

High Fat Diet Induced Lipotoxicity: Triglycerides or Cholesterol is to Blame?

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High fat diet-induced obesity is associated with lipid accumulation in adipose tissue, the arteries, and the liver. Lipid accumulation in these tissues can be adaptive, or can lead to lipotoxicity-induced insulin resistance, atherosclerosis and nonalcoholic fatty liver disease (NAFLD). Most NAFLD patients have simple fatty liver (steatosis) whereas 10-20% of them progress to the more severe form of nonalcoholic steatohepatitis (NASH), which can lead to liver failure. NASH is also linked to higher risk of cardiovascular disease. The pathogenesis of NASH involves multiple hits, including lipotoxicity, gut-derived signals, signals from the innate immune system such as toll like receptors (TLRs) or inflammatory cytokines, oxidative and endoplasmic reticulum (ER) stress. TGs and cholesterol accumulation may coexist in fatty liver, raising the possibility that type rather than the amount of fat determines the susceptibility of steatosis to inflammatory signals which promote NASH.

In my talk, I will present data suggesting that TG accumulation in hepatocytes may be an adaptive response in the liver as it is in adipose tissue, and may represent a way to preserve the function of hepatocytes. Consistent with this, hepatic TG accumulation is not uniformly associated with inflammation and liver injury.

Lipotoxicity due to free cholesterol accumulation in the liver, is an emerging aspect of NASH development which until recently has been underappreciated. This is supported by association studies in humans demonstrating dysregulation of cholesterol metabolism genes and free cholesterol levels with NAFLD. Furthermore, using nutritional and genetic models of hepatic steatosis, it was shown that free cholesterol accumulation but not TGs, sensitizes hepatocytes to TNF-induced apoptosis and NASH development. Future intervention studies are needed to define the precise role of specific changes in the accumulation of free cholesterol in NAFLD progression.