Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of hepatic pathology that resembles alcohol-induced liver disease but develops in individuals who are not heavy drinkers. NAFLD is likely to be the most common cause of chronic liver disease in many countries and may also potentiate liver damage induced by other agents, such as alcohol, industrial toxins, and hepatotrophic viruses. The lack of specific and sensitive noninvasive tests for NAFLD limit reliable detection of the disease. Often, NAFLD is diagnosed presumptively when imaging studies suggest hepatic steatosis or when liver enzyme elevations are noted in overweight or obese individuals with no other identifiable reason for liver disease. NAFLD is strongly associated with insulin resistance and dyslipidemia; however, whether it is a cause or a consequence of these other conditions in not clear. The natural history of NAFLD is also uncertain. Nevertheless, discrepancies between the apparently high prevalence of NAFLD in the population and the generally low prevalence of clinically significant liver disease, as well as the relatively low representation of NAFLD patients among liver transplant populations, have generated considerable skepticism about the clinical importance of NAFLD. The latter has reduced enthusiasm for aggressive diagnosis, treatment, and follow-up of patients with NAFLD. This review of the clinical literature and selected basic information about NAFLD challenges some of these assumptions.

NAFLD—What Is It?

The diagnosis of NAFLD requires a combination of invasive and noninvasive tests. Liver biopsy is the most sensitive test for detecting and staging fatty liver disease. Fatty liver (hepatic steatosis) is also the lesion at the most clinically benign end of the spectrum. Large (macro-) and small (micro-) vesicles of fat, predominately triglycerides, accumulate within hepatocytes without causing appreciable hepatic inflammation, liver cell death, or scarring. Cirrhosis is the lesion at the opposite end of the spectrum. By the time this degree of architectural distortion develops, hepatic steatosis has often disappeared. Steatohepatitis is an intermediate form of liver damage characterized by the appearance of focal hepatic inflammation and hepatocyte death on a background of hepatic steatosis. The inflammatory infiltrate includes polymorphonuclear leukocytes as well as mononuclear cells and is often prominent around ballooned hepatocytes, which sometimes contain Mallory’s hyalin. These foci of injury tend to predominate in acinar zone 3 and are variably associated with perisinusoidal, perivenular, or bridging fibrosis. Because all of these histologic features also occur in alcohol- or drug-induced fatty liver diseases, liver biopsy cannot reliably distinguish among the various causes of this entity.

Abnormal liver blood test values, particularly aminotransferases and gamma glutamyl transpeptidase, often trigger the evaluation that leads to the diagnosis of NAFLD. However, no single blood test is specific for NAFLD. Moreover, because liver enzymes can be normal, at least intermittently, in patients with any given histologic stage of NAFLD, the presence of normal or near-normal aminotransferase values does not exclude significant underlying liver damage. Classically, however, patients with NAFLD have slightly elevated liver enzyme values, deny excessive alcohol consumption, and have negative serologic tests for viral hepatitis, autoimmune liver disease, and congenital causes of chronic hepatitis. The utility of this “operational” definition has been validated by several investigators who performed liver biopsies in otherwise-unselected groups of asymptomatic adults with mildly elevated liver enzyme values of uncertain etiology. Fatty liver was demonstrated in 30%–40% and steatohepatitis, with varying degrees of fibrosis, was seen in an additional 15%–30%.

Thus NAFLD accounts for about 70% of the cases of “cryptogenic” chronic hepatitis in the general population. The prevalence of NAFLD is even higher in select obese or diabetic populations, in which liver biopsy demonstrates...
NAFLD in up to 90% of individuals with cryptogenic hepatitis. However, these diagnostic criteria probably underestimate the true prevalence of NAFLD. Not only do some patients with NAFLD have normal aminotransferase levels, but at least some patients with other types of liver disease also have NAFLD. The latter point is important, because NAFLD may influence the outcome of those other diseases. For example, recent evidence suggests that steatosis and steatohepatitis are major independent risk factors for cirrhosis in patients infected with hepatitis C. Conversely, other liver diseases can influence the outcome of NAFLD. This has been demonstrated for NAFLD patients who also have genetic hemochromatosis. Such individuals are significantly more likely to develop cirrhosis than NAFLD patients with a normal HFE genotype. Therefore, positive tests for viral hepatitis or hemochromatosis do not entirely exclude a diagnosis of NAFLD. Indeed, elevated serum ferritin levels may be a clue that nonalcoholic steatohepatitis (NASH) is present, because hyperferritinemia with or without increased transferrin saturation has been described in many NASH patients who do not have C282Y or H63D mutations in the HFE gene.

