Nonalcoholic Steatohepatitis and the Metabolic Syndrome

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ABSTRACT: Relatively recently, the liver has been recognized as a major target of injury in patients with insulin resistance or the metabolic syndrome. Insulin resistance is associated with fat accumulation in the liver, a condition called nonalcoholic fatty liver disease (NAFLD). Excess fat in the liver is not a benign condition. Some patients with NAFLD develop necroinflammatory changes in the liver called nonalcoholic steatohepatitis (NASH) and a fraction of those will develop cirrhosis. About 20% all adults have NAFLD and 2% to 3% of adults have NASH. Approximately 20% of patients with NASH are at risk for developing cirrhosis and subsequently dying from end-stage liver disease. The diagnosis of NASH requires a high index of suspicion, especially in obese patients over the age of 45 years who have diabetes, because these are the patients at greatest risk for developing cirrhosis. Treatment focuses on addressing the underlying insulin resistance with increased exercise and weight reduction. **KEY INDEXING TERMS:** Fatty liver; Cirrhosis; Insulin resistance; Liver biopsy; Alanine aminotransferase. **[Am J Med Sci 2005;330(6):326–335.]**

The liver is frequently a site of unrecognized injury in patients with insulin resistance. Chronic liver injury is typically silent in its progression, and the presence of liver disease in patients with progressively worsening insulin resistance may not be recognized until patients develop manifestations of the metabolic syndrome such as diabetes, hypertension, hyperlipidemia, and vascular disease. At this late stage, cirrhosis caused by decades of low-grade liver injury may be discovered. This review summarizes the current knowledge of liver disease associated with insulin resistance with respect to the epidemiology of the problem, its pathophysiologic underpinnings, and the results of various therapeutic trials.

Definitions: NAFLD and NASH

Insulin resistance is associated with the accumulation of fat in the liver. The fat accumulates as coalesced triglyceride droplets in hepatocytes that are either quite large and displace the hepatocyte nuclei to the periphery of cells or are small and give hepatocytes a "foamy" appearance. When pathologists examine liver biopsy samples, the presence of fewer than 5% of hepatocytes containing fat is considered normal. More than this is considered steatosis, and when the clinician corroborates the absence of significant alcohol consumption, a diagnosis of nonalcoholic fatty liver disease (NAFLD) is established. Patients with NAFLD can have only large droplets of hepatocellular fat, called *macrovesicular steatosis*, or a number of hepatocytes containing small droplets of fat, called *microvesicular steatosis*. Liver biopsies with only microvesicular steatosis are less common, and this lesion is most commonly associated with mitochondrial defects (e.g., alcohol, Reye syndrome, and valproic acid hepatotoxicity).

The NAFLD is an umbrella diagnosis describing excess fat in the liver that is identified either by liver biopsy or imaging studies, and nonalcoholic steatohepatitis (NASH) is found in a subset of NAFLD patients who have, in addition to excess fat, evidence of characteristic hepatocellular injury and necroinflammatory changes.[1] Typically, hepatocyte ballooning, cytoplasmic aggregates of cytoskeletal proteins called *Mallory bodies*, and variable degrees of fibrosis are identified. The amount of these changes needed to establish a diagnosis of NASH has been debated and continues to evolve.[1,2] The importance of distinguishing the presence of fat without substantial necroinflammatory changes, called *benign steatosis*, from NASH is that patients with NASH are at increased risk of progression to cirrhosis.[3]

