Fatty liver (steatosis) is an excessive accumulation of lipids within hepatocytes, most commonly in the form of large droplets of triglyceride (macrovesicular fat). The other form of fat accumulation, microvesicular steatosis with tiny fat droplets (such as fatty liver of pregnancy and Reye's syndrome), is quite rare and often rapidly fatal. In contrast, simple macrovesicular fatty liver was once considered quite benign and unimportant— an incidental finding with an obscure pathogenesis. Long considered a rather innocuous entity associated with obesity and diabetes, this form of steatosis was thought to progress rarely to advanced liver disease, particularly when not associated with alcohol use (1-3). Over the past two decades, it has become apparent that some of these patients have (or develop) a wide spectrum of lesions. Nonalcoholic fatty liver disease (NAFLD) is now recognized as a clinicopathological entity that extends beyond uncomplicated steatosis to steatohepatitis (fat plus inflammation, histologically resembling alcoholic hepatitis), steatonecrosis, advanced fibrosis, liver failure and, in some cases, hepatocellular carcinoma (2-7). In fact, nonalcoholic steatohepatitis (NASH) may frequently be a precursor of cryptogenic cirrhosis (8).

NASH is probably the crucial stage in the progression of NAFLD to advanced liver disease. NASH is usually asymptomatic. Frequently, the only clues to its presence are smooth hepatomegaly and/or elevated transaminase levels (6,9). The alanine aminotransferase (ALT) level exceeds the aspartate aminotransferase (AST) level in most cases, unless cirrhosis has supervened. Ultrasonography may reveal only the ‘bright’ appearance of the fatty liver. None of these findings is diagnostic. Of fundamental importance is the absence of excessive alcohol intake, which is best defined as more than 20 g/day for women or more than 30 g/day for men, although this may be difficult to confirm in practice (6). Hepatitis C and other liver diseases also must be excluded.

Liver biopsy is necessary to distinguish NASH from simple steatosis, to detect fibrosis or cirrhosis, and to exclude other forms of liver disease. Ludwig et al (10) coined the term, ‘NASH’ and pointed out its histological similarity to alcoholic hepatitis. The minimum diagnostic requirements are macrovesicular fat and lobular inflammation. Stricter criteria include evidence of hepatic degeneration and/or fibrosis (11,12). Hepatocellular injury manifests as ballooning degeneration (fluid accumulates and causes hepatocytes to swell) or, less commonly, as acidophilic degeneration (Mallory’s hyaline bodies) (9,12). A stronger definition would facilitate epidemiological and clinical investigations.

The true prevalence of NASH is unknown because the need for liver biopsy inherently creates a selection bias. NASH has been found in up to 11% of liver biopsy specimens and 6% of autopsies (10,13,14). It occurs more frequently in obese women who have type II diabetes or hypertriglyceridemia (6). Although it is often not recog-
nized as a serious problem in patients with type II diabetes, chronic liver disease rivals cardiovascular disease as a cause of excess mortality in this population (15).

Obesity remains the most consistent association. Most patients with NASH (60% to 95% in most series) are either overweight (body mass index [BMI] higher than 25 kg/m²) or obese (BMI higher than 30 kg/m²). They tend to have a central (truncal or abdominal) distribution of fat (6,16). Fatty liver is a very common finding in obese persons, affecting as many as 60% to 94% of those who are morbidly obese (17-19). Obesity, with its propensity to NASH, is a harbinger of fibrosis (3,13,20,21). NASH can also occur in non-obese men with normal blood glucose and lipid levels, but such persons seem to have milder histological findings and a better prognosis (22). Other risk factors for the progression of liver disease in obese subjects include advanced age, diabetes mellitus, AST level higher than the ALT level, and histological evidence of inflammation and fibrosis (20,23).

In this issue of the Journal, Zamin and colleagues (pages 303-307) evaluated the frequency of NASH in 912 obese persons referred to their outpatient clinic in Brazil. Sixty-eight had elevated aminotransferase levels. To define the apparent effects of obesity alone, they excluded those with alcohol use, diabetes mellitus or markers of viral hepatitis. Liver biopsy in 29 of the 33 remaining patients (ie, 3% of the total) revealed NASH of a relatively mild degree; four had steatosis. This frequency is less than the 18.5% of markedly obese individuals reported to have steatohepatitis in a Canadian autopsy series (13). The difference may reflect the problems inherent in autopsy studies. In addition, the Brazilian team excluded 12 diabetic patients and included only subjects with aminotransferase alterations.

