Chronic hyperglycemia may attenuate the serum-uric-acid-lowering effect of low-dose febuxostat in Japanese patients with type 2 diabetes mellitus

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Abstract

Aims This study investigated the independent predictors of the serum uric acid (sUA)-lowering effect of low-dose febuxostat, a novel xanthine oxidase inhibitor, in Japanese patients with type 2 diabetes mellitus (T2DM).

Materials and methods Data of 130 T2DM patients who had been taking febuxostat 10 mg once daily for elevated sUA (≥ 7 mg/dl) for at least 12 weeks were retrieved from medical records. Spearman's rank correlation coefficients were calculated to determine the correlations between sets of two independent continuous variables. Multiple stepwise linear regression analysis was used to determine independent predictors of the percent change of sUA levels after 12 weeks of febuxostat treatment ($\% \Delta$ sUA).

Results Among all patients, $\% \Delta$ sUA was significantly correlated with age ($\rho = 0.192$, $P = 0.030$) and mean glycated hemoglobin (HbA_{1c}) level ($\rho = -0.186$, $P = 0.036$). Multiple stepwise linear regression analysis of all patients revealed that major independent factors contributing to $\% \Delta$ sUA were mean HbA_{1c} ($\beta = -3.14$, $P = 0.022$) and mean glycated albumin ($\beta = -0.743$, $P = 0.013$) levels.

Conclusions High HbA_{1c} and glycated albumin levels significantly attenuated the sUA-lowering effect of low-dose febuxostat in Japanese patients with T2DM. Further detailed analysis using a larger population is warranted to confirm these findings.

Keywords Glycated hemoglobin · Glycated albumin · Febuxostat · Type 2 diabetes · Serum uric acid

Introduction

Lowering serum uric acid (sUA) levels below saturating levels to a target of <6.0 mg/dl is one of the major goals in the treatment of chronic gout and hyperuricemia to reduce or reverse clinical events such as gouty attacks and urolithiasis [1]. The main pharmacological methods employed for this purpose were xanthine oxidase (XO) inhibitors to reduce UA production [2]. Among the XO inhibitors, the purine analog allopurinol has been the main drug available for decades. However, allopurinol's side effects, although rare, can be serious, particularly hypersensitivity syndrome; they are more common in patients with renal dysfunction [3, 4]. Febuxostat, a novel non-purine analog XO inhibitor administered at a daily dose of 40–240 mg has been demonstrated to be at least as effective as allopurinol (≤ 300 mg/day) in lowering sUA levels to <6.0 mg/dl and may require fewer dose adjustments in patients with mild-to-moderate renal dysfunction [5, 6]. Approved daily doses are 40 and 80 mg in the USA and 80 and 120 mg in Europe. On the other hand, in Japan, for treating hyperuricemia, febuxostat is administered at a starting dose of 10 mg, gradually increasing to a recommended maintenance dose of 40 mg.

Continuous administration of febuxostat 10 mg was recently shown to substantially reduce sUA levels regardless of renal function [7]. However, predictors of the sUA-lowering effect of febuxostat and whether there are non- or poor responders have not been elucidated. The association between type 2 diabetes mellitus (T2DM) and gout has been established for more than a century and is frequently

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reaffirmed [8, 9]. However, the impact of T2DM on patient response to febuxostat has not been determined. Therefore, the aim of this study was to identify the independent predictors of sUA level reduction after 12 weeks of treatment with febuxostat 10 mg once daily in Japanese hyperuricemic patients with T2DM by using multiple stepwise linear regression analyses using the percent level reduction index as the dependent variable.