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The current definitions of NAFLD and NASH require the absence of significant alcohol consumption so as not to confuse these entities with alcoholic liver disease. How much alcohol is considered significant is debated. Certainly, consumption more than 60 g daily is worrisome. For the sake of studies, up to 20 g daily is usually considered insignificant. In the clinical management of patients, alcohol consumption between 20 and 60 g daily should be considered as a possible contributor to fat accumulation. These limits lead to the common question of how much of a particular beverage equates to 20 g of alcohol. The usual axiom is that 10 g of alcohol is found in one standard drink of distilled spirits, one beer, or one glass of wine. While there is some truth to this generalization, the actual amount of alcohol in these beverages is quite variable. One 12 fluid ounce beer may contain as little as 9 g of alcohol in the case of some light beers, up to 20 g for some regular domestic beers and as much as 32 g for malt liquors. A 4 fluid ounce glass of standard wine contains 13 g alcohol, whereas the same amount of a "fortified" wine contains 18 g alcohol. One of the difficulties in assessing alcohol consumption in wine drinkers is getting an idea of the volume consumed, since patients may have little idea of what 4 fluid ounces looks like in a glass. Asking how many bottles of wine are consumed daily or weekly provides a more accurate estimate, since a typical bottle of standard wine contains 750 ml of 13.5% (vol/vol) alcohol, which equates to 81 g alcohol. Thus, a bottle a day split between two people is 40 g daily for each consumer, an amount that could cause fatty liver, especially in women.

Epidemiology

Excess liver fat, or NAFLD, is present in 20% of adults in this country, and NASH is found in 2% to 3% of adults.[4–6] Although some clinicians continue to view these prevalence figures with skepticism, epidemiological data indicate that most patients with progressive liver disease due to NAFLD are not diagnosed. Multiple factors contribute to the underdiagnosis of NAFLD. These include the absence of symptoms and signs,[4] the poor sensitivity of liver enzymes to indicate the presence of disease,[7] and the absence of other reliable tests for detecting occult liver disease.

The full spectrum of NAFLD from benign steatosis to NASH and cirrhosis is also found in children.[8] Children with NASH are almost invariably obese and sedentary. The prevalence of NAFLD in children is unknown but may be growing in parallel with the rise in childhood obesity.

As insulin resistance and the metabolic syndrome have become increasingly prevalent and better understood, the presence of insulin resistance has become recognized as the most common underlying risk factor of the development of NASH.[9–17] In fact, some investigators have even suggested that the presence of fatty liver is a very early and sensitive indicator of insulin resistance.[18]

Many of the other risk factors identified in early studies of patients with NASH are now recognized as causes or other consequences of insulin resistance. Obesity, especially centripetal obesity, and sedentary lifestyle are two major risk factors for insulin resistance and are significant risk factors for NAFLD.[5,19] Female gender is no longer thought to be a risk factor for NASH. Although early series identified female gender as a risk factor, they may have suffered from substantial referral bias. Hyperlipidemia, most commonly hypertriglyceridemia, is associated with NAFLD but is not uniformly present in adults.

Now that insulin resistance is recognized as an underlying cause of NAFLD and NASH, future studies are needed to define the full spectrum of liver abnormalities and their prevalence in patients with insulin resistance. Major challenges to acquiring these data are the difficulties in defining insulin resistance and identifying the presence of NASH noninvasively.

Diagnosis

A diagnosis of NAFLD is often first suspected based on the results of imaging studies or unexplained elevations of aminotransferases. Identifying NASH in patients with NAFLD requires a liver biopsy, because there are currently no symptoms, signs, or reliable noninvasive markers that set NASH apart from the broader inclusive diagnosis of NAFLD.

NASH is not associated with any characteristic symptoms.[4] Many patients note fatigue and poor exercise tolerance. Vague, aching, right upper quadrant abdominal pain or fullness is often present but requires specific questioning to identify its presence. Few data exist regarding the prevalence and nature of this pain. It may be more common than is currently perceived and in some patients with severe pain, the symptoms can be difficult to discern from cholelithiasis.

