Effects of pharmacological reversal of hyperuricemia on features of the metabolic syndrome in patients with gouty arthritis

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Accepted 18 March 2018

ABSTRACT

Hyperuricemia has been associated in epidemiological studies with the development of obesity, hypertension, insulin resistance and type 2 diabetes. Nevertheless, it remains unclear whether lowering of serum uric acid (UA) alters any of the features of the metabolic syndrome. In this prospective study (ClinicalTrials.gov identifier: NCT01654276), 24 patients with gouty arthritis and hyperuricemia were treated for 6 months with the xanthine oxidase inhibitor febuxostat to lower serum UA to <6 mg/dL. Measurements of 24 hours ambulatory blood pressure (ABP) and serum and urine markers of the metabolic syndrome were measured at baseline and at the end of 6 months of febuxostat. The study population consisted of 18 men and 6 women, 18 of which completed the baseline and 6 months visits. Serum UA decreased significantly from 8.7±1.5 mg/dL at baseline to 4.4±1.1 mg/dL at 6 months (P<0.0001). During that time frame, there was no significant change in body mass index, systolic or diastolic blood pressure measured by 24 hours ABP monitor, serum glucose, insulin or homeostatic model assessment for insulin resistance, serum total and high-density lipoprotein-cholesterol, serum triglycerides or urine pH (P>0.05 for all). There was no correlation between parameters of the metabolic syndrome and the decline in serum UA or serum UA achieved at study end. In conclusion, in patients with gouty arthritis, UA lowering with febuxostat below 6 mg/dL had no significant impact on features of the metabolic syndrome.

Significance of this study

What is already known about this subject?

- In epidemiological studies, hyperuricemia has been associated with the development of obesity, hypertension, insulin resistance and type 2 diabetes.
- Some animal studies have suggested that elevation in serum uric acid plays a causal role in the development of metabolic syndrome features.
- Xanthine oxidase inhibitors such as allopurinol and febuxostat can potently lower serum uric acid, but it is not known if these medications can improve features of the metabolic syndrome in patients with hyperuricemia.

What are the new findings?

- In this clinical study conducted in patients with hyperuricemia and gouty arthritis, febuxostat significantly reduced serum uric acid, and maintained it below 6 mg/dL for 6 months.
- Despite reversing hyperuricemia, febuxostat did not significantly alter serum glucose, serum insulin, blood pressure (measured by ambulatory blood pressure monitors) or serum lipid profile.

How might these results change the focus of research or clinical practice?

- The association between hyperuricemia and the metabolic syndrome may be coincidental rather than causal.
- Future studies examining the link between hyperuricemia and metabolic syndrome may need to evaluate strategies for serum uric acid lowering starting at an earlier stage and for a longer period of time.

BACKGROUND

Hyperuricemia has been associated in epidemiological studies with the development of insulin resistance, obesity, hypertension and type 2 diabetes.[1–4] However, it remains unclear whether this association is causal or simply coincidental.

Experimental studies in rodents have suggested a causal effect of hyperuricemia in the development of hypertension and its associated kidney disease,[5] and inhibition of insulin signaling with induction of insulin resistance.[6] In humans, studies on the impact of hyperuricemia on metabolic risk factors have shown mixed findings: several large epidemiological reports suggest an independent impact of elevated serum uric acid (UA) on the development of type 2 diabetes[7–9] and hypertension.[10 11] Other studies failed to show an independent effect of serum UA on the development of these features.[12 13] Importantly, key confounders such as elevated body mass index (BMI), chronic kidney disease (CKD), alcohol

To cite: Marin M, Maalouf NM. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2018-000728

consumption and use of diuretics were not controlled for in all studies.

While a large number of reports have examined the association of hyperuricemia with various features of the metabolic syndrome, there is limited information on the impact of UA lowering on these features. A small prospective study in 14 patients with heart failure treated with the uricosuric agent benzbromarone for 8 weeks showed a significant reduction in insulin level but not in fasting plasma glucose.[14] Another placebo controlled cross-over trial in adolescents with hypertension showed that treatment with the xanthine oxidase inhibitor allopurinol resulted in a significant reduction of blood pressure compared with placebo.[15] However, a recent Cochrane review suggested that there is insufficient evidence to recommend the use of UA-lowering agents for the treatment of hypertension.[16]

To date, there is no information on the effects of the newer xanthine oxidase inhibitor febuxostat on the features of the metabolic syndrome in humans. We hypothesized that if hyperuricemia causes insulin resistance, dyslipidemia and hypertension, then lowering serum UA with febuxostat may result in improved insulin sensitivity and reversal of features of the metabolic syndrome in adults with gouty arthritis.