Abdominal imaging studies are often ordered instead of liver biopsy to confirm the clinical suspicion of NAFLD. This approach is rationalized because it avoids the risks associated with an invasive procedure. However, the risk of significant bleeding or death from "blind" percutaneous liver biopsy in patients with incidentally detected liver enzyme elevations is exceedingly rare, most likely far less than the figures derived from liver biopsy populations that included patients with conditions that increase biopsy-related morbidity and mortality, such as coagulopathy or liver tumor. In addition, the potential drawbacks of limiting diagnostic procedures to noninvasive tests must be considered. Ultrasonography is commonly used to screen for fatty liver disease. A recent study that correlated radiologic and histologic diagnoses in 24 healthy volunteers and 28 patients with elevated liver enzyme values demonstrated that ultrasound detection of fatty infiltration had a sensitivity of 67%, a specificity of 77%, a positive predictive value of 77%, and a negative predictive value of 67%. Thus, relying on ultrasound to diagnose fatty liver disease gives an incorrect diagnosis in 25% to 33% of patients. One study found computed tomography (CT) to be inferior to ultrasound in diagnosing fatty liver, mostly because associated hepatic iron overload produced a masking effect that decreased the sensitivity of CT scan. However, in another study, when test objects containing variable amounts of fat were scanned to generate a CT scan density calibration curve before patients with fatty livers were evaluated, an excellent correlation was seen between the hepatic fat content and liver-to-spleen density ratio. Thus calibrated CT scans might be useful in monitoring hepatic fat content. Proton nuclear magnetic resonance (NMR) spectroscopy has also been validated as a reliable test for quantifying liver fat. Hepatic triglyceride content assessed by proton NMR spectroscopy and by liver biopsy correlate almost perfectly. Thus, the latter approach seems to be the best noninvasive way for diagnosing and quantifying liver fat. However, the expense of various imaging modalities is not trivial (Table 1), and none of these can distinguish simple steatosis from NASH or "uncomplicated" NASH from NASH with fibrosis. Therefore, liver biopsy remains the most cost-effective and sensitive test for diagnosing and staging NAFLD.

### NAFLD—Who Gets It?

The absence of blood tests, imaging modalities, or histologic findings that can distinguish NAFLD from alcohol- or drug-induced fatty liver disease forces clinicians to rely heavily on other historical information, physical findings, and laboratory data to reach a final diagnosis of NAFLD. However, the success of this strategy rests on the validity of the assumptions made about "safe" levels of alcohol consumption, as well as the strength of the associations between NAFLD and gender, race, age, body mass index (BMI), and certain other medical conditions, such as dyslipidemia and insulin resistance.

<p>| Table 1. Comparison of the Expense and Limitations of Various Tests for Fatty Liver Disease |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Approximate Cost</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>$420</td>
<td>Insensitive, nonspecific</td>
</tr>
<tr>
<td>CT scan</td>
<td>$950</td>
<td>Insensitive, nonspecific</td>
</tr>
<tr>
<td>MRI</td>
<td>$970</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>$415</td>
<td>Invasive</td>
</tr>
</tbody>
</table>

### Profiling for NAFLD

Much of the NASH literature emphasizes the prevalence of the disease in obese, middle-aged women who do not drink alcohol, although a few series call attention to the fact that the disease also occurs in mildly overweight men who abstain from alcohol. Because most of the reported cases of NASH have been white, there has been some speculation that nonwhite races might be somewhat protected from NAFLD despite having an increased risk for other obesity-related health problems. Given this background information, clinicians
have been conditioned to favor NAFLD as the cause of abnormal liver enzyme values in patients who match the profile of the typical NASH patient and to look harder for other causes of liver disease in those who do not. However, it is important to acknowledge that this approach might be flawed, because despite the ethnic diversity of the general U.S. population, studies have often been limited to small, largely white, clinic-based samples influenced by selection bias related to referral patterns for abnormal liver tests. Given ethnic differences in obesity, type 2 diabetes, and dyslipidemias, all thought to be risk factors for NAFLD, it is conceivable that the previous small series have generated a somewhat distorted perspective of the distribution of NAFLD in the general U.S. population.

