Lowering Uric Acid With Allopurinol Improves Insulin Resistance and Systemic Inflammation in Asymptomatic Hyperuricemia

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Background: Hyperuricemia is an independent predictor of impaired fasting glucose and type 2 diabetes, but whether it has a causal role in insulin resistance remains controversial. Here we tested the hypothesis that lowering uric acid in hyperuricemic nondiabetic subjects might improve insulin resistance.

Methods: Subjects with asymptomatic hyperuricemia (n = 73) were prospectively placed on allopurinol (n = 40) or control (n = 33) for 3 months. An additional control group consisted of 48 normouricemic subjects. Serum uric acid, fasting glucose, fasting insulin, HOMA-IR (homeostatic model assessment of insulin resistance), and high-sensitivity C-reactive protein were measured at baseline and at 3 months.

Results: Allopurinol-treated subjects showed a reduction in serum uric acid in association with improvement in fasting blood glucose, fasting insulin, and HOMA-IR index, as well as a reduction in serum high-sensitivity C-reactive protein. The number of subjects with impaired fasting glucose significantly decreased in the allopurinol group at 3 months compared with baseline (n = 8 [20%] vs n = 30 [75%], 3 months vs baseline, $P < 0.001$). In the hyperuricemic control group, only glucose decreased significantly and, in the normouricemic control, no end point changed.

Conclusions: Allopurinol lowers uric acid and improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia. Larger clinical trials are recommended to determine if lowering uric acid can help prevent type 2 diabetes.

Key Words: uric acid, allopurinol, insulin resistance, inflammation

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An association of hyperuricemia and/or gout with hyperglycemia has been reported for more than 100 years and has been linked to a cluster of signs described as the metabolic syndrome.[1–7] Classically, hyperuricemia has been viewed as a secondary finding without functional significance in metabolic syndrome.[8,9] As such, measurement of uric acid has not been recommended in the workup of a patient with obesity or insulin resistance.

This viewpoint may need to be reconsidered. First, an elevated serum uric acid appears as an independent predictor for impaired fasting glucose or type 2 diabetes in 22 of 24 studies as well as in a meta-analysis (reviewed in Johnson et al.[10]). Second, experimental studies showed that uric acid may play a contributory role in causing diabetes via a number of actions, including inhibition of AMP-activated protein kinase, resulting in increased gluconeogenesis, and inflammation and oxidative stress in the pancreatic islet cells.[11–14] Lowering uric acid has also been reported to improve insulin resistance in animal models of metabolic syndrome.[15,16] Although interventional studies in humans are limited, lowering uric acid was reported to improve insulin resistance in subjects with congestive heart failure[17] and HbA1c levels in normotensive diabetic subjects.[18] However, no improvement in insulin resistance was observed with lowering uric acid in adult men administered large doses of fructose (200 g/d).[19]

Given these background data, we designed a prospective randomized study to determine if lowering uric acid with a xanthine oxidase inhibitor, allopurinol, can improve fasting glucose levels and insulin resistance in nondiabetic subjects with asymptomatic hyperuricemia.

MATERIALS AND METHODS

Patients and Study Design

This is a prospective, randomized, 3-month intervention trial conducted at Istanbul Medeniyet University, Goztepe Training and Research Hospital, between January 2014 and June 2014. The study was approved by the Istanbul Medeniyet University Ethics Committee and was conducted in accordance with the ethical principles set forth by the Declaration of Helsinki. This study was registered at ClinicalTrials.gov (study no. NCT02008968). All of the participants were included after signing informed consent forms. The primary end point of the study was whether allopurinol treatment would improve insulin resistance defined by homeostatic model assessment of insulin resistance (HOMA-IR) in asymptomatic hyperuricemic subjects without a history of diabetes mellitus compared with untreated hyperuricemic and normouricemic controls. A total of 121 consecutive patients attending the outpatient clinic with normal kidney function and fulfilling the inclusion criteria were recruited for the study. Of these, 73 patients were hyperuricemic (defined as serum uric acid >7 mg/dL for men and >6.5 mg/dL for women), whereas the remaining 48 patients were normouricemic. After entry into the study, the physician managing the patient was asked to randomly assign the hyperuricemic patient to receive either allopurinol 300 mg/d for 3 months or no treatment (ie, to serve as hyperuricemic control group). A flowchart of the study design is depicted

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Dr Johnson is an inventor of a patent at the University of Florida on lowering uric acid in the treatment of insulin resistance (US 2014/0107136 A1) that has been licensed to XORT Therapeutics.

