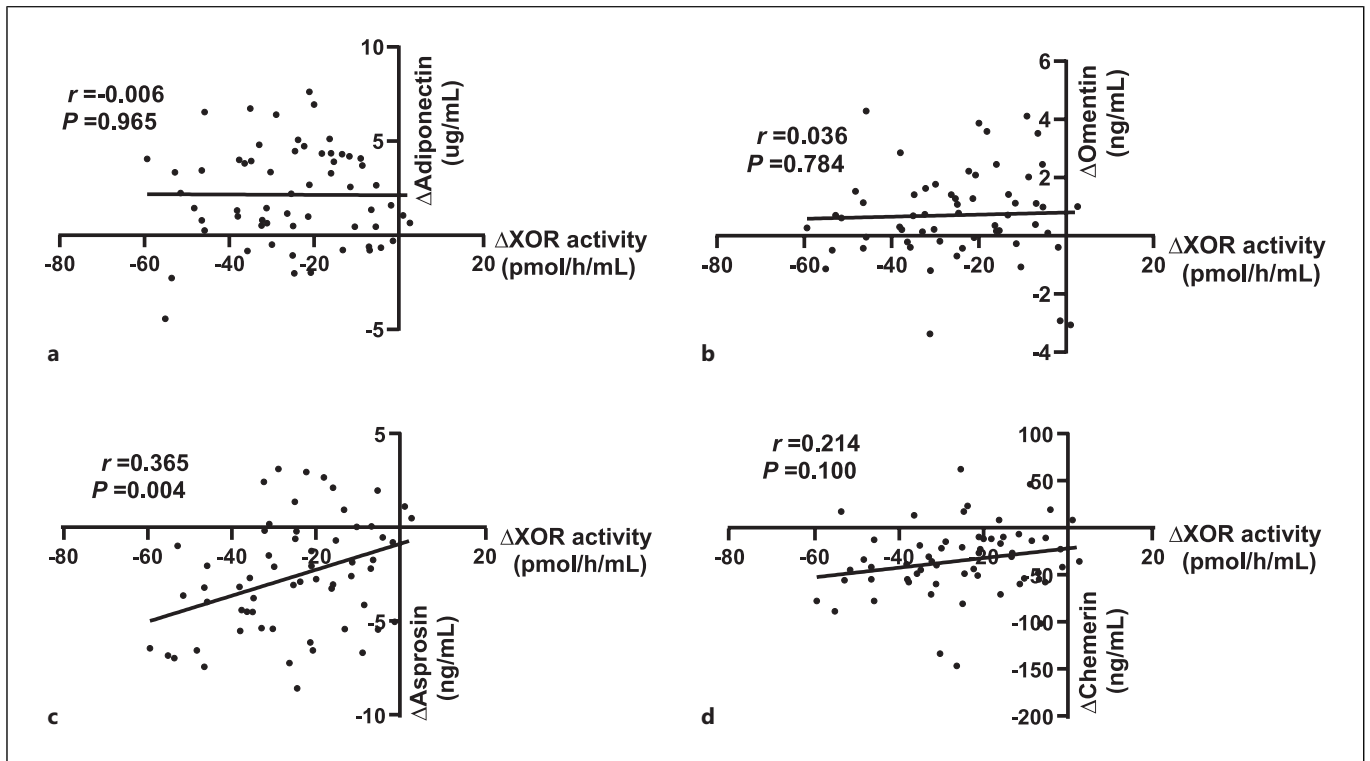


Fig. 5. a–d Correlation between Δ XOR activity and Δ adipokines.

Table 4. Multiple linear regression analysis of Δ asprosin

Variables	β	SE	Standardized β	t	p value
Constant	-1.589	1.288		-1.233	0.223
Δ SUA	-0.002	0.006	-0.061	-0.448	0.656
Δ TG	-0.341	0.299	-0.145	-1.141	0.259
Δ XOR	0.072	0.026	0.376	2.792	0.007

SUA, serum uric acid; TG, triglycerides; XOR, xanthine oxidoreductase.

and mice with insulin resistance [32]. Previous studies have shown that asprosin impairs insulin secretion mediated by TLR4/JNK-associated inflammation and suppresses insulin sensitivity through PKC δ -mediated ER stress [33, 34]. In addition, asprosin was found to inhibit browning of white adipocytes and promote Nrf2-mediated lipid deposition in adipose tissue [35]. Furthermore, circulating asprosin levels were significantly reduced after treatment with SGLT2 inhibitors or metformin in the newly defined T2DM group [36, 37]. Our study demonstrates for the first time that febuxostat

effectively reduces circulating asprosin levels in patients with overweight or obesity and asymptomatic hyperuricemia. Intriguingly, our findings suggest a positive correlation between the reduction in circulating asprosin and the inhibitory effect of febuxostat on XOR.

As the rate-limiting enzyme for uric acid formation in purine metabolism, XOR also plays a crucial role in oxidative stress, serving as a major enzymatic source of ROS [4, 6]. XOR may be a potential therapeutic target for metabolic abnormalities beyond hyperuricemia and has been shown to be implicated in inflammatory conditions [9]. Previous studies have reported a significant association between XOR activity and hyperuricemia, obesity, insulin resistance and dyslipidemia [7–9]. Febuxostat has been shown to reduce serum free fatty in gout and suppress adipocyte lipolysis [38]. Higa et al. [39] recently reported that febuxostat attenuates adipogenesis under oxidative conditions by suppressing ROS production and nuclear factor erythroid 2-related factor 2 (Nrf2) activation. XOR has been demonstrated to be abundantly expressed in adipose tissue of mice [40, 41]. The gene expression of XOR in visceral fat is upregulated in obesity [41]. XOR is positioned downstream of CCAAT/enhancer-binding protein beta (C/EBP β) and upstream of peroxisome proliferator-activated receptor γ

(PPAR γ) in the cascade of factors controlling adipogenesis, regulating PPAR γ activity [40]. Plasma XOR activity has been reported significantly correlated with levels of adipokines, notably FABP4, adiponectin, and FGF21 [13]. While this study did not find a correlation between XOR activity and HMW adiponectin or FGF21, it revealed a significant association between changes in asprosin levels and changes in XOR activity.

This study has several limitations. First, the number of study participants was relatively small. To mitigate bias, the randomized design of this study ensured an equal distribution of confounding factors between the control and febuxostat groups. However, further studies with larger numbers of participants are needed to confirm our findings. In addition, the follow-up period is short. Further studies with a longer follow-up period are needed to obtain more meaningful and comprehensive results.

Conclusion

We conducted a single-center, prospective, randomized, controlled clinical trial to investigate the effect of febuxostat on circulating adipokine profiles in patients with overweight or obesity and asymptomatic hyperuricemia. This study may provide important evidence that febuxostat could restore the imbalance in circulating adipokine levels in patients with overweight or obesity and asymptomatic hyperuricemia. Furthermore, we observed a positive correlation between changes in asprosin levels and changes in XOR activity. This study enhanced the clinical significance of febuxostat in patients with asymptomatic hyperuricemia.

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Statement of Ethics

The study was approved by the Ethics Committee of Huaian No. 1 People's Hospital (Approval No. KY-P-2018-010-01) and registered in the Chinese Clinical Trial Registry (ChiCTR1800017922). All participants signed a written informed consent form.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.D., K.A., Z.C., Y.L., and Y.B. collected the data. M.D., K.A., and L.M. performed the statistical analysis. All authors contributed to the interpretation of the data, the study design, and the manuscript writing. M.D. and K.A. revised the draft. L.M. finalized the manuscript.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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