To address this issue, we used the National Health and Nutrition Examination Survey (NHANES) III (conducted from 1988 to 1994 by the Centers for Disease Control) to assess the prevalence of NAFLD in the general U.S. population. Data on 12,241 adults (69% of the entire study sample) who had complete information on liver test values and other causes of liver disease were analyzed.

Elevated liver enzyme values were defined as any above-normal value of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or γ-glutamyltransferase (GGT) (>30 U/L), which is similar to definitions used in other studies and based on generally accepted laboratory normal values. A diagnosis of NAFLD was presumed if an individual had 1 or more elevated liver enzyme values and no evidence of an alternative explanation (e.g., negative testing for hepatitis B surface antigen and hepatitis C antibody, transferrin saturation <50%, consumption of fewer than 2 alcoholic drinks per day for men and less than 1 drink per day for women).

Surprisingly, we found that in every age group, men were significantly more likely to have NAFLD than women. The possibility that female hormones protect against NAFLD was further supported by evidence that NAFLD is twice as common in postmenopausal women as in premenopausal women (odds ratio [OR], 2.05; 95% confidence interval [CI], 1.43–2.94; P < 0.05) and postmenopausal women who receive hormonal replacement therapy are significantly less likely to have NAFLD than postmenopausal women who do not (OR, 0.69; 95% CI, 0.48–0.99; P < 0.05). Also, contrary to what we expected, even after adjusting for age and BMI, both non-Hispanic blacks and Mexican-Americans were significantly more likely to have NAFLD than non-Hispanic whites. However, as expected, NAFLD increased with increasing BMI, even after adjusting for age and ethnicity (Table 2). Consistent with other evidence that central adiposity is a major risk factor for NAFLD, we found that both men and women with greater waist circumferences are more likely to have NAFLD. Type 2 diabetes mellitus is associated with a 2-5-fold increased risk of NAFLD. Based on these results, it appears that we must modify our perception about the "typical" NAFLD patient—"she" is actually a "he," and he might not be white.

### Associated Conditions

**Obesity.** As indicated earlier, obesity is strongly associated with NAFLD. However, it is equally clear that some morbidly obese individuals do not have NAFLD, because the prevalence of NAFLD reportedly ranges from 50% to 90% in various obese cohorts. In the NHANES III population, only about 30% of obese men and 40% of obese women have NAFLD. Moreover, other studies have already shown that NAFLD definitely occurs in nonobese individuals and is particularly common in patients with congenital or acquired lipodystrophy, marked by a generalized paucity of adipose tissue. These findings suggest that obesity and NAFLD are common consequences of some other underlying disorder, or that obesity increases the risk of developing NAFLD after exposure to other insults.

With reference to the latter possibility, it is becoming apparent that obesity potentiates alcohol-related liver problems. For example, Bellentani et al. found ultrasound evidence of fatty liver in 46% of nonobese and 95% of obese heavy drinkers, demonstrating that obesity doubles the prevalence of alcohol-induced fatty liver disease. Another group has shown that obesity significantly increases the risk of alcohol-related cirrhosis. Thus, obesity conceivably could lower the threshold for alcohol-related liver disease. If this is true, then levels of

### Table 2. Adjusted Relative Odds of Cryptogenic Liver Enzyme Elevations (i.e., Presumed NAFLD) in NHANES III

<table>
<thead>
<tr>
<th>BMI categories (kg/m²)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>0.81</td>
<td>1.16</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>5.02*</td>
<td>3.92*</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>3.71*</td>
<td>3.92*</td>
</tr>
<tr>
<td>&gt;35.0</td>
<td>1.69-2.66 OR 95% CI</td>
<td>1.94-3.66 OR 95% CI</td>
</tr>
</tbody>
</table>

Note: Results are adjusted for age and ethnicity. OR, odds ratio; CI, confidence interval.

*P < 0.05.

Standard considered to be normal.
alcohol consumption considered "safe" for lean individuals might be dangerous for obese people.

