Nonalcoholic Fatty Liver Disease, Diabetes, Obesity, and Hepatocellular Carcinoma

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KEYWORDS

• Nonalcoholic steatohepatitis • Cirrhosis • Noncirrhotic • Insulin resistance
• Hepatocellular carcinoma • Obesity • Diabetes • Chemoprevention

KEY POINTS

- Obesity, type 2 diabetes mellitus (T2DM), and insulin resistance are strongly associated with nonalcoholic fatty liver disease (NAFLD) and increased incidence of hepatocellular carcinoma (HCC).
- HCC incidence is increasing as NAFLD becomes the most common cause of liver disease.
- HCC can develop in NAFLD patients without cirrhosis so cancers may be missed given the high prevalence of NAFLD and the limitations of current screening strategies.
- Activation of pathways that promote inflammation, insulin resistance, angiogenesis, and cellular proliferation seen in these diseases promote the development of HCC.
- Clinical studies to prevent the development of HCC in patients with obesity, T2DM or NAFLD are critically needed.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is now the most common liver disease in the United States, with more than 80 million Americans affected. It represents a spectrum of diseases ranging from isolated hepatic steatosis (IHS) to steatosis in association with inflammation and cellular injury—the progressive subtype of NAFLD referred to as nonalcoholic steatohepatitis (NASH). NASH is often but not always associated with varying degrees of fibrosis that can develop into cirrhosis and all of its associated complications.[1,2] The prevalence of the disease parallels the epidemic of the metabolic syndrome, namely obesity, type 2 diabetes mellitus (T2DM) and its other

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manifestations worldwide. It is no surprise that the mechanisms underlying the metabolic syndrome, insulin resistance, and obesity are also important in the development of both IHS and NASH.[3]

Hepatocellular carcinoma (HCC), known to occur most commonly in the setting of cirrhosis, is also increasing in incidence, and is now the second leading cause of cancer deaths worldwide.[4] Historically, the risk factors for HCC in the United States have primarily included alcoholic cirrhosis, hepatitis B virus (HBV) infection, hemochromatosis, and hepatitis C virus (HCV) infection. Because of its link to the HCV epidemic, HCC is considered the fastest growing cause of cancer mortality overall in the United States as well.[5] However, the clinical landscape of HCV is changing rapidly into a future where cure is not only probable, but will be nearly universal for those who have access to therapy. No doubt, this will reduce the development of HCV-related HCC in the future. Results of recent studies demonstrate that HCC is more prevalent in the setting of obesity and insulin resistance, and may occur in NAFLD patients without cirrhosis.[4] Therefore, if the incidence of obesity, diabetes, and NASH continues to increase, and the HCV-related association decreases with effective treatment strategies, NAFLD could become the most common cause of HCC in the United States and other developed countries. Indeed, in a recent retrospective cohort study that evaluated trends in HCC etiology among adult liver transplant recipients from 2002 to 2012, the number of patients undergoing liver transplant for HCC secondary to NASH increased by nearly 4-fold, whereas the number of patients with HCC secondary to HCV increased by only 2-fold.[6] During that same 10-year period, the prevalence of NASH-related HCC increased steadily, becoming the second leading etiology of HCC-related liver transplant in the United States (increasing from 8.3% in 2002 to 10.3% in 2007 and to 13.5% in 2012).

To clarify these relationships, this review discusses the pathophysiologic mechanisms that underpin the close relationship between obesity, insulin resistance, NAFLD, and the progression to HCC, both in the presence and absence of cirrhosis.

OBESITY, DIABETES, NONALCOHOLIC FATTY LIVER DISEASE, AND NONALCOHOLIC STEATOHEPATITIS AS RISK FACTORS FOR HEPATOCELLULAR CARCINOMA

The results of several studies have elucidated the relative risk of several disease processes that are implicated in the pathogenesis of HCC. In a population-based study, authors analyzed 6991 cases from the Surveillance, Epidemiology, and End Results–Medicare databases that link cancer registry data and Medicare enrollment during the period from1994 to 2007.[7] The authors estimated the population-attributable fractions (PAFs), that is, the proportions of cases that can be attributed to specific risk factors. They found that T2DM and/or obesity had the greatest PAF (36.6%), followed by alcohol-related disorders (23.5%), HCV (22.4%), HBV (6.3%), and rare genetic disorders (3.2%; **Fig. 1**). Although the relative risk of HCV for HCC incidence (39.9) was higher than the relative risk of T2DM and/or obesity (2.47), the high prevalence of T2DM and obesity in the United States accounted for more cases of HCC than HCV. However, the exact PAF of NAFLD remains to be determined, because NAFLD cases per se were not identified in the Surveillance, Epidemiology, and End Results database. Although the study was limited to age groups 68 years or older, it represented about 25% of the general population of the United States.[7]

In other studies, a direct relationship between obesity and HCC has been demonstrated. Available data suggest that obesity increases the risk of HCC 1.5- to 4-fold (**Table 1**).[8–10] In Danish and Korean studies, an association between obesity and an increased relative risk of HCC (1.9 and 1.56, respectively) was seen.[9,11] Data

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