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Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome

Takahiko Nakagawa*, Katherine R Tuttle, Robert A Short and Richard J Johnson

SUMMARY

The increasing incidence of obesity and the metabolic syndrome over the past two decades has coincided with a marked increase in total fructose intake. Fructose—unlike other sugars—causes serum uric acid levels to rise rapidly. We recently reported that uric acid reduces levels of endothelial nitric oxide (NO), a key mediator of insulin action. NO increases blood flow to skeletal muscle and enhances glucose uptake. Animals deficient in endothelial NO develop insulin resistance and other features of the metabolic syndrome. As such, we propose that the epidemic of the metabolic syndrome is due in part to fructose-induced hyperuricemia that reduces endothelial NO levels and induces insulin resistance. Consistent with this hypothesis is the observation that changes in mean uric acid levels correlate with the increasing prevalence of metabolic syndrome in the US and developing countries. In addition, we observed that a serum uric acid level above 5.5 mg/dl independently predicted the development of hyperinsulinemia at both 6 and 12 months in nondiabetic patients with first-time myocardial infarction. Fructose-induced hyperuricemia results in endothelial dysfunction and insulin resistance, and might be a novel causal mechanism of the metabolic syndrome. Studies in humans should be performed to address whether lowering uric acid levels will help to prevent this condition.

KEYWORDS essential hypertension, insulin resistance, metabolic syndrome, obesity, uric acid

REVIEW CRITERIA

We searched PubMed in June 2005 for articles published between 1983 and 2005, containing the terms "uric acid", "fructose", "obesity", "diabetes", "hypertension", "metabolic syndrome", "insulin resistance", "hypertriglyceridemia", "nitric oxide" and "endothelial dysfunction".

T Nakagawa is Research Assistant Professor in the Division of Nephrology, Hypertension, and Transplantation at the University of Florida, Gainesville, FL, KR Tuttle is the Medical and Scientific Director at The Heart Institute and Providence Medical Research Center, Spokane, Washington, DC, RA Short is a faculty member at Washington State University, Spokane, Washington, DC, and RJ Johnson is the J Robert Cade Professor of Nephrology and the Chief of the Division of Nephrology, Hypertension and Transplantation at the University of Florida, Gainesville, FL, USA.

Correspondence
*Division of Nephrology, Hypertension and Transplantation, PO Box 100224, University of Florida, Gainesville, FL 32610, USA
nakagt@medicine.ufl.edu

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INTRODUCTION

Obesity is epidemic. Prevalence has quadrupled in the past 25 years; 16% of children and 30% of adults in the US are now affected.[1] Many obese people suffer from the 'metabolic syndrome', which is characterized by insulin resistance, hypertriglyceridemia and hypertension.[2] Progression of the obesity epidemic has coincided with increased frequency of TYPE 2 DIABETES, and now affects more than 17 million individuals in the US.

A simple explanation for the obesity epidemic is that individuals ingest more calories than they consume. One contributory factor is ready access to foods high in fat and sugar. 'Fast foods' such as soft drinks, burgers, pizza, chips and pastries comprise nearly 20% of total energy intake for the average American.[3] Epidemiological studies implicate the introduction of 'Western diets' high in fatty meats and refined sugars in the epidemics of obesity, diabetes and hypertension currently occurring in Africa, Asia, South America, Australia/New Zealand and Oceania.[4,5] Not surprisingly, up to 45% of females and 30% of males are dieting at any given time.[6] Unfortunately, most studies show that, regardless of whether a low-fat or low-carbohydrate diet is followed, and despite often impressive weight loss in the first few months of a diet, long-term weight-reduction goals are seldom achieved because of poor adherence to the diet and high attrition rates.[7]

It is important to consider mechanisms of, and strategies for preventing and treating, the obesity epidemic. We propose that certain foods, particularly fructose-based sweeteners, cause the metabolic syndrome by increasing serum uric acid levels.

