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ORIGINAL RESEARCH

Febuxostat Improves Postprandial Glucose Regulation and Insulin Sensitivity in Hyperuricemic Individuals with Prediabetes or Newly Diagnosed Type 2 Diabetes: A Prospective Cohort Study

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Background: Hyperuricemia (HUA) has been linked to an elevated risk of impaired glucose metabolism. This study aimed to investigated the impact of the urate-lowering drug febuxostat on blood glucose levels, insulin sensitivity, and β-cell function in subjects with HUA who present with normoglycemia, prediabetes, or newly diagnosed type 2 diabetes (T2DM).

Methods: We assessed the glucose metabolism of participants with HUA using a 3-h oral glucose tolerance test (OGTT). Participants were categorized into two groups: those with HUA and normal glucose metabolism (NGM, n=28), and those with HUA and abnormal glucose metabolism (AbGM, n=32), including prediabetes (n=20) and newly diagnosed T2DM (n=12). Both groups received a daily dose of 40 mg febuxostat for 24 consecutive weeks and underwent 3-h OGTT at 12 and 24 weeks. Glucose, insulin, and C-peptide were measured to calculate insulin sensitivity (Stumvoll index, Gutt index) and β-cell function (Insulin Secretion-Sensitivity Index-2 and Disposition Index) indices. Differences in glucose levels and indices were analyzed by repeated measures ANOVA including interaction terms between groups and the time of visit.

Results: After 24 weeks of febuxostat treatment, subjects with HUA and AbGM showed significant reductions in postprandial 1-h (11.88±1.39mmol/L at baseline, 10.97±2.74mmol/L at 12 weeks, and 11.12±1.92mmol/L at 24 weeks, Ptime=0.031) and 2-h glucose (10.25±1.71mmol/L at baseline, 9.39±2.77mmol/L at 12 weeks, and 9.16±2.67mmol/L at 24 weeks, Ptime=0.014). Febuxostat significantly improved insulin sensitivity of subjects in the AbGM group, but did not affect β-cell function. Moreover, the improvement in insulin sensitivity in these subjects was not directly correlated with the improvement in uric acid. No significant changes were observed in subjects with NGM.

Conclusion: In subjects with HUA and prediabetes or newly diagnosed T2DM, febuxostat significantly enhanced postprandial glucose and insulin sensitivity, though it did not notably improve β-cell function. Further research is required to explore how febuxostat enhances insulin sensitivity.

Keywords: type 2 diabetes, prediabetes, hyperuricemia, insulin sensitivity, β-cell function

Introduction

The International Diabetes Federation Diabetes Atlas reported that the global prevalence of diabetes in adults was 11.1% in 2025.[1] In China, the prevalence of diabetes diagnosed according to ADA criteria was 12.6%. In addition, the standardized prevalence of prediabetes among Chinese adults is as high as 35.2%. Among them, individuals with prediabetes in China

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predominate with impaired glucose tolerance(IGT),[2] which is associated with a higher risk of cardiovascular and metabolic disease.[3] Fortunately, prediabetes and early-stage diabetes can be reversed, and effective interventions before diabetes develops can reduce the risk of future diabetes-related complications and cardiovascular disease.[4]

Hyperuricemia (HUA) is a metabolic disorder characterized by the disruption of purine metabolism. Elevated serum uric acid levels are associated with an increased risk of progression from prediabetes to diabetes.[5] Studies have shown that uric acid may promote abnormalities in glucose metabolism by promoting oxidative stress, inducing inflammatory responses, and disrupting insulin signaling pathways to promote insulin resistance.[6] HUA may also accelerate the development of diabetes by damaging and inducing apoptosis of pancreatic β-cells.[7] Furthermore, HUA may contribute to the development of chronic complications of diabetes, including macrovascular dysfunction, such as hypertension and stroke, and microvascular dysfunction, such as chronic kidney disease and peripheral artery disease.[8] These studies indict that HUA has an impact on all stages of diabetes and the development of its complications. Therefore, prompt and effective intervention for HUA is imperative.