One might even argue that some level of exogenous alcohol exposure is required to develop NAFLD. To evaluate this possibility, we reanalyzed the NHANES III data and looked at the prevalence of NAFLD in non-drinkers (i.e., those reporting fewer than 12 alcoholic drinks in their lifetime). This subgroup, representing 14% of the NHANES III population, was more likely to be female, nonwhite, older, and to have type 2 diabetes. Nevertheless, among these teetotalers, the overall prevalence of NAFLD is 21% (28% in men and 18% in women, P < 0.001). The pattern of associations with race, age, BMI, diabetes, and menopausal status is also nearly identical to that in the general population. Therefore, active exposure to alcoholic beverages is not required to develop NAFLD.

Might obesity so sensitize individuals to alcohol-related liver damage that they are injured by the small amounts of ethanol that are produced by their own intestinal flora? This is an interesting question given evidence that endogenous ethanol production is significantly increased in genetically obese, ob/ob mice that develop NAFLD spontaneously. We found a positive correlation between breath ethanol concentrations and obesity in a small group of individuals who denied recent consumption of alcoholic beverages. A group of Chilean investigators also presented preliminary evidence that malondialdehyde-acetaldehyde adducts, which form as a result of ethanol metabolism, are increased in the livers of morbidly obese patients undergoing gastric bypass surgery. Thus some cases of NASH might really be alcoholic steatohepatitis (ASH).

If NAFLD can be induced by exposure to small amounts of alcohol, then it is conceivable that other toxins might also contribute to the pathogenesis of NAFLD. This possibility is supported by evidence that obesity increases the risk of liver enzyme elevations after occupational exposure to certain industrial chemicals. Prescribed and over-the-counter medications might also promote NAFLD in susceptible individuals given that NAFLD-related comorbidities (e.g., diabetes, dyslipidemia, hypertension) often require medical treatment. Indeed, our analysis of NHANES III demonstrates that both men and women with NAFLD were more likely to have visited physicians during the past year than were individuals who had normal liver enzymes (men, OR 1.02; 95% CI 1.01–1.04; women, OR 1.03; 95% CI 1.01–1.04; P < 0.05). Therefore, it is likely that individuals with NAFLD might be taking more medications than individuals without NAFLD.

To evaluate the role of potential hepatotoxins in NAFLD pathogenesis, we looked at the prevalence of NAFLD in the 35% of the NHANES III population who took no prescription medication or acetaminophen in the past month. NAFLD was present in 21% of this subgroup (28% in men, 10% in women). Again, NAFLD was found to be more common in persons who are older, nonwhite, and postmenopausal and have higher BMI, higher waist circumference, and type 2 diabetes. Therefore, although obesity might potentiate the hepatotoxicity of alcohol and other chemicals, the latter are not required for NAFLD to develop.

Dyslipidemia. By definition, hepatic lipid homeostasis is disordered in NAFLD. However, whether dyslipidemia is a cause or a consequence of NAFLD is not clear. Assy et al., evaluated patients in the lipid clinic at their hospital and found that almost 2 of 3 of the patients had elevated liver enzyme values and that ultrasound findings revealed fatty liver disease in about half of the patients. Most of the patients with hypercholesterolemia had normal ultrasounds, whereas severe hypertriglyceridemia and mixed hyperlipidemia increased the risk of fatty liver disease by 5–6-fold. After adjusting for age, ethnicity, BMI, and type 2 diabetes, we found that both male and female NHANES III participants with a serum triglyceride level >200 mg/dL had about a 3-fold greater risk of having NAFLD than those with more normal triglyceride levels. In our analysis, a high-density lipoprotein (HDL) cholesterol level <35 mg/dL also almost doubled the risk of NAFLD. Taken together, these results confirm earlier reports documenting an association between certain dyslipidemias and NAFLD.

Insulin resistance and type 2 diabetes. Insulin resistance is strongly associated with conditions considered to be risk factors for NAFLD, including obesity and certain dyslipidemias. Therefore, insulin resistance may play a fundamental role in the pathogenesis of these disorders. Consistent with the possibility that insulin resistance plays a primary role in NAFLD pathogenesis, mild insulin resistance is very common at the earliest stages of NAFLD, and more severe insulin resistance (i.e., type 2 diabetes) correlates with more advanced stages of NAFLD. Moreover, in mice that have been genetically manipulated to overexpress lipoprotein lipase in the liver, hepatic insulin signaling is selectively inhibited and NAFLD develops. This finding has major clinical implications. For example, it helps us understand why blood glucose levels, glycosylated hemoglobin concen-
trations, and insulin-tolerance test results (all of which are heavily influenced by muscle insulin resistance) might be normal in some patients with NAFLD. This justifies our practice of using “guilt by association” with other insulin-resistant states to diagnose NAFLD.

