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HEPATIC STEATOSIS AND HEPATIC INSULIN RESISTANCE

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Abstract. Hepatic steatosis, considered the first step in the pathophysiologic continuum of non-alcoholic fatty liver disease, is estimated to afflict 30% of the US population and over 75% of patients with Type 2 diabetes. Non-alcoholic fatty liver disease is already emerging as the most common cause of chronic liver disease worldwide [1], a trend that will only worsen in the coming decades. More so, NAFLD is thought to be an independent determinant of cardiovascular disease (CVD) [4], in addition to clustering in individuals who already have multiple cardiovascular risk factors, a relationship that leads to an increased risk of undesired outcomes in this patient population. NAFLD is therefore a complex problem with implications far beyond the liver. Obesity and the metabolic syndrome are commonly associated with NAFLD, in fact so closely that hepatic steatosis has been proposed to become one of the diagnostic criteria of the metabolic syndrome. Yet the mechanistic sequence of the association between NAFLD and insulin resistance (and diabetes) is not fully understood. Studies have shown that NAFLD predicts the incidence of diabetes independently of traditional risk factors, including obesity, peripheral insulin resistance and the metabolic syndrome [6], suggesting that NAFLD would have a direct causal effect on the development of diabetes, perhaps by promoting hepatic insulin resistance. Uncontrolled diabetes also promotes or worsens hepatic steatosis, thus fueling a vicious cycle that closely ties the two conditions together.

Key words: NAFLD, hepatic insulin resistance, metabolic syndrome, CVD

In addition to the association with the metabolic syndrome and diabetes, NAFLD is thought to independently promote CVD. Studies have shown that individuals with hepatic steatosis have significantly greater carotid intima-media thickness (a marker of CVD) than those without steatosis [1], as well as impaired endothelial function and lower adiponectin levels – which promote CVD. The independent association between NAFLD and CVD is best supported by a large study that followed 2100 patients with Type 2 diabetes over 6 years and showed a hazard ratio (HR) of 1.96 for CVD in these patients, even after adjustment for gender, age, smoking, diabetes duration, HbA1c, LDL-cholesterol and medication use .

In conclusion, hepatic steatosis, diabetes and the metabolic syndrome are all intrinsic parts of the same disease process driven primarily by overnutrition, all promoting a metabolic milieu that further exacerbates each component, and ultimately leads to an increased risk of CVD morbidity and mortality. Several new diagnostic techniques are currently being developed in an effort to improve the diagnostic and staging accuracy of NAFLD. Fibroscan is a noninvasive method for evaluating liver stiffness through the use of pulse-echo ultrasound. It has the advantage of being noninvasive, it evaluates a large area of the liver thus eliminating sampling variability, and is more sensitive for detecting injury than currently used serological markers [2]. This method assumes that liver stiffness

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correlates well with the degree of fibrosis, yet it has one important weakness; fatty infiltration interferes with the wave velocity itself, thus results are less reliable in this population, rendering it as a more useful technique in liver conditions that are less associated with steatosis. Magnetic resonance elastography is another new technique that appears to have good diagnostic accuracy in staging fibrosis and is unrelated to BMI [3]. However, further studies are needed to clearly define its role in patients with hepatic steatosis and fibrosis.

New biochemical markers are also being evaluated as diagnostic tools, the most promising thus far being serum cytokeratin (CK) M30 and M65 antigens. A Japanese study showed higher levels of these biomarkers in NAFLD patients versus controls. In addition, increases in these antigens strongly correlated with increases in alanine transaminase (ALT) levels in NAFLD patients [3]. Another study showed CK M30 and M65 to have a sensitivity of 60.0 and 68.9% and a specificity of 97.4 and 81.6%, respectively, in diagnosing NASH .Improvement in hepatic steatosis with intensive lifestyle modifications was also achieved in patients with diabetes. The Look AHEAD trial evaluated the change in hepatic steatosis in patients with diabetes after 4 years of intensive lifestyle intervention strategies leading to weight loss. Compared with the control group, the intervention successfully reduced both hepatic steatosis and the risk of advancement of NAFLD [2]. Lifestyle changes and weight loss, if achieved and sustained, are the most effective means of preventing and reversing NAFLD in patients with and without diabetes.Bariatric surgery is an effective means to achieve significant long-term weight loss and provides researchers with a model to study the reversibility of the effects of morbid obesity on metabolism. Improvement in hepatic steatosis and even fibrosis was documented following all types of bariatric surgery, with the gastric bypass procedure being the most effective [3]. A study by Weiner of morbidly obese patients with NASH undergoing bariatric surgery (including Roux-en-Y gastric bypass, gastric banding and biliopancreatic diversion with duodenal switch) showed improvements in hypertension, Type 2 diabetes, steatosis, necro-inflammatory activity and hepatic fibrosis after surgery compared with baseline [4]. In a recent study of NAFLD patients receiving bariatric surgery, Bell and colleagues have shown significant improvements in the metabolic syndrome, grade and stage of liver disease, as well as liver histology [5].

Of note is the importance of paced weight loss following any weight-loss intervention. Andersen and colleagues have shown an increase in portal fibrosis in patients who lost weight at a rate higher than 1.6 kg/week following a gastric bypass procedure [6]. Similar case results are available in patients following severe diet restriction, thus moderation is recommended even where proven beneficial interventions are concerned.

Insulin resistance is a common complication of obesity and an important risk factor for diabetes and other metabolic complications. In the present study, we found that moderate weight loss increases both liver and skeletal muscle insulin sensitivity in obese adolescents. Our subjects had normal oral glucose tolerance and fasting plasma glucose concentrations. Therefore, the improvement in insulin sensitivity was not detectable by routine blood tests and required a sophisticated assessment of insulin action by evaluating glucose kinetics during basal conditions and experimentally induced hyperinsulinemia. These results demonstrate that moderate (~ 8%) weight loss has important beneficial metabolic effects in obese adolescents who do not have obvious evidence of metabolic abnormalities after evaluation by a standard medical examination.

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