Studies have shown that urate-lowering therapy can improve insulin resistance in subjects with HUA who have normal glucose tolerance[9,10] and reduce the risk of future type 2 diabetes (T2DM) in subjects with HUA.[11] This indicates that it may have beneficial effects in the development process of diabetes. Further research is necessary to clarify the specific effects of urate-lowering therapy on blood glucose levels, insulin secretion, and pancreatic β-cell function in subjects with HUA under different glucose metabolic conditions, including normoglycemia, prediabetes, and T2DM.

Febuxostat is a novel non-purine-selective xanthine oxidase inhibitor used for the treatment of HUA. As a urate-lowering drug, febuxostat has been shown to have better urate-lowering efficacy and safety profile compared to allopurinol, the standard medication for the treatment of HUA.[12] The objectives of this study are: (i) to explore the effects of febuxostat on blood glucose, insulin, insulin sensitivity, and β-cell function in subjects with HUA who have normal glucose metabolism, prediabetes, or newly diagnosed T2DM, and (ii) to determine whether this effect (if any), is associated with improvements in uric acid.

Materials and Methods

Study Design

The Department of Endocrinology and Metabolism at Shanghai Tenth People's Hospital conducted this 24-week open-label prospective cohort study to investigate whether febuxostat has beneficial effects on glucose metabolism in subjects with HUA who have NGM, prediabetes, or newly diagnosed T2DM. The primary endpoints were: (1) changes in fasting and postprandial blood glucose; (2) Changes in insulin sensitivity and pancreatic β-cell function. Participants with HUA were recruited based on the criteria of the American College of Rheumatology/European League Against Rheumatism,[13] Specifically, inclusion was limited to individuals aged between 18 and 75 years. Those with normal glucose metabolism, prediabetes, or newly diagnosed T2DM were recruited according to the World Health Organization (WHO) standards after confirmation through two screening 3-h oral glucose tolerance tests (OGTT).[14] NGM was defined as fasting blood glucose(FBG) ≤ 6.1 mmol/L and 2-h postprandial glucose(2h-PG) ≤ 7.8 mmol/L. Prediabetes was defined as impaired fasting glucose(IFG): 6.1mmol/L < FBG < 7.0 mmol/L and 2h-PG ≤ 7.8 mmol/L; IGT: FBG ≤ 6.1 mmol/L and 7.8 mmol/L < 2h-PG < 11.1 mmol/L; or IFG+IGT: 6.1 mmol/L < FBG < 7.0 mmol/L and 7.8 mmol/L < 2h-PG < 11.1 mmol/L. T2DM was defined as FBG ≥ 7.0 mmol/L or 2h-PG ≥ 11.1 mmol/L. Exclusion criteria included known diabetes mellitus; alanine aminotransferase(ALT), or aspartate aminotransferase (AST) levels ≥ 2.5 times the upper limit of normal; estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2; allergy to febuxostat; severe complications; undergoing urate-lowering therapy; and subjects trying to conceive.

This study was approved by the Ethics Committee of Shanghai Tenth People's Hospital. The study has been registered on the chictr.org website with the identification code ChiCTR-RIC-17011687. The investigation was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice, and all participants provided written informed consent.

Study Visits

During the baseline visit, researchers collected medical history, concomitant treatments, and alcohol consumption status. Physical examination includes body mass index (BMI), heart rate (HR), and blood pressure (BP). Anthropometric measurements were conducted by trained examiners. BMI was calculated by dividing weight (kg) by the square of height (m). BP was measured three times, and the average value was used for analysis.

Blood samples were collected after at least 12 hours of fasting. All laboratory measurements were performed using standard methods. A 3-h OGTT was conducted by adding 75 g of glucose to 200 mL of water. Plasma glucose levels were measured by a standard glucose oxidase assay to obtain a plasma glucose curve with values at baseline, 30 minutes, 60 minutes, 120 minutes, and 180 minutes.[15] Plasma insulin and C-peptide were measured with a two-site immunoenzymatic assay using a Tosoh 600 II analyzer (Tosoh Bioscience, South San Francisco, California) at all OGTT time points. We used the Stumvoll index and Gutt index to measure insulin sensitivity. Insulin Secretion-Sensitivity Index-2 (ISSI-2) and Disposition Index were used to assess β-cell function. The above parameters were calculated according to the formula in Supplemental Table 1.