Physical examination does not provide any findings that reliably indicate the presence of NAFLD or NASH. Because insulin resistance is present in most patients with NAFLD, the associated examination abnormalities of centripetal obesity, hypertension, and acanthosis nigricans may be seen in association with NAFLD. Hepatomegaly is said to be present in up to 75% of patients,[4] although it can be difficult to identify on physical examination in patients with marked abdominal obesity. Lipodystrophies are associated with NAFLD and NASH. An unusual distribution of body fat may suggest a diagnosis of lipodystrophy, but subtle lipodystrophic phenotypes can be difficult to identify.[20]

Laboratory testing can provide some clues to the

presence of NAFLD, although identifying NASH in patients with NAFLD requires a liver biopsy. Laboratory testing is essential in evaluating patients with suspected NAFLD to identify other causes of liver disease or concomitant diseases such as hepatitis C infection that may coexist with NAFLD.[21]

Serum levels of the aminotransferases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most commonly used tests to screen for unsuspected liver diseases such as NAFLD. Unfortunately, the aminotransferases lack specificity and sensitivity for NASH.[5] The prevalence of elevated serum ALT and AST levels in patients with NASH is unknown because the number of patients with normal levels having NASH is unknown. In morbidly obese subjects undergoing bariatric surgery, the entire spectrum of NAFLD from trivial disease to aggressive NASH and cirrhosis can be found, even in patients with normal aminotransferases.[5,7,22] A significant factor contributing to the poor sensitivity of aminotransferases for the detection of NAFLD and other chronic liver diseases is the methods used by clinical laboratories to define the upper limit of the reference range (commonly called the upper limit of normal, or ULN).[23] Because imaging and liver biopsy are needed to exclude NAFLD and NASH, these may exist in the reference populations used by laboratories to define their reference ranges. At this time, body mass index and clinical markers of insulin resistance that correlate with ALT elevations in population studies are not used to exclude patients from the reference population by clinical laboratories.[5,24] An important study using a carefully screened population recommended that the upper reference range for serum ALT activity should be 30 U/L for men and 19 U/L for women.[25] One problem with lowering the upper reference range to increase the sensitivity of the ALT would be the associated loss of specificity. Increasing the numbers of patients who have ALT values above the upper reference range could cause unnecessary testing until a new paradigm emerges for the clinical management of mildly elevated levels (e.g., 35 U/L).[26]

An important way in which measuring the ALT and AST levels can contribute to the diagnosis of NAFLD is to calculate the ALT-to-AST ratio. An AST value greater than the ALT value suggests either alcoholic liver disease or cirrhosis from any cause, whereas an ALT value greater than the AST value suggests the presence of NAFLD.[27] The role of fibrosis in causing the AST level to become greater than the ALT level was demonstrated in a series of 70 patients with NASH who were found to have AST-to-ALT ratios of 0.7, 0.9, and 1.4 when their liver biopsies demonstrated no fibrosis, mild fibrosis, or cirrhosis, respectively.[28]

Other laboratory tests in patients suspected of having NAFLD are needed to exclude other causes of liver disease or to identify concomitant diseases. Antibodies associated with autoimmune hepatitis, antinuclear antibody (ANA), and anti-smooth muscle antibody (ASMA), are sometimes found but usually in low titers.[29] High titers provide an additional reason to perform a liver biopsy to fully exclude autoimmune hepatitis. Measuring serum lipid levels can provide important information regarding the presence of the metabolic syndrome and associated abnormalities that require appropriate management. Defects in apolipoprotein B are associated with NAFLD and NASH. Identifying such rare patients with hypobetalipoproteinemia as a cause of NAFLD requires the astute observation of an unexpectedly and atypically low serum cholesterol. In patients younger than 35 years of age with NAFLD or NASH, Wilson disease must be fully excluded as an underlying disorder by measuring the serum ceruloplasmin and, when uncertainty exists, performing other tests such as collection of a 24-hour urine specimen for copper measurement and slit-lamp examination of the eyes for Kayser-Fleischer rings.