Materials and methods

Patients

Data of 130 patients with T2DM and aged 38–87 years who were prescribed febuxostat 10 mg once daily for at least 12 weeks for persistent (>12 weeks) elevation of sUA levels (≥ 7.0 mg/dl) were extracted from the medical records of the Fukui-ken Saiseikai Hospital. Patients were excluded if they had a history of T1DM, used any sUA-lowering pharmacotherapy within 6 months of starting febuxostat treatment, used any additional sUA-lowering pharmacotherapy other than febuxostat, or had any change in the use or dosage of hypoglycemic agents, including oral agents, glucagon-like peptide 1 (GLP-1) receptor agonists, or insulin, or use or dosage of antihypertensive or lipid-lowering drugs within 12 weeks of starting febuxostat treatment. Patients were also excluded if they had poor drug compliance (<75 %) as estimated from their medical records.

Parameters evaluated

Basic demographic data were sex; age; height; weight; baseline glycated hemoglobin (HbA_{1c}) level; baseline sUA level; diabetes duration; estimated glomerular filtration rate (eGFR); complications such as retinopathy, hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), and dyslipidemia (total cholesterol ≥ 220 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, and/or triglycerides ≥ 150 mg/dl); and orally administered hypoglycemic, antihypertensive, or lipid-lowering agents. Baseline HbA_{1c} and sUA levels were calculated as averaged levels measured within 12 weeks before starting febuxostat treatment. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. BMI ≥ 25 kg/m² was considered as being overweight.

The primary efficacy analysis evaluated the percent change of sUA level between baseline and week 12 (% Δ sUA), which was calculated as follows: % Δ sUA = [baseline sUA levels (mg/dl) – sUA levels 12 weeks after treatment (mg/dl)]/baseline sUA levels (mg/dl) $\times$ 100). The sUA levels were determined as part of SMA20 by the multichannel Olympus Au-5000 analyzer (Olympus Co., Tokyo, Japan) according to

the uricase method (reference range 4.0–6.5 mg/dl). HbA_{1c} was measured by high-performance liquid chromatography (HPLC) calibrated using Japan Diabetes Society (JDS) Lot 2 reference material [10] (reference range 4.6–6.2 %). Glycated albumin (GA) was measured using a Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co., Tokyo, Japan) by an enzymatic method using albumin-specific proteinase, ketamine oxidase, and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [11] (reference range 11.7–16.0 %).

Estimated glomerular filtration rate (eGFR) was calculated using the formula reported by Matsuo et al. [12]. This equation originated from the work of the Modification in Diet Renal Disease (MDRD) study group [13] adapted for Japanese individuals and is recommended by the Japanese Society of Nephrology: eGFR (ml/min 1.73 m⁻²) = $194 \times \text{SCr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female).

Statistical analysis

Data are expressed as mean $\pm$ standard deviation (SD) unless stated otherwise. Mean HbA_{1c} and GA levels were calculated as averaged HbA_{1c} and GA levels measured within 12 weeks of starting febuxostat treatment. As the relationships between the mean sUA, age, HbA_{1c} and GA levels, and % Δ sUA were nonlinear, correlations between sets of two independent continuous variables were investigated using Spearman's rank correlation coefficient method. Multiple stepwise regression analysis was used to search for independent predictors of % Δ sUA. First, all patient background variables considered clinically meaningful were estimated as independent variables for multivariate analysis, including sex, age, baseline BMI, baseline eGFR, diabetes duration, baseline sUA, and mean HbA_{1c} or GA level. However, because of significant correlations between age and BMI, age and eGFR, and age and diabetes duration on univariate analysis, we limited the number of independent variables in the multivariate analysis to four: sex, age, baseline sUA, and mean HbA_{1c} or GA. *F* value for inclusion of variables was set at 4.0 and level of significance at *P* < 0.05.

All statistical analyses were performed with the JMP version 5.1 (SAS Institute Inc., Cary, NC, USA). The study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki [14]. The protocol was approved by the ethics committee of the Fukui-ken Saiseikai Hospital.

