# Spectrum of Liver Disease in Type 2 Diabetes and Management of Patients With Diabetes and Liver Disease

KEITH G. TOLMAN, MD[1,2]
VIVIAN FONSECA, MD[3]
ANTHONY DALPIAZ, PHARMD[4]
MENG H. TAN, MD[5]

It is estimated that 20.8 million people, i.e., 7.0% of the U.S. population, have diabetes (1). Type 2 diabetes, with its core defects of insulin resistance and relative insulin deficiency, accounts for 90–95% of those with the disease. Another 5.2 million people are estimated to have undiagnosed type 2 diabetes. It is the sixth leading cause of death (1) in the U.S. and accounts for 17.2% of all deaths for those aged >25 years (2).

Liver disease is an important cause of death in type 2 diabetes. In the population-based Verona Diabetes Study (3), cirrhosis was the fourth leading cause of death and accounted for 4.4% of diabetes-related deaths. The standardized mortality ratio (SMR), i.e., the relative rate of an event compared with the background rate, for cirrhosis was 2.52 compared with 1.34 for cardiovascular disease (CVD). In another prospective cohort study (4), cirrhosis accounted for 12.5% of deaths in patients with diabetes.

Diabetes, by most estimates, is now the most common cause of liver disease in the U.S. Cryptogenic cirrhosis, of which diabetes is, by far, the most common cause, has become the third leading indication for liver transplantation in the U.S. (5,6). Virtually the entire spectrum of liver disease is seen in patients with type 2 diabetes. This includes abnormal liver enzymes, nonalcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure. In addition, there is an unexplained association of diabetes with hepatitis C. Finally, the prevalence of diabetes in cirrhosis is 12.3–57% (7). Thus, patients with diabetes have a high prevalence of liver disease and patients with liver disease have a high prevalence of diabetes.

The management of diabetes in patients with liver disease is theoretically complicated by liver-related alterations in drug metabolism, potential interactions between the drugs, and a low, albeit real, incidence of hepatotoxicity. In this article, we review the spectrum of liver disease found in patients with type 2 diabetes and the management of patients with concurrent diabetes and liver disease.

**METHODS** — A Medline search without limitations of date (as of October 2005), language, or humans was carried out by the authors. The following medical subject headings were used: "Diabetes Mellitus, type 2"; "Fatty Liver"; "Hepatitis, Toxic"; "Sulfonylurea Compounds"; "Thiazolidinediones"; "Rosiglitazone"; "Pioglitazone"; "Troglitazone"; "Hydroxymethylglutaryl-CoA Reductase Inhibitors"; "Metformin"; "Acarbose"; and "Gemfibrozil" and free-text terms: "fatty liver", "steatohepatitis", "nonalcoholic steatohepatitis", "nonalcoholic fatty liver disease", "drug-induced hepatitis", each drug name and "hepat*", and each drug name. When full-text articles were not available in the English language, abstracts were included in the search. Abstracts from national meetings through October 2006 were included. The Food and Drug Administration (FDA) Web site was searched for hepatotoxicity reports using the free-text terms listed above.

## SPECTRUM OF LIVER DISEASE IN TYPE 2 DIABETES

**SPECTRUM OF LIVER DISEASE IN TYPE 2 DIABETES** — The liver diseases seen in type 2 diabetes cover virtually the entire spectrum of liver disease.

### Abnormal liver enzymes

Elevation of serum alanine aminotransferase (ALT), while uncommon (0.5%) in apparently normal subjects (7), is common in patients with type 2 diabetes. In four clinical trials involving 3,701 patients with type 2 diabetes, between 2 and 24% of screened patients had liver enzyme tests above the upper limit of normal (ULN) (8). In these studies, investigators noted that ~5% of the patients had concomitant liver disease at baseline. In another report involving 13 clinical trials and 5,003 patients with type 2 diabetes, in which patients with serum ALT, aspartate aminotransferase (AST), or alkaline phosphatase >2.5 times ULN were excluded, 5.6% had serum ALT values between 1 and 2.5 times ULN (9). Evaluation of asymptomatic individuals with mild elevations of ALT and AST reveals that 98% have liver disease—most commonly, fatty liver disease and chronic hepatitis (10). The most common cause of a mild elevation of serum ALT is NAFLD (11), the most prevalent liver disease in type 2 diabetes.

