Why Is Nonalcoholic Fatty Liver Disease So Prevalent?

Nonalcoholic fatty liver disease (NAFLD), characterized by excess accumulation of fat in cells within the liver, is considered the most common liver disease (Delle Corte et al. 2011, Browning et al. 2004). This excess fat is associated with many adverse health effects, namely insulin resistance and dyslipidemia (McCullough 2004). There are many factors associated with this disease. Those factors include genetics, gender, ethnicity, family history, diet, lifestyle, prenatal environment, infant feeding, and conditions associated with metabolic syndrome (Brunt et al. 2015).

NAFLD develops in 20%–70% of the population due to genetic factors. Limited genome-wide analysis indicates at least six genes are associated with progressive NAFLD. Those genes include APOC3, GCKR, MBOAT7, PNPLA3, TM6SF2, TRIB1, and Kruppel-like factor plus possible single-nucleotide polymorphisms that may be attributable to differences in ethnic susceptibility (Romeo et al. 2008, NIH 2017). The PNPLA3 gene codes for adiponutrin, which is a unique enzyme found in fat cells and liver cells. Evidence based on a rat model indicates that adiponutrin participates in lipolysis and lipogenesis in fat cells and its activity appears to increase following a meal, whereas the activity is diminished during fasting (Oliver et al. 2011). This gene may be responsive to dietary and lifestyle variations and thus may be a biomarker to identify those at greater risk for disease development and progress as suggested in a mouse model (Smagris et al. 2015). TM6SF2 may be associated with the progression of NAFLD since it modulates triglyceride content in the liver. Overexpression of this gene in mice seems to affect VLDL and LDL cholesterol metabolism, thus impacting the risk of heart disease as well as liver disease (Ehrhardt et al. 2017).

Epidemiological data suggest considerable variations in the prevalence of NAFLD among countries. For example, within the United States, data from ultrasonography indicate a prevalence of 20%–50% of the general population. The prevalence appears to be highest among those identified as Hispanic (45%) and lowest among African-Americans (24%) (Browning et al. 2004). Among Asia-Pacific countries, the prevalence of NAFLD ranges from 15%–30%, whereas the range within Africa is 10%–20% (Sookoian and Pirola 2017).

A spectrum of dietary factors has been associated with the development and progression of nonalcoholic fatty liver disease. For several decades, many investigators have voiced concerns about the consumption of sucrose, particularly fructose, which they contend leads to diabetes, insulin resistance, cardiovascular disease, obesity, and even toxic effects (Yudkin 1972, Lustig 2009).

It is important to remember that glucose and fructose are metabolized differently. For example, glucose can be directly utilized as an energy source by all cells in the body whereas fructose cannot. In addition, glucose is the predominant energy source for human cells, particularly brain tissue, which is facilitated by a number of glucose transporters, such as the GLUT family. Within the cell, glucose is phosphorylated, converted to a phosphorylated fructose, and eventually converted to pyruvate. In contrast to glucose, fructose does not contribute to elevated blood glucose or elicit a postprandial insulin response. Not all tissues metabolize fructose (e.g., phosphorylation of dietary fructose). These enzymes are predominately in the GI tract and liver, with nominal fructose metabolizing enzymes in the kidneys. Only when dietary fructose is abnormally elevated is there a de novo synthesis of lipids from fructose in the liver (Tappy and Le 2012). It is also interesting to note that even those consuming a liter (106 g) of sugar, 53 g of fructose, ~25% total energy) of a sugar-sweetened beverage daily for 6 mo (Stanhope et al. 2009, Maersk et al. 2012). On the other hand, a short-term study (4 wk) among a small group of healthy human subjects (BMI ~20–35) fed ~30% of energy requirement from fructose (150 g) or glucose (150 g) indicated no differences in liver fat accumulation or body weight from baseline (Silbernagel et al. 2011). These results are similar to those reported by Johnston et al. (2013) among healthy overweight (BMI ~25–32) men fed 25% energy from monosaccharides for 2 wk and Bravo et al. (2013), who studied adult men and women (BMI ~25–32), which indicated...
changes in liver triglycerides were mediated during hypercaloric periods as opposed to levels of added sugars (8%, 18%, 30% of calories from HFCS or sucrose) during the 10 wk study period.

Two recent systematic reviews and meta-analyses indicated dietary fructose did not impact biomarkers of NAFLD. For example, Chung et al. (2014) noted that among the six observational studies and 21 intervention studies that met the inclusion criteria, elevated liver enzyme activities were confounded by excess energy intake, whereas the evidence to assess the potential association of fructose or glucose and NAFLD was insufficient. Similarly, Chiu et al. (2014) evaluated 13 human trials (seven isocaloric trials, in which fructose was exchanged isocalorically for other carbohydrates, and six hypercaloric trials, in which the diets were supplemented with excess energy (+21% –35% energy)) from high-dose fructose (+104–220 g/day). These mostly short-term studies (≤ 4 wk) indicated an isocaloric exchange of fructose for other carbohydrates did not induce NAFLD changes in nearly 300 healthy (typical BMI < 30) participants.

Thus the preponderance of high quality clinical evidence suggests fructose, when consumed at normal dietary levels, does not contribute to NAFLD in humans. These results are particularly important when fructose is consumed under isocaloric conditions for periods less than 10 weeks. Results from hypercaloric studies (excessive levels of fructose or glucose) for prolonged periods may confound the NAFLD issue, namely the association with excess energy intake rather than specific carbohydrates, such as fructose or glucose.

References cited are available via hyperlinks in the digital version of this column.