Results

Baseline clinical characteristics are presented in Table 1. At week 12, febuxostat treatment significantly reduced sUA levels from baseline (–2.0 mg/dl, *P* < 0.001); no

Table 1 Clinical characteristics of 130 patients with type 2 diabetes mellitus (T2DM) who received febuxostat 10 mg once daily at baseline and after 12 weeks of treatment

Characteristics	Baseline	Week 12
Sex (male/female)	104/26	
Age (years)	67 ± 13	
BMI (kg/m ²)	24.8 ± 4.2	24.6 ± 3.9
HbA _{1c} (%)	6.9 ± 0.9	7.0 ± 0.9
Diabetes duration (years)	7.0 ± 6.2	
Serum uric acid (mg/dl)	8.2 ± 0.9	6.2 ± 1.3
eGFR (ml/min 1.73 m ⁻²)	51.3 ± 20.8	52.5 ± 22.2
Complications		
Retinopathy (SDR/PPDR/PDR)	18/4/12	
Hypertension	102	
Antihypertensive agents (ARB/CCB/ACEI/diuretics/others)	82/67/11/8/7	
Dyslipidemia	86	
Lipid-lowering agents (statin/fibrates/ezetimibe)	56/6/3	
Antidiabetic medications (n)		
DPP-4 inhibitors	65	
Sulfonylurea	13	
α-Glucosidase inhibitors	32	
Glinide	3	
Thiazolidinediones	1	
SGLT2 inhibitors	1	
GLP-1 receptor agonists	1	
Insulin	40	

Baseline serum uric acid levels were calculated as averaged serum uric acid levels measured within 12 weeks before starting febuxostat treatment. Data are expressed as means ± standard deviations

BMI body mass index, HbA_{1c} glycated hemoglobin, eGFR estimated glomerular filtration rate, SDR simple diabetic retinopathy, PPDR preproliferative diabetic retinopathy, PDR proliferative diabetic retinopathy, ARB angiotensin-2 receptor blockers, CCB calcium-channel blockers, ACEI angiotensin-converting enzyme inhibitors, DPP-4 dipeptidyl peptidase 4, SGLT2 sodium-glucose cotransporter 2, GLP-1 glucagon-like peptide 1

significant changes in BMI, HbA_{1c}, and eGFR from the baseline were observed at week 12 ($P > 0.05$; Table 1).

Among all patients, %ΔsUA was significantly correlated with age ($\rho = 0.192$, $P = 0.030$) and mean HbA_{1c} level ($\rho = -0.186$, $P = 0.036$) (Fig. 1b, c). Meanwhile, %ΔsUA was not significantly correlated with baseline sUA, BMI, or eGFR, diabetes duration, or mean GA level ($\rho = 0.048$, $P = 0.589$; $\rho = 0.050$, $P = 0.572$; $\rho = -0.075$, $P = 0.397$; $\rho = -0.110$, $P = 0.172$; $\rho = -0.125$, $P = 0.223$, respectively; Fig. 1a, d).

To determine the independent determinants of %ΔsUA, multiple stepwise linear regression analysis was performed using %ΔsUA as the dependent variable; sex, age, baseline sUA, and mean HbA_{1c} or GA levels were independent variables. Results indicate that among all patients, the factors contributing significantly to %ΔsUA were mean HbA_{1c} ($P = 0.022$, $r^2 = 0.038$) alone when mean HbA_{1c}

level was used as an independent variable. In the resultant regression equation [%ΔsUA (%) = 46.84 – (3.14 × mean HbA_{1c} level; %)]. Coefficients for two-variable sets were significant ($P < 0.0001$). Mean HbA_{1c} levels alone accounted for 3.8 % of the total variance in %ΔsUA (Table 2).

Furthermore, results indicate that among all patients, factors contributing significantly to %ΔsUA were mean GA ($P = 0.0129$, $r^2 = 0.078$) and baseline sUA levels ($P = 0.0339$, $r^2 = 0.038$) when mean GA level was used as an independent variable instead of mean HbA_{1c} level (Table 3). In the resultant regression equation [%ΔsUA (%) = 15.25 – (0.743 × mean GA level; %) + (2.832 × baseline sUA; mg/dl)], coefficients for all two-variable sets were significant ($P < 0.0001$). Mean GA and baseline sUA levels collectively accounted for 11.6 % of the total variance in %ΔsUA (Table 3).