METHODS

Inclusion and exclusion criteria

Twenty-four adult patients with the diagnosis of gout were recruited in several clinics (general internal medicine, family practice, rheumatology), and Urgent Care Center in Parkland Hospital and UT Southwestern Medical Center in Dallas, Texas, USA. Inclusion criteria were age >21 years, personal history of gouty arthritis and hyperuricemia (defined as serum >7.0 mg/dL in men and >6.0 mg/dL in women). Exclusion criteria included current use of azathioprine, mercaptopurine, theophylline, losartan and probenecid, and use of febuxostat or allopurinol in the 3 months preceding study entry. Other exclusion criteria included treatment with insulin, uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg within the past 6 months), uncontrolled diabetes mellitus (HbA1c >8%), estimated GFR <60 mL/min by MDRD (representing CKD stage 3 or worse), elevated liver function tests (AST or ALT greater than three times the upper limit of normal) and pregnancy. Patients on antihypertensive medications or antidiabetes medications were asked to continue these drugs and follow-up with their treating physicians, and were closely followed for any changes in doses of medications throughout the study.

All participants provided written informed consent. This study is registered as NCT01654276 on the ClinicalTrials.gov site.

Study protocol

After a screening visit, participants who qualified were invited for an initial study visit during which they were fitted with an ambulatory blood pressure monitor (ABPM) (90217 Ultralite ABP Monitor Spacelab Healthcare, Issaquah, Washington, USA) that they wore for a complete 24 hours period. Blood pressure and pulse measurements were made every 20 min during awake hours and every 30 min during the night. Participants returned the next day in a fasting state for a blood draw and spot urine sample and to return the ABPM. At that point, treatment with febuxostat 40 mg by mouth once a day was initiated.

After 2 and 4 months of febuxostat therapy, participants returned for an ambulatory clinic visit during which a fasting blood sample was drawn for measurement of serum uric and liver function tests. If serum UA level was ≥6 mg/dL, the dose of febuxostat was titrated up to 80 mg/day, while the 40 mg dose was continued if serum UA was below this level. After 6 months of febuxostat therapy, participants returned for a second set of visits for 24 hours ABPM, and fasting blood and spot urine studies.

Measurements

Fasting serum studies were ran using Quest Laboratories for electrolytes, glucose, liver function tests, lipid profile and UA. Fasting serum insulin was measured using ELISA assay (Mercodia, Uppsala, Sweden). Urinary pH was measured by pH electrode. Urinary UA was measured by enzymatic assay. Urinary creatinine was measured by colorimetric analysis.

Statistical analysis

Descriptive statistics were used to summarize each of the time points, and results were analyzed using paired t-test comparing the pre-post febuxostat time points. Pearson's correlation coefficients were employed to evaluate the association among changes in serum UA (delta serum UA) and changes in HOMA-IR, blood pressure, lipid profile.

RESULTS

The study population consisted of 18 men and 6 women. Eighteen of the 24 subjects completed the baseline and 6 months visits. Of the six subjects who did not complete the study, one withdrew due to recurrent attacks of gouty arthritis within the first 3 months of therapy, one due to difficulty in returning for follow-up visits and four never started the study medication. The results in this report are therefore limited to the 18 subjects with available data at baseline and 6 months. Characteristics of these subjects are shown in table 1. Mean age was 56±8 years, while mean BMI was 33.1±5.3 kg/m^2. The study population was primarily composed of men (72%). Ethnicity was almost equally divided between Caucasians, African-Americans and Hispanics. Seventy-two per cent of the study participants had a previous history of hypertension, and 6% had a prior history of diabetes.