FRUCTOSE AND THE OBESITY EPIDEMIC

Fructose is a simple sugar present in honey and fruit. It constitutes 50% of table sugar (sucrose; a disaccharide consisting of one glucose and one fructose molecule) and accounts for 55% of the sugar content of high-fructose corn syrup

(HFCS). HFCS was introduced in the US in 1967 as a more stable and less expensive alternative to table sugar. It is currently used in many foods, particularly soft drinks, baked goods, candies/sweets, jams/preserves, yogurts, and sweetened and packaged products. While yearly per capita sucrose intake decreased from 44 to 30 kg between 1966 and 2001, HFCS consumption increased from 0 to 29 kg.[8,9] So, in the US, there has been an approximately 30% increase in total fructose intake, contributing to a 25–30% increase in total sweetener consumption, over the past 35 years.[10]

Over the past 25 years, the increased fructose intake correlates with the acceleration of the obesity epidemic.[10] Ingestion of soft drinks, which are high in HFCS, is associated with an increased risk of obesity in adolescents[11] and of type 2 diabetes in young and middle-aged women.[12] Similarly, excessive consumption of fruit juice, which is also high in fructose, is associated with obesity in children.[13] Feeding fructose to rats causes rapid development of the metabolic syndrome, including obesity, hypertension, insulin resistance, hypertriglyceridemia and hyperinsulinemia.[14,15]

There are several reasons why fructose, as opposed to other sugars, might cause obesity.[14] Fructose is phosphorylated in the liver by fructokinase. Further metabolism generates glycerol-3-phosphate, which is crucial in the synthesis of triglycerides. Fructose administration markedly enhances triglyceride synthesis,[15,16] which increases intramyocellular triglyceride content in the skeletal muscle, causing insulin resistance.[17] Evidence indicates that fructose does not suppress appetite to the same degree as glucose. Glucose ingestion causes transient elevation of serum glucose and insulin. The latter then stimulates leptin release, signaling the brain to stop eating. Ingestion of fructose decreases postprandial glucose levels. Subsequently lower insulin and leptin levels result, thereby predisposing the individual to continue to eat.[16]

FRUCTOSE-INDUCED HYPERURICEMIA AND THE METABOLIC SYNDROME

We have identified another mechanism by which fructose might cause the metabolic syndrome. We propose that development of the metabolic syndrome is related to the unique ability of fructose to increase serum uric acid levels. Oral or intravenous ingestion of fructose results in a rapid (30–60 min) increase in serum uric acid in humans, which might be sustained;[18–21] glucose and other simple sugars do not have the same effect. The effect of fructose intake on serum uric acid is greatest in patients with gout and their children.[18–20]

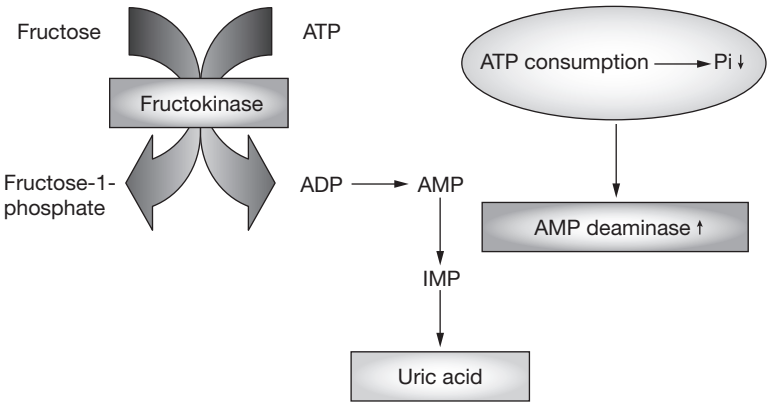

Figure 1 Fructose-induced production of uric acid in the hepatocyte.

ATP acts as a phosphate donor during phosphorylation of fructose by fructokinase in hepatocytes (Figure 1). ADP is generated, and is further metabolized to various purine substrates.[14] The rapid depletion of phosphate during these reactions stimulates AMP deaminase. The combination of increased substrate (via oral ingestion of fructose) and enzyme (AMP deaminase) upregulates urate production.[22]

High levels of uric acid could lead to endothelial dysfunction and reduced bioavailability of endothelial nitric oxide (NO). Soluble uric acid potently reduces NO levels in cultured human and bovine endothelial cells.[23,24] Decreased levels of plasma nitrites (NO breakdown products) in hyperuricemic rats can be restored if uric acid concentration is lowered with allopurinol.[23] Vasorelaxation of arterial rings in response to acetylcholine, a process that is mediated by NO, is blocked by uric acid (T Nakagawa *et al.*, unpublished data). In humans, serum uric acid concentration varies inversely with plasma NO during the day; urate levels peak in the morning when plasma NO is low.[25] Lowering uric acid levels using allopurinol also improves endothelial function in patients with heart failure, diabetes and hypercholesterolemia, and in heavy smokers.[26–30]