After that, participants were instructed to take 40 mg of febuxostat once daily. Study participants returned to the clinical outpatient after 12 and 24 weeks of medication to repeat all examinations during the baseline visit. During the administration of the study medication, the safety of all participants was closely evaluated. Adverse events, as well as the mental and physical condition of each subject, were meticulously recorded by the investigator at each visit. All study data were collected by the researchers using a custom-built mini-program system (Supplemental Figure 1).

Statistical Analyses

Assuming an anticipated dropout rate of 20%, we estimated that enrolling 70 participants (35 per group) would provide the trial with more than 80% statistical power to detect a significant difference in insulin sensitivity before and after febuxostat intervention, at a significance level of 0.05 using a two-tailed test. The sample size was calculated based on the insulin resistance (HOMA-IR) values from previous studies, where the mean HOMA-IR value after 24 weeks of febuxostat intervention was 2.15 ± 0.48, compared with the baseline value of 2.69 ± 0.81.[16]

We used the Kolmogorov–Smirnov test to examine the distribution of parameters. Continuous variables that follow a normal distribution and those that do not are represented by the mean ± standard deviation and the median (quartile), respectively. Categorical variables are expressed as frequency (percentage). For continuous variables, comparisons of mean values before and after treatment are conducted using paired two-tailed Student's *t*-test for normally distributed variables and the paired two-tailed Wilcoxon signed-rank test for non-normally distributed variables. The unpaired two-sided Student's *t*-test and Mann–Whitney *U*-test were used for comparison between groups of normally and nonnormally distributed parameters, respectively. Categorical variables were compared using the chi-square test or Fisher's exact test.

To investigate the response of blood glucose, insulin, and C-peptide to OGTT at 12 and 24 weeks of medication, we plotted the response curves of glucose, insulin, and C-peptide at fasting, 30 minutes, 60 minutes, 120 minutes, and 180 minutes during OGTT for each group. We used repeated measures ANOVA to compare the mean levels of glucose, insulin, and C-peptide at each time point before and after medication between and within the two groups, as well as the mean levels of insulin sensitivity (Stumvoll index and Gutt index) and β-cell function (ISSI-2 and Disposition index). At return visits at 12 and 24 weeks after medication, we also assessed the prevalence of prediabetes and T2DM in each group and compared the prevalence within each pair of groups using the chi-square test. The associations between indices with statistically significant changes over time and laboratory parameters were investigated in participants of the NGM and AbGM groups, both at baseline and considering the changes from baseline to 24 weeks after treatment.

Two-tailed P-value of <0.05 was considered statistically significant. In all of the above analyses, P-values for pairwise comparisons were adjusted using Bonferroni correction. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) software, and graphs were made using GraphPad Prism 8.0.

Results

Participants

The study recruited a total of 212 subjects with HUA aged between 18 and 70 years from March 2022 to August 2024. Participants who had a history of diabetes (n=35), abnormal liver function (n=40), or were receiving urate-lowering treatment (n=65) were excluded at the baseline survey. The final sample included 72 subjects, comprising 37 subjects with NGM and 35 subjects with AbGM (23 with prediabetes and 12 with newly diagnosed T2DM). In the NGM and AbGM group, 9 (24.32%) and 3 (8.57%) subjects, respectively, withdrew from the study. The most common reasons for withdrawal were being busy with work and loss to follow-up. A total of 60 subjects underwent per-protocol analysis, including 28 participants with NGM and 32 participants with AbGM (20 with prediabetes and 12 with newly diagnosed T2DM) (Supplementary Figure 2).

Table 1 lists the baseline demographic and clinical characteristics of participants in the NGM group (n=37) and the AbGM group (n=35). All subjects in this study were male (72, 100%). subjects in the AbGM group (52.16 ± 12.37 years) were older than those in the NGM group (44.00 ± 12.68 years). In terms of blood glucose, subjects in the AbGM group had significantly higher FBG (5.78 ± 0.60 vs 4.99 ± 0.40), 2h-PG (10.25 ± 1.71 vs 6.53 ± 0.88), and HbA1c (5.93 ± 0.56