From the [1]Division of Gastroenterology, University of Utah School of Medicine, Salt Lake City, Utah; the [2]Department of Pharmacology, University of Utah School of Medicine, Salt Lake City, Utah; the [3]Division of Endocrinology, Tulane University, New Orleans, Louisiana; the [4]Department of Pharmacy, University Hospitals and Clinics, Salt Lake City, Utah; and [5]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.

Address correspondence and reprint requests to Keith G. Tolman, MD, Department of Internal Medicine, University of Utah School of Medicine, 30 N. 1900 East, Salt Lake City, UT 84132. E-mail: keith.tolman@hsc.utah.edu.

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K.G.T. is on the scientific advisory boards for TAP Pharmaceuticals, Takada, Santarus, Merck, Johnson & Johnson, and InterMune and is on the speakers bureau for TAP Pharmaceuticals, Takeda, Schering, Roche, Eli Lilly, Santarus, InterMune, and G.D. Searle. V.F. is a consultant for and on the speakers bureau for Eli Lilly, Novartis, Takeda, Pfizer, and Sanofi-Aventis and has received grants from GlaxoSmithKline, Novartis, Takeda, AstraZenca, Pfizer, Sanofi-Aventis, Eli Lilly, and the National Institutes of Health.

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVD, cardiovascular disease; FDA, Food and Drug Administration; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SMR, standardized mortality ratio; TNF, tumor necrosis factor; TZD, thiazolidinedione; ULN, upper limit of normal.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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## NAFLD

The most common chronic liver disease in the U.S. is NAFLD (5). It is defined as fatty liver disease in the absence of <20 g alcohol/day. NAFLD, which resembles alcoholic liver disease, consists of a spectrum of liver disease from steatosis (fatty infiltration of the liver) to nonalcoholic steatohepatitis (NASH), which consists of steatosis plus inflammation, necrosis, and fibrosis. The prevalence of NAFLD in diabetes is estimated at 34–74% (12–17) and, in diabetes with obesity, at virtually 100% (18). While once considered a benign process, NASH has been found to lead to cirrhosis and, in some cases, to hepatocellular carcinoma (13,19–21). Of patients with NAFLD, 50% have NASH and 19% have cirrhosis at the time of diagnosis (18,22,23) While these studies are subject to selection bias, the prevalence is undoubtedly very high.

The pathogenesis of NAFLD is only partially understood. Hepatic steatosis reflects an imbalance between the uptake and synthesis of fatty acids by the liver and their oxidation and export. Patients with type 2 diabetes have dyslipidemia, which is characterized by elevated plasma triglycerides, decreased HDL cholesterol, and predominance of small LDL, a pattern also seen in patients with NAFLD (24). A central abnormality in the pathogenesis of steatosis appears to be insulin resistance resulting in lipolysis, which increases circulating free fatty acids (25), which are then taken up by the liver as an energy source. The fatty acids overload the hepatic mitochondrial β-oxidation system, leading to accumulation of fatty acids in the liver (26). Indeed, some investigators suggest NAFLD to be the hepatic manifestation of the insulin resistance syndrome (22,27–29). NAFLD does not universally progress to NASH, and the precise pathogenesis of steatohepatitis is yet to be determined. However, dysregulation of peripheral lipid metabolism seems to be important.

Lipid metabolism is, in part, regulated by adipokines, including tumor necrosis factor (TNF)-α and adiponectin. TNF-α, which interferes with insulin signaling thereby favoring steatosis, is elevated in fatty liver disease albeit not specific to type 2 diabetes (30,31). TNF-α is also proinflammatory and, thus, may play a role in the pathogenesis of the inflammation in NASH (32,33). Adiponectin, in contrast to TNF-α, is antilipogenic and anti-inflammatory and, thus, may protect the liver from lipid accumulation and inflammation. Adiponectin levels are decreased in conditions associated with NAFLD, including insulin resistance (34), obesity (35), type 2 diabetes (36,37), and NAFLD (36). Adiponectin and TNF-α therefore have opposing effects. The net effect of increased TNF-α and decreased adiponectin is prosteatotic and proinflammatory.