Table 1 Characteristics of study participants

Age (years)	**56±8**
Gender (% female)	28%
Ethnicity (% African-American/Caucasian/Hispanic)	33/39/28
Height (cm)	170±11
Weight (kg)	96.1±17.9
Body mass index (kg/m^2)	33.1±5.3
History of hypertension (%)	72%
History of diabetes (%)	6%

Data are expressed as percentage or mean±SD.

Table 2 Changes in outcomes between baseline and following 6 months of febuxostat treatment

	Baseline	6 months	P value*
BMI (kg/m^2)	33.1±5.3	33.4±5.9	0.82
Serum UA (mg/dL)	8.7±1.5	4.4±1.1	<0.0001
Serum creatinine (mg/dL)	0.98±0.18	0.98±0.22	0.88
Systolic BP† (mm Hg)	130±16	126±14	0.17
Diastolic BP† (mm Hg)	79±9	75±9	0.070
Serum glucose (mg/dL)	104±15	107±30	0.64
Serum insulin (mU/L)	13.3±6.3	14.0±6.1	0.69
HOMA-IR	1.77±0.82	1.86±0.83	0.66
Serum total cholesterol (mg/dL)	204±39	196±46	0.42
Serum HDL-cholesterol (mg/dL)	47±11	49±16	0.51
Serum triglycerides (mg/dL)	190±83	175±107	0.40
Urine UA (mg/dL)	381±189	208±137	0.0032
Urine creatinine (mg/dL)	1411±794	1332±669	0.68
Fractional excretion UA	0.04±0.02	0.04±0.02	0.62
Urine pH	5.58±0.46	5.58±0.43	0.99

*P value for baseline vs 6 months results by paired t-test.
†Systolic and diastolic blood pressure measured by 24 hours ambulatory blood pressure monitoring.
BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; UA, uric acid.

Serum UA decreased significantly from 8.7±1.5 mg/dL at baseline to 4.4±1.1 mg/dL at 6 months (P<0.0001) (table 2, figure 1A). There was concomitant significant decrease in urinary UA (381±189 to 208±137 mg/dL; P=0.0032), but no significant change in fractional excretion of UA (figure 1B). Weight and BMI did not change significantly during the 6 months study period (table 2). During the same time frame, there were non-significant changes in ambulatory blood pressure measurements (systolic blood pressure: 130±16 mm Hg at baseline vs 126±14 mm Hg at 6 months, P=0.17; diastolic blood pressure: 79±9 to 75±9 mm Hg, P=0.070, table 2). One subject experienced a sizeable (>25 mm Hg) drop in systolic and diastolic blood pressure (figure 2A and B) requiring discontinuation of a diuretic agent during the course of the study, while antihypertensive medications were unchanged in the remaining participants. There was no significant correlation between the change in blood pressure and change in serum UA (figure 2C and D).

Measurements of glucose metabolism were not significantly different between baseline and 6 months (fasting serum glucose: 104±15 to 107±30 mg/dL, P=0.64; fasting serum insulin levels 13.3±6.3 to 14.0±6.1 mU/L, P=0.69; HOMA-IR 1.77±0.82 to 1.86±0.83, P=0.66, figure 3A, B and C). Changes in serum glucose and insulin were not significantly correlated with change in serum UA (figure 3D and E).

Serum lipid profile (including fasting total cholesterol, HDL-cholesterol and triglycerides) did not change significantly during the course of the study (table 2). Fasting urine pH did not significantly change during the study (table 2).

DISCUSSION

This study was designed to determine whether lowering serum UA levels in patients with gouty arthritis using the xanthine oxidase inhibitor febuxostat improves features of the metabolic syndrome including insulin resistance, hypertension and dyslipidemia. We found no significant difference in any of the features of the metabolic syndrome after 6 months of treatment with febuxostat despite reducing serum UA below 6 mg/dL.