Obtaining a liver biopsy sample is the only way to establish a diagnosis of NASH with certainty.[1,30] The decision to perform a liver biopsy to evaluate elevated liver enzymes or imaging evidence of NAFLD must balance the risks associated with a biopsy and the benefits of establishing the diagnosis and excluding other causes of liver disease.[31,32] The latter point is not trivial. At least one third of patients suspected of having NALFD on clinical grounds were found in one study of biopsies to have other causes of elevated liver enzymes.[33] In the past, liver biopsies might not have changed the clinical management of most patients with NASH, but as NASH is better understood and new treatment options emerge, the need to establish a firm diagnosis and recommend appropriate treatment will likely increase.[27,33,34] At this time, the decision to perform a liver biopsy in a patient suspected of having NAFLD or NASH must take into account the presence of risk factors for advanced disease (see below) and the patient's level of interest in establishing the diagnosis.

Imaging studies can identify the presence of fat (i.e., NAFLD) when the amount of excess fat is significant. Although each imaging modality has its strengths and weaknesses, no imaging study can assess the necroinflammatory changes or fibrosis that distinguish NASH from less worrisome forms of NAFLD.[35–37] Imaging studies often incidentally provide the first evidence that a patient has otherwise unsuspected NAFLD, and a common clinical problem is how to approach such a patient with an incidental finding of NAFLD. Although a rational and cost-effective approach has not been developed, a reasonable algorithm is to assess alcohol consumption, estimate insulin sensitivity, exclude other

causes of liver disease, and use this information to determine whether a liver biopsy should be recommended.

Ultrasonographic examination is the least costly and invasive imaging method, but it lacks both specificity and sensitivity. Fat in the liver confers a ″bright″ appearance on an ultrasonogram, but significant fibrosis without fat can have a similar appearance.[35] Nonetheless, ultrasonography remains a commonly used method of identifying the NAFLD as a cause of unexplained liver enzyme elevations. Computed tomography (CT) imaging of the liver is more sensitive but also more costly than ultrasound for detecting NAFLD.[35] Neither ultrasonography nor CT can identify necroinflammatory changes or early fibrosis that signify the presence of NASH. With the use of CT, the fatty liver has a lower density than a normal liver and the amount of fat can be estimated numerically by comparing the liver density to spleen or paraspinal muscle density. A difference between liver and spleen densities of greater than 10 Hounsfield units indicates excess liver fat,[38] as does a liver-to-spleen ratio of less than 1. Magnetic resonance imaging and magnetic resonance spectroscopy are the most sensitive yet most expensive means of detecting NAFLD.[35] Nuclear medicine techniques to image diffuse process in the liver such as NAFLD have been abandoned in favor of ultrasonography, CT, and magnetic resonance techniques because of the very low sensitivity and specificity of nuclear scans in this setting.

Imaging studies of patients with NAFLD often identify lesions called *focal fat* and *focal sparing*, both of which turn out to provide insights into the role of hyperinsulinemia in the pathogenesis of NAFLD. Focal fat can be caused by aberrant venous drainage of insulin-enriched pancreatic blood into specific regions of the liver near the porta hepatis.[39] In contrast, focal sparing is caused by variations in the blood supply such that non-portal blood that is not enriched in insulin reaches specific areas of the liver. Focal sparing adjacent to the gallbladder is common (up to 80% of patients) and results from a localized blood supply to a small area of the liver that originates from the gallbladder blood supply.[40] Rarely, focal sparing can also occur adjacent to the falciform ligament due to non-insulin-enriched blood reaching the liver from an aberrant gastric vein that fails to join the portal vein before it enters the liver.[39,41]

Natural History

Early studies of small cohorts followed for relatively short periods suggested that NASH was a relatively benign disease. Unfortunately, this perception has persisted despite accumulating evidence that NASH is now the most common form of chronic liver disease that leads to cirrhosis, hepatocellular carcinoma, and death.[4,42] The best estimates at this time are that 2% to 3% of all adults in this country have NASH, about 20% of those with NASH go on to develop cirrhosis, and 30% to 40% of patients with cirrhosis receive a liver transplant or die of liver-related complications (Figure 1).[43] About 10% to 12% of liver transplants are now performed because of liver disease caused by NASH. This prevalence in transplant candidates probably substantially underrepresents the true prevalence of people with cirrhosis caused by NASH. End-stage liver disease caused by NASH is often associated with vascular disease, complicated diabetes, or massive obesity, and these comorbidities likely cause many of these patients to be ineligible for transplantation.

