Nonalcoholic fatty liver disease (NAFLD) is common, with an estimated prevalence of 3%-20% in Western and Asian regions. A small but significant proportion of patients develop cirrhosis and hepatocellular carcinoma and may die from their disease. The principal metabolic abnormality underlying NAFLD is insulin resistance, which manifests clinically as the metabolic syndrome with features of central obesity, dyslipidemia, glucose intolerance and hypertension. Central obesity is common among NAFLD patients and reflects an increase in visceral adipose tissue, which appears to be particularly resistant to the effects of insulin. Importantly, body mass index, a routine measure of obesity, may not detect central obesity particularly among Asian populations.

Insulin resistance increases adipose lipolysis, resulting in efflux of free fatty acids (FFA) into the serum, which are then delivered to the liver. The FFA are in turn esterified into triglycerides and incorporated into very low density lipoproteins (VLDL). Excess triglyceride-rich VLDL secretion by the liver leads to hypertriglyceridemia. In addition, insulin resistance inhibits peripheral lipoprotein lipase activity, reducing VLDL clearance and increasing serum triglyceride levels further. When triglyceride delivery to the liver or hepatic de novo synthesis exceeds triglyceride export or oxidation, fatty liver results. Hyperlipidemia is found in 21% to 61% of patients with NAFLD and conversely, NAFLD is found in up to 50% of patients with hyperlipidemia. However, it is unclear whether hyperlipidemia has prognostic significance.

In this issue of the Journal, Hatzitolios and colleagues enrolled a select group of 72 non-diabetic NAFLD patients with hyperlipidemia, in an open-label, uncontrolled study of 24 weeks’ duration. Patients with hypertriglycerideremia (n=23) were given omega-3 fatty acids (5 mL, thrice daily), patients with predominant hypercholesterolemia (n=28) were given atorvastatin (20 mg daily), and obese dyslipidemic patients (n=28) were prescribed orlistat (120 mg, thrice daily). Endpoints were safety and efficacy as judged by change in aminotransferase levels and resolution of fatty infiltration on liver ultrasound. After 24 weeks, all patients had reductions in triglyceride and cholesterol levels. Similarly, all patients had significant reductions in aminotransferase levels, although only the group receiving orlistat had complete normalization in all patients. This was also the only group that lost a significant amount of weight over the treatment period. When ultrasonography was repeated at the end of treatment, a normal liver echopattern was observed in 86% of patients receiving orlistat, 61% of those on atorvastatin, and 35% of those taking omega-3 fatty acids.

These promising results have also been echoed in a few other smaller pilot studies. A diet high in polyunsaturated fatty acids has been shown to be associated with liver enzyme improvement in obese subjects with fatty liver. Similarly, atorvastatin and orlistat have improved liver enzymes as well as liver steatosis in a handful of patients over 6-12 months.

However, promising data from uncontrolled trials without histological endpoints can be misleading. Ultrasonography is insensitive at detecting low grades of hepatic steatosis and cannot assess the more sinister pathological changes of inflammation or fibrosis. Improvement of liver enzymes over time does not correlate sufficiently with improvement in fibrosis stage to be clinically useful. In addition, improvement may simply reflect 'regression to the mean', as NAFLD patients with high enzymes naturally fluctuate between normal and abnormal levels over time. Hatzitolios and colleagues attempted to minimize this phenomenon by including only patients with persistently raised aminotransferase levels.

Revealingly, after several pilot studies had suggested ursodeoxycholic acid to be beneficial in the treatment of nonalcoholic steatohepatitis, a subsequent large randomized placebo-controlled trial that examined liver histology as well as liver enzymes demonstrated it was no better than placebo. Therefore, before omega-3 fatty acids, atorvastatin or orlistat can be suggested for routine treatment among patients with NAFLD, further evidence with adequately powered randomized, placebo-controlled trials with histological endpoints need to be performed. Unfortunately, no treatment has been proven to be efficacious with these stringent criteria. Until then, it is notable that the intervention in this study that was associated with weight loss (and presumably improvement in insulin resistance) achieved the greatest normalization of liver enzymes and hepatic echopattern. Therefore, measures that improve insulin resistance such as weight loss and exercise may be the most important directive we can give patients at present.

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