Metabolic syndrome and nonalcoholic steatohepatitis

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There is evidence for a systematic liver involvement in conditions associated with the metabolic syndrome. Obesity, diabetes and dyslipidemia *per se* cause hepatic fat infiltration, whose pathogenesis is directly linked to insulin resistance and increased FFA flux. Most patients with metabolic diseases have bright liver at ultrasounds, and the prevalence of raised aminotransferases is around 15%. These two conditions characterize the whole spectrum of nonalcoholic fatty liver disease (NAFLD), and the association with metabolic diseases is so tight that NAFLD is now considered the hepatic manifestation of the metabolic syndrome. Less clear is the association of raised blood pressure and steatosis. Also hypertensive patients show a 15% prevalence of high liver enzymes, but the association might be spurious and mediated by obesity/diabetes. Fatty liver, the first NAFLD step, remains a non-progressive disease in the large majority of cases, but a few patients (10% or more) also have necroinflammation and fibrosis (nonalcoholic steatohepatitis – NASH), which are responsible for disease progression to cirrhosis (the large part of cases with cryptogenic cirrhosis) and eventually to hepatocellular carcinoma. In Western countries, the metabolic pathway to advanced liver disease accounts for a remarkable proportion of cases awaiting liver transplantation (5-15%, depending on the disease burden of viral hepatitis). It is remarkable that also lean, non-diabetic subjects with NAFLD are insulin resistant, suggesting that genetic factors may be the basis for the metabolic as well as the hepatic disorder.

A few questions, however, remain unsolved. Firstly, who will develop a progressive disease? The “two-hit” theory suggesting that oxidative stress or any other additional pathogen might be responsible for progression has never been fully substantiated. Oxidative stress is associated with NASH, but why oxidative stress develops in a few cases and not in others? Cytokine and adipokine levels and response to individual pathogens, modulated by genetic variability and polymorphisms, might be a possible answer. Secondly, because of their metabolic disease, NAFLD patients are at high risk of cardiovascular events, and cardiovascular involvement has been demonstrated in several studies with different techniques (carotid Doppler sonography, flow-mediated vasodilation, etc.). But why in a few cases prognosis remains ultimately dictated by progressive liver disease, and in others cardiovascular events occur? Only large-scale prospective studies will answer these questions. Finally, is there any rationale and effective treatment of NAFLD, apart from the treatment of associated metabolic disorders? The lack of surrogate markers to rely upon, coupled with the long natural history of disease, constitutes a barrier to a rapid definition of this issue.