To our knowledge, no other interventional study has evaluated the impact of febuxostat on features of the metabolic syndrome in humans, although febuxostat administration significantly lowered blood pressure, serum triglycerides and insulin in rats fed a high-fructose diet.[17] Interventional studies using other UA-lowering agents in different groups of human subjects have been performed with conflicting results. The uricosuric agent benzbromarone significantly reduced serum insulin without altering serum glucose in a randomized cross-over trial in 14 patients with congestive heart failure,[14] whereas the xanthine oxidase inhibitor allopurinol did not impact serum insulin or glucose in patients with non-insulin-dependent diabetes.[18] Allopurinol use

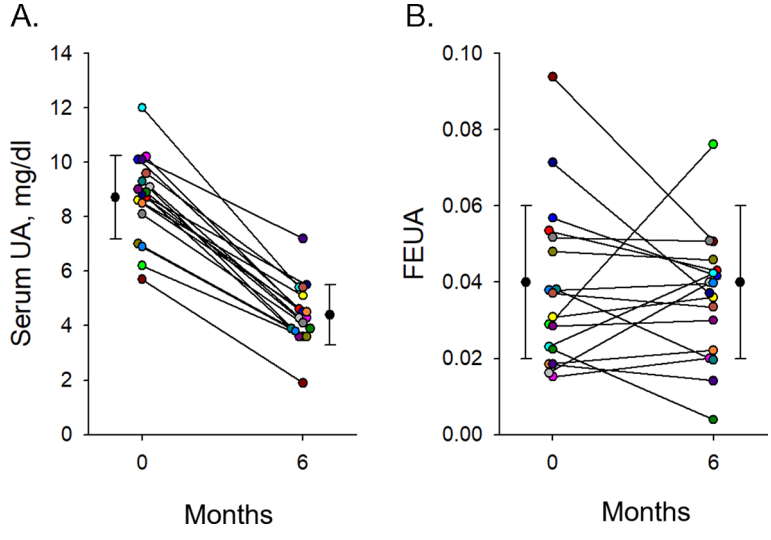

Figure 1 Changes in serum uric acid (UA) (A) and fractional excretion of uric acid (FEUA, B). Lines represent individual changes. Outer dot (●) with error bars represent mean±SD.

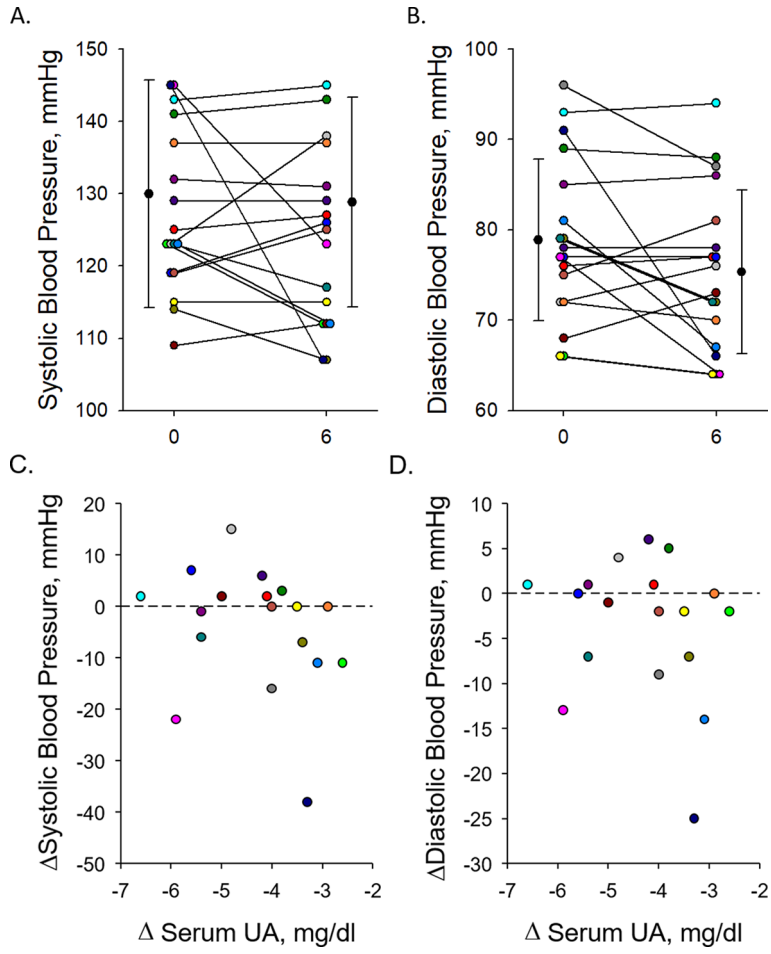

Figure 2 Changes in 24 hours ambulatory systolic (A) and diastolic blood pressure (B). Lines represent individual changes. Outer dot (●) with error bars represent mean±SD. Net change in 24 hours ambulatory systolic (C) and diastolic blood pressure (D) before and after treatment vs change in serum uric acid (UA).