The mechanism of cell injury remains unclear. Fatty acids in the liver induce formation of free radicals (38), which cause lipid peroxidation and induce proinflammatory cytokines (39). The lipid peroxidation leads to the release of malondialdehyde and 4-hydroxynonenal, which in turn causes cell death and protein cross-linkage. This results in the formation of Mallory's hyaline in the hepatocyte (40) and activation of the stellate cells, which leads to collagen synthesis and fibrosis (41). The net effect of these processes is necrosis, formation of Mallory's hyaline, inflammation, and fibrosis—the characteristic histologic features of NASH.

The natural history of NAFLD is similar to that of alcoholic liver disease. The progression from steatosis to steatohepatitis to cirrhosis and, in some patients, to hepatocellular carcinoma over a period of many years is well established (13,42). The prognosis worsens with each stage of disease. Why some patients progress while most do not is not known. The only reliable way, to date, of determining this progression is liver biopsy, which may have significant economic implications (good or bad) for the management of patients with type 2 diabetes.

## Cirrhosis in diabetes

Cirrhosis is an important cause of death in diabetes. An autopsy study in the U.S. has shown that patients with diabetes have an increased incidence of severe fibrosis (19). In the Verona study, the SMR for cirrhosis was 2.52, greater than the 1.34 for CVD. If the patient was being treated with insulin, the SMR increased to 6.84 (3). Cryptogenic cirrhosis, primarily diabetes 5, is the third leading indication for liver transplantation in this country (6).

The association of cirrhosis and diabetes is complicated by the fact that cirrhosis itself is associated with insulin resistance. Impaired glucose tolerance is seen in 60% and overt diabetes in 20% of patients with cirrhosis. Insulin-mediated glucose disposal has been shown to be reduced by ~50% in cirrhotic patients (43). However, the onset of type 2 diabetes in cirrhotic patients is associated with decreased rather than increased insulin secretion (44). This interplay of associations has made it difficult to sort out the pathogenesis of cirrhosis in diabetes. Nevertheless, the association is incontrovertible and has implications for the treatment of diabetes in patients with cirrhosis.

## Hepatocellular carcinoma in diabetes

Numerous studies have confirmed a fourfold increased prevalence of hepatocellular carcinoma in patients with diabetes as well as an increased prevalence of diabetes in patients with hepatocellular carcinoma (45–48). It is not known whether the increased prevalence of hepatocellular carcinoma is unique to diabetes or the increased prevalence of cirrhosis, the precursor lesion of hepatocellular carcinoma. The pathogenic sequence of events leading to hepatocellular carcinoma appears to be insulin resistance, increased lipolysis, lipid accumulation in the hepatocytes, oxidative stress, and cell damage followed by fibrosis and cell proliferation, which are procarcinogenic (49–52).

## Acute liver failure

The incidence of acute liver failure appears to be increased in patients with diabetes: 2.31 per 10,000 person-years compared with 1.44 in the background population (53,54). It remains unclear whether it is diabetes, medications, or some other factor that accounts for the increased risk of acute liver failure. Troglitazone was factored out in these studies.

## Hepatitis C in diabetes

The prevalence of hepatitis C virus (HCV) is higher in patients with diabetes than in the general population (55–63). Specifically, the prevalence of HCV antibodies is 4.2% in the diabetic population compared with 1.6% in the comparator group. The relative odds of HCV-infected patients developing diabetes is 2.1 (95% CI 1.12–3.90) (58). Patients with HCV are more likely to develop diabetes (21%) than patients with hepatitis B (10%), suggesting that HCV, rather than liver disease per se, predisposes patients to diabetes. Furthermore, patients who are transplanted for HCV (and universally become reinfected) are more likely to develop diabetes than those who are transplanted for other liver diseases (61). Taken together, these observations suggest that HCV may play a pathogenetic role in type

2 diabetes. Recent studies suggest that the core protein of HCV impairs insulin receptor substrate signaling, which plays an important role in the metabolic effects of insulin (64,65).