Decreased endothelial NO in turn results in development of insulin resistance and obesity. A contributory mechanism to this phenomenon is inhibition of insulin-dependent NO production, which is crucial for the enhancement of blood flow that allows glucose delivery to the skeletal

GLOSSARY

TYPE 2 DIABETES
Referred to as maturity-onset diabetes; it is not usually dependent on insulin injections and control is achieved through changes in lifestyle

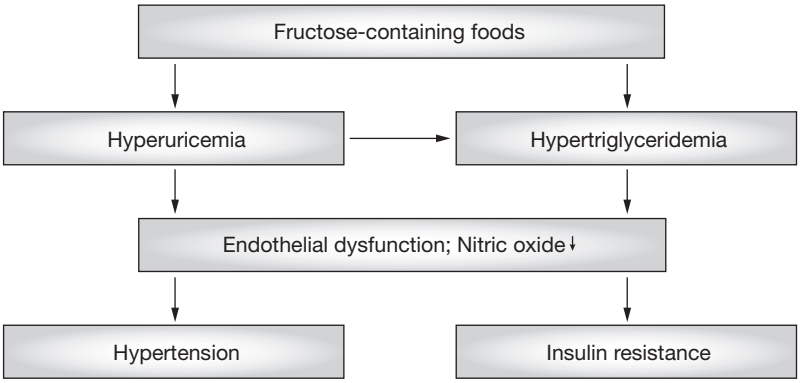

Figure 2 Proposed pathway of fructose-induced metabolic syndrome.

Box 1 Evidence supporting involvement of uric acid in development of insulin resistance.

- Uric acid predicts, and is an integral component of, the metabolic syndrome.[36–41]
- Serum uric acid levels are elevated in secondary insulin-resistance syndromes (e.g. gout, transplantation, pre-eclampsia and diuretic use).[42–45]
- Elevated serum uric acid levels correlate with increased frequency of obesity and insulin resistance in the US, in developing countries, and in studies of immigrant populations.[47–57]
- Experimental hyperuricemia induces diabetes and hypertension in animals.[34,35]
- Fructose-induced hyperuricemia in rats leads to hypertension, insulin resistance, obesity and hypertriglyceridemia; these conditions are ameliorated by decreasing uric acid levels. (REFS 14,16 and T Nakagawa *et al.*, unpublished data.)
- Fructose ingestion increases serum uric acid levels[18–21] and correlates with progression of the obesity epidemic.[10–13]
- Uric acid-induced endothelial dysfunction with impaired NO production might mediate development of insulin resistance and hypertension.

muscle and adipose tissues.[31] Mice deficient in endothelial NO synthase develop features of the metabolic syndrome including hypertension, insulin resistance and hypertriglyceridemia.[32] In studies in which NO synthesis was blocked in rats *in vivo* with L-NAME (N-nitro-L-arginine methyl ester), rates of insulin-dependent glucose uptake into skeletal muscle and adipose tissue were significantly decreased and insulin resistance developed.[33]

We therefore propose that rapid ingestion of fructose causes a transient increase in serum uric acid that limits endothelial NO bioavailability. By this theory, uric acid-induced NO inhibition would occur while concomitant intake of glucose stimulated insulin secretion. The consequence would be inhibition of insulin-mediated NO release, and slowing of rates of glucose delivery to skeletal muscle (Figure 2). The physiological response would be to increase insulin levels to overcome the acquired insulin resistance, leading to hyperinsulinemia. As less glucose would be delivered to skeletal muscle than is normal for the level of insulin, it is possible that signaling in the central nervous system could sustain ingestion.