Even more exciting, the molecular basis for insulin resistance has been discovered recently. Two groups have reported that IKK-beta, the kinase that activates nuclear factor beta, is chronically activated in ob/ob mice and several other murine models of insulin resistance. The investigators used pharmacologic and genetic strategies to inhibit IKK-beta in these animals and proved that insulin resistance was abolished. The next challenge is to identify the genetic and environmental factors that promote the sustained activation of this enzyme. At least 1 clinically relevant IKK-beta activator is well recognized: tumor necrosis factor (TNF)-alpha. Moreover, not only does TNF-alpha activate IKK-beta, but also the result-

ant induction of NF-kB promotes the transcription of TNF-alpha, suggesting a self-reinforcing, positive-feedback mechanism that could maintain chronic insulin resistance.

NAFLD—Who Cares?

Prevalence

Diseases that are endemic or become epidemic generally attract our attention. For example, there is no doubt that hepatitis B is an important disease in China (with a prevalence of 8% to 15%). Screening for diabetes has become routine in the United States, because this disease develops in 5% of American adults. Most general practitioners are on the alert for hepatitis C, which affects about 2% of the U.S. population. To judge whether NAFLD should be placed on our national health-alert “radar screen,” it is important to define its prevalence here. The prevalence of NAFLD in European and Japanese population-based studies is estimated to be 14%–21%. However, no U.S. population-based study of NAFLD has been reported. Such studies are difficult because, as discussed previously, no single blood test, imaging study, or histologic parameter is 100% sensitive or specific for NAFLD.

Using the biopsy-validated operational criteria that define NAFLD as the most likely cause of abnormal liver enzymes in adults who have no other obvious cause of liver disease, our analysis of NHANES III suggests that NAFLD is by far the most common cause of elevated liver enzyme values in American adults. We found that 27% of adults have an elevated AST, ALT, or GGT level, and that 79% of these cases cannot be explained by other common causes of liver disease. Thus, NAFLD is the most likely explanation for the elevated liver enzyme values observed in 23% of the general U.S. adult population. This represents approximately 31 million people. According to our definition, 31% of men and 16% of women have NAFLD.

Further studies will be required to determine whether or not 1 out of every 4–5 American adults actually has NAFLD. It is possible that this incidence rate is inflated because the cut-off values that we used to diagnose elevated liver enzyme values were unrealistically low. An analysis of liver enzyme values in NHANES III participants demonstrates that none of these values are distributed normally. For example, the median value for AST was 19 (range, 6–517), the median ALT value was 13 (range, 1–486), and the median GGT value was 20 (range, 1–1342). Therefore, using a cut-off value of 30 identifies an individual whose liver enzyme values definitely exceed the median. When the same data are reanalyzed using more stringent criteria for elevated liver enzymes (i.e., ≥1.5 times normal), the overall prevalence of NAFLD decreases to 11% (14% in men, 8% in women), but the pattern and magnitude of the associations discussed previously persist. Because liver biopsies were not performed in NAHNES III, confirmatory histopathology is lacking. Moreover, tests to exclude unusual causes of chronic hepatitis, such as alpha-antitrypsin deficiency, Wilson’s disease, and autoimmune hepatitis, were not performed. However, it is unlikely that these rare conditions account for most of the liver enzyme elevations in the general population. It also seems that alcohol or medication use cannot be blamed, because our subsidiary analyses in subgroups that did not drink or take medications showed findings similar to those in the entire population. Given that several studies have demonstrated NAFLD histology in most of their cases with elevated cryptogenic liver enzyme values and that the prevalence of NAFLD in the NHANES III population is very similar to the prevalence of NAFLD in population-based studies from Western Europe and Japan, it seems safe to conclude that NAFLD is the most common cause of liver enzyme elevations in American adults.