There are other peculiarities in the HCV-diabetes connection including HCV genotype specificity. There are six genotypes of HCV, with genotype 1 being the most prevalent in the U.S. The prevalence of fatty liver disease is disproportionately high in HCV genotype 3 (66), presumably secondary to insulin resistance (67,68). Patients with hepatitis C and fatty liver disease have elevated levels of TNF-α and reduced levels of adiponectin, which in combination are proinflammatory and prosteatotic (69,70), leading to oxidative stress in mitochondria (71) and steatosis in many genotype 3 patients (72–74). Finally, there is an association of diabetes with α-interferon treatment of HCV infection. Type 1 diabetes occurs more frequently in patients treated with interferon for HCV versus other conditions (75). The latency of diabetes ranges from 10 days to 4 years after starting treatment.

The interaction between HCV infection, diabetes, and interferon is the subject of intensive investigation. In the meantime, given the strong epidemiologic evidence for the increased prevalence of HCV in diabetes, it seems reasonable that all patients with type 2 diabetes and persistently elevated serum ALT should be screened for HCV.

## TREATMENT OF PATIENTS WITH TYPE 2 DIABETES AND LIVER DISEASE

— The severity of type 2 diabetes and the type and severity of liver disease influence the therapy. There are few clinical trials that specifically target patients with coexistent diabetes and liver disease, and all are limited by small numbers of patients. We will review the management of type 2 diabetes in patients with liver disease as well as the management of liver disease specifically associated with type 2 diabetes.

## MANAGEMENT OF DIABETES IN PATIENTS WITH CONCOMITANT LIVER DISEASE

### Lifestyle modification

Treatment of type 2 diabetes in patients with liver disease may be compromised by poor nutritional status and general health. More than 50% of patients with severe liver disease are malnourished. A number of uncontrolled studies indicate that weight loss decreases hepatic steatosis (76–78). The durability of weight loss on hepatic steatosis remains to be determined (79). Low-glycemic, low-calorie diets with a weight loss of 1–2 kg/week seem reasonable. Low-fat diets should be avoided (80,81). Some have suggested that a Mediterranean diet (i.e., high complex carbohydrates, high monounsaturated fats, moderate amounts of wine, and low amounts of red meat) is preferred in patients with type 2 diabetes and NAFLD (82,83). Exercise improves peripheral insulin sensitivity (84), albeit not specific to patients with diabetic liver disease. Alcohol should be avoided not only because of its toxic effects on the liver, but also because of its high caloric content and potential interaction with sulfonylureas (85,86).

### Pharmacologic therapy

Pharmacologic therapy of type 2 diabetes in patients with liver diseases is, for the most part, the same as that without liver disease. While there are theoretical concerns about altered drug metabolism and hepatotoxicity, only patients with evidence of liver failure such as ascites, coagulopathy, or encephalopathy have altered drug metabolism. Furthermore, there is no evidence that patients with liver disease are predisposed to hepatotoxicity (87). Underlying liver disease, however, may compromise the diagnosis and increase the severity of drug-induced liver disease.

First-line therapy with metformin is appropriate in most patients but not recommended in patients with advanced hepatic disease because of a perceived increased risk of lactic acidosis. Recent trials have shown some benefit in patients with fatty liver and type 2 diabetes (88–91). Given that insulin resistance is the core defect in fatty liver disease, the case can be made for thiazolidinediones (TZDs) as front line therapy in these patients. Recent trials with pioglitazone and rosiglitazone have shown improvement in ALT and liver histology (92–97). Weight gain is a concern with TZDs, and cost is prohibitive for many patients. If metformin or TZDs are contraindicated, pharmacotherapy can begin with a secretagogue such as a sulfonylurea with rapid advancement to insulin if glycemic control is not achieved.