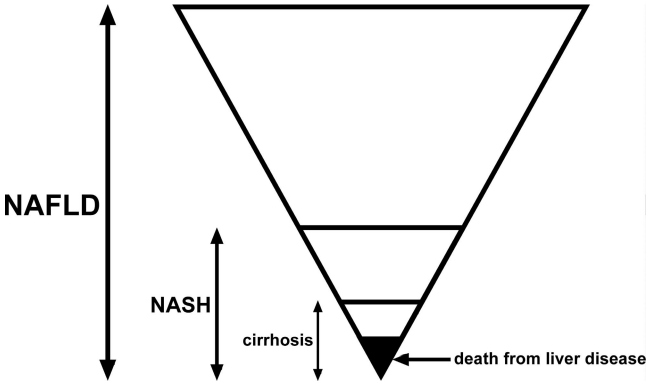

Figure 1. The inverted NAFLD pyramid. About 20% of adults have excess fat in the liver, shown here as an inverted pyramid. Of these people, 10% to 15% have NASH and 20% of those with NASH are at risk for developing cirrhosis. Up to 30% to 40% of those with NASH cirrhosis will die from end-stage liver disease.

Accurately assessing the natural history of NAFLD has proven difficult because the older data are compromised by a number of factors, including variable definitions of NAFLD and NASH, possible unrecognized coexistence of hepatitis C virus, the prolonged period of follow-up needed to identify progression, and probably a failure to recognize cirrhosis as a contributor to death from the known complications of insulin resistance and the metabolic syndrome. As awareness of occult liver disease in patients with insulin resistance increases, more patients may be recognized as having significant underlying liver disease while being treated for other complications, such as cardiovascular disease and diabetes. Some investigators have suggested that NASH has been a silent and unrecognized contributor to death from obesity, cardiovascular disease, and diabetes.[44] The presence of such silent cirrhosis has been well documented in morbidly obese patients undergoing bariatric surgery.[45]

Recognizing that most patients with cryptogenic cirrhosis once had NASH as the underlying cause of their cirrhosis has greatly expanded the understanding of NASH as a risk for cirrhosis. In patients with cryptogenic cirrhosis, a liver biopsy typically

