# The Fructose Nation

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There is growing miasma in our national correspondence over the increasing heft and metabolic dysfunction of everyday Americans. The origin of this mounting poundage has many parents, not the least of which is our appetite for nutritive (read caloric) sweeteners in processed foods and beverages. The culprit derivatives taking most heat today are various formulations of added fructose. Bray *et al.*[1] drew attention to the association of obesity with increasing fructose consumption in a landmark paper several years ago.

Fructose is everywhere because it is highly soluble in water, more so than glucose,[2] makes bread crusts browner, cookies softer, and everything sweeter. The vast majority of sweeteners are nutritive, although nonnutritive sweeteners like acesulfame and sucralose (chlorinated sucrose) are increasingly in use. The recent shortage of sucralose suggests some retreat from fructose may already be under way. Even so, concern remains that unfettered consumption of fructose is contributing to rampant obesity, metabolic syndrome, and insulin-resistant diabetes.[3] It seems we have morphed insidiously into a fructose nation.

It did not start out like this. For eons, humans sweetened their food with cane or beet sugar containing sucrose. Sucrose is metabolized into dextrose and fructose by disaccharidases in the gut and is the only sweetener allowed to label as commercial sugar. By the mid-19th century, however, the use of cornstarch as a laundry stiffener ushered in a new era for agrocorn.[4] Chemists figured out how to make dextrose and anhydrous sugar from cornstarch after the Civil War, and the marketplace for corn-based sweeteners became a nascent industry. Corn syrups came next. Syrup manufactured from the dregs of corn germ led to the development of commercial dextrose, which quickly became an economical competitor of natural sucrose by the early 1900s, but that is not the end. With better corn syrup technology, chemists were eventually able to isomerize dextrose into fructose, producing a commercially successful derivative known as high-fructose corn syrup.

Fructose is sweeter than sucrose,[1] and high-fructose corn syrup became a main staple of the sweetener industry beginning in 1967.[5] How much fructose do we eat today? A lot. Americans increased their overall consumption of nutritive sweeteners by 41% between 1959 and 1997, to an amount nearly 10 yr ago totaling 70 kg per capita per year.[6] The addition of high-fructose corn syrup to the national diet during a comparable interval[7] increased exposure to fructose in high-fructose corn syrup from near zero to 29 kg per capita per year[3] and a few years ago represented a large fraction of our current appetite for nutritive sweeteners.[1,6] In past decades, even back to Osler, fructose was also touted as a preferred sugar substitute for individuals with diabetes because its metabolism lowers blood glucose and insulin responses.[8] Now this notion seems quaint and probably ill-advised.[9]

If sucrose has been around for centuries and is partly metabolized to fructose, why only now do we censure fructose in the epidemic of obesity[10] and metabolic syndrome?[3] Opinion varies. Many foods need sweetening or no one will buy or make them. Sucrose consumption a few decades ago was largely influenced by whoever did meal preparation at home.[6] Today we snack more frequently and super-size what we consume, and with reliance on vending machines and fast foods for quick calories, nimble commercial interests now influence our quantity of fructose per serving. This transition has been facilitated by perverse incentives in congressional farm bills that encouraged commodity farmers to grow more corn in the past 25 yr.[11] Although entrenched supply-chain economics are hard to repurpose, much of our current corn production may have alternative use in new ethanol-based fuels.

So what is the problem with fructose? Fructose is metabolized differently than glucose. Unlike glucose, which is stored as glycogen, fructose is absorbed by the gut and converted into triglycerides by the liver.[12] Fructose also elevates uric acid levels through effects on an ADP-IMP pathway in hepatocytes.[13] The resulting dyslipidemia and hyperuricemia facilitate insulin resistance,[14] aggravate hypertension,[13] and accelerate endothelial dysfunction.[15] Attenuation of nitric oxide levels is an important pathogenic mechanism as a final common pathway to poor blood flow.[3,16] What we end up with is a familiar caloric additive provoking a new spate of metabolic dysfunction.[3]

Johnson and colleagues[17] have been studying this problem in rats using diets rich in fructose that produce a metabolic syndrome with glomerular hypertension. In this issue of *JASN*, their group moves the story a step further by showing that exposure to thiazide diuretics in fructose-consuming

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rats makes metabolic syndrome worse.[18] It is interesting that these rats are not obese, perhaps because the study period was too short, or, as recently observed, obesity may not be the only driver of metabolic syndrome.[19]

Thiazide diuretics have long been linked with glucose intolerance in humans.[20,21] An elevated blood glucose in this setting is largely attributable to hypokalemia that renders glucose uptake less effective. Thiazides, which are a traditional mainstay for treating hypertension in populations with metabolic syndrome and diabetes, also raise blood levels of uric acid.[22] Proper attention to potassium replacement and the lowering of serum uric acid with allopurinol in rats on high-fructose diets consuming thiazides ameliorate the aggravating circumstances of metabolic syndrome.[18]

Where do we go from here? It is important not to reach conclusions too quickly. Some think a commercial conversion to nonnutritive sweeteners in processed foods and beverages is the answer to the fructose problem. Nonnutritive sweeteners are quite potent; sucralose, for example, is 600 times sweeter than sucrose but has a metallic aftertaste that needs abatement.[23] Mixing in inulin can improve palatability,[24] and nephrologists will enjoy that piece of trivia. Although a change to nonnutritive sweeteners would reduce exposure to fructose, there is a curve ball and the irony is this: Consumables laced with nonnutritive sweeteners seemingly produce less satiety and only marginal weight loss because they are not appetite suppressants.[25] Although controversial, disconnecting nutritive sweeteners from free-living diets may not address passive overeating. Worse yet, low-income populations are more affected because high-energy foods and beverages cost less than low-energy consumables.[26] Put another way, most of us probably cannot win for losing.