SUPPORTING EVIDENCE

Several lines of evidence support our hypothesis (Box 1). Fructose-fed rats develop hyperuricemia, endothelial dysfunction, insulin resistance and the metabolic syndrome.[14] If fructose-induced hyperuricemia is prevented by administration of allopurinol, the development of obesity, hyperinsulinemia, hypertension and hypertriglyceridemia is significantly attenuated (T Nakagawa *et al.*, unpublished data). Two older studies showed that rats made hyperuricemic using different uricase inhibitors develop hypertension, hyperglycemia and hypertriglyceridemia.[34,35] These data are consistent with recent work demonstrating a strong causal relationship between experimentally induced hyperuricemia and hypertension.[36]

Further support for our hypothesis is the fact that elevated serum uric acid independently predicts development of the metabolic syndrome; for example, increased serum levels of uric acid independently predict development of obesity,[37] insulin resistance[38] and hypertension.[36,39] In a secondary analysis, we examined whether serum uric acid might predict the development of hyperinsulinemia in 60 nondiabetic adults admitted with first-time myocardial infarction (45 males and 15 females; mean age 57 ± 9 years, range 39–80 years). Fasting serum uric acid, plasma insulin and a series of cardiovascular risk factors were measured in the first month following myocardial infarction, and 6 and 12 months later. The power of serum uric acid to predict hyperinsulinemia (defined as a plasma insulin concentration >12 μU/ml) at 6 and 12 months was determined using a multiple logistic regression model that controlled for gender, age >60 years,

calculated (MDRD FORMULA) glomerular filtration rate <60 ml/min, insulin levels at baseline and at 6 months, and baseline BMI ≥27 kg/m^2.

At baseline, 28 of 60 patients (47%) had serum uric acid levels ≥5.5 mg/dl (mean 6.6 ± 0.8 mg/dl) and 32 patients had serum uric acid levels <5.5 mg/dl (mean 4.9 ± 0.5 mg/dl). Patients with higher (≥5.5 mg/dl) serum uric acid levels at baseline were more likely to develop hyperinsulinemia at 6 months (ODDS RATIO 5.47, 90% CI 1.6–17.7, $n = 60$, $P = 0.01$) and 12 months (odds ratio 3.4, 90% CI 1.1–10.4, $n = 53$, $P = 0.04$) (Figure 3).

Hyperuricemia and endothelial dysfunction are common in subjects with the metabolic syndrome; hyperuricemia is an integral component of the metabolic syndrome in both children and adults.[40,41] Elevated uric acid concentrations are also evident in other insulin-resistant conditions, such as gout,[42] pre-eclampsia[43] and transplantation,[44] and during low-dose diuretic treatment.[45] Altered bioavailability of endothelial NO is also common in subjects with the metabolic syndrome, hypertension and/or vascular disease.[46]

Epidemiological studies have established a link between the increasing prevalence of the metabolic syndrome and an elevated population mean serum uric acid concentration. Notwithstanding different methods of determining uric acid levels, there has been a general increase in population mean uric acid in the US—levels have risen in men from <3.5 mg/dl in the 1920s,[47] to approximately 5.0 mg/dl in the 1950s,[48] to 5.5 mg/dl in the 1960s,[49] and to 6.0–6.5 mg/dl in the 1970s.[50,51] Similar changes over time have been reported in Germany.[52] The escalation of serum uric acid levels during the twentieth century correlates not only with the frequency of diabetes and obesity, but also with a progressive increase in hypertension. In the 1930s, 10–11% of the US population were affected by hypertension.[53] Today, the incidence of hypertension has tripled to 30%.

A study in Rochester, MN, detected a twofold increase in the incidence of gout between 1977 and 1995.[54] The onset and increasing impact of gout in indigenous populations, such as the Maori of New Zealand, also parallels the increased frequency of diabetes, hypertension and obesity that accompanied their adoption of the Western diet.[55] Developing countries such as the Seychelles currently have high frequencies of hyperuricemia that correlate closely with parameters of the metabolic syndrome, particularly hypertrigylceridemia and hypertension.[56] Similarly, studies of immigrants have linked dietary changes

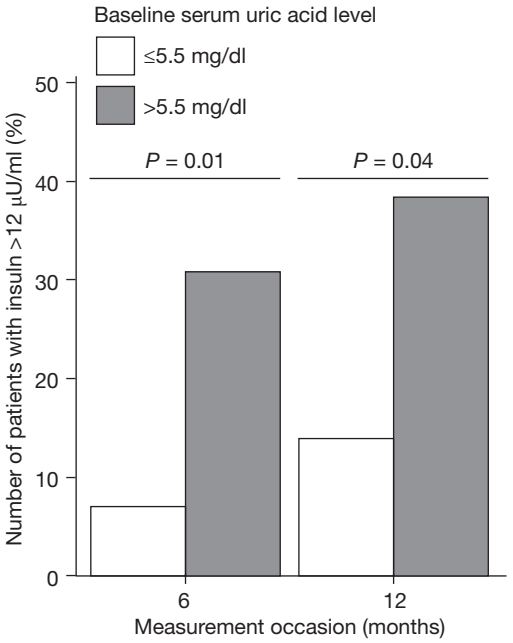

Figure 3 Uric acid predicts hyperinsulinemia in first-time myocardial infarction patients.

