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MINI REVIEW

Non-alcoholic steatohepatitis in morbidly obese patients

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Summary The hepatic complications of morbid obesity range from steatosis to steatohepatitis (Non-alcoholic steatohepatitis [NASH]), fibrosis, cirrhosis and finally hepatocellular carcinoma. The pathophysiological mechanisms of the progression of a normal liver to a liver showing steatosis and then steatohepatitis are complex, including, per se, insulin-resistance, iron accumulation, oxidative stress and hepatocyte death. An imbalance in anti- and pro-inflammatory factors may be the trigger. These factors can originate from intra- or extrahepatic sites, particularly the adipose tissue and the gut. This review will provide insight into the current diagnosis and understanding of hepatic inflammation including non-invasive markers of NASH (markers of hepatocyte death), intrahepatic mechanisms (regulation of the immune and inflammatory response, hepatocellular iron deposition, hepatocyte death) and extrahepatic factors (from adipose tissue and gut) in morbidly obese patients.

Introduction

The liver receives 80% of its blood supply from the gut through the portal vein, which is rich in bacterial products, environment toxins and food antigens. Seventy percent of the cells in the liver are hepatocytes, which fulfill the metabolic and detoxifying needs of the body. The remaining cells comprise the non-parenchymal cells, including endothelial cells, stellate cells, Kupffer cells (resident macrophages) and lymphocytes. Emerging evidence suggests that the liver could play an important role in the body's immune response [1]. In obesity, the activation of the immune system in the liver by intra- and extrahepatic factors plays a key role in liver complications. In extrahepatic sites, an alteration in the properties of the gut and an increase in inflammation of adipose tissue during obesity influence the progression of liver diseases.

The incidence of overweight and obesity is rapidly increasing in many Western countries. Weight and height is used to calculate the body mass index (BMI). Overweight and obesity is defined according to the WHO

Abbreviations: NASH, Non-alcoholic steatohepatitis; NAFLD, Non-alcoholic fatty liver disease; LPS, Lipopolysaccharide; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TNF, Tumor necrosis factor; IL, Interleukin.

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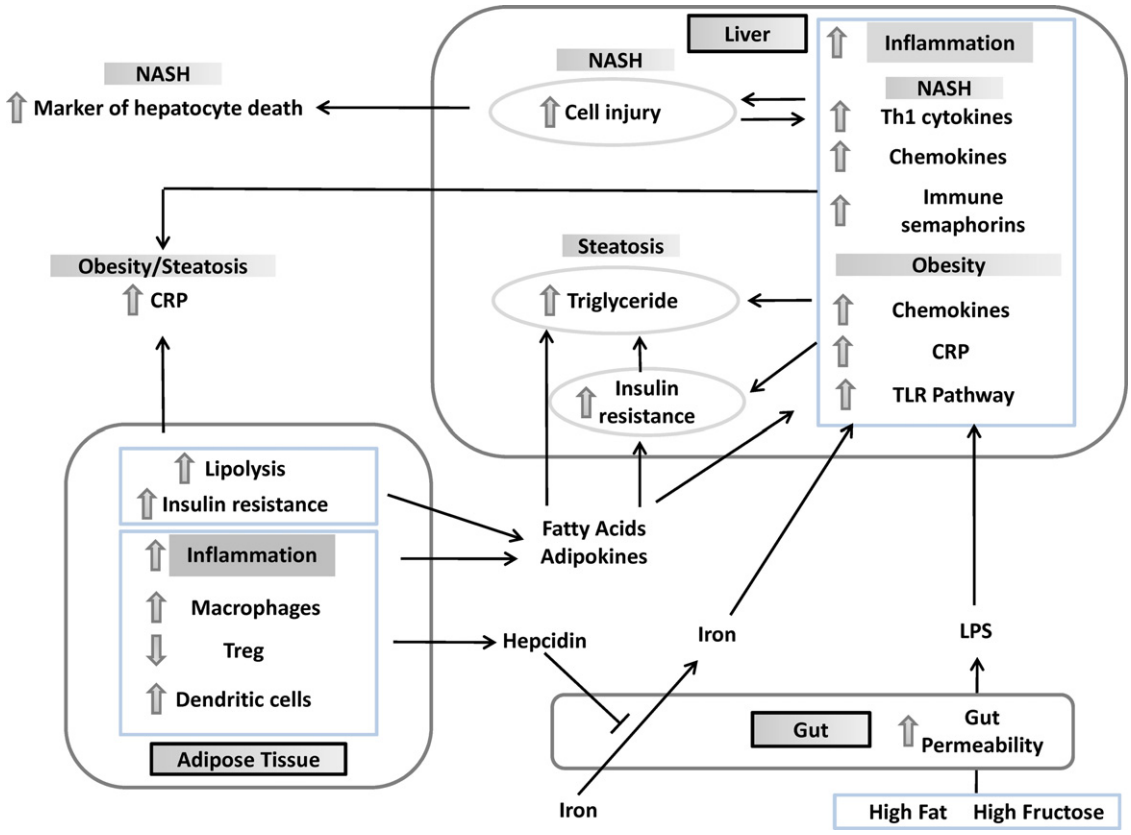

