The Impact of Obesity on Liver Histology

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KEYWORDS

• Nonalcoholic fatty liver disease • Steatosis • Nonalcoholic steatohepatitis
• Cryptogenic cirrhosis • Hepatocellular adenoma • Hepatocellular carcinoma

KEY POINTS

- Obesity and metabolic syndrome produce changes in the liver's normal role in lipid and energy metabolism that cause a sequence of histopathologic changes.
- Steatosis is caused by an increase in hepatocellular fat vacuoles that parallels increased body mass index. Death of a small number of steatotic hepatocytes can produce liver enzyme elevation and focal nonspecific inflammation.
- Steatohepatitis occurs when there is cytoskeletal damage in genetically susceptible individuals resulting in loss of normal keratin filaments, ballooning degeneration of affected liver cells, and formation of Mallory-Denk bodies.
- In patients with steatohepatitis, activation of hepatic stellate cells produces intralobular fibrosis in the perisinusoidal spaces, whereas periportal ductular reaction causes activation of portal myofibroblasts and periportal fibrosis. With continuing fibrogenesis, there is progression to bridging fibrosis and cirrhosis.
- Hepatocellular carcinoma may develop in the cirrhotic liver, but both hepatocellular adenoma and hepatocellular carcinoma may occur in fatty liver disease before cirrhosis develops.

NORMAL LIVER AND NONSPECIFIC OR PHYSIOLOGIC STEATOSIS

The liver plays a central role in lipid metabolism, and consequently lipids (primarily triglycerides) may accumulate in the liver (primarily in hepatocytes) whenever there is an imbalance between the delivery of fat to the liver from the diet or from adipose tissue stores and the export of fat as a component of very-low-density lipoproteins. Small lipid droplets, identifiable only by electron microscopy or fat stains, are normally present in the cytoplasm of hepatocytes,[1] but under conditions of metabolic imbalance, stress, or cellular injury in many pathologic processes, lipid droplets become large enough to visualize by light microscopy as clear vacuoles in hepatocytes cytoplasm.

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Fat stains performed on frozen sections of livers from autopsies of hospitalized adults[2] and children dying of trauma[3] have shown that some degree of microvesicular steatosis is nearly always present, even though it is often not appreciated with routine paraffin-embedded sections. Similar population-based histologic studies of liver biopsies have not been performed in normal living subjects, because liver biopsies are seldom performed without a clinical indication, but proton nuclear magnetic resonance spectroscopy detects some hepatic triglyceride in all normal individuals, with a minimum of 1.9% of tissue by weight.[4]

OBESITY-RELATED STEATOSIS AND NONALCOHOLIC FATTY LIVER DISEASE

The presence of hepatocyte fat vacuoles that can be detected in routine hematoxylin-eosin–stained sections can be considered steatosis. Any alteration of the lipid transport and lipoprotein secretion may cause sufficient enlargement of normal lipid droplets to qualify, and minor degrees of unexplained steatosis are common. Traditionally, steatosis has been graded histologically by the proportion of affected parenchyma as mild (<1/3), moderate (1/3 to 2/3), or marked (>2/3) (**Fig. 1**).[5] This grading has the disadvantage of including many cases with only a few affected hepatocytes in the same category as those that have 32% fat; so, in recent years, a lower limit of 5% fat, as estimated by a pathologist, has often been used as a defining feature of NAFLD.[6] This practice is supported by the nuclear magnetic resonance studies showing that 95% of individuals with normal body mass index (BMI) and no risk factors for fatty liver disease had less than 5.5% hepatic triglyceride by weight.[4] Even experienced pathologists, however, routinely overestimate the amount of fat when compared with quantitative measurements by digital image analysis and computer-assisted morphometry,[7] with estimates typically doubling the amount of fat that is actually present, so liver biopsies estimated to have 5% fat may actually have much less.

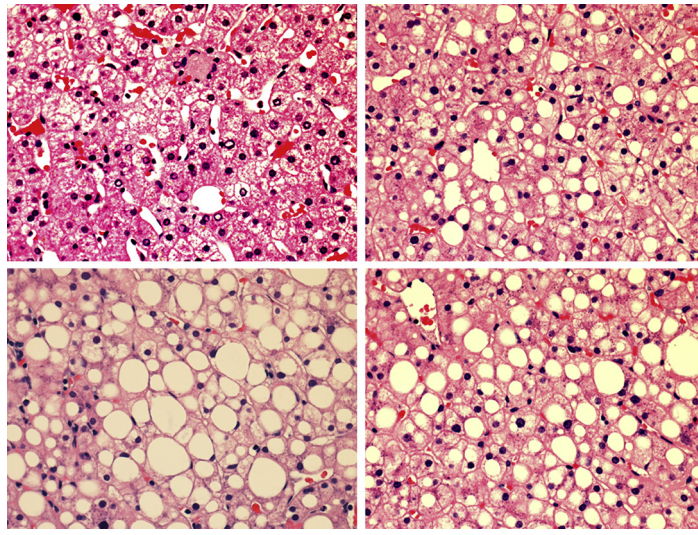

Fig. 1. Degrees of steatosis. None (*upper left*)—hepatocytes have no visible cytoplasmic fat vacuoles. Mild (*upper right*)—fat vacuoles occupy greater than 5% but less than 33% of hepatocyte cytoplasm. Moderate (*lower right*)—fat vacuoles occupy greater than 33% of hepatocyte cytoplasm. Marked (*lower left*)—fat vacuoles occupy greater than 66% of hepatocyte cytoplasm.