with elevated serum uric acid concentrations, increased frequency of hypertension, and higher fasting plasma glucose levels.[57]

Ingestion of alcohol (especially beer and hard drinks) and foods rich in purines (such as fatty red meats [beef, pork and lamb], shellfish, lobster, dark fish and organ meats) also increases levels of serum uric acid. Increased consumption of these types of food correlates with an increased risk of gout,[58] and with the global epidemic of hypertension, diabetes, obesity and cardiovascular disease.[59] It is likely that the increase in fatty meat consumption had a role in increasing rates of obesity during the early twentieth century; however, it is unlikely to have been the predominant mechanism behind the rise in obesity during the past 20 years. The average per capita intake of red meat decreased by a little more than 10% between 1980 and 2001,[8] and so does not correlate with the marked increase in obesity observed during this time.

Once frank diabetes develops, serum uric acid levels fall. This action is a function of glycosuria stimulating renal urate excretion. So, serum concentrations of uric acid are elevated in insulin resistance but not necessarily in diabetes.[60] Interestingly, in studies of type 2 diabetes, persistent hyperuricemia has been associated with progression of renal disease, whereas hypouricemia correlates with poor metabolic control, hyperfiltration and decreased risk of

GLOSSARY

MDRD FORMULA
Used to calculate glomerular filtration rate; developed as a result of the Modification of Diet in Renal Disease study conducted by Levey *et al.* in 1999

ODDS RATIO
Ratio of odds of an event in intervention group to odds in control group; when <1 for an undesirable outcome, the intervention reduced the risk

renal-disease progression.[61] One might posit that this phenomenon is the result of the fact that experimental hyperuricemia promotes glomerular hypertension and renal vasoconstriction,[62] both of which can induce and accelerate renal injury.[63]

We propose that hyperuricemia has a role in inducing insulin resistance that could become less important once insulin resistance and obesity are established. It is well documented that obesity itself causes insulin resistance, either as an effect of increased triglycerides in adipocyte and muscle cells,[18] or because associated hyperglycemia and/or advanced glycation endproducts impair endothelial cell-dependent release of NO.[64,65] Hyperuricemia might therefore be more important in the development phase of insulin resistance than in maintenance of prediabetic and diabetic states.

The renin–angiotensin system has a key role in mediating the endothelial and vascular effects associated with experimental hyperuricemia[66] and fructose-induced endothelial dysfunction,[67] and in rats in which NO synthesis is chronically inhibited.[68] Preservation of endothelial function by angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in response to hyperuricemia or other mechanisms might explain why these agents have been found to reduce the incidence of type 2 diabetes.[69]

COUNTERING ARGUMENTS

There are countering issues to the above propositions to consider. First, fructose has been considered safe for consumption by diabetics as it does not elevate glucose levels to the extent of glucose itself;[70] however, if fructose causes insulin resistance, its benefit as a nonglucose carbohydrate source might be nullified. Second, several studies indicate that uric acid is elevated in the metabolic syndrome because insulin enhances uric acid reabsorption.[71] This evidence does not, however, negate the possibility that uric acid might also cause hyperinsulinemia. Third, there are certain populations, particularly in Oceania, whose serum uric acid levels are elevated without concomitant obesity, hypertension or cardiovascular disease.[72] It is possible that these individuals have the advantage of mechanisms that confer protection; for example, the raw cocoa ingested by the Kuna Indians of Panama contains flavonoids that enhance NO release from endothelial cells.[73] Finally, one study found that infusion of uric acid into human volunteers did not impair brachial artery reactivity, a reflection of endothelial function.[74] Our more recent studies, however, indicate that the mechanism of urate-induced endothelial dysfunction could be a consequence of a urate oxidant-based reaction, rather than a direct effect of uric acid (A Angerhofer *et al.*, unpublished data). As such, direct infusion studies might not reproduce the physiological mechanism by which uric acid exerts its effect.