significantly lowered blood pressure in adolescents with primary hypertension,[15] and a meta-analysis including 10 randomized controlled and prospective trials using allopurinol found a net decline in systolic and diastolic blood pressure.[19] Still, a recent Cochrane review suggested that there is insufficient evidence to recommend the use of UA-lowering agents for the treatment of hypertension.[16] There is also limited information regarding the impact of urate-lowering agents on lipid profile. Allopurinol use for 3 months was associated with a significant decrease in low-density lipoprotein-cholesterol in 12 patients with end-stage renal disease,[20] but had no significant impact on lipid profile in patients with CKD[21] or non-insulin-dependent diabetes.[18]

Similar to some of these prior reports with other urate-lowering agents, our study found no significant impact of febuxostat on serum insulin or glucose or on lipid profile, despite a significant reduction in serum UA. There was a trend towards lower diastolic blood pressure (P=0.070), and it is conceivable that with a larger sample size, the impact of febuxostat on blood pressure would have become statistically significant. The website www.ClinicalTrials.gov describes a few larger studies currently being conducted to assess the impact of febuxostat on blood pressure.

Few features of our study need to also be considered. First, the duration of treatment (6 months) may be insufficient to produce a change in metabolic syndrome features and studies with longer duration of treatment may be warranted. Second, our study participants all had gouty arthritis, and results may not necessarily be applicable to patients with asymptomatic hyperuricemia without gout. Third, the average age of our subjects was 56±8 years. Prior studies have suggested that pharmacological reduction of serum UA may having a greater lowering in blood pressure in younger individuals,[22] possibly due to a greater burden of cardiometabolic risk factors with advancing age (that overwhelm the effect of hyperuricemia), or to more permanent changes that occur with prolonged hyperuricemia including reduction in vascular wall elasticity. Finally, we feel that it is unlikely that lowering serum UA concentration below the achieved level of 4.4 mg/dL would have yielded different results, as higher risk for diabetes, hypertension, dyslipidemia and coronary artery disease was observed at serum UA levels >5.0–6.0 mg/dL in past epidemiological studies.[2 7 11]

One major limitation of our study is the absence of a placebo arm. A placebo-controlled study would have