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in Figure 1. All of the groups had levels of serum uric acid, high-sensitivity C-reactive protein (hsCRP), and HOMA-IR at baseline and at the end of the 3-month study period. Lifestyle and physical activity were not modified in any of the group of patients, and medications were not changed throughout the study period.

Inclusion criteria: clinically asymptomatic hyperuricemia; exclusion criteria: presence of diabetes mellitus, hypothyrodism, hyperthyroidism, kidney and liver disease, or history of allergy to allopurinol. In addition, patients with a previous diagnosis of gout and current use of thiazide diuretics, allopurinol, or uricosuric agents were excluded. Finally, an unwillingness to participate in the study also qualified for exclusion. An additional control group with normal serum uric acid level that also had no evidence for the same comorbid conditions (see above) was included (n = 48). The patients were monitored for potential adverse effects of allopurinol via system review and a comprehensive physical examination.

Blood Pressure Measurement

Hypertension was defined as a systolic blood pressure (SBP) more than 140 mm Hg or diastolic BP (DBP) more than 90 mm Hg on repeated measurements or the use of antihypertensive drugs. The arterial BP was measured by a physician 3 times after a 15-minute resting period in the morning, and mean values were calculated for SBP and DBP for all participants.

Laboratory Measurements

Blood sampling was performed in the morning, after 12 hours of fasting. Samples (6–8 mL) of venous blood were collected from each subject in the morning between 8:00 and 9:00 AM, after an overnight fast. Serum uric acid levels were determined in all samples. All assays were performed with a Cobas 8000 autoanalyzer c 701 module using its own kits (Roche Diagnostics, Indianapolis, Ind). In all patients, we measured fasting plasma glucose, total serum cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein cholesterol. Measurements of hsCRP were done by a photometric kit. The basal insulin level was measured by Beckman Coulter UniCel DxI 800 autoanalyzer (California, USA). An insulin resistance score (HOMA-IR) was computed using the following equation: HOMA-IR was defined as fasting plasma glucose (milligrams per deciliter) × immunoreactive insulin (micro international units per milliliter)/405.[20] Impaired fasting glucose was accepted as fasting blood glucose level from 100 to 125 mg/dL.[21]

Statistical Methods

Summary statistics at baseline were generated for key demographic and baseline characteristics. These include N, mean, SD, minimum, median, and maximum. Data were summarized for each of the 3 groups. Baseline differences for continuous variables were compared among the 3 groups using a Kruskal-Wallis test. For discrete variables, sex and hypertension, a χ^2 test was performed. Change from baseline for HOMA-IR, insulin, glucose, uric acid, and hsCRP was summarized by N, mean, SD, first and third quartiles, and the median. Change (from a difference of zero) was tested by signed rank test, as the end points of interest were not normally distributed and the resulting residuals from an analysis of variance were unlikely to meet normality assumptions. Analysis of change between the groups was performed on the ranked change values as well as for untransformed variables.

RESULTS

Baseline Demographics

Table 1 shows the baseline characteristics of the 3 groups of subjects (asymptomatic hyperuricemia, asymptomatic hyperuricemia treated with allopurinol, and normouricemic groups). As expected, subjects with hyperuricemia tended to be more hypertensive, hyperlipidemic, and insulin resistant than normouricemic controls. Comparison among the 3 groups showed that age, uric acid, glucose, insulin, HOMA-IR, creatinine, and presence of hypertension differed significantly (Table 1).

Correlation Analysis of Subjects' Variable

Serum fasting insulin levels negatively correlated with HDL cholesterol levels ($r = -0.216$, $P = 0.02$). In contrast, there were no statistically significant correlations between fasting insulin with body mass index (BMI), triglyceride, HDL, fasting glucose, and hsCRP levels. Serum uric acid levels were positively correlated with HOMA-IR index ($r = 0.244$, $P = 0.007$; Fig. 2) but no correlation with fasting insulin and hsCRP was observed.

