

Gersch MS, Mu W, Cirillo P, Reungjui S, Zhang L, Roncal C, Sautin YY, Johnson RJ, Nakagawa T. Fructose, but not dextrose, accelerates the progression of chronic kidney disease. *Am J Physiol Renal Physiol.* 2007 Oct;293:F1256-61.

Background

All authors hold appointments with the Division of Nephrology, Dialysis and Transplantation at the University of Florida; Michael Gersch is also associated with the North Florida/South Georgia Veterans Health System, Gainesville, Florida.

Richard Johnson seems to have staked out a niche in the area of fructose effects on kidney function and related diseases. His recent articles have attempted to implicate dietary fructose in kidney disease, hypertension, obesity, the metabolic syndrome, diabetes, hyperuricemia and cardiovascular disease (1-3). Reference 1, also authored by Johnson, was one of three papers critiqued in a recent Letter to the Editor accepted by the *American Journal of Clinical Nutrition* (4).

Takahiko Nakagawa is a frequent collaborator with Johnson. The two are also co-inventors on patent applications filed by the University of Florida related to the role of fructose in hypertension and the metabolic syndrome. It is clear from this patent activity and References 1 and 3 that Johnson and Nakagawa hope to extend this line of research into commercial applications.

Hypothesis

The authors have adopted the hypothesis of Bray *et al* (5) that fructose/HFCS are uniquely responsible for the obesity/metabolic syndrome epidemic. They have extended the Bray hypothesis to suggest in this paper that fructose/HFCS are also unique contributors to chronic kidney disease.

Justifications

The authors' justifications for this study are summarized below:

- Fructose consumption has steadily increased over the past 30 years in parallel to the growth of the obesity/metabolic syndrome epidemic.
- Over the past 30 years, fructose has become a standard part of the American diet.
- If we consider the animal and epidemiological data, it is reasonable to hypothesize that fructose consumption in our diet may be among the factors that contribute to the epidemic of the metabolic syndrome and, consequently, to the epidemic of chronic renal disease.
- Fructose consumption by CKD patients may actually be placing them at an increased risk for progression of their CKD.
- The 60% fructose diet is the classical model of fructose-induced metabolic syndrome described in the literature. Though it is 4-times the level that many

people consume, it is common to use higher-dose treatments in animals to achieve a statistically significant result in a limited time frame.

Experimental Design

Forty-two 150-g male rats were randomized and received a diet of 60% fructose, 60% glucose or standard rat chow control (complex carbohydrates in place of purified sugars). At 6-weeks, all animals received a left nephrectomy and two-thirds right nephrectomy (five-sixths nephrectomy) to model renal insufficiency (failure) — the remnant kidney model. Assigned diets were continued for 11 additional weeks following surgery, after which the study was terminated by animal sacrifice.

Results

Observed in fructose but not glucose or control rats:

- increased proteinuria (protein excretion), blood urea nitrogen (a renal function measure) and monocyte chemoattractant protein-1 (MCP-1);
- decreased creatinine clearance;
- enlarged kidneys and worsened kidney morphology (glomerular sclerosis, tubular atrophy, tubular dilation, cellular infiltration); and
- higher mortality (3 fructose rats died; all other rats survived to the end of the study).

Author Conclusions

1. Consumption of a high-fructose diet greatly accelerates progression of chronic kidney disease in the rat remnant kidney model.
2. It is possible that fructose consumption by clinical patients may be contributing to the development or progression of CKD. Restriction of dietary fructose may slow the progression of CKD in these patients.

Critique

- In contending that fructose consumption has steadily increased over the past 30 years due to fructose and HFCS use in commercial foods, the authors mislead readers into believing that sweeteners alone have increased. In truth, consumption of total calories has increased 24% in the past 30 years; it is significant that increases in fat and cereal grains have out-paced increases in added sugars consumption over that period.
- The authors justify their 60% fructose vs. 60% glucose experimental diets (% calories) as acceptable in animal studies in order to accelerate the development of disease. However, the fructose variable exposes rats to 7.5-times the level reported by Park & Yetley (6) for the general human population (8% of calories); it is clearly not physiological.
- Furthermore, no one in the world eats a diet pure in either fructose or glucose to the exclusion of other sugars. We are daily exposed to fructose from fruits and vegetables and nutritive sweeteners (sucrose, HFCS, honey, fruit juice concentrates, crystalline fructose). But the simple sugar most consumed by humans is glucose from sources like cereal grains; food ingredients like starches,

maltodextrins, corn syrups and glucose; fruits and vegetables; and nutritive sweeteners.

- Forshee *et al* calculated the fructose-to-glucose ratio at 0.78 in the typical diet (7). Despite the authors' claims to the contrary, this ratio has likely not changed significantly since sucrose became a staple of the American diet over a hundred years ago. It certainly didn't change with the introduction of HFCS 30 years ago, since HFCS has the same sugars composition as sucrose and largely replaced sucrose in foods and beverages.
- The authors report upsets in rat kidney physiology and function at grossly elevated fructose concentrations and atypical fructose:glucose ratios. However, they offer no proof that fructose/HFCS adversely affect rats at typical human fructose consumption levels or at the fructose:glucose ratio found in the typical human diet. The results of this study cannot be considered predictive of human dietary outcomes. And it is inappropriate for the authors to extrapolate results from an animal model featuring so extreme a diet to humans.
- Most importantly, the authors fail to prove their hypothesis that restricting dietary fructose would slow the progression of chronic kidney disease at realistic human fructose exposure levels, or that this is even an important public health issue.

References

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