

# Calorie Control Council Response to Lê *et al* “Effects of four-week high-fructose diet on gene expression in skeletal muscle of healthy men”

Lê KA, Faeh D, Stettler R, Debard C, Loizon E, Vidal H, Boesch C, Ravussin E, Tappy L. *Diabetes Metab.* 2008 Feb;34:82-5.

## Background

This study is a collaboration between research labs at the University of Bern (Boesch) and University of Lousanne (Lê, Faeh, Stettler, Tappy) in Switzerland; Pennington Biomedical Research Center, Baton Rouge, LA (Ravussin); and université Lyon-1, faculté de médecine Lyon-Sud, Oullins, France (Debard, Loizon, Vidal). Pennington is the pre-retirement home of George Bray.

## Hypothesis

The authors hypothesized that the deleterious effects of a high-fructose diet may not be detectable at the whole-body level; subtle molecular changes may be occurring in peripheral tissues. Their aim was to investigate whether fructose may induce early molecular changes in skeletal muscle prior to the development of whole-body insulin resistance.

## Justifications

- Over the past decades, fructose consumption has dramatically increased and several authors have suggested that fructose may play a role in the onset of metabolic disorders (1, 2).
- In rodents, a high-fructose diet leads to insulin resistance and ectopic (out of place) lipid deposition.
- In healthy humans, a four-week high-fructose diet alters lipid homeostasis, but does not affect insulin sensitivity or intramyocellular lipids.

## Experimental Design

Muscle biopsies were taken from five healthy men who had participated in a previous four-week high-fructose study, during which insulin sensitivity, and intrahepatocellular lipids and intramyocellular lipids were assessed before and after fructose. The mRNA concentrations of 15 genes involved in lipid and carbohydrate metabolism were quantified before and after high-fructose by real-time quantitative PCR (polymerase chain reaction) technique.

## Author Conclusions

- High-fructose significantly increased one gene product (stearoyl-CoA desaturase-1 [+50%]) and decreased three others (glucose transporter-4 [-27%], acetyl-CoA carboxylase-2 [-48%] and peroxisomal proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  [-26%]). All other genes showed no significant changes.
- These high-fructose-mediated changes may be early markers of insulin resistance.

## Critique

- The number of subjects used in this study was very low = 5 subjects. Individual genetic variation could skew the results dramatically with such a small number of subjects.
- There were no controls for fructose or extra calories in the experiment; each subject was self-controlled, where measurements taken during a two-week, baseline isocaloric period were compared with those after four weeks of high-fructose supplementation. *This means that the effect claimed for fructose could equally have been caused by excess calories or carbohydrates in the test diet.*
- Dietary compliance was poorly controlled: the study was carried out on an outpatient basis with no accurate monitoring of outside food intake over the six-weeks duration.
- During the high-fructose phase of the study, the isocaloric diet was supplemented with and additional 1.5 g fructose/kg body weight/day. Though this was advertised as an 18% energy supplement, it resulted in a minimum fructose exposure of 25% of calories; the actual upper limit of exposure is unknown, since outside food intake was not monitored or restricted.
- In summary, this experiment was sloppily carried out and little validity should be given to the results until they are repeated under more rigorous conditions.

## References

1. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr.* 2004 Apr;79:537-43.
2. Havel PJ. Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr Rev.* 2005 May;63:133-57.