CONCLUSIONS

It was over 100 years ago that Osler prescribed diets low in fructose as a means to prevent gout. He wrote in his 1893 text[75] that "The sugar should be reduced to a minimum. The sweeter fruits should not be taken". This brilliant insight gels with our proposition that foods that elevate serum uric acid levels induce transient endothelial dysfunction, which in turn causes insulin resistance and hypertension to develop. The primary dietary inductive factors are foods containing fructose or table sugar, and fatty meats that contain high concentrations of purines. We have outlined a mechanistic pathway that at least partially explains why low-carbohydrate diets such as the Atkins diet, and more classic eating plans, are successful to some degree. Adherence to most diets can decrease uric acid levels in concert with weight loss.[76] Importantly, once a person becomes obese and diabetic, insulin resistance will be driven primarily by the obesity itself, as a consequence of elevated intramuscular triglyceride levels.[18] Clinical studies of either low-fructose diets and/or lowering uric acid levels with allopurinol as a means of preventing or treating the early metabolic syndrome, should be considered. Such a trial is urgent given the magnitude of the metabolic syndrome epidemic.

KEY POINTS

- Increased ingestion of fructose in processed foodstuffs has correlated with development of the obesity epidemic
- Hypothesis: fructose-mediated elevation of serum uric acid levels has a role in development of the metabolic syndrome
- By the proposed hypothesis, transient hyperuricemia would exert its effect by limiting bioavailability of endothelial nitric oxide, leading to insulin resistance and hypertension
- Low-fructose diets or allopurinol-mediated lowering of serum uric acid levels might prevent or successfully treat early stage metabolic syndrome