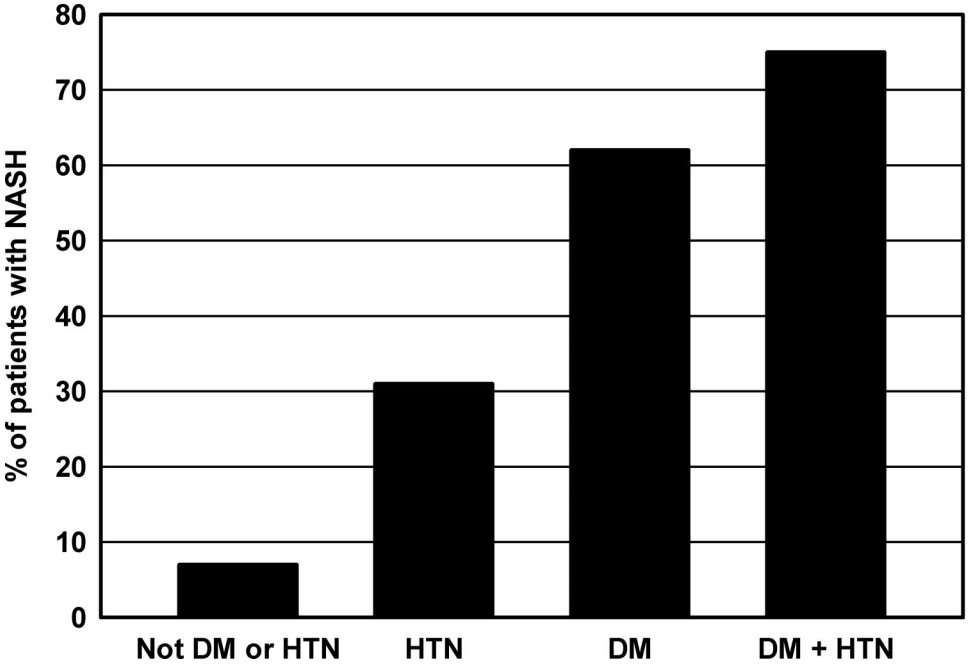

Figure 2. The risk of having NASH increases with the presence of components of the metabolic syndrome in obese individuals. (From Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121:91–100. With permission of Elsevier.)

demonstrates relatively bland cirrhosis.[46,47] Features of the metabolic syndrome such as diabetes and obesity are overrepresented in patients with cryptogenic cirrhosis[48] and NASH often occurs after liver transplantation for cryptogenic cirrhosis as it does in patients with known NASH.[49–51]

Hepatocellular carcinoma is a devastating complication of cirrhosis and it is now recognized to be a complication of NASH cirrhosis, just as it is for other forms of cirrhosis.[52–56] The notion that the growth stimulus provided by chronic hyperinsulinemia increases the risk of liver cancer as it does for other cancers has been suggested.[53,55,57]

Optimal management of patients with NASH requires the ability to predict which patients with NAFLD are at greatest risk for progression to cirrhosis. One study of severely obese patients with NAFLD undergoing bariatric surgery (body mass index >35) found that insulin resistance, hypertension, and elevated ALT levels predicted the presence of NASH.[12] In fact, three-quarters of these patients who had both hypertension and diabetes also had NASH, whereas only 7% with neither condition had NASH (Figure 2). The presence of diabetes and hypertension was also predictive of advanced fibrosis. A patient's age was found to be critical in another study in which significant fibrosis was present in only 4% of NASH patients under the age of 45 yet 40% of those older than 45 years.[58] Taken together, current data indicate that the greatest risk for advanced liver fibrosis is in patients with obesity, diabetes, age over 45 years, and an AST-to-ALT ratio greater than 1.0.

Pathophysiology

By definition, accumulation of excess triglyceride in hepatocytes is necessary for the development of NAFLD. Fat either is delivered to hepatocytes in the form of free fatty acids bound to albumin or is synthesized de novo within hepatocytes, primarily from excess carbohydrate. Circulating free fatty acids delivered to the liver originate primarily from adipose tissue, although a small fraction of circulating free fatty acids is made up of short-chain fatty acids absorbed directly from the small bowel during food digestion. Because little dietary fat is delivered directly to the liver, a low-fat diet may do little to decrease the amount of fat delivered to the liver, yet a diet composed of excessive carbohydrates may rapidly increase the liver fat through stimulation of de novo synthesis. Free fatty acids in the liver have two major fates: they can be delivered to hepatocyte mitochondria where they serve as a source of energy production or they can be converted into triglyceride and secreted into the circulation as very low density lipoprotein. In general, processes that increase the delivery of fat to the liver or impair its metabolism and secretion lead to NAFLD.

Peripheral insulin resistance and the resulting compensatory hyperinsulinemia interfere with these homeostatic mechanisms of energy balance, leading to the accumulation of fat in the liver. Normally, circulating insulin levels rise after a meal and promote glucose uptake by muscle and adipose tissue. Elevated post-prandial insulin levels also normally signal adipocytes to stop releasing free fatty

acids and hepatocytes to stop the production of glucose. Downregulating these metabolic steps after a meal is appropriate, since circulating free fatty acids are not needed by muscle and the liver for energy production and blood levels of glucose do not need to be supported by hepatic gluconeogenesis.

