

Richard J. Johnson,¹ Tony Merriman,² and Miguel A. Lanasa¹

Causal or Noncausal Relationship of Uric Acid With Diabetes



Diabetes 2015;64:2720–2722 | DOI: 10.2337/db15-0532

Humans and great apes have higher serum uric acid due to mutations that reduced activity and then silenced the uricase gene about 15 million years ago (1). Uricase degrades intracellular urate in the liver, resulting in low serum uric acid. Parallel silencing of uricase occurred in lesser apes, suggesting natural selection for higher serum uric acid. Uric acid is an antioxidant in the extracellular environment, reacting with superoxide (to make allantoin) and with peroxynitrite (to make triuret). These antioxidant properties of uric acid were proposed to be beneficial by protecting against aging and cancer-associated oxidative stress (2).

A different hypothesis has also been proposed (3). The uricase mutation occurred during a period of global cooling that caused seasonal famines for ancestral apes living in Europe due to loss of fruit availability during winter months. The primary food for these ancestral apes was fruit rich in fructose, a nutrient that predisposes to increased hepatic and visceral fat stores and insulin resistance due to its unique metabolism in which transient ATP depletion occurs (4). The nucleotide turnover generates urate intracellularly with a rise in serum uric acid. The intracellular urate causes mitochondrial oxidative stress and inhibits AMPK, resulting in liver fat accumulation, gluconeogenesis, and metabolic syndrome (5,6). Inhibition of uricase amplifies the effects of fructose to induce metabolic syndrome, whereas expressing the ancestral uricase in human liver cells blocks the effects of fructose to induce fat accumulation and gluconeogenesis (1,7,8). This suggests uric acid may be a survival factor that enhances the metabolic effects of fructose during famine (3).

The introduction of diets rich in sugar and umami (purine-rich) foods has led to a remarkable rise in serum uric acid and a widespread increase in obesity and diabetes (9). Elevated serum uric acid consistently predicts the development of obesity and diabetes (9,10). Lowering serum uric acid prevents insulin resistance in fructose-dependent and fructose-independent animal models

of metabolic syndrome (11,12). A pilot randomized clinical study reported that lowering uric acid with a uricosuric agent improves insulin resistance (13), and we completed a randomized trial that showed that lowering uric acid with allopurinol also improves insulin resistance in hyperuricemic individuals (M. Takir, O. Kostek, O. Elcioglu, A. Bakan, A. Erek, A. Ozkok, H. Mutlu, O. Telci, A. Semerci, A. Riza Odabas, A. Covic, G. Smits, M.A.L., S. Sharma, R.J.J., and M. Kanbay, unpublished data). In contrast, we did not show improvement in insulin resistance by lowering serum uric acid in subjects administered fructose, but this may relate to the high doses (200 g/day) administered (14).

In this issue of *Diabetes*, Sluijs et al. (15) challenge the uric acid-insulin resistance hypothesis using a genetic epidemiological approach known as Mendelian randomization. A “genetic score” consisting of 24 single nucleotide polymorphisms identified from genome-wide association studies was developed that explained 4% of the variance in serum uric acid. Using two studies that included over 40,000 subjects with diabetes, they show that the genetic score predicts serum uric acid as expected, but not diabetes. They conclude that serum uric acid is not causal in diabetes and that “uric acid-lowering therapies may therefore not be beneficial in lowering diabetes risk” (15).

It is critical to question how one proves causality. Adapting Koch’s postulates, one might conclude uric acid is likely causal for diabetes (Table 1) (8–14). However, one must always be open to the possibility that a hypothesis may not be correct. Mark Twain is said to have remarked, “It ain’t what you don’t know that gets you into trouble, it’s what you know for sure that just ain’t so.” Thus, the article by Sluijs et al. is important as it emphasizes that more research is needed, especially “black swan” studies aimed at disproving a hypothesis.

Nevertheless, there are limitations with using epidemiology to address causality, as the underlying premise is that the linkage between the factor and the outcome is direct. For example, the Framingham Heart Study erred in

¹Division of Renal Diseases and Hypertension, University of Colorado, Aurora, CO

²Department of Biochemistry, University of Otago, Dunedin, New Zealand

Corresponding author: Richard J. Johnson, richard.johnson@ucdenver.edu.

