Narrative Review: Hepatobiliary Disease in Type 2 Diabetes Mellitus

Keith G. Tolman, MD; Vivian Fonseca, MD; Meng H. Tan, MD; and Anthony Dalpiaz, PharmD

Diabetes mellitus is the fifth leading cause of death in the United States; an estimated 17 million people are affected. Liver disease is one of the leading causes of death in persons with type 2 diabetes. The standardized mortality rate for death from liver disease is greater than that for cardiovascular disease. The spectrum of liver disease in type 2 diabetes ranges from nonalcoholic fatty liver disease to cirrhosis and hepatocellular carcinoma. The incidence of hepatitis C and acute liver failure is also increased. Nonalcoholic fatty liver disease is now considered part of the metabolic syndrome, and, with alcohol and hepatitis C, is the most common cause of chronic liver disease in the United States. Weight reduction and exercise are the mainstays of treatment for nonalcoholic fatty liver disease, but there are promising results with the new thiazolidinediones (pioglitazone and rosiglitazone) as well as metformin and 3-hydroxy-3-methylglutaryl coenzyme A inhibitors.

Diabetes mellitus is the fifth leading cause of death in the United States; an estimated 17 million people are affected (1). Of these, 90% have type 2 diabetes. Many, however, are unaware that they have the disease, and thus the number of people actually affected is probably much greater (2).

Only recently has liver disease been recognized as a major complication of type 2 diabetes. The standardized mortality ratio (that is, the relative risk compared to the background population) for death due to cirrhosis is greater than for cardiovascular disease (3). In this review, we discuss the spectrum of liver disease in type 2 diabetes, including nonalcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, hepatitis C, acute liver failure, and cholelithiasis. In addition, we review the metabolic effects of type 2 diabetes on the liver, the hepatotoxicity of antihyperglycemic medications, and the treatment of diabetes in patients with liver disease.

METHODS

We searched MEDLINE for the primary literature using Medical Subject Heading and free-text terms. The search also included the bibliographies of each citation for relevant articles. When full-text articles were unavailable, we included abstracts in the search. The U.S. Food and Drug Administration (FDA) Web site was also searched for reports of hepatotoxicity.

THE METABOLIC EFFECTS OF TYPE 2 DIABETES ON THE LIVER

Carbohydrate and lipid metabolism are affected by the insulin resistance and relative insulin deficiency in type 2 diabetes. Insulin resistance decreases glucose uptake in skeletal muscle and increases adipocyte lipolysis. The lipolysis results in increased circulating plasma free fatty acids, which, in turn, may lead to more insulin resistance. In effect, a vicious cycle is started. Alternatively, the elevated plasma free fatty acids, which occur secondary to obesity, may induce peripheral insulin resistance. Whatever the mechanism, the net effect is increased storage of fat in the liver (Figure 1).

Carbohydrate Metabolism

The elevated plasma free fatty acid level resulting from insulin resistance negatively affects glucose homeostasis by increasing hepatic glucose production and decreasing peripheral clearance (4, 5). Under physiologic conditions, compensatory hyperinsulinemia would suppress hepatic gluconeogenesis and glycogenolysis, thus restoring glucose homeostasis. Patients with type 2 diabetes, however, are resistant to these suppressive effects of insulin (6). The elevated free fatty acid level does not increase plasma insulin levels sufficiently to overcome the hepatic and peripheral effects of insulin resistance (7). In this way, reduced glucose utilization leads to hyperglycemia, which, in turn, contributes to the vascular complications of diabetes.

Lipid Metabolism

Patients with type 2 diabetes frequently have dyslipidemia characterized by elevated plasma triglyceride levels; reduced high-density lipoprotein cholesterol levels; and a predominance of small dense low-density lipoprotein particles, a pattern frequently seen in nonalcoholic fatty liver disease (8). The major cause of hypertriglyceridemia is hepatic overproduction of triglyceride-rich very-low-density lipoprotein (VLDL) and apolipoprotein B (apoB) caused by hyperinsulinemia and the increased availability of free fatty acid substrate (9, 10). In healthy humans, insulin decreases VLDL-1 apoB release. However, patients with type 2 diabetes do not adequately suppress hepatic VLDL-1 apoB production, which leads to hypertriglyceridemia (10). Decreased lipoprotein lipase activity in fat and skeletal muscle contributes to the reduced clearance of triglyceride-rich lipoproteins (8, 11, 12).