Patients with insulin resistance have impaired responses by muscle, adipose tissue, and the liver to insulin, causing compensatory increases in pancreatic insulin secretion to keep glucose levels within the normal narrow range. Chronic hyperinsulinemia causes triglyceride to accumulate in hepatocytes by favoring the formation of triglyceride instead of mitochondrial beta-oxidation, yet possibly impairing the secretion of triglyceride into the circulation. Compounding this dysfunctional metabolic handling of fat in the liver is the continued release of free fatty acids by peripheral adipose tissue in the fed state because of insulin resistance at the level of adipocytes.

Why fat-laden hepatocytes are prone to injury has not been fully established. Lipid peroxidation and oxidant stress have been proposed as one link between the accumulation of fat and subsequent injury.[59] This appealing theory is largely based on animal models, and there is little evidence that confirms a causal role of oxidant stress in the pathogenesis of liver injury in humans with NASH. Although markers of oxidant stress in the liver and in the serum are increased, treatment trials of various antioxidants have generally been disappointing. This may be due to a lack of efficacy of currently used antioxidants; alternatively, oxidant stress may not be critical to the pathogenesis of NASH and studies finding elevated indices of oxidant stress could be measuring epiphenomena. Alternative explanations of liver injury and inflammation in NASH include cytotoxicity of free fatty acids and impaired mitochondrial ATP production resulting in energy depletion. These mechanisms of injury are not mutually exclusive, and a combination of these and yet undiscovered mechanisms could be important.

The formation of scar tissue, or fibrogenesis, is the most serious consequence of sustained necroinflammation because it is this process that leads to the development of cirrhosis. Why some individuals develop fibrosis in response to chronic liver injury while others do not is unknown, but roughly a third of patients with any form of chronic liver disease appear to be at risk for developing fibrosis and are therefore at risk for progressing to cirrhosis. Interstitial hepatic stellate cells are the primary source of excess extracellular matrix production, and these cells have been shown to be activated in NASH.[60,61] Chronically elevated insulin levels may contribute to the activation of hepatic stellate cells to a fibrogenic phenotype, thus potentially predisposing patients with hyperinsulinemia to hepatic fibrogenesis.[62] The clinical correlate of this may be the increased risk of hepatic fibrosis in patients with diabetes.[12,63,64]

Clinical Management

No effective treatment strategies or interventions that prevent NASH have been identified by reliable clinical trials.[65] A number of agents and interventions have been examined in small trials and case series; although the initial results that reach publication are often encouraging, the findings are often not corroborated by subsequent more rigorous studies. For example, a pilot study of ursodeoxycholic acid suggested a benefit, but a subsequent well designed and appropriately powered trial determined that it was no better than placebo.[66]

Improving insulin sensitivity is a rational approach given the central role of insulin resistance in the development of NASH. Increased physical activity is probably the best means of improving insulin sensitivity.[67–69] For example, a study of more than 50,000 nurses demonstrated that less television watching and more physical activity prevented the onset of diabetes, a disease that represents the final stages of insulin resistance.[70] Several small trials have found that exercise may be an effective means of treating fatty liver.[71,72]

Weight loss in patients with overweight or obesity also improves insulin sensitivity. Achieving sustained weight loss to treat NAFLD and NASH has been the subject of a number of small trials and case series.[73] These trials each have their weaknesses and no firm conclusions can be drawn. A continued trend in the dietary management of obesity is the use of low-carbohydrate diets in place of the carbohydrate-based food pyramid. Although low-carbohydrate diets may have short-term benefits, sustained benefits have not been found in the absence of sustained lifestyle modifications that include exercise.[74–76] Failure of standard treatment options for obesity has led to increasing use of obesity surgery, which, at a price in terms of risks and side effects, can improve insulin sensitivity and its complications.[77–79] The procedures as they are currently performed are not associated with the aggressive liver disease caused by the jejunoileal bypass operation performed for obesity three decades ago. Early results of the current bariatric surgical approach suggest that the NASH associated with severe obesity may improve after the roux-en-Y gastric bypass.[22,80–83]