NASH also occurs in children (24). The increasing prevalence of obesity in this population is alarming. Over 20% of adolescents are overweight (above the 85th percentile of BMI), and 8% to 17% are obese (above the 95th percentile of BMI) (25). The prognosis for NASH in children is unknown, but the long course of disease may eventually culminate in fibrosis and cirrhosis. There is a worldwide epidemic of obesity, in both developed and developing countries (26,27). In the United States, for example, 59.4% of men and 50.7% of women are overweight, as defined by a BMI higher than 25 kg/m² (28). This level of adiposity is often associated with insulin resistance (29). Generally, as the frequency of obesity increases in adults, so will the prevalence of NAFLD. The risk of NASH also extends to lean men and women, even if they do not have diabetes or hyperlipidemia (7,22).

Insulin resistance is the unifying theme for all of these risk factors, and can lead to NASH, independent of the presence of diabetes mellitus or obesity (30,31). It occurs before the development of cirrhosis, which itself can cause hyperinsulinemia (32,33). NASH may be part of the so-called metabolic syndrome or syndrome X, which includes impaired glucose tolerance, hyperlipidemia and hypertension (33). Because of the central role of insulin resistance in this cluster, the disorder is also known as the insulin resistance syndrome. The visceral obesity in some apparently lean men would explain their developing NASH, in association with the metabolic syndrome. The splanchic fat might supply the excess triglycerides that are then stored in the steatotic liver. In patients with simple steatosis, the accumulation of triglycerides in hepatocytes generally reflects an imbalance between hepatic triglyceride synthesis (or input) and secretion (output). This result is simple steatosis. Only a minority of persons with simple steatosis develop steatohepatitis and fibrosis (2,5).

A second event or 'hit' is necessary to produce inflammation and liver damage (34). A most attractive explanation for such injury invokes abnormal lipid peroxidation and oxidative stress (9,35). In this model, an increased generation of reactive oxygen metabolites and carbon-centred free radicals initiates the peroxidation of fatty acid side chains in cell membranes and thus produces cell damage. As with alcohol-related liver disease, there is heightened expression of hepatic cytochrome P450 2E1 (CYP2E1). The end products of lipid peroxidation (eg, aldehyde products) are capable of activating hepatic stellate cells (which produce collagen), causing hepatocyte degeneration (and can form Mallory bodies) and upregulating proinflammatory cytokines and adhesion molecules. These effects lead to inflammation, cell injury and fibrosis – ie, NASH and its sequelae. Besides CYP2E1 induction, the high levels of fatty acids within the liver might provide another source of oxidative stress through peroxisomal beta-oxidation, producing hydrogen peroxide. Hydrogen peroxide, in the presence of free iron, is converted to highly reactive hydroxyl radicals (9,34,36). Iron overload has been associated with both steatosis and hepatic fibrosis. Once again, the common denominator appears to be insulin resistance. The importance of liver iron to the pathogenesis of steatohepatitis, however, has not been conclusively established.

Another candidate for this ‘second hit’ is bacterial endotoxin, because it induces the production of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) (37). This concept evolved from efforts to explain the propensity of obese patients undergoing jejunoileal bypass surgery to develop NASH; the liver injury was mitigated by metronidazole therapy. Such surgery promotes portal bacteremia, while obesity apparently increases the sensitivity of the liver to endotoxin-induced damage. Indeed, some cases of NASH have bacterial overgrowth and increased serum TNF-α levels, even though the infected bypassed loop of the small intestine is not ‘leaky’ and endotoxemia is not evident (38).

The story is approaching a full circle. TNF-α can induce insulin resistance, through modulation of the tyrosine kinase activity of the insulin receptor, and is involved in iron regulation. Furthermore, because TNF-α is overexpressed in adipose tissue, increased serum levels are found with obesity. Two polymorphisms in the TNF-α gene promoter, one at 308 (termed the TNF2 allele) and the other at 238 (the TNFA allele), are associated with increased expression of this cytokine. The 238 TNF-α polymorphism
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is more prevalent in persons with NAFLD, perhaps representing a genetic predisposition (39).

The trigger that sets off the liver injury in NASH is not known with certainty. There are, however, therapeutic implications to the presence of the common factors of obesity and insulin resistance (29). Even though weight loss seems to be an obvious benefit, there is little evidence that it improves liver histology, and weight reduction is notoriously difficult to maintain (40). Furthermore, any acute weight reduction acts to lower hepatic levels of the endogenous antioxidant, glutathione, and is known to worsen the liver disease (35).

Several pharmacological interventions have been tried. Pilot studies with ursodeoxycholic acid have shown enough promise to warrant a well-designed, multicentred study, currently underway. Ingestion of therapeutic dosages of antioxidants such as vitamin E deserves further study (41), but such an approach merely addresses the effect rather than the cause. Lipid-lowering drugs are not consistently effective for NASH, perhaps because they do not reverse insulin resistance (40). Aggressive control of diabetes with insulin or sulfonylureas, which actually aggravates the hyperinsulinism, also has failed. More promising is the use of metformin, which directly tackles the problem of insulin resistance and defective glucose production in type II diabetes.

REFERENCES