© 2015 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

See accompanying article, p. 3028.

Table 1—Koch's postulates adapted to uric acid and diabetes

1. An elevated serum uric acid predicts the development of diabetes (epidemiology) (9,10).
2. Experimentally raising uric acid with fructose causes insulin resistance in rats (11).
3. Lowering serum uric acid improves insulin resistance in fructose-dependent and -independent models of metabolic syndrome (11,12).
4. Cellular mechanisms by which uric acid can induce diabetes have been identified (8).
5. A pilot study reported that lowering serum uric acid improves insulin resistance in subjects with hyperuricemia (13), but this was not shown in subjects administered high doses of fructose (14).

suggesting serum uric acid is not a true risk factor for heart disease because it was not independent of high blood pressure (16). Later, they realized serum uric acid is an independent risk factor for hypertension (17), and, hence, the relationship of uric acid with cardiovascular disease could still be causal, but indirect (18). Indeed, the evidence that uric acid is causal in hypertension is strengthening (19).

The genetic score in the article by Sluijs et al. (15) is largely based on genes that modulate uric acid transport between extracellular and intracellular environments and, hence, may dissociate the physiological serum-intracellular relationship. Furthermore, the transporter with the highest influence on the genetic score is *SLC2A9*, which has opposing effects on the kidney and portal circulation, such that knocking it down in the kidney leads to a fall in serum uric acid, while knocking it down in the intestine causes a rise in portal and serum uric acid. As uric acid-mediated metabolic effects result primarily from the intracellular actions of uric acid in the liver, it is interesting that knockdown of intestinal *SLC2A9* results in features of metabolic syndrome that were prevented by lowering serum uric acid (20). The genetic score did not predict diabetes after removing the two major uric acid-associated transporters (*SLC2A9* and *ABCG2*), but one still does not know how the score alters the extracellular-intracellular equilibrium. If serum uric acid is an indirect reflection of intracellular urate, which we postulate is the direct cause of insulin resistance, then the genetic score may dissociate this relationship and lead to the incorrect notion that serum uric acid is not causal as a risk factor for diabetes.

Additional Mendelian randomization studies failed to show a relationship of genetic score with hypertension and insulin resistance and kidney function or, in some cases, showed protection (see Supplementary Table 8 [15]) (21). Other studies show positive relationships of uric acid-raising alleles with hypertension, obesity, insulin resistance, and cardiovascular and kidney disease (22–31).

More research needs to be done. Pathway analyses in Mendelian randomization studies, such as those that focus

on mechanism (glycolysis vs. transport) or site (how it affects intracellular levels), might provide better insights into causality. Ultimately, we recommend establishing causality by direct experimental investigation, followed by large randomized controlled clinical trials to determine whether lowering serum uric acid, and especially intracellular, can slow the development of metabolic syndrome and diabetes.

Duality of Interest. R.J.J. is listed as an inventor on patents on uric acid and its role in blood pressure and insulin resistance (U.S. patents 7,799,794B2 and 8,557,831) and has shares in XORT, a start-up company developing novel xanthine oxidase inhibitors. No other potential conflicts of interest relevant to this article were reported.

References

1. Kratzer JT, Lanaspá MA, Murphy MN, et al. Evolutionary history and metabolic insights of ancient mammalian uricases. *Proc Natl Acad Sci U S A* 2014; 111:3763–3768
2. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci U S A* 1981;78:6858–6862
3. Johnson RJ, Andrews P. The fat gene: a genetic mutation in prehistoric apes may underlie today's pandemic of obesity and diabetes. *Sci Am*. In press
4. Ishimoto T, Lanaspá MA, Le MT, et al. Opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. *Proc Natl Acad Sci U S A* 2012;109:4320–4325
5. Lanaspá MA, Cicerchi C, García G, et al. Counteracting roles of AMP deaminase and AMP kinase in the development of fatty liver. *PLoS One* 2012;7:e48801
6. Lanaspá MA, Sanchez-Lozada LG, Choi YJ, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. *J Biol Chem* 2012;287:40732–40744
7. Tapia E, Cristóbal M, García-Arroyo FE, et al. Synergistic effect of uricase blockade plus physiological amounts of fructose-glucose on glomerular hypertension and oxidative stress in rats. *Am J Physiol Renal Physiol* 2013;304:F727–F736
8. Cicerchi C, Li N, Kratzer J, et al. Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: evolutionary implications of the uricase loss in hominids. *FASEB J* 2014;28:3339–3350
9. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, et al. Sugar, uric acid, and the etiology of diabetes and obesity. *Diabetes* 2013;62:3307–3315
10. Kodama S, Saito K, Yachi Y, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care* 2009;32:1737–1742
11. Nakagawa T, Hu H, Zharikov S, et al. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 2006;290:F625–F631
12. Baldwin W, McRae S, Marek G, et al. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. *Diabetes* 2011;60:1258–1269
13. Ogino K, Kato M, Furuse Y, et al. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail* 2010;3:73–81
14. Perez-Pozo SE, Schold J, Nakagawa T, Sánchez-Lozada LG, Johnson RJ, Lillo JL. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. *Int J Obes (Lond)* 2010;34:454–461
15. Sluijs I, Holmes MV, van der Schouw YT, et al. A Mendelian randomization study of circulating uric acid and type 2 diabetes. *Diabetes* 2015;64:3028–3036

16. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7–13
17. Sundström J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. *Hypertension* 2005;45:28–33
18. Johnson RJ, Tuttle KR. Much ado about nothing, or much to do about something? The continuing controversy over the role of uric acid in cardiovascular disease. *Hypertension* 2000;35:E10
19. Feig DI, Madero M, Jalal DI, Sanchez-Lozada LG, Johnson RJ. Uric acid and the origins of hypertension. *J Pediatr* 2013;162:896–902
20. DeBosch BJ, Kluth O, Fujiwara H, Schürmann A, Moley K. Early-onset metabolic syndrome in mice lacking the intestinal uric acid transporter SLC2A9. *Nat Commun* 2014;5:4642
21. Hughes K, Flynn T, de Zoysa J, Dalbeth N, Merriman TR. Mendelian randomization analysis associates increased serum urate, due to genetic variation in uric acid transporters, with improved renal function. *Kidney Int* 2014;85:344–351
22. Mallamaci F, Testa A, Leonardis D, et al. A polymorphism in the major gene regulating serum uric acid associates with clinic SBP and the white-coat effect in a family-based study. *J Hypertens* 2014;32:1621–1628; discussion 1628
23. Mallamaci F, Testa A, Leonardis D, et al. A genetic marker of uric acid level, carotid atherosclerosis, and arterial stiffness: a family-based study. *Am J Kidney Dis* 2015;65:294–302
24. Testa A, Mallamaci F, Leonardis D, et al; MAURO Study Investigators. Synergism between asymmetric dimethylarginine (ADMA) and a genetic marker of uric acid in CKD progression. *Nutr Metab Cardiovasc Dis* 2015;25:167–172
25. Voruganti VS, Nath SD, Cole SA, et al. Genetics of variation in serum uric acid and cardiovascular risk factors in Mexican Americans. *J Clin Endocrinol Metab* 2009;94:632–638
26. Parsa A, Brown E, Weir MR, et al. Genotype-based changes in serum uric acid affect blood pressure. *Kidney Int* 2012;81:502–507
27. Shafiu M, Johnson RJ, Turner ST, et al. Urate transporter gene SLC22A12 polymorphisms associated with obesity and metabolic syndrome in Caucasians with hypertension. *Kidney Blood Press Res* 2012;35:477–482
28. Voruganti VS, Laston S, Haack K, et al. Serum uric acid concentrations and SLC2A9 genetic variation in Hispanic children: the Viva La Familia Study. *Am J Clin Nutr* 2015;101:725–732
29. Sun X, Zhang R, Jiang F, et al. Common variants related to serum uric acid concentrations are associated with glucose metabolism and insulin secretion in a Chinese population. *PLoS One* 2015;10:e0116714
30. Kleber ME, Delgado G, Grammer TB, et al. Uric acid and cardiovascular events: a Mendelian randomization study. *J Am Soc Nephrol*. 18 March 2015 [Epub ahead of print]. DOI: 10.1681/ASN.2014070660
31. Voruganti VS, Franceschini N, Haack K, et al. Replication of the effect of SLC2A9 genetic variation on serum uric acid levels in American Indians. *Eur J Hum Genet* 2014;22:938–943