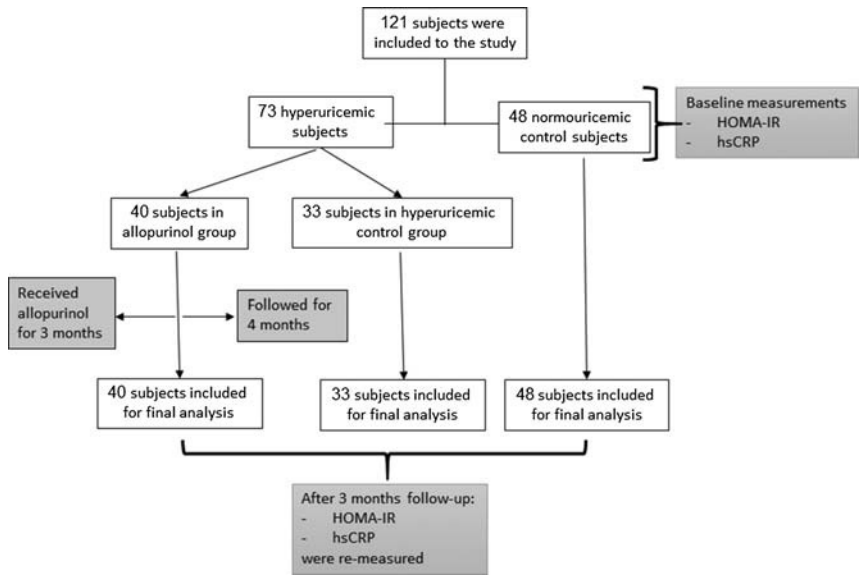

FIGURE 1. Flow diagram of the study.

TABLE 1. Baseline Clinical Characteristics and Laboratory Values of the Study Population

	Hyperuricemic Control Group (n = 33)	Allopurinol Group (n = 40)	Normouricemic Control Group (n = 48)	*P*
Mean age, y	49.88 ± 12.46	52.15 ± 15.86	45.3 ± 10.7	0.011
Male sex, n (%)	11 (33)	25 (62.5)	5 (10.4)	0.02
Hypertension, n (%)	20 (60.6)	19 (47.5)	25 (52.1)	<0.0001
BMI, kg/m^2	30.9 ± 4.86	30.11 ± 4.39	30.43 ± 6.46	0.73
Uric acid, mg/dL	7.45 ± 0.9	7.86 ± 0.62	4.55 ± 0.86	<0.0001
Creatinine, mg/dL	1.07 ± 0.2	0.9 ± 0.15	0.81 ± 0.18	<0.0001
Glucose, mg/dL	93.06 ± 8.24	102.6 ± 9.04	93.23 ± 8.18	<0.0001
Insulin, μU/mL*	14.4 (10.0–19.0)	12.7 (8.3–12.4)	9.8 (6.1–14.8)	0.041
HOMA-IR index*	3.2 (2.2–4.1)	3.1 (1.9–4.3)	2.2 (1.3–3.4)	0.044
HsCRP, mg/L*	0.4 (0.2–0.9)	0.3 (0.3–0.9)	0.3 (0.2–0.7)	0.145
LDL cholesterol, mg/dL	120 ± 33	138 ± 40	119 ± 38	0.049
HDL cholesterol, mg/dL	47 ± 10	48 ± 13	52 ± 14	0.276
Triglyceride, mg/dL*	145 (116–193)	174 (117–239)	119 (102–164)	0.029
Total cholesterol, mg/dL	200 ± 40	224 ± 53	200 ± 42	0.031
Medications, n (%)				
RAAS blockers, n (%)	16 (48.5)	19 (47.5)	20 (41.7)	>0.05
Diuretic, n (%)	0	0	0	
Beta-blocker, n (%)	0	0	1 (2)	

Data are shown as mean ± SD or median (25th–75th percentile) as appropriate. Comparison among groups was made by 1-way analysis of variance test or Kruskal-Wallis and χ^2 test. Value of $P < 0.05$ was considered to show a statistically significant result.

*Median (interquartile range).

HDL indicates high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system.

Effect of Allopurinol Therapy on Fasting Glucose, Fasting Insulin, and HOMA-IR Index

Treatment with allopurinol for 3 months was associated with a significant improvement in the primary end point, including fasting blood glucose, fasting insulin, and the HOMA-IR index (Table 2; Fig. 3A–C). A decrease in hsCRP was also observed (Fig. 3D). In the hyperuricemic control group, serum glucose decreased significantly (although by approximately one third seen in the allopurinol group) and, in the normouricemic control, no end point changed significantly. The allopurinol group showed a significant improvement in HOMA-IR ($P < 0.0001$), insulin ($P < 0.0001$), uric acid ($P < 0.0001$), and hsCRP ($P < 0.0001$) compared with the hyperuricemic control group, with only a trend in improvement in glucose ($P = 0.07$). Importantly, the number of patients with impaired fasting glucose levels were significantly lower in the allopurinol group at 3 months compared with baseline (n = 8 [20%] vs n = 30 [75%], 3 months vs baseline, $P < 0.001$). The change in serum uric acid levels in the 3 groups had no significant correlations with changes in fasting insulin, fasting glucose, HOMA-IR, and hsCRP.

