Obesity and the liver: nonalcoholic fatty liver disease

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The increasing prevalence of nonalcoholic fatty liver disease (NAFLD) parallels the rise of obesity and its complications. NAFLD is a common cause of cirrhosis and a leading indication for liver transplant. Genetic susceptibility, dietary composition, and exercise habits influence the development of NAFLD, and insulin resistance results in widespread metabolic perturbations with a net effect of triglyceride accumulation in the liver. Some patients will develop hepatocyte cellular injury and fibrosis of the liver, which can progress to cirrhosis and require liver transplant. Treatments targeting the pathophysiological mechanisms of NAFLD exist, but carry some potential risk and are not universally effective. Weight loss and lifestyle changes remain the most effective and safest approach, but sustainable change is difficult for most patients to achieve. Future work will continue to focus on developing effective and safe interventions to prevent the development of advanced liver disease, whereas efforts in the public health domain continue to combat obesity. (Translational Research 2014;164:312–322)

Abbreviations: ApoC3 = apolipoprotein C III; CK-18 = cytokeratin-18; DAG = diacylglycerol; ER = endoplasmic reticulum; HCC = hepatocellular carcinoma; LPS = lipopolysaccharide; LXR = liver X receptor; MET = metabolic equivalent of task; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PNPLA3 = patatin-like phospholipase domain containing 3; ROS = reactive oxygen species; SREBP-1 = sterol regulatory element-binding protein 1; TLR4 = toll-like receptor 4

INTRODUCTION

The exploding rate of obesity in the United States over the past several decades has led to an increased prevalence of diabetes and cardiovascular disease as well as nonalcoholic fatty liver disease (NAFLD). NAFLD is present in ~20%–30% of adults in the United States and ~10% of children.[1-3] NAFLD represents a spectrum of disease with most patients having only steatosis; however, a sizable number of patients can also develop inflammation, cellular injury, and fibrosis, termed nonalcoholic steatohepatitis (NASH). The cellular injury in NASH is characterized by ballooned hepatocytes, which frequently contain Mallory-Denk bodies.[4] Patients with NAFLD found to have only steatosis are unlikely to progress to cirrhosis; however, steatosis can accelerate other forms of liver disease.[5-7] Patients found to have NASH represent a subset of those with NAFLD at the greatest risk of progressing to cirrhosis, and it is estimated that ~3%–5% of the general population has NASH.[8] NASH now represents the third most common indication for liver transplantation, although at its current trend it is expected to soon eclipse alcohol as an indication for liver transplantation (Fig 1).

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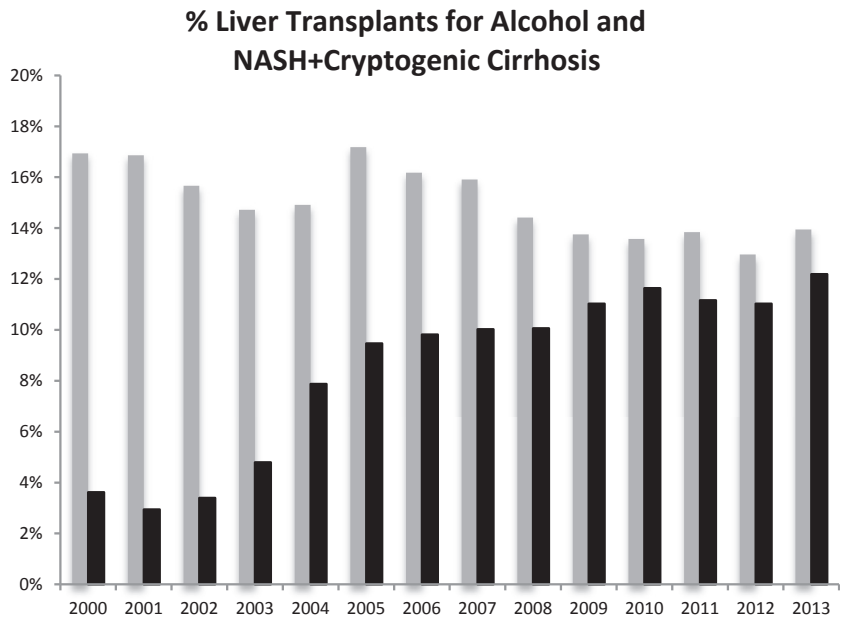

Fig 1. Percentage of liver transplants for alcohol and NASH±cryptogenic cirrhosis. The number of patients transplanted with a primary diagnosis of NASH±cryptogenic cirrhosis (black) has steadily risen and is nearly equal to the number of patients transplanted with primary diagnosis of alcohol (gray). Hepatitis C remains the most common indication for liver transplant. Patients with a primary diagnosis of hepatocellular carcinoma are excluded. http://optn.transplant.hrsa.gov. NASH, nonalcoholic steatohepatitis.

In addition to increasing rates of transplantation for NASH, increased prevalence of obesity and diabetes in potential cadaveric donors has led to increased organ discard rate exacerbating the mismatch between supply and demand for liver transplants.[9]

The rising rate of childhood obesity has also led to the development of NAFLD in the pediatric population. Estimates based on elevated Alanine Aminotransferase and an autopsy series suggest a prevalence of pediatric NAFLD of ~8%–10%.[10] Risk factors for pediatric NAFLD mirror those for adult NAFLD and children with NASH can even progress to cirrhosis and require liver transplantation.[11] Similar histologic changes are often noted in pediatric NASH compared with adult NASH; however, some cases of pediatric NASH present with less hepatocyte ballooning and more portal-based inflammation and fibrosis.[4,10]

Although NAFLD leads to increased morbidity and mortality from liver disease, the most frequent cause of morbidity and mortality in the NAFLD population remains cardiovascular. Efforts continue to better understand the pathophysiology of NAFLD and develop treatments addressing those patients who develop NASH and have progressive liver disease. However, NAFLD should continue to be viewed as the hepatic manifestation of the metabolic syndrome and treatment of associated diabetes, hyperlipidemia, and hypertension are equally as important as the treatment of the actual liver disease. This review will discuss current understanding of the pathophysiology of NAFLD and its management.

PATHOGENESIS OF NAFLD

Fat accumulation in the liver is the culmination of dysregulation of fatty acid influx to the liver, fatty acid efflux, and hepatic de novo lipogenesis. Circulating adipokines and cytokines mediate and result from this process. Insulin resistance is near universally present in NAFLD and diabetes is a very frequent finding in those patients who develop NASH. Lipotoxicity, mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum (ER) stress are involved in hepatic injury. Adipose tissue distribution and genetic factors influence this process, and gut microbiota may also play a role (Fig 2).

Genetics. Certain groups tend to have a higher prevalence of NAFLD with Mexican-Americans having a particularly high burden (~24%) compared with non-Hispanic whites (~18%) and non-Hispanic blacks (~14%).[1] There may be some differences based on alternate dietary patterns; however, genetic factors are a significant contributor to these differences. Patatin-like phospholipase domain containing 3 (*PNPLA3*) is a gene strongly associated with susceptibility to develop steatosis and progressive liver disease and may explain some of the racial differences. The