References

1 Hedley AA *et al.* (2004) Prevalence of overweight and obesity among children, adolescents, and adults, 1999–2002. *JAMA* **2:** 2847–2850
2 Weiss R *et al.* (2004) Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* **350:** 2362–2374
3 Block G (2004) Foods contributing to energy intake in the U.S.: data from NHANES III and NHANES 1999–2000: *J Food Comp Analysis* **17:** 439–447
4 Johnson RJ *et al.* (2005) Uric acid, evolution, and primitive cultures. *Sem Nephrol* **25:** 3–8
5 Yusuf S *et al*. (2001) Global burden of cardiovascular diseases. Part I: General considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* **104:** 2746–2753
6 Serdula MK *et al.* (1999) Prevalence of attempting weight loss and strategies for controlling weight. *JAMA* **282:** 1353–1358
7 Foster GD *et al.* (2003) A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* **348:** 2082–2089
8 United States Department of Agriculture Economic Research Service report. [http://www.ers.usda.gov/data/foodconsumption/spreadsheets/sweets.xls]
9 US Census Bureau (2003) Health and Nutrition. No. 214 Per Capita Consumption of Major Food Commodities: 1980 to 2001. In: *Statistical Abstract of the United States: 2003*, 143. Washington DC: US Census Bureau
10 Bray GA *et al.* (2004) Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* **79:** 537–543
11 Ludwig DS *et al.* (2001) Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet* **357:** 505–508
12 Schulze MB *et al.* (2004) Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA* **292:** 927–934
13 Dennison BA *et al.* (1997) Excess fruit juice consumption by preschool-aged children is associated with short stature and obesity. *Pediatr* **99:** 15–22
14 Hallfrisch J (1990) Metabolic effects of dietary fructose. *FASEB J* **4:** 2652–2660
15 Lingelbach LB and McDonald RB (2000) Description of the long-term lipogenic effects of dietary carbohydrates in male Fischer 344 rats. *J Nutr* **130:** 3077–3084
16 Teff KL *et al.* (2004) Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. *J Clin Endocrinol Metab* **89:** 2963–2972
17 Zammit VA *et al.* (2001) Insulin stimulation of hepatic triacylglycerol secretion and the etiology of insulin resistance. *J Nutr* **131:** 2074–2077
18 Perheentupa J and Raivio K (1967) Fructose induced hyperuricemia. *Lancet* **2:** 528–535
19 Emmerson BT (1974) Effect of oral fructose on urate production. *Ann Rheum Dis* **33:** 276–280
20 Stirpe F *et al.* (1970) Fructose-induced hyperuricemia. *Lancet* **2:** 1310–1311
21 Fox IH and Kelley WN (1972) Studies on the mechanism of fructose-induced hyperuricemia in man. *Metabolism* **21:** 713–721
22 Smith CM *et al.* (1977) Fructose-induced adenine nucleotide catabolism in isolated rat hepatocyte. *Can J Biochem* **55:** 1237–1240
23 Khosla UM *et al.* (2005) Hyperuricemia reversibly inhibits endothelial dysfunction in rats. *Kidney Int* **67:** 1739–1742
24 Kang DH *et al.* (2003) Uric acid induced C-reactive protein (CRP) expression via upregulation of angiotensin type 1 receptors (AT_1) in vascular endothelial cells and smooth muscle cells [abstract #136]. *J Am Soc Nephrol* **14**
25 Kanabrocki EL *et al.* (2000) Circadian relationship of serum uric acid and nitric oxide. *JAMA* **283:** 2240–2241
26 Butler R *et al.* (2000) Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. *Hypertension* **35:** 746–751
27 Doehner W *et al.* (2002) Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* **105:** 2619–2624
28 Farquharson CA *et al.* (2002) Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* **106:** 221–226
29 Cardillo C *et al.* (1997) Xanthine oxidase inhibition with oxypurinol improves endothelial vasodilator function in hypercholesterolemic but not in hypertensive patients. *Hypertension* **30:** 57–63
30 Guthikonda S *et al.* (2003) Xanthine oxidase inhibition reverses endothelial dysfunction in heavy smokers. *Circulation* **107:** 416–421
31 Scherrer U *et al.* (1994) Nitric oxide release accounts for insulin's vascular effects in humans. *J Clin Invest* **94:** 2511–2515
32 Cook S *et al.* (2003) Clustering of cardiovascular risk factors mimicking the human metabolic syndrome X in eNOS null mice. *Swiss Med Wkly* **133:** 360–363
33 Roy D *et al.* (1998) Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues *in vivo* is NO dependent. *Am J Physiol* **274:** E692–E699
34 Wexler BC and Greenberg BP (1977) Effect of increased serum urate levels on virgin rats with no arteriosclerosis versus breeder rats with preexistent arteriosclerosis. *Metabolism* **26:** 1309–1320
35 Wexler BC (1982) Allantoxanamide-induced myocardial necrosis in Sprague-Dawley vs. Spontaneously Hypertensive Rats. *Proc Soc Exp Biol Med* **170:** 476–485
36 Johnson RJ *et al.* (2005) The resurrection of uric acid as a causal factor in hypertension. *Hypertension* **45:** 18–20
37 Masuo K *et al.* (2003) Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension* **42:** 474–480
38 Nakanishi N *et al.* (2003) Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type 2 diabetes in Japanese male office workers. *Eur J Epidemiol* **18:** 523–530
39 Sundström J *et al.* (2005) Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. *Hypertension* **45:** 28–33
40 Vuorinen-Markkola H and Yki-Järvinen H (1994) Hyperuricemia and insulin resistance. *J Clin Endo Metab* **78:** 25–29
41 Costa A *et al.* (2002) Uric acid concentration in subjects at risk of type 2 diabetes mellitus: Relationship to components of the metabolic syndrome. *Metabolism* **51:** 372–375
42 Berkowitz D (1966) Gout, hyperlipidemia, and diabetes interrelationships. *JAMA* **197:** 117–120
43 Thadhani R *et al.* (2004) Insulin resistance and alterations in angiogenesis. Additive insults that may lead to preeclampsia. *Hypertension* **43:** 988–992
44 Pascual E (1994) Hyperuricemia and gout. *Curr Opin Rheumatol* **6:** 454–458

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Competing interests

The authors declared competing interests; go to the article online for details.