Figure 1 Liver complications in morbidly obese patients: modifications in hepatic inflammation and in the immune response play an important role in the development of liver complications associated with obesity. Intra- and extrahepatic factors are involved. In obesity, increased inflammation of the adipose tissue (decrease in Treg, accumulation of M1 macrophages and dendritic cells) leads to insulin-resistance and lipolysis. The release of fatty acids and cytokines/chemokines could modify inflammation of the liver. The inflammation of the adipose tissue, which is associated with elevated CRP levels, also enhances the expression of hepcidin. The latter could delay hepatocellular iron deposition by inhibiting intestinal iron absorption. A high-fat diet and a high-fructose diet could modify the gut permeability leading to endotoximemia (LPS). These factors including fatty acids, adipokines and LPS are involved in the modification in the hepatic insulin pathway and inflammation. Increased inflammation in steatotic liver enhances cells death (by apoptosis and necrosis), which leads to the increase in circulating levels of hepatocyte death markers. Upregulation of specific pro-inflammatory Th1 cytokines, chemokines and immune semaphorines could be related to non-alcoholic steatohepatitis (NASH) liver.

definitions [2] as, respectively, $25 \leq \text{BMI} < 30\,\text{kg/m}^2$ and $\text{BMI} \geq 30\,\text{kg/m}^2$. Obesity is further categorized into moderate ($30 \leq \text{BMI} < 35\,\text{kg/m}^2$), severe ($35 \leq \text{BMI} < 40\,\text{kg/m}^2$) and morbid ($\text{BMI} \geq 40\,\text{kg/m}^2$). This pandemy is not only associated with the development of type 2 diabetes, hypertension, and cardiovascular diseases, but also has negative effects on liver function. In the general population, the estimated prevalence of non-alcoholic fatty liver diseases (NAFLD) ranges from 5.4% to 24% [3]. The spectrum of these hepatic abnormalities extends from isolated steatosis (triglyceride accumulation) to steatohepatitis (steatosis with inflammation) (Non-alcoholic steatohepatitis [NASH]), steatofibrosis, which sometimes leads to cirrhosis and hepatocellular carcinoma. NAFLD is one of the three main causes of cirrhosis [4—6] and increases the risk of liver-related death and hepatocellular carcinoma [7]. Despite this major public health concern, apart from lifestyle changes, NAFLD is still difficult to treat as no large study has shown any efficacy of pharmacological treatments for NAFLD. Currently, the diagnosis of NASH requires a liver biopsy, an invasive technique that can be harmful.

However, the molecular mechanisms responsible for the progression to NASH are still unclear. A ''two-hit'' model has been proposed [8]. Peripheral insulin-resistance may represent the ''first hit'' in the pathogenesis of NAFLD, which leads to hepatic steatosis. Combined hyperglycemia and hyperinsulinemia promote de novo lipid synthesis and structural defects in mitochondria within hepatocytes [9—11]. Moreover, insulin-resistance of adipose tissue leads to an enhanced free fatty acid flux to the liver that contributes to steatosis [10,11]. Steatotic hepatocytes may be vulnerable to a ''second hit'' induced by cytokines (such as tumor necrosis Factor-α, TNFα) and oxidative stress, which leads to the development of steatohepatitis and fibrosis [12,13]. In addition, the induction of CYP2E1, bacterial endotoxins and hepatic iron accumulation could play an important role in the development of steatohepatitis.