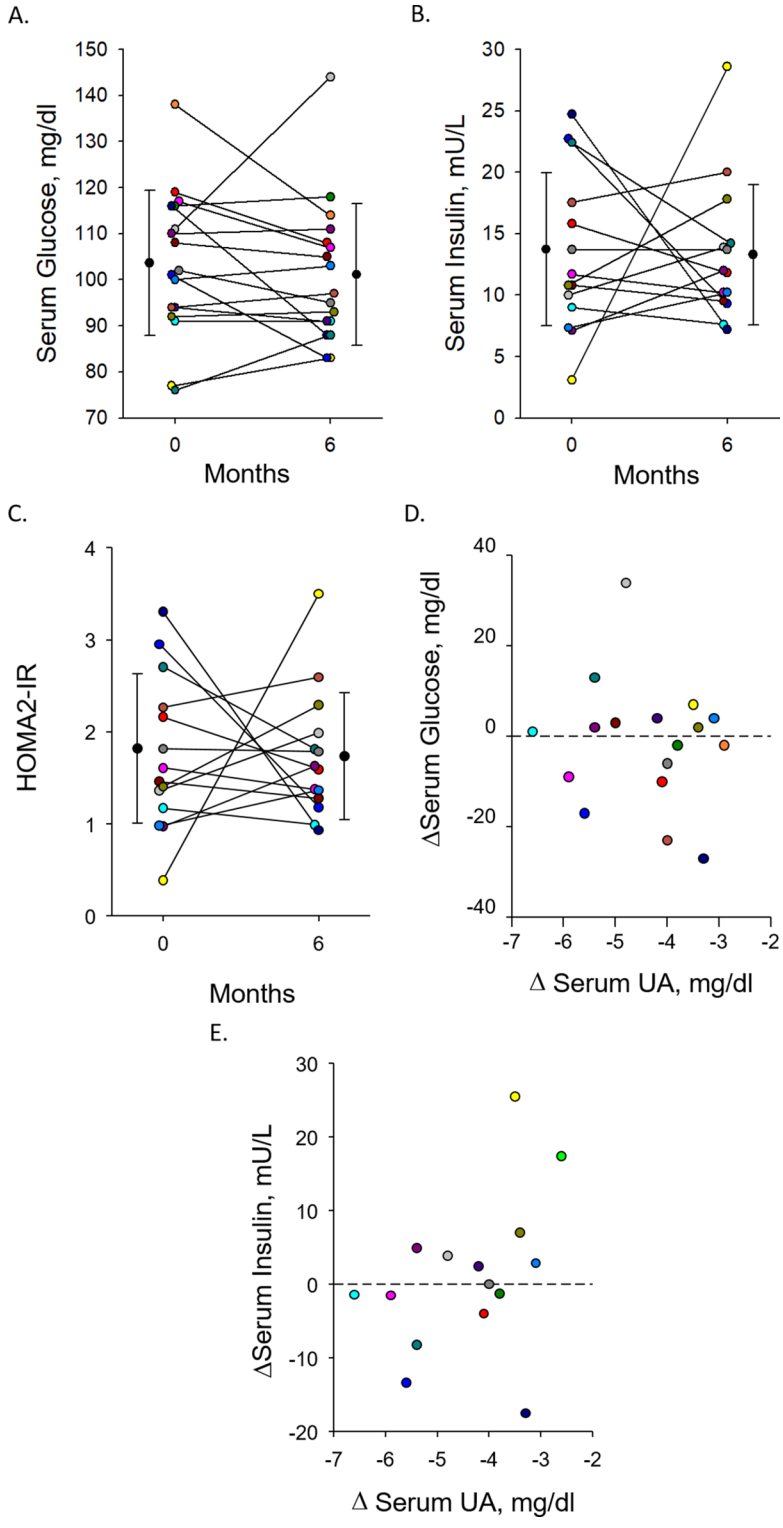

Figure 3 Changes in serum glucose (A), insulin (B) and homeostatic model assessment for insulin resistance (C). Lines represent individual changes. Outer dot (●) with error bars represent mean±SD. Net change in serum glucose (D) and serum insulin (E) levels before and after treatment vs change in serum uric acid (UA).

allowed us to determine with more certainty the impact of febuxostat on metabolic syndrome features. However, our study participants all suffered from symptomatic hyperuricemia (due to gouty arthritis), and a placebo arm would not have been ethical in this study population.

CONCLUSIONS

In this uncontrolled study, UA lowering with febuxostat below 6 mg/dL had no significant impact on features of the metabolic syndrome in patients with gouty arthritis. These findings should be considered when planning additional

studies regarding lowering UA and various features of the metabolic syndrome.

Acknowledgements The authors deeply appreciate the help of the research nursing staff: Reena John, Ann Heard-Sakhaee and Carolyn Griffith for their help in carrying out the study protocol, John Poindexter for figure preparation and technical support and Beverley Huet for statistical analysis.

Contributors MM contributed to subject recruitment, follow-up, data collection and drafting of manuscript. NMM contributed to subject recruitment, study conduct and supervision, data analysis and manuscript review.

Funding This study was funded in part by an investigator-initiated grant (MSA-NC-FEB-137) to Dr Maalouf from Takeda Pharmaceuticals (USA). This grant provided research costs to UT Southwestern.

Disclaimer Takeda Pharmaceuticals had no role (either direct or indirect) in study design, data collection and analysis, decision to publish or preparation of the manuscript. The authors had no other relationship or involvement with Takeda Pharmaceuticals.

Competing interests This study was funded in part by an investigator-initiated grant (MSA-NC-FEB-137) to Dr Maalouf from Takeda Pharmaceuticals (USA). This grant provided research costs to UT Southwestern.

Patient consent Obtained.

Ethics approval The study was reviewed and approved by the Institutional Review Board at the University of Texas Southwestern Medical Center.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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