Although a proverbial stretch from current studies in rats, more attention to potassium stores[27] and uric acid levels[28] may hypothetically help patients with metabolic syndrome, particularly if they are taking thiazide diuretics for control of hypertension. Only further human study will tell, but the sweetener epidemic is here. There is paradoxic subtext to the meaning of sugar-free, and with apologies to Pogo, the enemy is us.

## DISCLOSURES

None.

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See the related article, "Thiazide Diuretics Exacerbate Fructose-Induced Metabolic Syndrome," on pages 2724–2731.

# A New Approach to Idiopathic Nephrotic Syndrome

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Minimal-change disease (MCD) and primary FSGS are important causes of idiopathic nephrotic syndrome (INS) and, in the case of FSGS, end-stage renal failure. Intriguing features of these diseases include their frequent response to steroids, their association with immune abnormalities, the existence of a circulating permeability factor, and, in the case of FSGS, the tendency for disease to recur in some patients after transplantation. An article published in this issue of *JASN*[1] shows that immune reconstitution of immunodeficient mice with cells from patients with INS induces a MCD-like lesion. This new story provides further evidence for INS being a disease of the immune system.

In 1974, Shalhoub[2] proposed the now-famous hypothesis that "lipoid nephrosis," what we now call MCD, is a disorder of T cell function resulting in the production of a circulating lymphokine toxin (later termed a vascular permeability factor) based on limited humoral immunity and immune effectors in glomeruli, remissions with measles infection or with corticosteroids and cyclophosphamide, and reports of disease occurring with Hodgkin's disease or thymoma. Although we now know more about INS, we still do not know how it occurs; neither do we have targeted, effective, and nontoxic therapies. We know that the podocyte, the primary glomerular cell type affected in INS, is critical to the maintenance of glomerular structure and function,[3] and podocytes are directly affected by treatments for MCD/FSGS.[4] Moreover, some cases of "idiopathic" FSGS are due to genetic mutations in podocyte-specific proteins.[3] The recurrence of disease after transplantation, the control of posttransplantation FSGS with plasmapheresis or immunoabsorption, and the resolution of proteinuria after transplantation of nephrotic kidneys into recipients with ESRD that is not due to FSGS support the pathogenicity of this still-elusive circulating factor or factors.[5]

Given the association of MCD with allergy and atopy in children,[6] it has been hypothesized that aberrant T helper cell 2 cytokine production drives this disease. Human podocytes express receptors for IL-4 and IL-13 and respond to either cytokine,[7,8] and recent evidence in IL-13–overexpressing rats confirms IL-13 as a possible factor in MCD.[9] Although disease has been associated with raised serum or peripheral blood mononuclear cell Th2 cytokines, not all studies are concordant.[10] Assessment of immune abnormalities in patients with MCD and primary FSGS are confounded by the tendency of childhood relapses of MCD to be associated with viral infection, by questions of "cause *versus* consequence,"[11] and by differences in methods of assessing cytokine production. Models of primary INS do exist. Transfer of supernatant from lymphocytes or T cell hybridomas of patients with nephrotic syndrome[12] or a posttransplantation FSGS factor into rats results in proteinuria.[13] The Buffalo/Mna rat strain develops nephrotic syndrome that is caused by immune abnormalities, perhaps with some additional intrarenal podocytic genetic abnormality.[14,15]

In this issue of *JASN*, Sellier-Leclerc *et al.*[1] use an innovative approach, humanizing NOD/SCID mice, to implicate further an "immature" immune system in the pathogenesis of FSGS. Owing to severe combined immunodeficiency, these mice act as a "blank immunologic palette" into which human cells can be transplanted and engrafted and the resultant effects studied *in vivo*. Researchers have used these mice in studies of human lymphocyte development and HIV infection.[16] Using human CD45 as a common leukocyte marker, immune cells from patients or control subjects were able to reconstitute an immune system in these mice to some degree. CD34 defines an immature cell population that has the capacity to differentiate into T cells, B cells, or myeloid cells. Transfer of immature $CD34^+$ cells from patients with MCD or FSGS (but not control subjects) resulted in albuminuria and an MCD-like lesion in mice with electron microscopic–defined podocyte changes very similar to those seen in humans. The nature of the reconstitution was such that mature $CD3^+$ cells were not seen in the periphery, counting against a mature T cell subset being culpable, and lack of regulatory T cell function also seemed unlikely.

Progenitor $CD34^+$ cells differentiating into T lymphocytes are positively and negatively selected in the thymus. In humans, the T cell repertoire is most actively defined in early childhood, although T cell selection can occur throughout life. Data from other studies suggest that the dysregulated release of less than fully mature cells from the thymus is important in the pathogenesis if INS.[17] The validity of humanizing SCID mice

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