DISCUSSION

In this study, 73 subjects with asymptomatic hyperuricemia were administered allopurinol or continued as controls and were followed for 3 months. Treatment with allopurinol led to a significant decrease in serum uric acid and was well tolerated without significant side effects. The striking finding was a robust improvement in fasting glucose, fasting insulin, and HOMA-IR in the allopurinol group. In addition, hsCRP, which is considered a marker of systemic inflammation, was also improved with allopurinol. When compared with the hyperuricemic control group, a significant improvement was observed in insulin resistance (HOMA-IR), fasting insulin, and hsCRP, but not in serum glucose. These data suggest that allopurinol can improve insulin resistance in

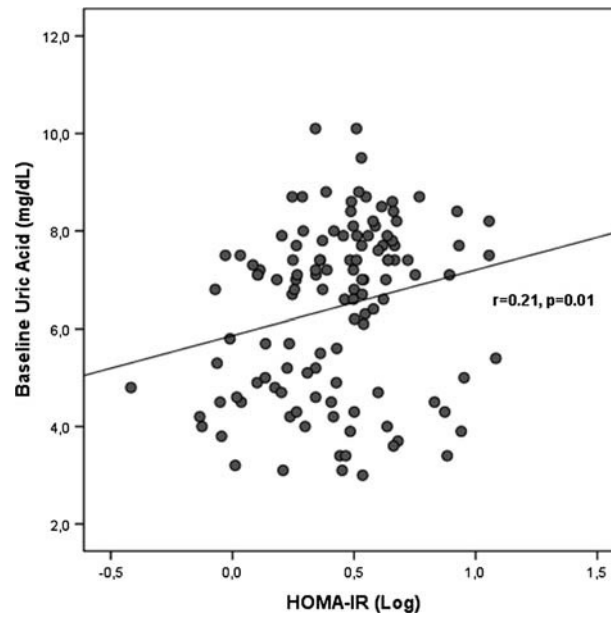

FIGURE 2. The association between baseline serum uric acid level and HOMA-IR (Log).

