Non-alcoholic fatty liver disease and fructose: Bad for us, better for mice

Frank A. Anania*

Emory University School of Medicine, Division of Digestive Diseases, Room 248, The Whitehead Biomedical Research Building, 615 Michael Street, NE, Atlanta, GA 30322, USA

COMMENTARY ON:


AND


© 2011 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Pediatricians have been telling us for some time that fructose consumption is a serious problem in their population. The two studies cited from Hepatology this past year represent the tip of an iceberg that has the potential to affect more than just the pediatric population. At a time when Western governments are grappling with staggering debt, the problems associated with metabolic syndrome, including a steep increase in type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) in our youth, is certainly cause for great concern especially in North America.

High fructose corn syrup (HCFS) has been a staple of the American diet since 1970 and as the article by Abdelmalek et al. report accounts for roughly 10% of dietary intake in the US. HCFS is contained in many processed foods commonly found on US grocery shelves. Recently the European Union put a production quota of foods containing HCFS. In 2005, this quota was set at 303,000 tons; in comparison, the EU produced an average of 18.6 million tons of sugar annually between 1999 and 2001. So, while it is not banned in the EU, its consumption (known as iso-glucose) is limited. (http://wiki.answers.com/Q/High_fru-cose_corn_syrup_banned_in_Europe#ixzz18lyWnsCr). Fructose, a five carbon sugar is often found in fruit beverages that along with HCFS-sweetened sodas are routinely sold to children around the globe. The fundamental problem with a corn based syrup or fructose diet is their fate vis-a-vis hepatic intermediary metabolism that converts such ingredients into long chain fatty acids (LCFA) by committing hepatic fructose uptake to fructose-1-phosphate as opposed to fructose-1,6-bisphosphate (Fig. 1).

Increased storage of free fatty acids (FFA) not only occurs in liver and white adipose tissue (WAT) but also skeletal muscle. FFA storage in white adipose tissue, or WAT, and myocellular fat are states of inflammation which paradoxically release more FFA into circulation and impair normal uptake of glucose following consumption of meals and insulin secretion. In the liver, the result of increased FFA from WAT and impaired glycogen synthesis paradoxically results in hepatocyte insulin resistance, in which more glucose is released into circulation[1]. Based on the intermediary metabolism of fructose, it is clear that an alarming trend is occurring with far reaching implications for the health of young adults in the near future.

It is with this background that two recent articles in Hepatology were published. The article by Abdelmalek et al. comes from data collected from the NIH sponsored NASH Clinical Research Network Data Base [2]. It comes as no surprise that younger people in America consume more beverages with fructose and increased caloric consumption. I will comment on the correlation found with serum uric acid. The most important finding was that when the investigators controlled for age, sex, body mass index (BMI), and total caloric intake they found that daily fructose consumption was associated with a significantly higher fibrosis stage; however, in older adults these data were associated with increased hepatic inflammation or grade but not a higher (fibrosis) stage on liver biopsy. This retrospective analysis is provocative but there are also many shortcomings to the study; these include the fact that the number of patients was relatively small and that the consumption of the fructose-containing beverages was self-reported. Moreover, biopsies for the study were done three months after the study was initiated. No significant or new information was reported on ethnicity (e.g. Hispanics) or race (e.g. African- or Asian-Americans).
Nonetheless the conclusions by the authors, regardless of any concerns about study design, are straightforward and startlingly clear: the world’s youth should significantly reduce the amount of fructose-containing beverages they are consuming, and with this restriction, consume far fewer daily calories that are a source for de novo hepatic biosynthesis of long chain fatty acids. The authors also emphasize the growing importance of AMP kinase in the pathogenesis of non-alcoholic fatty liver disease (NASH) and that hyperuricemia was found in those subjects consuming more than seven servings of fructose per week. While the authors contend that an elevated uric acid may be yet another marker of metabolic syndrome due to the depletion of ATP in the genera-

Fig. 1. Biochemistry of excess fatty acid synthesis as a consequence of hepatic fructose uptake.
tion of fatty acids from high fructose consumption, they also note that, in adjusting for total calorie intake between no fructose consumers and daily consumers, the serum urate concentrations were no longer significant. Further studies concerning serum urate as a marker for NASH will be necessary to make more definitive conclusions.

In the second Hepatology paper published late last year, the investigators put C57Bl/6j mice on a diet similar to the ALIOS (adult-lifestyle induced obesity syndrome) diet that Tetri introduced in 2008 [3]. The major difference was that the present study was conducted for 16 weeks with a significant concentration of sucrose and fructose along with a high fat diet (HFHC) compared to mice fed the high fat diet alone (HF). As anticipated, all the mice fed on either diet developed physiologic markers of metabolic syndrome and insulin resistance; however, the animals fed on the HFHC diet had additional markers for increased fibrosis including histological hepatic fibrosis: increased α-smooth muscle actin mRNA, α1 collagen mRNA, transforming growth factor beta one (TGFβ1) mRNA and livers with significantly higher content of hydroxyproline. The authors attribute this progression of ‘non-alcoholic steatofibrosis’ as a consequence of coenzyme Q9 activation which results in increased reactive oxidant species (ROS) and activation of hepatic and systemic macrophages that increased type 1 collagen gene expression. While this study provides a mechanism for fibrosis that is in-sync with Day’s two hit hypothesis [4], work in the field has nuanced this model recently. Emerging thought would imply that increased de novo lipogenesis, adipocytokine release from WAT, and increased translocation of intestinal FFA may all play a role in the development of hepatocyte lipotoxicity. Sanyal [5], Gores [6] and others have repeatedly published that such lipotoxicity can be deadly to hepatocytes and set off an unfolded protein response (UPR) that leads to cell death by apoptosis and recruitment of pro-inflammatory mediators. In neither article little discussion concerning the role of the gut microbiome—clearly changed upon consuming diets loaded with fat and probably carbohydrate—was mentioned. These dietary changes degrade intestinal tight junctions and significantly reduce paracellular permeability [7,8]. Whatever the case, the merits of long term feeding of mice with both diets high in fat and carbohydrate and little exercise is a far better approach to studying human disease in rodents than denying them methionine or choline! What is also clear from both articles—one from a human database and the other in a more realistic mouse model of human food consumption—is that the continuous consumption of juices and foods laden with high fructose corn syrup should be

significantly reduced in our food supply. In Europe fructose consumption may be easier to control, but in North America a task to reduce consumption is easier said than done. The American food industry, where profits have been made, in large part, on the use of fructose in corn syrup, would have no appetite to put North American youth on a diet free of HFCS.

Conflict of interest

The author who has taken part in this study declared that he does not have anything to disclose regarding conflict of interest with respect to this manuscript.

Acknowledgments

The author acknowledges financial support of his work by the US Public Health Service National Institutes of Diabetes, Digestive, and Kidney Diseases (NIDDK) R01DK062092, R01DK075397. R24DK064399 to Emory University Division of Digestive Diseases Research Development Center (DDRDC).

References