**Insulin secretagogues.** Sulfonylureas are generally safe in patients with liver disease but may not overcome the insulin resistance and defects in insulin secretion seen in patients with coexistent alcoholic liver disease and pancreatic damage (84). Sulfonylureas with a short half-life such as glipizide or glyburide are preferred in these patients. Patients with decompensated cirrhosis, i.e., encephalopathy, ascites, or coagulopathy, may have a reduced ability to counteract hypoglycemia, and thus, the response to therapy should be monitored closely. Historically, chlorpropamide (84,98–100) was associated with hepatitis and jaundice.

Clinical trials assessing the efficacy of meglitinides in the treatment of patients with liver disease have not been reported. The pharmacokinetics and tolerability of nateglinide in patients with cirrhosis is not significantly different than in control subjects (101). Repaglinide and nateglinide have not been associated with hepatotoxicity.

**Biguanides.** Metformin may be particularly useful in obese patients in whom it may cause mild weight loss (102). It is relatively contraindicated in patients with advanced liver disease or in binge drinkers because it may predispose to lactic acidosis. It is unclear whether the liver disease or alcohol is the predisposing factor. Metformin has not been reported to cause hepatotoxicity and has shown some benefit in patients with NAFLD (88–91).

**α-Glucosidase inhibitors.** The α-glucosidase inhibitors may be particularly useful in patients with liver disease because they act directly on the gastrointestinal tract to decrease carbohydrate digestion and thus glucose absorption, thereby decreasing postprandial hyperglycemia

A randomized double-blind trial evaluated the use of acarbose for the control of postprandial hyperglycemia in 100 patients with compensated liver cirrhosis and type 2 diabetes treated with insulin (103). Glycemic control improved significantly in both the fasting and postprandial state. In a recent placebo-controlled cross-over trial in patients with hepatic encephalopathy, acarbose significantly decreased fasting and postprandial glucose as well as A1C (104). There was also a reduction in blood ammonia levels, which paralleled an increase in bowel movement frequency. It was speculated that the increased bowel frequency favored the proliferation of saccharolytic bacteria while reducing the proliferation of proteolytic bacteria, resulting in a reduction in intestinal ammonia production.

Acarbose frequently causes mild transient elevations of ALT and, on rare occasions, severe liver disease (105–107).

While the labeling of acarbose has a warning for patients with liver disease, it appears to be safe and effective in patients with hepatic encephalopathy and type 2 diabetes. Miglitol, another α-glucosidase inhibitor, has not been associated with hepatotoxicity.

**TZDs.** TZDs may be especially useful because they enhance insulin sensitivity, the underlying defect in NAFLD. There has been concern about their potential hepatotoxicity because of the experience with troglitazone (since withdrawn from the U.S. market). However, in pre-approval clinical trials of rosiglitazone and pioglitazone, threefold elevations of ALT were seen with the same frequency for rosiglitazone (0.26%), pioglitazone (0.2%), and placebo (0.2 and 0.25%) (Physicians' Desk Reference 2005, Avandia Tablets and Actos Tablets). Lebovitz et al. (9) have reported that there was no difference in the incidence of liver abnormalities in patients treated with rosiglitazone, placebo, metformin, or a sulfonylurea in trials involving >5,000 patients. Rosiglitazone, in fact, decreased serum ALT by a mean of 5 units/l (9), as did pioglitazone in another trial (8). Furthermore, in the latter trial (8), serum ALT three times ULN occurred less frequently in the pioglitazone group (0.9%) than in the metformin (1.9%) or gliclazide (1.9%) groups.

The risk of acute liver failure with rosiglitazone and pioglitazone is much less than that with troglitazone (108,109). At the time of that review (109), 68 cases of "hepatitis" or "acute liver failure" due to rosiglitazone and 37 cases due to pioglitazone had been reported to the Food and Drug Administration (110–116). However, attestation as to cause was not provided, and many cases were confounded by concomitant medications and cardiovascular events (fluid retention and heart failure).