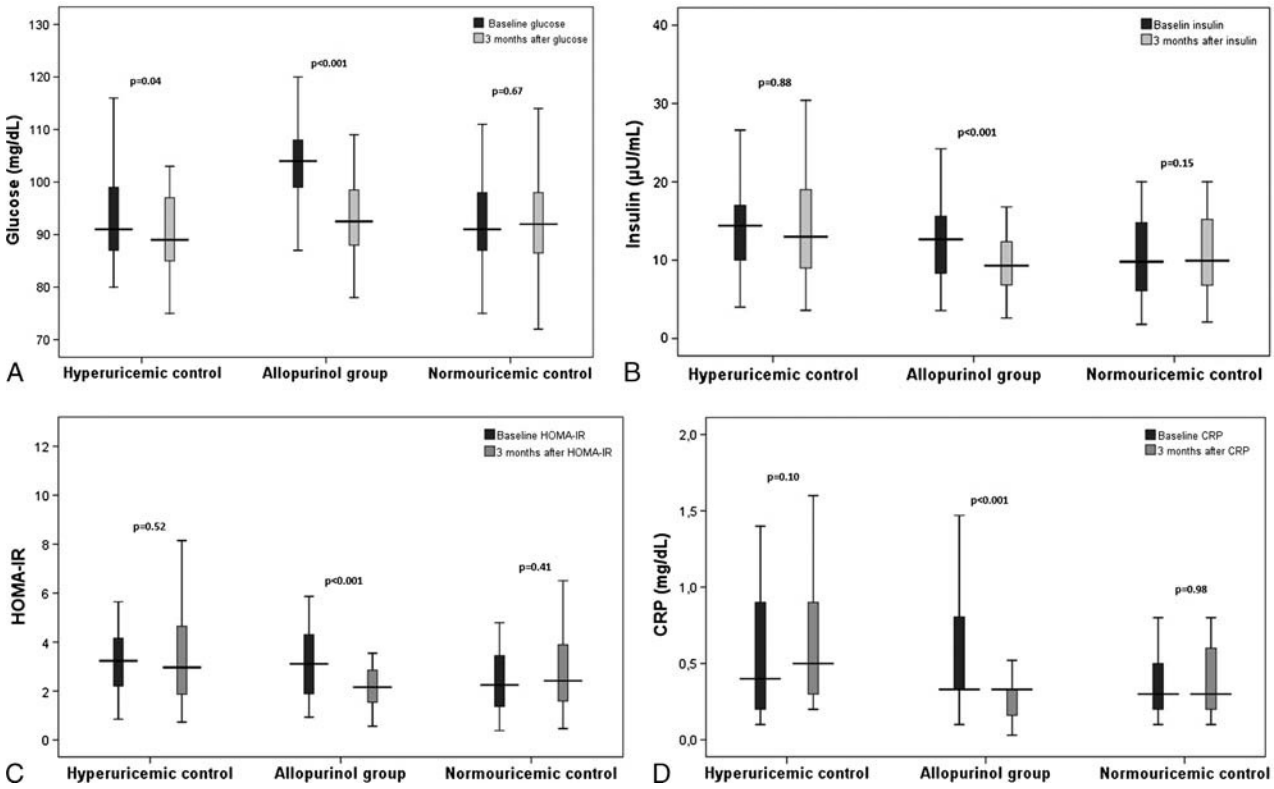

FIGURE 3. A, Glucose at baseline and third month after. B, Insulin at baseline and third month after. C, HOMA-IR at baseline and third month after. D, HsCRP at baseline and third month after.

hyperuricemic subjects and is consistent with the hypothesis that xanthine oxidase and/or uric acid may have a contributory causal role in insulin resistance.

Uric acid is a purine degradation product that is best recognized as a cause of gout and kidney stones. Recent studies suggest that uric acid may offer survival benefits, especially under conditions of food deprivation.[21,22] In animal models, hyperuricemia has been shown to stimulate fat stores in the liver,[12,23] to raise blood pressure,[24,25] and to stimulate foraging response-like behavior.[26] Indeed, one of the reasons fructose has been postulated to be so effective at inducing metabolic syndrome is via its ability to generate uric acid during its metabolism.[11,15,27]

Hyperuricemia is one of the most important predictors of insulin resistance and diabetes. However the exact pathophysiological mechanism by which uric acid influences insulin resistance needs to be clarified. Uric acid probably contributes to insulin resistance by adversely affecting various tissues such as islet cells, liver, endothelium and adipocytes.[12,14,28–30]

High uric acid levels were found to inhibit the proliferation of pancreatic β cells, increase the production of reactive oxygen species and impair the glucose stimulated insulin secretion in both in vitro and in vivo studies.[14,31] Further examination on signal transduction pathways revealed AMPK and ERK pathways were responsible for the adverse effects of uric acid on islet functions.[31]

TABLE 2. The Mean Serum Uric Acid, Glucose, Insulin, and HOMA-IR Score at Baseline and 3 Months Later

	Hyperuricemic Control Group (n = 33)			Allopurinol Group (n = 40)			Normouricemic Control Group (n = 48)		
	Baseline	3 Mo	*P*	Baseline	3 Mo	*P*	Baseline	3 Mo	*P*
Uric acid, mg/dL	7.45 ± 0.9	7.07 ± 0.90	0.13	7.86 ± 0.62	6.27 ± 0.95	<0.001	4.55 ± 0.86	4.65 ± 0.82	0.05
Glucose, mg/dL	93.06 ± 8.24	90 ± 7.5	0.04	102.6 ± 9.04	92.3 ± 8.2	<0.001	93.23 ± 8.18	92.4 ± 9.15	0.67
Insulin, μU/mL*	14.4 (10.0–19.0)	13.0 (9.0–19.0)	0.88	12.7 (8.3–12.4)	9.3 (6.8–12.4)	<0.001	9.8 (6.1–14.8)	9.9 (6.8–15.2)	0.15
HOMA-IR index*	3.2 (2.2–4.1)	2.9 (1.8–4.6)	0.52	3.1 (1.9–4.3)	2.1 (1.5–2.8)	<0.001	2.2 (1.3–3.4)	2.4 (1.6–3.8)	0.41
HsCRP, mg/dL*	0.4 (0.2–0.9)	0.5 (0.3–0.9)	0.10	0.3 (0.3–0.9)	0.3 (0.2–0.3)	<0.001	0.3 (0.2–0.7)	0.3 (0.2–0.6)	0.98
IFG, n (%)	6 (18.2)	3 (9.1)	0.37	30 (75)	8 (20)	<0.001	10 (20.8)	8 (16.7)	0.72

Data are presented as median (25th–75th percentile). Analysis of change within a group, Wilcoxon signed rank test and McNemar.