Table 1 The Baseline Demographic and Clinical Characteristics

Index	Normal Glucose Metabolism (n=37)	Abnormal Glucose Metabolism (n=35)	*P* value
Age (years)	44.00±12.68	52.16±12.37	**0.015***
SBP (mmHg)	134.81±13.59	138.47±13.19	0.300
DBP (mmHg)	87.96±8.64	85.28±8.09	0.224
BMI (kg/m^2)	26.20 (23.77, 28.40)	26.38 (24.01,28.05)	0.830
LDL (mmol/L)	3.29±0.75	2.88±0.84	0.052
TC (mmol/L)	5.38±0.80	5.00±0.93	0.096
TG (mmol/L)	2.80±1.39	3.05±1.82	0.550
ESR (mm/h)	5.00 (2.00, 15.00)	8.00 (4.00,14.00)	0.188
CRP (mg/L)	1.47 (0.61, 2.56)	1.93 (0.82, 3.50)	0.548
SUA (μmol/L)	561.04±70.10	581.75±89.27	0.327
ALT (U/L)	38.39±34.20	37.13±18.34	0.856
AST (U/L)	25.29±12.96	24.34±8.06	0.733
γ-GT (U/L)	49.11±39.49	40.84±15.02	0.277
Creatinine (μmol/L)	86.29±16.55	89.72±14.81	0.400
Cystatin C (μmol/L)	0.91±0.18	0.98±0.27	0.221
eGFR (mL/min/1.73 m^2)	93.57±21.32	85.64±18.12	0.124
HbA1c (%)	5.59±0.35	5.93±0.56	**0.007****
HbA1c (mmol/mol)	37.63±3.79	41.36±6.07	**0.007****
FBG (mmol/L)	4.99±0.40	5.78±0.60	**<0.001****
2h-PG (mmol/L)	6.53±0.88	10.25±1.71	**<0.001****
Insulin (mIU/L)	12.41±6.70	14.44±6.88	0.252
2h-Insulin (mIU/L)	118.88±76.04	164.57±106.34	0.064
C peptide (ug/L)	3.15±1.12	3.25±0.85	0.693
2h-C peptide (ug/L)	13.53±4.11	15.87±4.94	0.052
Insulin sensitivity			
Stumvoll index	0.11±0.01	0.09±0.01	**<0.001****
Gutt index	74997.04±2.17	74,989.90±3.61	**<0.001****
β-cell function			
ISSI-2	867.95±348.73	457.75±167.17	**<0.001****
Disposition index	19.12±23.40	5.27±3.76	**0.004****

Note: Data are mean±SD or median (quartile) unless otherwise indicated. Bold numbers indicate that the p-value is less than 0.05.*p<0.05; **p<0.01.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; SUA, serum uric acid; γ-GT, Gamma-glutamyl transferase; 2h-Insulin, 2-hour postprandial insulin; 2h-C peptide, 2-hour postprandial C peptide.

vs 5.59 ± 0.35) compared to the NGM group (all P ≤ 0.007). Compared to the NGM group, subjects in the AbGM group had lower insulin sensitivity (as indicated by the Stumvoll index and Gutt index) (both P < 0.001), and lower β-cell function, as indicated by the ISSI-2 and Disposition index (both P < 0.005).

Effect of Febuxostat on Glycemic Control, Insulin and C-Peptide Levels

We first evaluated the OGTT glucose response curves before and after medication. As shown in Figure 1A, the differences in glucose response patterns between the two groups reflected differences in the β-cell function. Specifically, at each time point of OGTT, the glucose levels of the AbGM group were higher than those of the NGM group before and after medication (all p < 0.001). In the AbGM group, the 1h-PG and 2h-PG significantly decreased after 12 and 24 weeks of medication (P < 0.05). However, in the NGM group, there were no significant changes in glucose levels at any time point of the OGTT.

We also evaluated the insulin release curves and C-peptide release curves before and after medication. As shown in Figure 1B, the AbGM group had lower insulin levels at 30 minutes postprandial (P < 0.03) and higher insulin levels at 3-h postprandial (P < 0.01) compared to the NGM group. In the NGM group, there were no significant changes in insulin levels at any time point of the OGTT after 12 and 24 weeks of treatment. In the AbGM group, insulin levels at 1-hour postprandial (P = 0.029) and 2- hour postprandial (P = 0.002) significantly decreased compared to baseline levels after 12 and 24 weeks of medication. Notably, the insulin secretion peak in the NGM group occurred at 1-hour postprandial before and after treatment, while in the AbGM group, the peak shifted from 2-hour to 1-hour postprandial after 24 weeks of medication, reflecting an improvement in insulin secretion phases. Similar to the insulin release curves, the AbGM group had lower C-peptide levels at 30 minutes postprandial compared to the NGM group (P < 0.03), and higher C-peptide levels at 3-hour postprandial (P < 0.01). However, after medication treatment, there were no significant changes in C-peptide levels at any time point in either group (Figure 1C).