It is currently recommended that serum ALT levels be evaluated before the initiation of rosiglitzone and pioglitazone therapy and that therapy not be initiated if there is evidence of active liver disease or if the serum ALT level exceeds 2.5 times ULN (product labeling, 2005). Monitoring is recommended periodically thereafter as clinically indicated rather than every 2 months as previously recommended. Paradoxically, TZDs are emerging as the treatment of choice for NASH (92–97).

**Insulin.** Insulin treatment is frequently required in patients with diabetes and liver disease. Insulin requirements, however, may vary. For example, in patients with decompensated liver disease, the requirement may be decreased due to reduced capacity for gluconeogenesis and reduced hepatic breakdown of insulin. However, patients with impaired hepatic function may have an increased need for insulin due to insulin resistance (43). Thus, careful glucose monitoring and frequent dose adjustments of insulin may be necessary.

In patients with hepatic encephalopathy who require high-carbohydrate diets, resulting in postprandial hyperglycemia, rapid-acting insulin analogs such as insulin lispro, aspart, or glulisine may be particularly useful.

### Other drugs used in the management of disorders associated with type 2 diabetes

Statins are frequently used in patients with type 2 diabetes to treat hyperlipidemia and prevent cardiovascular events. Statin therapy, like all cholesterol-lowering therapy including bariatric surgery (117,118), causes minor but transient elevations in liver enzymes (119). However, the liver adapts with continuing therapy, and there are no long-term consequences of these abnormalities. Severe liver damage and liver failure are very rare (119). Paradoxically, statins are currently used to treat NAFLD (120,121), and recent studies suggest that statins are hepatoprotective in patients with HCV (122).

All of the ACE inhibitors have been implicated in hepatic injury including fulminant hepatic failure (123–126). The reactions are mostly hepatocellular, but cholestatic reactions have also been reported. Although losartan has been associated with hepatotoxicity (127) it has also been used to treat fatty liver disease (128). There are no current recommendations for hepatic monitoring of these idiosyncratic events.

Even aspirin is potentially hepatotoxic albeit at very high doses. Hepatotoxicity has not been described at doses used for cardioprotection.

## MANAGEMENT OF LIVER DISEASE IN PATIENTS WITH CONCOMITANT TYPE 2 DIABETES AND LIVER DISEASE

### Abnormal liver function tests

Given the fact that at least 50% of patients with type 2 diabetes have NAFLD, all patients with type 2 diabetes should have an ALT and AST test done as part of their initial evaluation. At least 95% of patients with a confirmed minor elevation of ALT or AST have chronic liver disease independent of the degree of elevation. Thus, it is always necessary to obtain a specific diagnosis (10). The most likely etiologies of minor elevations of ALT/AST are NAFLD, hepatitis C, hepatitis B, and alcohol. Moderate social drinking, i.e., <20 g/day, does not cause an elevation of liver enzymes. The initial workup should include testing for hepatitis C (anti-HCV or HCV PCR), hepatitis B (HBV surface antigen), hemochromatosis (iron and iron saturation), and an abdominal ultrasound. Patients with hepatitis C, hepatitis B, and increased iron saturation need referral for further workup and treatment. Ultrasound has a positive predictive value of 96% for detecting NAFLD in the absence of other liver diseases (129). Unfortunately the negative predictive value is only 19%; thus, patients with a negative ultrasound will also need referral. The impact of this approach on cost of care and manpower is not known, and the cost-effectiveness of screening ALT has not been established, although the American Association for the Study of Liver Disease is now recommending yearly ALT screening for everyone.

### Fatty liver disease

The diagnosis of NAFLD or NASH should be suspected in any patient with type 2 diabetes, especially if there are abnormal liver function tests. It should be specifically looked for in all obese patients with type 2 diabetes. ALT is typically elevated two- to threefold above ULN but is often normal. Mild elevations of serum alkaline phosphatase and glutamyl transferase may be present. Serum ferritin levels are frequently elevated, while iron and iron-binding capacity are normal (42,130).

