

# Non alcoholic steatohepatitis

## Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease ranging from simple steatosis to inflammatory steatohepatitis (NASH) with increasing levels of fibrosis and ultimately cirrhosis. NAFLD is closely associated with obesity and insulin resistance, and is now recognized to represent the hepatic manifestation of metabolic syndrome.<sup>1</sup> Clinical importance of non-alcoholic fatty liver disease has grown in recent years, mainly in consequence of the obesity epidemics, sedentary habits and high calorie diet adopted by people of western countries, reflecting the increase in cardiovascular and endocrine metabolic diseases. It has been considered the most common liver disease and the most frequent cause of elevated aminotransferases and cryptogenic cirrhosis.<sup>2</sup> Hepatocellular carcinoma is a well-recognized complication of NASH related cirrhosis.<sup>1</sup> Several systems have been proposed for the histologic assessment of NAFLD, of which the Kleiner NAFLD activity score (NAS) is probably the most well established.<sup>3</sup>

The pathogenesis of NAFLD for long has been explained by the two hit theory. According to the traditional view, hepatic fat accumulation (i.e. pure fatty liver) is the first hit and the prerequisite for hepatocyte injury to develop, whereas cytokines, adipokines, bacterial endotoxin, mitochondrial dysfunction and/or endoplasmic reticulum stress represent the second hit for the progression to NASH.<sup>3,4</sup> The traditional 'two-hit' pathophysiological theory has been challenged as knowledge of the interplay between insulin resistance, adipokines, adipose tissue inflammation and other less recognised pathogenetic factors have increased over the last decade. In particular, it has been suggested that hepatic steatosis may represent an epiphenomenon of several distinct injurious mechanisms rather than a true 'first hit'.<sup>4,5</sup> For this reason, the initial 'two-hit' theory for explaining the progression from NAFLD to NASH is now being modified by the 'multiple parallel hits' hypothesis. In the 'multiple-hit' model, the first hit is insulin resistance and its associated metabolic disturbances. Hyperinsulinaemia, caused by insulin resistance, results in an increased hepatic de novo lipogenesis and impaired inhibition of adipose tissue lipolysis that ultimately leads to an increased efflux of free fatty acids from the adipose tissue to the liver. After the initial hepatic fat infiltration, the liver becomes extremely vulnerable to a series of hits that may follow, leading to hepatocyte injury and finally progressing from simple steatosis to NASH and fibrosis. Such multiple pathogenetic factors may include oxidative damage, dysregulated hepatocyte apoptosis, activation of the profibrogenic transforming growth factor (TGF)-beta pathway, dysregulation of multiple adipokines and hepatic stellate cell activation. All of these factors can act in complicated way to enhance the development and progression of the hepatic lesions through the NAFLD spectrum.<sup>4,6</sup>

The American Association for the Study of Liver Diseases has recently discussed the key endpoints and specific trial design issues that are germane for development of diagnostic biomarkers and treatment trials in patients with NASH. In terms of potential for progression, the recommendations suggest to classify patients within the NAFLD spectrum into two main categories, i.e. non-alcoholic steatohepatitis (NASH); and 'not steatohepatitis, with steatosis' (a category traditionally defined as 'pure fatty liver' or 'simple steatosis'). In general, only one-third of patients in the spectrum of NAFLD develop

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NASH, which is histologically defined by the presence of lobular inflammation, portal inflammation, cellular ballooning and fibrosis. By contrast, 'not steatohepatitis, with steatosis' is characterised by simple fat infiltration or steatosis with minimal inflammation.<sup>4,7</sup> For patients with early stage NASH, about 9% to 20% will progress to cirrhosis over a period of 5-10 years. In contrast, 'not steatohepatitis, with steatosis' tends to be stable over time.<sup>8,9</sup>

Imaging modalities commonly used in the diagnosis of NAFLD include ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). The newer imaging modalities which are being used in diagnosis of NAFLD are MR elastography and ultrasound elastography.<sup>1,10</sup> However, despite the availability of newer imaging modalities and serum markers for presumptive diagnosis of NAFLD, liver biopsy still remains the gold standard for definite diagnosis of non-alcoholic fatty liver disease. The most widely used histological grading and staging is the NAFLD activity score developed by Kleiner et al.<sup>11</sup> The grading of the score is the sum of scores for various degrees of steatosis, lobular inflammation and hepatocellular ballooning.<sup>11</sup> The quest for accurate tools to stage NAFLD related liver injury stems from a variety of recent developments. First the prevalence of NAFLD has grown to epidemic proportions; it is currently the most common cause of abnormal liver biochemistry and cryptogenic cirrhosis, and a frequent indication for liver transplantation. Second, it is now well recognized that NAFLD exists as a spectrum consisting of two major phenotypes (simple steatosis and steatohepatitis) that have drastically different clinical implications.<sup>3,5</sup>

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## Conflict of interest

The author declares no conflict of interest.

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