Pathogenesis and Diagnosis of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is a result of hepatic fat accumulation (steatosis) with prevalence of 25% to 45% worldwide. Around 30% of patients with NAFLD develop hepatocellular inflammation and injury with or without fibrosis, i.e. the nonalcoholic steatohepatitis (NASH). In contrast, 30% to 60% of NASH patients have a normal ALT level. Nevertheless, it is estimated that 20% of patients with NASH develop cirrhosis as compare to less than 4% of those with NAFLD. The risks for disease progression are diabetes, metabolic syndrome, hypertension, obesity, and dyslipidemia.

Evidence from epidemiology, biochemistry, and therapy supports the pathophysiological abnormality in NAFLD is insulin resistance, which leads to increased lipolysis, triglyceride synthesis, increased liver triglyceride accumulation and uptake of free fatty acids. Important regulators of liver insulin sensitivity are fat derived hormones (e.g. adiponectin, leptin, and resistin), which are controlled by activation of multiple receptors, membrane glycoproteins, and cytokines.

The pathogenesis of NASH include genetic, gut microbial factors, metabolic, and environmental. Visceral fat tissue alters lipid and glucose metabolism leading to hepatic fat accumulation with subsequent oxidative stress, lipotoxicity, inflammation, and apoptosis.

Hepatic steatosis is diagnosed on medical imaging. The sensitivity of ultrasound is 93% in steatosis of >33%. The sensitivity declines with concomitant fibrosis, particularly in steatosis of <30%. MRI and MR spectroscopy can detect steatosis of >5.56%, however, with limited affordability and availability. The newly available controlled attenuation parameter (CAP, e.g. Fibroscan) is promising and more feasible. Hepatic fibrosis is the only histological feature to predict hepatic decompensation and death in NAFLD. NAFLD fibrosis score (http://nafldscore.com/) provide high accuracy clinical and laboratory parameters to predict severe fibrosis and liver-related outcomes. MR elastography (MRE) have higher accuracy than Vibration-controlled transient elastography (Fibroscan) or elastography (or ultrasound) with acoustic radiation force impulse (ARFI) for hepatic fibrosis. Furthermore, transient elastography has limitations in obesity or severe steatosis.

However, once again, MRE is limited by higher cost and lower availability.

Liver biopsy remains the gold standard for the diagnosis and staging of NASH, however, with the limitations of invasiveness and sampling error. NASH diagnosed on biopsy predicts fibrosis progression and subsequent poor outcomes. Candidates for biopsy include those with metabolic syndrome, diabetes, high NAFLD fibrosis score (>0.675), ALT elevation (e.g. >1.5x) for >6m, suspected other concomitant liver disease or suspected early cirrhosis.