

The Effect of Fructose on Renal Biology and Disease

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ABSTRACT

Dietary fructose intake is increasing. It is increasing primarily from added sugars, including sucrose and high fructose corn syrup, and correlates epidemiologically with the rising prevalence of metabolic syndrome and hypertension worldwide. The administration of fructose to animals and humans increases BP and the development of metabolic syndrome. These changes occur independently of caloric intake because of the effect of fructose on ATP depletion and uric acid generation. Fructose ingestion may also be a risk factor for kidney disease that includes glomerular hypertension, renal inflammation, and tubulointerstitial injury in animals. We suggest excessive fructose intake should be considered an environmental toxin with major health implications.

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Fructose is a simple sugar, a monosaccharide that is present primarily in added dietary sugars, honey, and fruit. The primary sources of fructose in the American diet are from sucrose, a disaccharide containing 50% fructose and 50% glucose bonded together, and high fructose corn syrup (HFCS), which is a mixture of free fructose and free glucose, usually in a 55/45 proportion. Intake of fructose has increased dramatically over the last century, has accelerated since the introduction of HFCS in the 1970s,¹ and likely contributes to the epidemic of human obesity.² Although the mean intake of fructose is currently about 74 g/day,³ many individuals, especially adolescents, African American adults, and Hispanic adults, are ingesting as much as 30% of their diet as added sugars. This represents >25 times what was ingested in the United Kingdom in 1700.

FRUCTOSE METABOLISM

Fructose is distinct from glucose in its initial metabolism. The Glut5 transporter in

the intestine absorbs fructose with 60 to 70% being taken up by Glut2 and possibly other transporters in the liver and 30 to 40% by the kidney, adipose tissue, and other organs. Although fructose can be metabolized by hexokinase, most fructose is metabolized by fructokinase (ketohexokinase), which phosphorylates fructose to fructose 1-phosphate (Figure 1). Unlike glucose, whose phosphorylation is tightly regulated so that ATP levels are never depleted, the phosphorylation of fructose results in a decrease in intracellular phosphate and ATP depletion, resulting in transient inhibition of protein synthesis. Adenosine monophosphate is generated and broken down by adenosine monophosphate deaminase, resulting in the generation of inosine monophosphate and eventually uric acid. Uric acid rises in the cell and may transiently increase by 1 to 2 mg/dl in the circulation. Fructose-1-phosphate is then metabolized by aldolase B and other enzymes, eventually generating the acyl glycerol, diacylglycerol, with the formation of glycogen and triglycerides.⁴

FRUCTOSE AND HYPERTENSION

Recent studies suggest that fructose is a mediator of hypertension, and the mechanism may involve the ability of fructose to raise uric acid. First, epidemiologic studies link fructose intake to the development of hypertension. In the NHANES (1999–2004) survey, a tight association of sugar-sweetened drinks with uric acid levels and hypertension was observed in adolescents.⁵ Similarly, in the NHANES (2003–2006) survey, fructose intake from added sugars correlated with the presence of elevated BP.³ Second, the ingestion of fructose-rich drinks raises BP. For example, the acute ingestion of 60 g of fructose (comparable to two 12-oz soft drinks), but not glucose, will increase BP in young healthy adults. We also reported that the administration of 200 g of fructose per day for 2 weeks raises both clinic and 24-hour ambulatory BP in healthy adult men in association with a significant rise in fasting levels of serum uric acid.⁶ In this study, one half of the patients were randomized to receive allopurinol, and in this group, the serum uric acid was lowered and the rise in BP prevented.⁶

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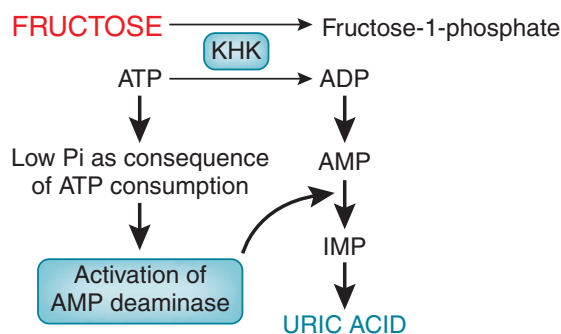


Figure 1. A pathway by which fructose is metabolized into uric acid. KHK, ketohexokinase.