*Median (interquartile range).

HOMA-IR indicates homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IFG, impaired fasting glucose.

Furthermore, proinflammatory and prooxidative effects of uric acid on pancreatic β cells were prevented by the organic anion transport inhibitor, probenecid that blocks the entry of uric acid into the cells.[14]

Uric acid may also lead to insulin resistance by mitochondrial oxidative stress and steatosis in liver.[12] Another possible role of uric acid on insulin resistance is through the inhibition of the vasodilatory effects of insulin, leading to decreased delivery of glucose to the skeletal muscles causing peripheral insulin resistance.[15,29] Lowering uric acid levels with allopurinol was demonstrated to decrease local inflammation and increase adiponectin levels in adipose tissue and improved insulin sensitivity in the hyperuricemic mouse model.[16]

Serum uric acid levels are controlled in most mammals by uricase, an enzyme in the liver that degrades uric acid, eventually generating allantoin. However, a series of mutations occurred in ancestral humans (hominoids) during the Oligocene, culminating in the complete loss of uricase in the mid-Miocene.[32] The loss of uricase in the Miocene occurred during global cooling that led to decreased availability of fruits, especially in Europe, leading to seasonal famine that eventually resulted in extinction of the apes in this region. Nevertheless, studies of the fossil record suggest that a European ape returned to Africa to become the ancestor of African apes and humans.[33,34] This has led to the hypothesis that the uricase mutation may have occurred in Europe where it would have resulted in a survival advantage during times of reduced fruit (fructose) availability.[35,36] Indeed, the ability of fructose to increase features of metabolic syndrome in rats can be enhanced if uricase is inhibited.[37] Moreover, the ancestral uricase has been recently resurrected and has been shown to decrease fat synthesis and gluconeogenesis in human liver cells (HepG2 cells) in response to fructose and starvation, respectively.[32,38] Hence, it is likely that the uricase mutation may have functioned like a "thrifty gene," as postulated by Neel[39] more than 50 years ago. However, uric acid levels have been increasing in the last century, particularly in response to increasing sugar (sucrose) and high fructose in the diet.[40,41] In turn, hyperuricemia has emerged as a potential candidate for driving hypertension, diabetes, fatty liver, and obesity.[10,42]

Allopurinol is known to have allergic and hepatotoxic adverse effects.[43] Thus, it should be carefully used with good patient follow-up. Patients who are planned to be treated with allopurinol should be informed about the toxicity of the drug. It is obvious that lifestyle modification is the first-line and the safest treatment modality to improve insulin sensitivity and cardiovascular health. Head-to-head clinical trials are needed to compare the efficacy and safety of allopurinol and lifestyle modifications. At this time, treatment with allopurinol is discouraged until such trials are completed because of the possible toxicity of allopurinol.

There are several limitations of the study. First, the subjects were enrolled based on inclusion criteria, but choice of allopurinol versus control was performed by the treating physician, and hence, the study was not a pure randomization. As a consequence, there were some differences noted at baseline among groups, of which the major difference was a higher percentage of men in the allopurinol group compared with the hyperuricemic controls. The sex difference likely accounts for the slightly higher baseline uric acid in the allopurinol versus hyperuricemic control group as well. Nevertheless, the observation that there was little change in insulin resistance parameters in the control group compared with the allopurinol group suggests that the changes in insulin resistance are valid. The second weakness is that the study does not determine if the beneficial effects of allopurinol on insulin resistance are caused by lowering uric acid or another aspect of allopurinol, such as the blocking of xanthine oxidase–associated oxidants or an off-target effect of allopurinol. However, the prior report that a uricosuric (benzbromarone) was able to also improve insulin resistance in a small number of patients with congestive heart failure[17] would be consistent with the effect being caused by uric acid. Finally, we did not have the information on change in BMI, weight, or lipid measurements to see if there were effects of allopurinol on these parameters. Possible weight changes might have effects on serum uric acid levels, glycemic markers, insulin resistance, and inflammation; however, we could not evaluate the relationships between these parameters and weight changes because we did not have the information about the changes in weight.

In conclusion, allopurinol treatment of subjects with asymptomatic hyperuricemia resulted in a marked improvement in insulin resistance and systemic inflammation. Larger clinical trials are indicated to determine if lowering uric acid can help prevent type 2 diabetes.

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