Ultrasound studies may reveal a diffuse increase in echogenicity, so-called "bright" liver. The sensitivity of ultrasound in patients with elevated ALT is 89% with a specificity of 93% for detecting steatosis (131). If the ultrasound reveals fatty liver, it is appropriate to look for etiologies other than diabetes such as dyslipidemia. There are shortcomings to this approach. The sensitivity of ultrasound decreases greatly as hepatic steatosis decreases to 30% or less (132). Most patients with NAFLD found incidentally or by screening ultrasound have a normal ALT. These observations suggest that the sensitivity of ultrasound overall is really

not very high. In patients with abnormal ALTs and other diseases ruled out, the positive predictive value of ultrasound is 96% but the negative predictive value only 19% (129). Magnetic resonance spectroscopy is capable of quantitative assessment of steatosis (133) but is not indicated for routine clinical practice. Thus, the gold standard for diagnosis of NAFLD remains the liver biopsy. Furthermore, the diagnosis of progressive liver disease (i.e., NASH), the precursor of cirrhosis, can only be made by liver biopsy. However, certain patients including those with reversed ALT-to-AST ratio, hypertriglyceridemia, and thrombocytopenia are at high risk for progressive disease (134,135).

## Treatment of NAFLD

Most patients do not need to be treated. Only patients with biopsy-proved NASH or the risk factors listed above should be treated. Whether or not all patients need a liver biopsy is controversial in that the sensitivity of the risk factors for progressive disease is not known. It is also not known whether treatment, other than bariatric surgery, affects the ultimate prognosis. The treatment consists of measures to lose weight as well as pharmacologic intervention. There are no FDA-approved treatments and, in fact, no FDA guidelines for approving drugs for NAFLD.

**Exercise and weight reduction.** The initial treatment of NASH consists of weight loss and exercise, which enhance insulin sensitivity and result in reduction of steatosis (136–141). Rapid weight reduction, however, may increase necrosis, inflammation, and fibrosis (117,118,142). This paradoxical effect is thought to be due to an increase in circulating free fatty acids due to increased lipolysis seen with fasting. The ideal rate of weight loss is not known, but l.5 kg/week has been recommended (143). The ideal content of the diet is not known. However, saturated fatty acids increase insulin resistance, and for that reason a Mediterranean diet, i.e., a diet enriched with monounsaturated fatty acids and low-glycemic carbohydrates, seems reasonable (82,83). Recent studies have demonstrated that bariatric surgery either improves or completely reverses steatosis in patients with obesity with or without diabetes (141,144).

**Pharmacologic therapy.** Pharmacologic therapy of NAFLD is evolving. While many studies have shown improvement in steatosis, there are neither long-term studies to determine whether they alter the natural history of the disease nor studies to indicate whether relapse occurs after treatment withdrawal. Gemfibrozil (145), vitamin E (146), metformin (88–91), betaine (147), pioglitazone (92–96), rosiglitazone (97), atorvastatin (120, 121), losartan (128), orlistat (148), and pentoxifylline (149) have all been tried and have all been shown in small trials to improve liver enzymes. Modest histologic improvement over 6–12 months is seen with some of the agents. Long-term outcome trials with the various treatment modalities are yet to be completed.

Given that insulin resistance is central to the pathogenesis of NAFLD, insulin-sensitizing agents should have utility (even in the absence of diabetes), and there is increasing evidence that they do (80–90,92–97). Five studies using pioglitazone from 16 to 48 weeks have been published, and a large multicenter placebo-controlled trial is near completion (94). All have shown improvement in serum ALT and most in histology (92–96). One study showed an increase in adiponectin, a decrease in A1C, enhanced insulin sensitivity, and improved hepatic histology including steatosis, inflammation, and fibrosis (150). There have been three trials including a placebo-controlled trial with rosiglitazone (97,151,152). A 24-week study with rosiglitazone showed histologic improvement (97). In another study of 30 patients treated with rosiglitazone 8 mg/day for 48 weeks, there was significant improvement in ALT, AST, γ-glutamyl transferase, and insulin sensitivity. Of the 22 patients who had histologic evaluation, steatosis improved in 13, and fibrosis improved in 8 (152). This study was confounded by the use of statins. Interestingly, in the recently presented French multicenter trial known as FLIRT (French Multicenter Trail), ~50% of the patients had ALT and/or histologic improvement, but nondiabetic patients were more likely than diabetic patients to respond (153).