Using drugs to improve insulin sensitivity may have an important role in treating patients who are unable to increase physical activity or lose weight. Two types of drugs are currently available to improve insulin sensitivity, the thiazolidinediones (TZDs, or "glitazones") and metformin. Experimentally, the TZDs reduce fat accumulation in the liver and muscle of diabetic animals and humans,[84] sug-

gesting that they could be beneficial in patients with NASH. The first clinically available TZD, troglitazone, caused idiosyncratic hepatotoxicity and is no longer available. Troglitazone, rosiglitazone, and pioglitazone have all been evaluated in pilot studies with promising initial results.[85–88] Larger, placebo-controlled trials are now underway with the available TZDs. Weight gain can be associated with the use of TZDs and this can be discouraging to patients. Additionally, one patient treated with rosiglitazone experienced a sudden rise in aminotransferase levels that correlated with short-term concomitant use of corticosteroids,[89] underscoring the need to examine the value of these agents as a treatment for NASH within the structure of clinical trials. Metformin improves insulin sensitivity in patients with type 2 diabetes, but whether it is useful in the treatment of NASH is uncertain. A pilot study of 20 patients with NASH treated with 1.5 g metformin daily for 4 months demonstrated improved liver enzymes and insulin sensitivity,[90] yet it did not reduce liver fat content in a study of diabetic subjects.[84]

Because oxidant stress may be important in the development of NASH, antioxidants might prove to be effective therapies. One pilot study demonstrated that vitamin E at daily doses ranging from 400 to 1200 IU improved liver enzymes in children,[91] but a pilot study in adults found that vitamin E did not offer significant benefits beyond those achieved with exercise.[72] Another small study in adults suggested that a combination of vitamin E and vitamin C improved NASH, yet the control group experienced a similar benefit.[92]

In summary, the central role of insulin resistance in the pathogenesis of NASH suggests that interventions directed at improving insulin sensitivity might be beneficial in stopping disease progression or reversing established disease. As more complex studies are designed and executed, a therapeutic approach to NASH may emerge that combines a multidisciplinary approach to obesity, insulin resistance, sedentary lifestyle, dietary imbalances, and genetic variations.

Special Issues

Use of HMG-CoA Reductase Inhibitors ("Statins")

The HMG-CoA reductase inhibitors, or "statins," cause occasional aminotransferase elevations, and the manufacturers of these drugs routinely recommend not using them in patients with known liver disease. Despite these warnings, there are no data indicating that patients with preexisting chronic liver disease are any more susceptible to serious liver injury than patients without liver disease. This issue was examined in a survey of a university practice and found that patients who had elevated liver enzymes before starting a statin tended to have overall improvement in their liver enzymes during treatment with the drug.[93] A reasonable approach is to use the statins when needed to treat hypercholesterolemia with appropriate routine monitoring of liver enzymes as recommended in patients with normal liver enzymes.

Hepatitis A Vaccination

Although severe hepatitis A leading to liver failure or liver transplantation is rare, preexisting liver disease may increase the likelihood of developing acute liver failure after hepatitis A infection. To prevent such serious outcomes, the Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices recommend that all patients with chronic liver disease receive hepatitis A vaccinations. The vaccine, given as two injections over 6 months, is highly effective and well tolerated. When a diagnosis of NAFLD or any other form of chronic liver disease is established, it is reasonable to recommend the vaccine.

How Much Alcohol Is Allowable?

Whether small amounts of alcohol such as one glass of wine per week are harmful in patients with NAFLD is unknown. No widely accepted recommendation for the amount of alcohol allowed has been established for patients with nonalcoholic chronic liver disease, but most clinicians recommend a maximum consumption that ranges from complete abstinence to one drink (10-20 g ethanol) weekly. The Italian Dionysos population study found no adverse consequences of daily alcohol consumption not exceeding 30 g, but few clinicians are comfortable recommending this generous upper limit to patients. On the other hand, there are no data to indicate that the occasional (e.g., weekly) single drink poses a danger to the liver. Decisions regarding the amount of allowable alcohol should be made based on the patient's desires and expectations and on the severity of underlying liver disease.

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