Fig. 1 Distribution plots between percent change of sUA levels (% Δ sUA) (mg/dl) and baseline UA level (a), age (b), baseline glycosylated hemoglobin (HbA_{1c}) level (c), and mean glycated albumin level (d)

Table 2 Independent predictors of percent change in serum uric acid (% Δ sUA)

	β coefficient	R^2	P value
% Δ sUA (mg/dl)			
Mean HbA _{1c} level	-3.137	0.038	0.0220
Total R^2	0.038		

Independent variables were sex (female = 0, male = 1), age, baseline sUA (mg/dl), and mean HbA_{1c} (%) levels

Sex, age and baseline sUA level were not retained in the model because they were not significant predictors. Values represent independent contributions of each predictor in the model to r^2

% Δ sUA percent change of serum uric acid level between baseline and week 12, HbA_{1c} glycated hemoglobin

Table 3 Independent predictors of percent change in serum uric acid (% Δ sUAC) level

	β coefficient	R^2	P value
% Δ sUA (mg/dl)			
Mean glycated albumin level	-0.743	0.078	0.0201
Baseline sUA level	2.832	0.038	0.0339
Total r^2	0.116		

Independent variables were sex (female = 0, male = 1), age, baseline sUA (mg/dl), and mean glycated albumin level (%) levels

Sex and age were not retained in the model because they were not significant predictors. Values represent independent contributions of each predictor in the model to r^2

% Δ sUA percent change of serum uric acid level between baseline and week 12

Discussion

Multiple stepwise regression analysis showed mean HbA_{1c} and GA levels contribute significantly to the percent of sUA-lowering effect of low-dose febuxostat (10 mg once daily) in Japanese patients with T2DM. To our knowledge, this is the first report to demonstrate a significant relationship between long-term glycemic control markers and the sUA-lowering effect of febuxostat. Therefore, the reason febuxostat-mediated sUA reduction is negatively influenced by chronic hyperglycemia should be discussed precisely with each patient by referring to previous reports.

It is well known that increased oxidative stress and oxidative damage are present in T2DM [15]. Oxidative stress results from the formation of reactive oxygen species (ROS), which are generated by various pathways, such as xanthine oxidase (XO), nicotinamide adenine dinucleotide phosphate, reduced (NADPH) oxidase, and mitochondrial respiratory enzymes [16]. Kuppusamy et al. [17] report that patients with T2DM have significantly increased levels of XO accompanied by decreased levels of antioxidant enzymes compared with controls, suggesting the possible contribution of XO to oxidative stress. Furthermore, they report a strong positive relationship (regression $r = 0.34\text{--}0.51$) between HbA_{1c} and XO activity according to Pearson's correlation analysis in three different ethnic groups. In addition, Desco et al. [18] report that XO plays an important role in the generation of free radicals in diabetes and that XO activity increases in the liver and plasma of diabetic animals; therefore, they speculate that the increase in plasma XO activity in diabetic animals may be explained by the increase in the hepatic release of this enzyme. XO generates superoxides, which are dismutated by superoxide dismutase to form hydrogen peroxide. Hydrogen peroxide can then form a potent hydroxyl radical in the presence of redox-active ions such as ferrous and cuprous ions; this can accelerate the cellular and vascular damage that results in diabetes vascular complications [19]. Although the underlying molecular mechanisms by which hyperglycemia induces XO activation remain unclear, if this phenomenon persists, low-dose febuxostat alone may be insufficient for suppressing elevated XO activity, which is part of the reason febuxostat-mediated sUA reduction is negatively influenced by chronic hyperglycemia. In addition, hyperuricemia induced by frank hyperglycemia [20, 21] may further activate XO through compensatory positive feedback mechanisms. Therefore, the extent that each factor, including hyperglycemia itself and hyperglycemia-induced hyperuricemia, independently influences serum XO activity should be investigated further.