More recently, two groups have administered low-fructose diets. In a study in Mexico City, Madero *et al.* found that a low-fructose diet reduces serum uric acid, with a significant decrease in BP in obese adults (M. Madero *et al.*, submitted). In another study of 810 adults involving behavior intervention, a reduction in one sugar-sweetened beverage per day translated into a reduction of 1.8 mmHg systolic and 1.1 mmHg diastolic blood pressure at 18 months.⁷ Interestingly, in the latter study, the effect was independent of serum uric acid, but because it is the intracellular uric acid levels that mediate the vascular effects, it may still be dependent on a uric acid–driven pathway.

In contrast to the above studies, Forman *et al.*⁸ was unable to find an association of fructose intake with hypertension in studies based on nurses and health professionals. However, in these groups, a large amount of fructose was from natural fruits, which are known to be high in antioxidants and flavonols that can block the pro-hypertensive effects of fructose in animals; in addition, ascorbate also lowers uric acid by stimulating renal excretion. Also challenging the fructose hypothesis has been the observation that fructose does not increase BP very effectively in laboratory rats, except during active ingestion. This may be because rats carry the enzyme uricase and, as such, show a blunted uric acid response to fructose.

FRUCTOSE AND METABOLIC SYNDROME

Excessive intake of fructose, primarily in the form of added dietary sugars, has

also been linked epidemiologically with the development of obesity, diabetes, and nonalcoholic fatty liver disease. More importantly, the administration of fructose to humans induces all of the features of metabolic syndrome. In a study by Stanhope *et al.*,⁹ a diet containing 25% fructose was administered for 6 weeks to overweight adults; control subjects received 25% glucose. Subjects on the high-fructose diet developed insulin resistance, visceral obesity (measured by computed tomography scan), and postprandial dyslipidemia. In the Menorca⁶ study, the administration of 200 g fructose per day resulted in a 25% increase in metabolic syndrome, with a significant increase in fasting triglycerides, a fall in HDL cholesterol, a rise in systolic and diastolic BP, and a worsening of insulin resistance measured using the homeostasis model assessment index.

Studies in animals have also found that fructose induces all features of the metabolic syndrome, especially when administered at high doses.¹⁰ However, metabolic syndrome can be induced with concentrations of fructose as low as 20% if it is administered with glucose, either as sucrose or HFCS, likely because the presence of glucose accelerates fructose absorption.¹¹

Furthermore, a striking finding is that the effects of fructose to induce metabolic syndrome are independent of energy intake and can even be induced in the setting of caloric restriction.¹² For example, we found that a 40% sucrose diet (which contains 20% fructose) given to rats at approximately 90% of reg-

ular intake for 4 months induces hypertriglyceridemia, insulin resistance, fatty liver, and β islet dysfunction with the development of frank diabetes; in contrast, control rats administered starch show much less metabolic disturbance (Roncal *et al.*, submitted).

The mechanism for the development of metabolic syndrome may relate to the influx of free fatty acids with intracellular lipid accumulation in nonadipocyte tissues such as the liver.¹³ Fructose is also known to induce oxidative stress and mitochondrial dysfunction, resulting in a stimulation of peroxisome proliferator-activated receptor gamma coactivator 1- α that drives insulin resistance.¹⁴ Finally, there is some evidence that the rise in intracellular uric acid may have a role in mediating insulin resistance, perhaps by direct effects on the adipocyte¹⁵ or possibly by impairing endothelial nitric oxide release in response to insulin, which subsequently blocks blood flow and hence delivery of glucose to peripheral tissues such as skeletal muscle.¹⁶