HEPATOBIARY DISORDERS ASSOCIATED WITH DIABETES

Hepatobiliary disorders occur more frequently in patients with type 2 diabetes. These disorders include nonalcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, hepatitis C, acute liver failure, and cholelithiasis.
**Nonalcoholic Fatty Liver Disease**

Nonalcoholic fatty liver disease refers to a broad spectrum of liver disease ranging from steatosis (blunt fatty infiltration of hepatocytes) to nonalcoholic steatohepatitis (steatosis plus inflammation, necrosis, or fibrosis) to cirrhosis and, in some patients, to end-stage liver disease and hepatocellular carcinoma. Nonalcoholic fatty liver disease resembles alcoholic liver disease (13). Its prevalence is as high as 50% in patients with type 2 diabetes and 100% in patients with diabetes and obesity. Of these affected patients, 50% have steatohepatitis and 19% have cirrhosis (14–16). Nonalcoholic fatty liver disease (from all causes) is the most prevalent liver disease in the United States (17).

The pathogenesis of nonalcoholic fatty liver disease is partially understood. Steatosis reflects the net retention of lipids within hepatocytes. This results from an imbalance between the uptake and synthesis of fatty acids and their oxidation and export. Angulo (18) has described these mechanisms in detail. The most consistent pathogenic factor is insulin resistance, leading to enhanced lipolysis, which, in turn, increases circulating free fatty acids (14). The increase in fatty acids overloads the mitochondrial \( \beta \)-oxidation system, and fatty acids accumulate in the liver. Fatty acids induce the cytochrome P450 4A and \( \alpha \) isoform isoenzymes—lipooxygenases that can generate free oxygen radicals (19). Reactive oxygen species promote disease progression by both lipid peroxidation and cytokine induction (20). Lipid peroxidation leads to the release of malondialdehyde and 4-hydroxynonenal. These substances cause cell death and protein cross-linkage, resulting in the formation of Mallory's hyaline in the hepatocyte (21). They also activate stellate cells, which leads to collagen synthesis and fibrosis (22). Cytokine induction promotes inflammation (23). Taken together, these are the characteristic histologic features of nonalcoholic fatty liver disease. The diagnosis of nonalcoholic fatty liver disease is suspected in patients who do not use alcohol and have mildly elevated aminotransferase levels. The clinical features are nonspecific. Most patients do not have signs or symptoms of liver disease; however, some report malaise or a sense of fullness in the right upper quadrant. Hepatomegaly may be present.

Laboratory studies reveal mild elevations of alanine aminotransferase (ALT) and aspartate aminotransferase levels. Serum alkaline phosphatase and \( \gamma \)-glutamyltransferase levels may be mildly elevated. Serum ferritin levels are elevated in almost half of the patients (24, 25). The hepatic iron index and iron level, however, are usually normal. Indicators of more advanced disease include a ratio of aspartate to alanine aminotransferase greater than 1 and higher levels of plasma triglycerides (24). Iron overload

**Figure 1.** Some metabolic effects of insulin resistance in skeletal muscle, fat, and liver.

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**Figure 1.** Some metabolic effects of insulin resistance in skeletal muscle, fat, and liver.

- **Insulin resistance**
  - **Skeletal muscle**
    - Increased FFA levels
    - Decreased glucose uptake and clearance
    - Hyperglycemia
  - **Fat**
    - Increased lipolysis
    - Decreased triglyceride clearance
    - Increased FFA levels
  - **Liver**
    - Increased glucose production
    - Decreased triglyceride clearance
    - Increased VLDL production
    - Hypertriglyceridemia

**FFA =** free fatty acid; **VLDL =** very-low-density lipoprotein.
The Liver and Diabetes

Figure 2. Ultrasonographic findings from a patient with steatosis.

Top. Fatty liver showing a so-called "bright liver." Bottom. The dark areas appear as masses and represent areas of liver that are spared from fatty infiltration—the so-called "phantom tumor."

Imaging studies are helpful in diagnosing steatosis. The disorder appears as a diffuse increase in echogenicity (so-called "bright liver") on ultrasonography, which has a sensitivity of 89% and a specificity of 93% for detecting steatosis (Figure 2, top) (29). Areas of focal fat-sparing appear as masses (so-called "phantom tumor") (Figure 2, bottom) (30). Magnetic resonance spectroscopy allows quantitative assessment of steatosis (31). However, only liver biopsy can assess the severity of damage and the prognosis.