Effects of Febuxostat on Indices of Insulin Sensitivity and β-Cell Function

Table 2 summarizes the baseline and 24 weeks values for several indicators of insulin sensitivity and β-cell function in two study groups. Between-group analysis showed that the insulin sensitivity indicators (Stumvoll index and Gutt index) of the NGM group before and after administration were consistently higher than those of the AbGM group. In the repeated measures ANOVA model, the insulin sensitivity indicators of the AbGM group significantly increased after medication compared to the baseline level (P values were all ≤0.01), while the NGM group showed no significant changes before and after treatment (Figure 2). Similar to insulin sensitivity, the insulin β-cell function (ie, ISSI-2 and Disposition index) of the NGM group was consistently higher than that of the AbGM group before and after medication. But febuxostat treatment had no effect on islet β-cell function variables of both groups.

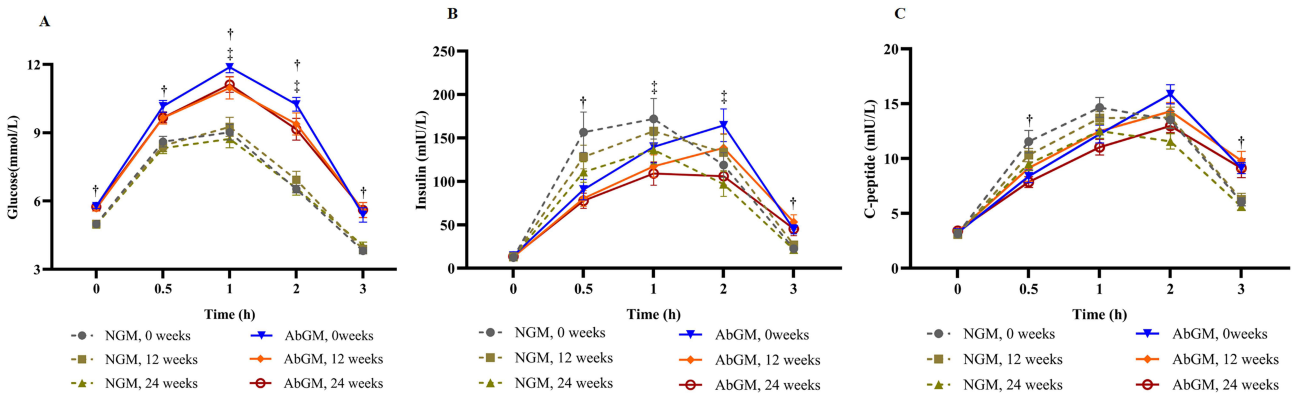

Figure 1 The OGTT results for two groups at baseline, 12 weeks post-treatment, and 24 weeks post-treatment are shown, including (**A**) glucose response, (**B**) insulin response, and (**C**) C-peptide response. Error bars show the standard error of the sample mean. †denotes P < 0.05 for the comparison between NGM and AbGM group; ‡denotes P < 0.05 for the comparison between post-treatment and baseline in AbGM group.

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Table 2 Laboratory Tests Before and After Medication in the Study Population