FRUCTOSE AND RENAL DISEASE

The possibility that fructose may have a role in chronic kidney disease is increasingly likely, given its potential role in driving hypertension and diabetes. Indeed, the observation that metabolic syndrome is a significant risk factor for chronic kidney disease¹⁷ raises the possibility that fructose may have a causal role. Nevertheless, there is currently only one human study that examines the relationship of intake of sugar-containing beverages with renal disease. Specifically, the NHANES (1999–2004) found that intake of two or more sugar-containing beverages was associated with an increased risk of having albuminuria.¹⁸

However, experimental studies support fructose intake as a mechanism for kidney injury. For example, we found the administration of fructose (60% diet) to rats induces renal hypertrophy with tubular cell proliferation and low-grade tubulointerstitial injury, generating

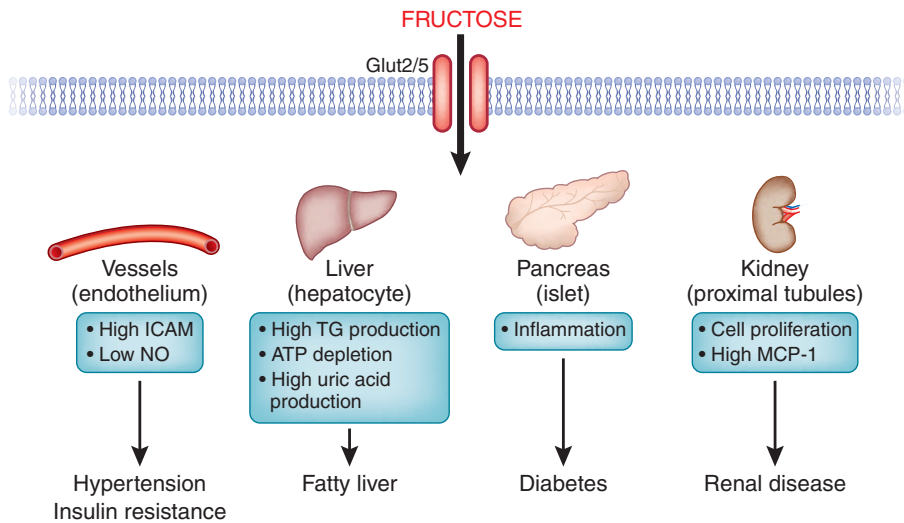


Figure 2. Effects of fructose in the development of hypertension, fatty liver, diabetes, and renal disease.

chemotactic factors such as monocyte chemoattractant protein-1 by tubular cells and intercellular adhesion molecule-1 in renal microvascular endothelial cells.^{19–22} We also found the administration of fructose (60% diet) exacerbates proteinuria, worsens renal function, and accelerates glomerulosclerosis in the remnant kidney model; importantly, these abnormalities are not observed in rats fed an equivalent glucose-based diet.²² Finally, micropuncture studies documented that fructose intake results in glomerular hypertension and reduced renal blood flow in association with the development of preglomerular vascular disease.²³ These findings are similar to what is observed in hyperuricemic rats, and consistent with this hypothesis, we found that lowering uric acid blocks these hemodynamic effects.²³

CONCLUSIONS

There is increasing evidence that excessive intake of fructose may have a myriad of unfortunate health effects, including raising BP, inducing the metabolic syndrome, causing fatty liver, and possibly causing or accelerating renal disease (Figure 2). Given that many physicians recommend low-protein diets for subjects with chronic kidney disease, which could translate into a high-carbohydrate, high-fructose diet, we recommend that

protein restriction should also include restricting added sugars containing fructose. We also believe that more clinical studies are needed to determine the effect of dietary fructose restriction or of lowering uric acid in subjects with chronic kidney disease.

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DISCLOSURES

Drs. Johnson and Nakagawa are listed as inventors on several patent applications related to lowering uric acid as a means to prevent or treat metabolic syndrome or hypertension. Dr. Johnson also has a book in the lay press, *The Sugar Fix* (Rodale, and Simon and Schuster).

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