The histologic features of steatohepatitis, which include steatosis, inflammation, ballooning hepatocyte necrosis, Mallory's hyaline, and fibrosis, are indistinguishable from those of alcoholic liver disease (Figure 3). As the disease advances toward cirrhosis, the steatosis and necro-inflamatory response recede (27). The natural history of nonalcoholic fatty liver disease from steatosis to steatohepatitis to cirrhosis and, finally, to hepatocellular carcinoma is well established (25, 32); however, it is not known why some patients progress while others do not. The prognosis worsens with each stage of progression. In one study, 56% of all patients died after a mean follow-up period of 8.3 years (27).

Treatment of fatty liver consists of good metabolic control and weight reduction. Weight loss improves insulin sensitivity and usually results in reduction of steatosis (33–37), but the necroinflammation and fibrosis may worsen if the weight reduction is rapid (38, 39). This paradoxical effect may be caused by increased circulating free fatty acids from the increased lipolysis seen with fasting. The most effective rate of weight loss is not known, but approximately 1.5 kg per week has been recommended (33). The content of the diet is a matter of debate. Given:

Figure 3. Liver biopsy specimens from persons with steatohepatitis.

Top. Liver biopsy specimen showing fatty infiltration with so-called chicken-wire appearance. Bottom. Liver biopsy specimen showing fatty liver with accompanying inflammatory infiltrate and fibrosis (nonalcoholic steatohepatitis). (Hematoxylin-eosin stain; original magnification, X40.)
that saturated fatty acids increase insulin resistance, a diet enriched with unsaturated fatty acids is theoretically reasonable.

Pharmacologic therapy with gemfibrozil (40), vitamin E (41), metformin (42, 43) ursodeoxycholic acid (44-46), betaine (47), pioglitazone (48-51), rosiglitazone (52), and atorvastatin (53, 54) has been investigated. Angulo (55) recently reviewed these therapies. All have been shown to improve liver enzyme levels. Betaine, vitamin E, and rosiglitazone (subsequently withdrawn from the market) led to modest histologic improvement. One prospective controlled study with ursodeoxycholic acid and diet showed improvement or normalization in liver enzyme levels (45). Another prospective controlled study of 166 patients did not show histologic improvement after 2 years (46).

Given that insulin resistance is the most consistent feature of fatty liver disease, it is reasonable to use insulin-sensitizing agents. A 6-month study with pioglitazone and vitamin E showed histologic improvement (49). Another study showed improvement in glycemic control and hepatic lipid content after 16 weeks (46). A recent study showed improvement in biochemical and histologic features of fatty liver disease after pioglitazone treatment for 48 weeks (51). A study using rosiglitazone showed improvement in insulin sensitivity, hepatic fat content, necroinflammation, and fibrosis at 24 weeks (52).

A pilot study showed atorvastatin to improve inflammation, ballooning degeneration, and Mallory's hyaline (53).

Cirrhosis in Diabetes

Cirrhosis is one of the leading causes of death in patients with diabetes (5). The Verona Diabetes Study was a population-based study that used standardized mortality ratios to compare the cause of death in patients with type 2 diabetes to that in the general population. The standardized mortality ratio for cirrhosis was greater than for cardiovascular disease (2.52 vs. 1.54). Furthermore, the ratio for cirrhosis was higher in patients treated with insulin (6.84), again raising the possibility that hyperinsulinemia predisposes to liver disease. Alternatively, patients who take insulin may have a longer duration of diabetes, with more time to develop cirrhosis.

Most of the evidence that diabetes causes cirrhosis is indirect. The prevalence of diabetes is disproportionately increased in patients with cryptogenic cirrhosis (56). The most common cause of cryptogenic cirrhosis is steatohepatitis, the most common cause of which is type 2 diabetes (13, 57–61). However, the steatohepatitis regresses when the disease progresses to cirrhosis; thus, the association is difficult to determine. Nevertheless, the epidemiologic association is strong (17), and there is convincing evidence that steatohepatitis progresses to cirrhosis (32, 62). A confounding factor is that cirrhosis itself is associated with impaired glucose tolerance in 60% of patients and overt diabetes in 20% (63). Furthermore, insulin resistance is a characteristic feature of cirrhosis, even in the absence of diabetes (64).