Index	Normal Glucose Metabolism			Abnormal Glucose Metabolism		
	Pre-Febuxostat	Post-Febuxostat	*P* value	Pre-Febuxostat	Post-Febuxostat	*P* value
BMI (kg/m2)	26.20 (23.95, 28.39)	26.27 (24.00, 28.49)	0.600	26.12 (24.99, 27.66)	26.61 (25.03, 27.07)	0.379
LDL (mmol/L)	3.30±0.76	3.44±0.90	0.231	2.91±0.88	3.21±0.89	**0.041***
TC (mmol/L)	5.39±0.81	5.44±0.85	0.672	5.05±0.93	5.18±1.03	0.410
TG (mmol/L)	3.30±0.76	3.44±0.90	0.194	3.19±1.89	2.49±1.23	**0.005****
ESR (mm/h)	5.00 (2.00, 15.00)	5.00 (2.00, 10.00)	0.516	8.00 (4.00, 13.50)	8.00 (4.00, 13.75)	0.976
CRP (mg/L)	1.47 (0.61, 2.56)	1.16 (0.65, 1.57)	0.115	1.86 (0.82, 3.03)	1.28 (0.60, 3.17)	0.585
SUA (μmol/L)	561.04±70.10	351.00±86.73	**<0.001****	581.75±89.27	354.41±112.25	**<0.001****
ALT (U/L)	37.89±34.74	33.81±29.80	0.585	37.89±18.61	32.11±18.52	0.132
AST (U/L)	25.22±13.21	23.37±7.41	0.487	24.11±7.64	24.79±11.76	0.758
γ-GT (U/L)	47.04±38.67	50.33±48.85	0.561	40.89±15.58	45.35±30.45	0.371
Cr (μmol/L)	86.30±16.87	82.48±17.34	**0.036**	88.14±13.51	85.93±13.62	0.261
Cyc-C (μmol/L)	0.91±0.18	0.89±0.20	0.537	0.94±0.23	0.94±0.21	0.912
eGFR (mL/min/1.73 m^2)	93.88±21.66	99.76±25.02	**0.036***	87.59±17.55	89.86±15.50	0.350
HbA1c (%)	5.59±0.35	5.64±0.52	0.641	5.96±0.58	5.95±0.60	0.886
HbA1c (mmol/mol)	37.63±3.79	38.11±5.68	0.641	41.36±6.07	41.53±6.53	0.886
Insulin sensitivity						
Stumvoll index	0.11±0.01	0.11±0.01	0.801	0.09±0.01	0.10±0.12	**0.015***
Gutt index	74997.04±2.17	74,997.34±1.91	0.153	74,989.90±3.61	74,990.89±3.23	**0.004****
β-cell function						
ISSI-2	876.11±348.24	758.32±206.24	0.072	492.75±180.72	462.99±145.67	0.153
Disposition index	19.12±23.40	11.55±5.95	0.088	5.27±3.76	5.04±3.50	0.756

Notes: Data are mean±SD or median (quartile) unless otherwise indicated. Bold numbers indicate that the p-value is less than 0.05.*p<0.05; **p<0.01.

When investigating the simple correlations between insulin sensitivity and anthropometric and laboratory parameters in subjects of the AbGM group, the Stumvoll index and Gutt index were consistently negatively correlated with 2h-PG and 2-h postprandial insulin (P values were all < 0.01). The Gutt index was also negatively correlated with baseline BMI, ALT, AST, and the change value of HbA1c (P values were all < 0.05). Insulin sensitivity was consistently not significantly correlated with uric acid (Supplemental Table 2).

Reversal and Progression of Prediabetes and T2DM in AbGM Group

To assess the impact of febuxostat on subjects with AbGM, we evaluated the reversal and progression of glucose metabolism in those subjects after medication. After 24 weeks of febuxostat treatment, among the 20 participants with

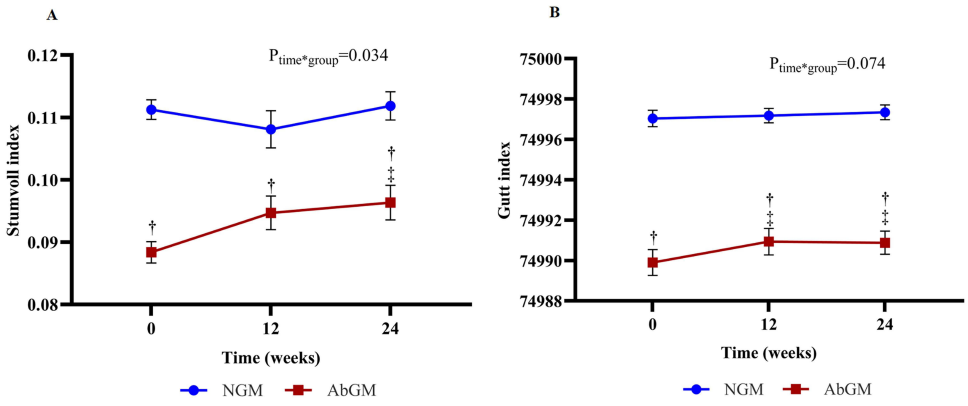

Figure 2 Comparison between the NGM and AbGM groups at baseline, 12 weeks post-treatment, and 24 weeks post-treatment for (**A**) Stumvoll index and (**B**) Gutt index. Error bars show the standard error of the sample mean. †denotes P < 0.05 for the comparison between NGM and AbGM group; ‡denotes P < 0.05 for the comparison between post-treatment and baseline in AbGM group; *denotes the interaction between time and group.