45 Lindholm LH *et al.* (2003) Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid profile in a North of Sweden Efficacy Evaluation (ALPIN study). *J Hypertens* **21:** 1563–1574
46 Deedwania PC (2003) Mechanisms of endothelial dysfunction in the metabolic syndrome. *Curr Diab Rep* **3:** 289–292
47 Fishberg AM (1924) The interpretation of increased blood uric acid in hypertension. *Arch Int Med* **34:** 503–507
48 Hall AP *et al.* (1967) Epidemiology of gout and hyperuricemia. *Am J Med* **42:** 27–37
49 Mikkelsen WM *et al.* (1965) The distribution of serum uric acid values in a population unselected as to gout or hyperuricemia. Tecumseh, Michigan. 1959–1960. *Am J Med* **39:** 242–251
50 Glynn RJ *et al.* (1983) Trends in serum uric acid levels. 1961–1980. *Arthritis Rheum* **26:** 87–93
51 Freedman DS *et al.* (1995) Relation of serum uric acid to mortality and ischemic heart disease. *Am J Epidemiol* **141:** 637–644
52 Gresser U *et al.* (1990) Uric acid levels in Southern Germany in 1989. A comparison with studies from 1962, 1971, and 1984. *Klin Wochenschr* **68:** 1222–1228
53 Robinson SC and Brucer M (1939) Range of normal blood pressure. A statistical and clinical study of 11,383 persons. *Arch Int Med* **64:** 409–444
54 Arromedee E *et al.* (2002) Epidemiology of gout: Is the incidence rising? *J Rheumatol* **29:** 2403–2406
55 Lennane GAQ *et al.* (1960) Gout in the Maori. *Ann Rheum Dis* **19:** 120–125
56 Conen D *et al.* (2004) Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. *BMC Public Health* **4:** 1–9
57 Kagan A *et al.* (1974) Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California. Demographic, physical, dietary and biochemical characteristics. *J Chron Dis* **27:** 345–364
58 Choi HK *et al.* (2004) Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* **350:** 1093–1103
59 Johnson RJ and Rideout BA (2004) Uric acid and diet: insights into the epidemic of cardiovascular disease. *N Engl J Med* **350:** 1071–1073
60 Tuomilehto J *et al.* (1988) Plasma uric acid level and its association with diabetes mellitus and some biological parameters in a biracial population of Fiji. *Am J Epidemiol* **127:** 321–336
61 Bo S *et al.* (2001) Hypouricemia and hyperuricemia in type 2 diabetes: two different phenotypes. *Eur J Clin Invest* **31:** 318–321
62 Sánchez-Lozada LG *et al.* (2005) Mild hyperuricemia induces severe cortical vasoconstriction and perpetuates glomerular hypertension in normal rats and in experimental chronic renal failure. *Kidney Int* **67:** 237–234
63 Kang DH *et al.* (2002) A role for uric acid in renal progression. *J Am Soc Nephrol* **13:** 2888–2897
64 Beckman JA *et al.* (2002) Inhibition of protein kinase C β prevents impaired endothelium-dependent vasodilation caused by hyperglycemia in humans. *Circ Res* **90:** 107–111
65 Hogan M *et al.* (1992) Advanced glycosylation endproducts block the antiproliferative effect of nitric oxide. Role in the vascular and renal complications of diabetes mellitus. *J Clin Invest* **90:** 1110–1115
66 Mazzali M *et al.* (2001) Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* **38:** 1101–1106
67 Shinozaki K *et al.* (2004) Evidence for a causal role of the renin angiotensin system in vascular dysfunction associated with insulin resistance. *Hypertension* **43:** 255–262
68 Pollock DM *et al.* (1993) Angiotensin blockade reverses hypertension during long-term nitric oxide blockade. *Hypertension* **21:** 660–666
69 Yusuf S *et al.* (2001) HOPE Study Investigators. Ramipril and the development of diabetes. *JAMA* **286:** 1882–1885
70 Osei K *et al.* (1987) Metabolic effects of fructose as a natural sweetener in the physiological meals of ambulatory obese patients with type 2 diabetes. *Am J Med* **83:** 249–255
71 Galvan AQ *et al.* (1995) Effect of insulin on uric acid excretion in humans. *Am J Physiol* **268:** E1–E5
72 Prior IAM *et al.* (1966) Hyperuricemia, gout and diabetic abnormality in Polynesian people. *Lancet* **1:** 333–338
73 Fisher ND *et al.* (2003) Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens* **21:** 2281–2286
74 Waring WS *et al.* (2004) Hyperuricaemia does not impair cardiovascular function in healthy adults. *Heart* **90:** 155–159
75 Osler W (1893) Gout. In: *The Principles and Practice of Medicine*, edn 2, 287–295.New York: Appleton
76 Dessein PH *et al.* (2000) Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout; a pilot study. *Ann Rheum Dis* **59:** 539–543