Nature vs nurture: genetic susceptibility and weight loss in hepatic steatosis

K Huang

Department of Medical Genetics, Centre for Molecular Medicine and Therapeutics, University of British Columbia, 980 West 28th Avenue, Vancouver, British Columbia, Canada V5Z 4H4.

e-mail: khuang@cmmt.ubc.ca

Apolipoprotein C3 gene variants in non-alcoholic fatty liver disease

Petersen et al. (2010)


Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the Western countries (1), affecting approximately a quarter of the population. Fatty liver is associated with cardiovascular disease (2) and metabolic conditions including diabetes, insulin resistance, obesity and high blood pressure (3, 4).

Excess lipid accumulation in the liver cells is not only a mediator of metabolic syndrome but also accompanied by a range of histological alterations varying from hepatic steatosis, a hallmark of NAFLD, to non-alcoholic steatohepatitis, with time progressing to manifest cirrhosis [reviewed in (1)]. There are several mechanisms by which excess triglycerides are acquired and accumulate in hepatocytes. In adipose tissue, insulin resistance induces an impaired antilipolytic action of insulin and increased release of fatty acids (5, 6). Elevated plasma concentrations of glucose and fatty acids may promote hepatic fatty acid and triglyceride uptake and synthesis, and impair β-oxidation (7). As a result, an accumulation of triglycerides in the liver will occur, leading to hepatic steatosis (Fig. 3).

Although an association between hepatic steatosis and insulin resistance is well accepted, it remains unclear whether there is a genetic basis for this association. Previous studies have suggested that two single-nucleotide polymorphisms (SNPs) in the gene encoding apolipoprotein C3 (APOC3) may be associated with hypertriglyceridemia (8–11). These two SNPs, rs2854116 (T-455C) and rs2854117 (C-482T), are located in the promoter region of APOC3. The variant alleles at each SNP are each associated with higher apoC3 expression in vitro (12). Therefore, the authors set out to examine whether these SNPs might confer a predisposition to hepatic steatosis and insulin resistance.

Genetic screening for these two APOC3 SNPs was examined in a cohort of Asian Indian men, a group known to have a high prevalence of NAFLD. These selected subjects did not have the typical risk factors for NAFLD, including excessive alcohol consumption, obesity, overt insulin resistance, or type 2 diabetes. The variant allele carriers had an average of 30% increase in their plasma apoC3 (13). The enhanced expression of apoC3 correlates to an elevation in both fasting plasma and hepatic triglyceride concentrations (13). Proton nuclear magnetic resonance studies detected hepatic steatosis in 38% of subjects with one or more of the variant alleles but in none of those without these alleles. Individuals with hepatic steatosis also showed marked insulin resistance, measured by 3-h oral glucose tolerance test (13).

How might an increase in apoC3 lead to hepatic steatosis? It has been previously shown that apoC3 causes hypertriglyceridemia by inhibiting the catabolism and the clearance of triglyceride-rich lipoproteins (14). Indeed, in this study, the subjects with high-expression alleles had increased levels of fasting serum triglycerides, increased post-prandial levels of circulating triglyceride-rich chylomicrons, and a decreased ability to clear triglyceride from plasma after an intravenous triglyceride challenge (13). Thus, the increased levels of apoC3 impair the clearance of diet-derived triglyceride-rich particles, resulting in increased hepatic delivery of triglycerides, which in turn leads to hepatic steatosis (Fig. 3).

The association between the two SNPs in APOC3 promoter and hepatic steatosis was also found in a cohort of non-Asian Indian men who also did not have the typical risk factors for steatosis (13). These findings confirm the association between the increased expression of apoC3 and hepatic triglyceride accumulation, while suggesting that racial or ethnic factors also influence susceptibility to steatosis.

Interestingly, despite the predominant genetic predisposition in this Asian Indian cohort, with a gradual weight loss of an average of 5.5 kg, subjects with hepatic steatosis and insulin resistance
had a significant reduction in the liver triglyceride content, plasma glucose as well as insulin concentrations (13). A marked improvement in insulin sensitivity was evident, suggesting life-style modification (i.e. weight loss) is extremely effective in controlling the progression of hepatic steatosis.

With the identification of various genetic and epigenetic factors, doctors may eventually be able to identify patients who are at risk for hepatic steatosis as well as patients with steatosis who are particularly at risk for further progressing to steatohepatitis and cirrhosis. Preventive strategies and treatments can then be introduced to minimize the health risks attributable to fatty liver.

References