Table 3 Reversal and Progression of Prediabetes and Type 2 Diabetes in AbGM Group

	Prediabetes			Type 2 Diabetes		
	Before	**After**	***P* value**	**Before**	**After**	***P* value**
Normal	–	8 (40.00%)	**<0.001****	–	3 (25.00%)	**0.007****
Prediabetes	20	9 (45.00%)		–	4 (33.33%)	
IFG	1	1		–	0	
IGT	15	7		–	3	
IFG+IGT	4	1		–	1	
Type 2 diabetes	–	3 (15.00%)		12	5 (41.67%)	

Note: Bold numbers indicate that the p-value is less than 0.05. **p<0.01.

prediabetes, 3 (15.00%) developed T2DM, 8 (40.00%) returned to normal, and 9 (45.00%) remained in the prediabetes stage. In subjects with newly diagnosed T2DM, 3 (25.00%) out of 12 participants returned to normal, 4 (33.33%) returned to prediabetes, and 5 (41.67%) remained in the newly diagnosed T2DM stage. Overall, among the AbGM group (n=32), 3 (9.38%) experienced progression in blood glucose, 15 (46.88%) experienced blood glucose reversal, and 14 (43.75%) maintained their initial status (Table 3).

Changes in the Secondary Endpoint Before and After Medication

In the laboratory tests of the two groups of subjects, we observed a significant increase in low-density lipoprotein cholesterol (LDL) and a significant decrease in triglycerides in the AbGM group. In the NGM group, we observed a decrease in serum creatinine and a significant increase in eGFR. Both groups showed a significant decrease in serum uric acid level (Table 2).

Discussion

The main findings of this survey on subjects with HUA and different glucose metabolism statuses are: (i) After 24 weeks of treatment with the urate-lowering drug febuxostat, the postprandial blood glucose in subjects with HUA and AbGM significantly decreased; (ii) After 24 weeks of treatment with febuxostat, the insulin sensitivity of subjects with HUA and AbGM significantly improved; (iii) The results of correlation analysis showed that the improvement of insulin sensitivity in participants with HUA and AbGM was not directly correlated with the short-term reduction in uric acid levels.

Hyperuricemia impairs insulin signaling and pancreatic β-cell function by inducing inflammatory response and oxidative stress, which are important mechanisms for the development of T2DM.[17] Previous studies have shown that urate-lowering treatment has a positive impact on FBG and insulin resistance, suggesting that it may be able to reverse or delay the progression of diabetes by reversing the toxic effects of elevated serum uric acid on insulin sensitivity and pancreatic β-cells. In this study, we explored the effects of the urate-lowering drug febuxostat on subjects with HUA and different glucose tolerances. The study found that after 24 weeks of treatment with febuxostat, the levels of 1h-PG, 2h-PG, 1-h postprandial insulin and 2-h postprandial insulin in subjects with HUA and AbGM were significantly reduced. Insulin sensitivity is significantly improved, as indicated by the Stumvoll index and the Gutt index, while β-cell function showed no significant changes. The same beneficial effects were not observed in subjects with HUA and NGM. We observed a significant decrease in triglycerides and a significant increase in LDL in the AbGM group. This may be due to lifestyle changes, such as alterations in dietary habits, although their BMI has not changed significantly.