Clinical Impact

Debate persists over whether someone with incidentally detected liver enzyme elevations has a disease. Generally, this is believed to be true for patients with alcoholic liver disease, chronic viral hepatitis, sclerosing cholangitis, or primary biliary cirrhosis. Studies of patients with these disorders suggest that 10%–30% develop cirrhosis. Virtually identical findings have been reported in the small series of NAFLD patients who have had a biopsy. Moreover, given the high incidence of NAFLD in the
general population, it is not surprising that this disease is now considered the most common cause of cryptogenic cirrhosis. In chronic liver diseases, liver-specific morbidity and mortality is generally restricted to patients with cirrhosis. However, it is important to recall that the risk of developing clinically significant complications of cirrhosis is relatively low (about 25%–30% per decade), and liver-related mortality rarely occurs in the absence of advanced portal hypertension. Patients with well-compensated alcohol-induced cirrhosis have only an approximate 10% risk of dying from liver disease in 10 years. Matheoni et al. reported an 11% 8-year liver-related mortality rate in their small series of patients with NAFLD-induced cirrhosis, suggesting that the natural history of NAFLD is likely to be similar to that of other causes of chronic hepatitis.

Sometimes liver transplant registries are used to gauge the clinical impact of a particular type of liver disease. Using these criteria, NAFLD does not seem to be a very serious type of liver disease; only 1%–2% of liver transplant recipients carry a pretransplant diagnosis of NAFLD. However, this conclusion probably should be revised, because patients with cryptogenic cirrhosis constitute a large subset of transplant recipients and many patients with cryptogenic cirrhosis have NAFLD. Also, NAFLD-related comorbidities, such as diabetes and dyslipidemias, predispose patient with NAFLD to cardiovascular and renal diseases that are generally contraindications for liver transplantation. Thus many patients with advanced NAFLD may die without being listed for liver transplantation. This possibility is supported by evidence that cirrhosis is the 10th-leading cause of death in middle-aged adults and that half of these liver-related deaths are attributed to cryptogenic cirrhosis.

There is also growing evidence that NAFLD contributes to the progression of other liver diseases. For example, a recent study identified hepatic steatosis related to visceral adiposity as the major independent risk factor for fibrogenesis related to chronic hepatitis C infection, whereas viral burden had absolutely no relevance to disease progression. Moreover, NAFLD is likely to interfere with the therapy for other liver diseases given the high prevalence of NAFLD in the general population, the increasing reliance on living donor liver transplantation as a treatment for end-stage liver disease, and the fact that fatty liver grafts are at high risk for primary nonfunction after transplantation. Finally, even in the absence of liver-specific complications, individuals with NAFLD were more likely to visit doctors, take medications, and to report poor health status than other individuals surveyed in NHANES III, suggesting that patients with incidentally noted liver enzyme elevations are not truly asymptomatic.

**NAFLD—What Can We Do?**

The fact that no proven therapy for NAFLD exists is one of the most often-voiced rationalizations for avoiding aggressive diagnostic testing of patients with presumed NAFLD. Without a doubt, more information about the natural history of NAFLD and the results of large, randomized prospective treatment trials for patients with this disease is needed to guide future decisions. In the meantime, a number of reasonable treatment options are available.

**Putative Treatments**

**Lifestyle modification.** The preliminary results from a large, multicenter trial indicate that lifestyle modifications (e.g., diet and exercise) significantly reduce the risk of developing type 2 diabetes. Given the strong association between insulin resistance and NAFLD, it is reasonable to recommend such lifestyle modifications as a treatment for NAFLD, although at this point it is not clear whether this approach will help individuals who have already developed diabetes or who have histologically advanced NAFLD. Several small studies have demonstrated that weight loss improves liver enzyme elevations in patient with NAFLD, however, it is equally true that rapid, extreme weight loss, such as that induced by weight-reduction surgery, accelerates hepatic decompensation in some patients with NAFLD. A more careful evaluation of the techniques used to induce weight loss might be informative because little is known about the relative importance of changing diet composition as opposed to general caloric restriction. At least in rats and mice, evidence clearly indicates that diets with high sucrose or fat content are more likely to cause insulin resistance and hepatic steatosis than are equienergetic diets enriched with glucose or protein. Also, because exercise is an important component of most successful weight loss programs and physical activity enhances muscle insulin sensitivity, it is not clear whether merely increasing physical activity would provide the same benefits as dieting for patients with NAFLD.

