

Calorie Control Council Response to Thuy *et al*

“Nonalcoholic fatty liver disease in humans is associated with increased plasma endotoxin and plasminogen activator inhibitor 1 concentrations and with fructose intake”

Thuy S, Ladurner R, Volynets V, Wagner S, Strahl S, Konigsrainer A, Maier KP, Bischoff SC, Bergheim I. Nonalcoholic fatty liver disease in humans is associated with increased plasma endotoxin and plasminogen activator inhibitor 1 concentrations and with fructose intake. *J Nutr.* 2008 Aug;138:1452-5.

Background

This article is a collaboration of three German laboratories: Department of Nutritional Medicine, University of Hohenheim, Stuttgart; Department of General, Visceral and Transplant Surgery, Tübingen University Hospital; and Liver Center, City Hospital, Esslingen. The purpose of the study is to better understand the biochemical and pathological changes associated with the development of nonalcoholic fatty liver disease (NAFLD) so that improved therapies can be developed.

Author Justification

High dietary carbohydrate intake is claimed to be a key factor in the development of NAFLD, increasing the odds of later stages of the disease. In animal studies, fructose at levels up to 60% of calories is reported to increase lipid accumulation in the liver leading to insulin resistance, elevated plasma triglycerides and oxidative stress. The authors previously reported that moderate fructose consumption in mice could lead to increased intestinal translocation of bacterial endotoxin, induction of hepatic tumor necrosis factor alpha and subsequent liver steatosis¹ (1). Simultaneous treatment with antibiotics almost completely blocked the effect of fructose on mouse liver.

Aim

Assess dietary intake, endotoxin and PAI-1 concentration of NAFLD patients and controls to further investigate the mechanisms involved in the development of NAFLD in humans.

Experimental Design

The dietary intakes of 12 NAFLD patients and 6 control subjects were assessed. Measurements of several biochemical markers of NAFLD were made: plasma endotoxin and plasminogen activator inhibitor (PAI)-1, hepatic PAI-1 and toll-like receptor (TRL) 4 mRNA.

Results

- Fructose intake, endotoxin and PAI-1 concentration increased in NAFLD patients;
- Endotoxin and PAI-1 concentration are related;
- Carbohydrate intake and PAI-1 concentration are related.

Author Conclusions

1. Endotoxin and its receptor TLR4 and plasma PAI-1 concentration, dietary fructose intake and PAI-1 are associated with NAFLD in humans.
2. Hepatic TLR4 expression, plasma PAI-1 and endotoxin concentrations are related.
3. Hepatic PAI-1 expression might be related to total carbohydrate and sugar intake.

¹ Abnormal retention of lipids within a cell.

4. Results are consistent with the concept that intestinal permeability and flora, as well as dietary pattern [read 'fructose intake'] and PAI-1, are important in the pathogenesis of NAFLD in humans.
5. Further studies are needed to explore the molecular mechanisms responsible.

Critique

- In the authors' previous paper (1), mice were given *ad libitum* water; water + artificial sweetener (cyclamate, Sunett and saccharin); or 30% aqueous solutions of glucose, sucrose or fructose. It appears from examination of the data that the mice took in approximately 55% of calories as fructose, comparable to the level (60-65%) commonly used to induce metabolic abnormalities in rats (see ex., RJ Johnson). The upsets attributed to fructose clearly are inappropriate as extrapolated to humans, due to the exaggerated exposures, single-sugar protocol and mouse-human differences.
- The link between fructose intake and NAFLD in the current paper is very weak:
 - Fructose intakes were teased from patient dietary recall of recent meals during nutritionist interviews, a widely acknowledged imprecise method.
 - The difference in total fructose (free + sucrose) intake between NAFLD patients and controls was about 10 g/d = 40 kcal/d. The average daily calorie intake between the two groups was about 2200 kcal. Thus, NAFLD patients took in an extra 1.8% of calories as fructose; a rather modest difference.
 - The difference in sucrose intake between patients and controls was about 9 g/d = 36 kcal. NAFLD patients took in an extra 1.6% of calories as sucrose; not much less than the fructose variable.
- That fructose, but not sucrose, differences were statistically significant may be attributable to the low numbers of subjects (12 NAFLD; 6 control). Statisticians would consider this study to have low statistical power, which earns it low credibility in the long run.

References

1. Bergheim I, Weber S, Vos M, et al. Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. *J Hepatol* 2008;48:983-92.