In our study, the AbGM group observed a significant improvement in insulin sensitivity after 24 weeks of medication, mainly manifested in the decrease of postprandial insulin, and the peak of postprandial insulin secretion was advanced from 2-h postprandial to 1-h. Surprisingly, in our study, there was no direct significant correlation between the improvement of insulin sensitivity and uric acid. In fact, febuxostat may significantly improve insulin sensitivity and glucose tolerance through anti-inflammatory and antioxidant effects that are independent of hyperglycemia improvement. Febuxostat reduces oxidative stress by inhibiting xanthine oxidase activity, decreasing ROS generation, and directly

mitigating oxidative damage. It also alleviates inflammation by inhibiting oxidative stress-induced signaling pathways (such as NADPH oxidase and NF-κB pathways) and suppressing the expression and secretion of key inflammatory cytokines (such as IL-1β, IL-6, and MCP-1). Additionally, it enhances the body's antioxidant defenses by modulating the activity of antioxidant enzymes (such as superoxide dismutase and catalase), further reducing oxidative damage to cells. These anti-inflammatory and antioxidant effects may be independent of blood glucose improvements and significantly enhance insulin sensitivity and glucose tolerance. In models of diabetic nephropathy and atherosclerosis, febuxostat reduces organ inflammation and improves function by decreasing inflammatory cell infiltration and cytokine expression, while slowing disease progression. These mechanisms contribute to its significant protective effects in models of metabolic syndrome, atherosclerosis, and diabetic nephropathy.[18–20] The current findings extend these findings to include participants with prediabetes and newly diagnosed T2DM, who represent the early stages of glucose dysregulation. In addition, the Gutt index at baseline was significantly negatively correlated with BMI, ALT and AST, which can be explained by non-alcoholic fatty liver disease and insulin resistance caused by overweight/obesity.[21]

A study on the effect of febuxostat on insulin resistance in subjects with primary gout showed that after 24 weeks of febuxostat treatment, fasting glucose, insulin, and HOMA-IR significantly decreased, and this may be achieved by reducing oxidative stress.[16] This is not exactly the same as our findings, and although we also observed an increase in insulin sensitivity, we did not observe significant improvements in fasting blood glucose and insulin in participants in both the NGM and AbGM groups, so the parameter HOMA-IR calculated from them also did not show significant improvement. This may be attributed to the different subject groups in the two studies. The former targeted subjects with primary gout, who may have a more severe oxidative stress response than the hyperuricemia subjects in our study. The more significant relief of inflammation led to significant improvements in fasting blood glucose and insulin. As confirmed, in the former study, the high-sensitivity C-reactive protein levels of gout were significantly higher than those of normal subjects, while the C-reactive protein levels of the HUA included in our study were within the normal range.

Our study was the first to discover the positive effect of febuxostat on postprandial blood glucose in AbGM subjects. In China, among subjects with abnormal glucose metabolism, the main issue is IGT,[22] which was also reflected in our prediabetic subjects (15/20, 75.00%). IGT is associated with a higher risk of diabetes.[23] The effect of febuxostat on postprandial blood glucose may provide a dual beneficial impact for subjects with hyperuricemia who have early abnormalities in glucose metabolism. Further mechanistic studies are needed.

This prospective cohort study has several advantages. First, the study includes subjects with HUA and three different glucose metabolism statuses: normal glucose metabolism, prediabetes, and newly diagnosed T2DM, comprehensively assessing the effects of febuxostat on subjects with HUA and different glucose metabolism statuses. Second, each subject underwent a 3-h OGTT before and after medication. The data of blood glucose, insulin, and C-peptide at fasting and postprandial time points are complete. Third, both insulin sensitivity and pancreatic β-cell function is described using two validated indices. This study also has some limitations. First, the sample size is relatively limited. Second, because the incidence of HUA in male is much higher than that in female.[24] This study only includes male with HUA, so it is not possible to compare the sex differences in the effects of febuxostat. Third, our study lacks a control group that does not use febuxostat to further illustrate the effect of the drug. Fourth, the study was conducted in an open-label manner, which may introduce bias due to the potential influence of participants' and researchers' expectations on the outcomes.

In conclusion, the findings of our study suggest that febuxostat has the potential to enhance insulin sensitivity in subjects with HUA who have prediabetes and newly diagnosed T2DM. Additionally, it appears to lower postprandial blood glucose and insulin levels which may contribute to reversing or delaying the progression of T2DM. Further research is required to explore how febuxostat enhances insulin sensitivity.

Data Resource and Availability

The data were analyzed or generated during the study and are available on request from the corresponding authors.

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Disclosure

The authors report no potential conflicts of interest to this work.

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