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EDITORIAL

# In NAFLD, You Are What You Eat, Not Simply How Much You Eat

On May 20, 2016, the Food and Drug Administration (FDA) published a set of new regulations.[1] These new labeling requirements were the result of FDA review of new scientific data "on the associations between nutrients and chronic diseases, health-related conditions, physiological endpoints, and/or maintaining a healthy dietary pattern." The proposal drew over 500 public comments, the majority of which were related to classifications of fats and carbohydrates, signifying that (1) there is great public interest in the topic of nutrition, (2) there exists great confusion regarding how one categorizes nutrients, and (3) more science is needed to determine definitively which nutrients and what quantity of these nutrients promote health or disease.[1]

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, the article by Duwaerts et al[2] is, therefore, a timely publication that addresses the relative contribution of total caloric intake versus dietary nutrient content to the nonalcoholic fatty liver disease (NAFLD) epidemic. The authors used an isocaloric, mouse NAFLD model to investigate the effects of common dietary components on hepatic and adipose tissue lipid metabolism and glucose homeostasis. Mice were fed chronically for 6 months with a chow or 1 of 4 high-carbohydrate (sourced from either sucrose or starch), high-fat (sourced from either oleate or palmitate) diets. Although all combinations of the isocaloric diet increased hepatic steatosis compared with chow-fed mice, mice fed the starch-oleate diet exhibited the greatest degree of hepatic steatosis, hepatic inflammation, and glucose intolerance, arguably a surprising finding given the reported cardiovascular health benefits of oleate-rich diets.[3]

Based on *in vivo* metabolic tracer studies and analyses of liver and white adipose tissue depots, the authors concluded that combined high-carbohydrate/high-fat diets increase hepatic triglyceride content because of increased hepatic *de novo* lipogenesis. The authors observed additionally that white adipose tissue mass was reduced significantly in mice fed the oleate-containing diets compared with chow-fed animals, suggesting that adipocyte lipolysis and subsequent hepatic uptake of circulating free fatty acids may also contribute to the hepatic steatosis they observed. They tested this hypothesis by *in vivo* measurement of white adipose tissue lipogenesis and *ex vivo* measurement of lipolysis and concluded that, although adipocyte *de novo* lipogenesis is reduced in both oleate groups, lipolysis contributes significantly only to mice fed a starch-oleate diet. Moreover, they observed that the starch-oleate diet caused the greatest amount of white adipocyte inflammation and necrosis by histology, gene array analysis, and flow cytometry analysis of NK cell infiltration. Notably, these findings were reproduced by mice fed a stereotypical Western diet.

Of additional interest is that the starch palmitate combination caused hepatic steatosis and hyperinsulinemia with preserved glucose tolerance and enhanced white adipose tissue *de novo* lipogenesis. These findings suggest that one of the earliest events in NAFLD is indeed hyperinsulinemia, which, under normal conditions, prevents adipose tissue lipolysis and enhances hepatic *de novo* lipogenesis. Although the Duwaerts et al study was limited to 6 months, if these mice had continued to age on this diet, it is conceivable that they would eventually develop tissue insulin resistance with resultant adipocyte lipolysis and increased hepatic gluconeogenesis. Examination of these temporal associations not only would strengthen these data, but also is critical to our understanding of NAFLD pathophysiology, especially as we develop new targets for therapy.

NAFLD is a systemic disease, not simply a disease of the liver; and patients with the nonalcoholic steatohepatitis subtype of NAFLD have impaired insulin signaling at the level of adipose tissue, muscle, and liver (reviewed in Carr et al),[4] likely explaining why NASH patients who receive a liver transplant remain at risk for disease recurrence.[5] The work of Duwaerts et al is consistent with the mechanistic hypothesis that damage of white adipose tissue particularly by starch-oleate contributes to hepatic injury, although this was not examined directly. This study demonstrates clearly that nutrient composition (not simply total caloric intake) matters in the pathogenesis of NAFLD and supports the findings of other groups who have demonstrated similarly that the combination of high-carbohydrate/high-fat diet promotes liver injury.[6,7]

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**Conflicts of interest**
The author is sub-investigator for Intercept Pharmaceuticals.

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