Becker et al. [22] recently reported that among patients with moderate renal impairment (estimated creatinine

clearance 30–59 ml/min), febuxostat 40 mg exhibited lower efficacy in patients with gout and diabetes than in patients with gout alone; meanwhile, febuxostat 80 mg exhibited equivalent efficacy between groups; however, baseline HbA_{1c} levels were not specifically described.

Conversely, some previous reports show that treating patients with allopurinol, which is widely used in clinical practice, prevents glutathione oxidation and lipoperoxidation in human T1DM [18], is effective in improving endothelial vasodilator function in hypercholesterolemic, but not in hypertensive patients [23], and has a protective effect against endothelial dysfunction in diabetic patients with mild hypertension [24]. Furthermore, Kushiya et al. [25] reported that oral administration of allopurinol in ApoE-knockout mice impaired plasma lipoprotein clearance and induced atherosclerosis within a short period, markedly ameliorating lipid accumulation and calcification in the aorta and aortic root.

Febuxostat inhibits XO-dependent UA formation 1000-fold more potently [50 % inhibitory concentration (IC₅₀) = 1.8 nM for febuxostat vs. 2.9 μM for allopurinol] and has superior potency to allopurinol for inhibiting endothelium-associated XO [26]. Febuxostat suppresses plaque formation, reduces arterial oxygen species levels, and improves endothelial dysfunction in ApoE2/2 mice without affecting plasma cholesterol levels [27]. In high-risk cardiac surgery patients with hyperuricemia, febuxostat but not allopurinol lowers oxidized LDL level, oxidative stresses, and pulse wave velocity [28], indicating febuxostat has superior potency compared to allopurinol in the inhibition of XO-derived ROS production. Accordingly, clinicians may want to more aggressively reduce hyperglycemia-mediated elevated XO activity at an early stage using sufficient doses of XO inhibitors, especially febuxostat.

However, judging from the r^2 values, the contribution of mean HbA_{1c} ($r^2 = 0.038$) and mean GA ($r^2 = 0.078$) levels to the %ΔsUA is very small. Therefore, many other factors may contribute to the %ΔsUA, including homeostasis model assessment of insulin resistance (HOMA-IR), because UA metabolism is affected by insulin resistance [29]. However, we could not perform multivariate analysis including HOMA-IR because fasting immunoreactive insulin (IRI) levels were not measured in most patients.

The major limitations of this study are its retrospective analytic design and limited number of patients. Study duration may also be a limitation, because the extent of sUA-lowering response may not have been fully elucidated over this time frame. To date, few reports describe the effect of febuxostat 10 mg once daily over a long-term period. The only article regarding this subject was published in 2014, in which 96 patients with 8 weeks of

treatment with febuxostat 10 mg daily were evaluated [7]; in that study, UA levels and eGFR were significantly ameliorated. Considering these findings, 12 weeks was determined to be a sufficient evaluation period for our study. Furthermore, as mentioned above, other markers that may have affected febuxostat-mediated UA reduction were not measured, such as HOMA-R, XO activity, and UA urine excretion volume [20].

In conclusion, this 12-week retrospective study of Japanese hyperuricemic patients with T2DM provides evidence that high HbA_{1c} and GA levels significantly attenuate the sUA-lowering effect of low-dose febuxostat. Long-term analysis of a larger population using more detailed clinical parameters is warranted to confirm these findings.

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Compliance with ethical standards

Conflict of interest None of the authors has conflicts of interest to declare.

Human rights statement and informed consent All procedures conducted in this study were in accordance with the ethics committee of Fukui-ken Saiseikai Hospital and with the Declaration of Helsinki of 1964 and later revision. Informed consent or substitute for it was obtained from all patients for being included in the study. Identifying information of patients were not included in our written descriptions.

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