Metformin has shown mixed results in human trials (88–91) with some improvement in ALT but not in histology. Two long-term trials initiated by the National Institutes of Health are underway. At this time, treatment with metformin is not recommended outside of clinical trials. In the meantime, it seems reasonable to treat patients with NASH and type 2 diabetes with TZDs, recognizing that the patients may gain weight. In the absence of a histologic diagnosis of NASH, only those with risk factors for progressive disease as mentioned above should be treated. TZDs, despite shortcomings, are emerging as the treatment of choice even in the absence of diabetes.

Three prospective controlled studies using ursodeoxycholic acid, which reduces apoptosis and has cytoprotective properties, have been conducted. The results have been mixed (121,154,155). There is increasing interest in this agent because of its antiapoptotic effect as nonspecific or add-on therapy.

Statins may reduce hepatic fat content in patients with hyperlipidemia and NASH (120,121). Atorvastatin and ursodeoxycholic acid were evaluated in a small comparative trial of 44 obese adults with NASH, including 10 patients with diabetes. Normolipidemic patients received ursodeoxycholic acid, 13–15 mg · $kg^{-1}$ · $day^{-1}$, and hyperlipidemic patients received atorvastatin, 10 mg daily for 6 months. Liver chemistries improved in both groups; however, an increase in liver density, suggesting a decrease in fat content, occurred only in the atorvastatin group.

Oxidative stress has been shown to be important in the pathogenesis of NASH. It seems reasonable, therefore, to try therapy with antioxidants. Pilot studies with vitamin E have been conducted (146,156–158) with promising results, but a meta-analysis of high-dose vitamin E revealed an increase in overall mortality (159).

TNF-α is proinflammatory and increased in NASH. Pentoxifylline is a methylxanthine compound that inhibits TNF-α. It is used in the treatment of alcoholic hepatitis. A pilot study (149) has shown improvement in liver enzymes in patients with NASH. However, the high incidence of side effects led to early withdrawal in many patients, and it seems unlikely that it will find a place in the treatment of NASH.

In summary, the ideal therapy for NAFLD is yet to be identified, and no evidence-based recommendations can be made. Outside of clinical trials, therapy should be directed toward the underlying etiology.

**Hepatitis C.** The most effective treatment of HCV is a combination of pegylated α-interferon and ribavirin (160). Interferon, however, affects insulin sensitivity and glucose tolerance. Studies in nondiabetic patients report that interferon impairs glucose tolerance (161–163). A recent trial, however, failed to

detect a difference in insulin sensitivity and glucose tolerance after 6 months of interferon treatment (164), while another study reported that fasting plasma glucose and fasting immunoreactive insulin decreased during interferon treatment (72). The practical implications of the observed changes in glucose homeostasis in patients being treated with interferon are not known. Given the unpredictable effect of interferon in diabetes, it is reasonable to monitor diabetes carefully when using interferon.

**SUMMARY** — Type 2 diabetes is associated with a large number of liver disorders including elevated liver enzymes, fatty liver disease, cirrhosis, hepatocellular carcinoma, and acute liver failure. In addition, there is an unexplained association with HCV. The SMR for cirrhosis is higher than that for CVD in type 2 diabetes. Many consider NAFLD to be part of the insulin resistance syndrome. However, the presence of liver disease (unless decompensated) has little implication for the specific treatment of diabetes, and the presence of diabetes has little implication for the specific treatment of liver disease. Patients with decompensated liver disease are more susceptible to hypoglycemia and require careful monitoring. There continues to be a need for long-term placebo-controlled trials for the treatment of NAFLD and for the treatment of diabetes in patients with liver disease.

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