**Insulin-sensitizing medications.** Mouse models of insulin resistance and fatty liver disease have shown that treatment with metformin or thiazolidinediones improves both conditions. Caldwell et al. reported that treatment with troglitazone significantly improved liver enzyme abnormalities and somewhat improved hepatic histology in a small series of patients with NAFLD. Recently, metformin therapy was shown to significantly improve liver enzyme values and hepatic steatosis in another small group of patients with NAFLD.
ever, there has been some hesitancy about recommending either drug as a general therapy for NAFLD because of potential treatment-related toxicity. Troglitazone was withdrawn as a first-line therapy for type 2 diabetes because of rare, but potentially fatal, hepatotoxicity. Phenformin, the parent compound of metformin, is known to cause life-threatening lactic acidosis; thus metformin is contraindicated in patients with liver disease. Nonetheless, results of the same diabetes prevention trial that demonstrated the efficacy of lifestyle modifications also indicated that metformin was well tolerated in that large population of obese, insulin-resistant subjects and significantly decreased the incidence of overt diabetes. The safety and efficacy of troglitazone could not be evaluated, because that arm of the study was terminated prematurely because of concerns about potential hepatotoxicity. It remains plausible that second-generation thiazolidinediones, which appear to have less intrinsic hepatotoxicity, might be beneficial in treating NAFLD. Leptin might also have some role as a therapy for selected patients with NAFLD. In lipodystrophic mice that develop leptin deficiency caused by lipoatrophosis, associated insulin-resistance and hepatic steatosis have been cured with leptin therapy, suggesting that leptin might be helpful for lipodystrophic patients with NAFLD.

**Antioxidants.** A few trials have demonstrated that treatment with vitamin E improves liver enzyme abnormalities in patients and certain animal models with fatty liver disease. Vitamin E is also well tolerated and cheap, making it a particularly attractive potential treatment for this common and indolently progressive disease. Other antioxidants, such as betaine, also appear to have some efficacy. Perhaps the benefits of antioxidants are not so surprising now that the links between NAFLD and insulin-resistance and between insulin resistance and the IKK-beta pathway have been established. Oxidant--and inflammatory--stresses are known to activate the IKK-beta pathway, therefore, treatments such as vitamin E that reduce oxidative stress and inflammation should inhibit IKK-beta activation. Interestingly, this may be a common mechanism of action for several agents thought to improve NAFLD. For example, studies in mice and cultured hepatocytes demonstrate that both metformin and thiazolidinediones inhibit the proinflammatory cytokine TNF-α, a potent activator of IKK-beta.

**Ursodeoxycholic acid.** A small study demonstrated that ursodeoxycholic acid improves liver enzyme abnormalities in NAFLD. Although data supporting its efficacy in NAFLD is sparse, hepatologists are very familiar with this drug, which is commonly used to treat cholestatic liver diseases, and it has become a popular therapy for NAFLD. The mechanism for the putative beneficial effect of ursodeoxycholic acid in NAFLD is uncertain, and the results of at least one large ongoing trial should clarify whether or not more extensive scrutiny of this agent is justified.

**Lipid-lowering drugs.** The National Institutes of Health is assembling a multicenter network to conduct large natural history and treatment trials for patients with NAFLD. Meanwhile, basic scientists from a number of disciplines are chipping away the mysteries of NAFLD pathogenesis. Soon, we may know enough about the

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**Figure 1.** Polymorphisms of genes that regulate inflammatory responses and exposure to certain environmental factors might influence the extent of IKKbeta activation and hence, the development of hepatic insulin resistance and NAFLD.
genetic and environmental factors to be able to counsel individuals about their risk for NAFLD. Current data suggest that both "nature" (i.e., genetic control of inflammatory responses) and "nurture" (i.e., epigenetic causes of oxidative stress/inflammation) contribute to this type of liver disease (Figure 1). Hence, individuals who have inherited the "bad" tendency to have sustained inflammatory responses might be better off minimizing the consumption of alcohol or foods that stimulate cellular oxidant production and trigger inflammation or taking medications to improve their antioxidant/anti-inflammatory defenses, whereas others with "good" inflammation-control genes can be reassured that they can safely enjoy these pleasures.

References

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