The treatment of patients with decompensated cirrhosis is liver transplantation. Steatosis, however, may recur (54).

Hepatocellular Carcinoma in Type 2 Diabetes

The incidence of hepatocellular carcinoma is increased in patients with diabetes. This was first described by Lawson and colleagues (65), who noted a 4-fold excess of patients with diabetes among 105 patients with hepatocellular carcinoma. The national cancer registries in Sweden and Denmark have also recorded a 4-fold increase in the incidence of hepatocellular carcinoma in patients with diabetes (66, 67). A recent prospective study from Japan has confirmed this association (68), as has a retrospective study from the Department of Veterans Affairs (69).

The sequence of events leading to hepatocellular carcinoma seems to be hyperinsulinemia, increased lipolysis, lipid accumulation in the hepatocytes, and oxidative stress with formation of reactive oxygen species. The oxidative stress leads to both DNA damage and cell death. Healing occurs by cell proliferation and fibrosis, which leads to cirrhosis. However, several genetic alterations occur along the way, including defects in DNA mismatch repair proteins. This results in microsatellite (70–72) and chromosomal instability, both of which predispose to malignant transformation (73).

Another early event in carcinogenesis is binding of the insulin-like growth factor I receptor, which is a membrane-bound receptor found on hepatocytes and other cells. This event activates insulin receptor substrate-1, which induces cell proliferation and inhibits transforming growth factor β-mediated apoptosis (74–77). In this way, insulin is proproliferative. However, cells with increased insulin receptor substrate-1 are highly tumorigenic (74, 79). The cell proliferation provides a milieu for genetic damage because replicating cells lose DNA, including potential tumor suppressor genes (79, 80). Furthermore, chromosomal instability during cell replication may lead to 1 daughter cell having 3 copies of a chromosomal arm, while the other has only 1 copy. If the lost chromosomal arm contains a tumor suppressor gene, such as p53, that cell may be conferred a growth advantage. Studies have demonstrated such chromosomal damage in hepatocellular carcinoma (81, 82), albeit not specific to type 2 diabetes.

Hepatitis C in Diabetes

Strong epidemiologic evidence shows that the prevalence of hepatitis C virus (HCV) in patients with type 2 diabetes is greater than that in the general population (83, 84), and emerging evidence shows that HCV contributes to the development of diabetes (85–87). The relative odds of HCV-infected patients developing diabetes is 2.1 (95% CI, 1.12 to 3.90). Furthermore, 4.2% of patients with diabetes compared with 1.6% in a comparator group have HCV antibodies.
Given the strong epidemiologic link between type 2 diabetes and HCV (83, 85, 86, 88, 89), could HCV have a role in the development of diabetes? Some evidence supports this view. Patients infected with HCV have a higher incidence of diabetes than do patients with hepatitis B virus infection (21% vs. 10%, respectively) (88). Furthermore, HCV-infected patients who have had liver transplantation have a higher incidence of diabetes than do patients who receive transplants for other liver diseases (89). Finally, the interferon treatment of HCV infection improves glucose tolerance (90, 91) when HCV is eradicated. Taken together, these studies suggest that HCV may indeed cause type 2 diabetes. Of note, HCV genotype 2 is disproportionately represented in diabetes associated with HCV (88). However, the prevalence of fatty liver disease is highest in genotype 3 (92). Patients with genotype 3 have insulin resistance and presumable will develop type 2 diabetes (93). Alcohol is an independent risk factor for steatosis in HCV and accelerates the course of hepatitis C (94); this finding indicates that fatty liver may be the link in this interplay of diseases. Patients with HCV and fatty liver seem to be relatively resistant to treatment with interferon (95). Interferon, however, reduces steatosis in patients with HCV genotype 3 (96).

Acute Liver Failure in Diabetes

A recent cohort study that used the database of the U.S. Department of Veterans Affairs indicates that diabetes increases the risk for acute liver failure (97). The study included 173,643 patients with a hospital discharge diagnosis of diabetes (99.5% with type 2) and 650,620 patients without diabetes and was done before the introduction of troglitazone. It excluded patients with preexisting or subsequent liver disease. The risk for acute liver failure was significantly greater in patients with diabetes (incidence rate, 2.31/10,000 person-years) than in those without (1.44/10,000 person-years). Chan and colleagues have reported similar results (98).

Cholelithiasis in Diabetes

There is a 2- to 3-fold increased prevalence of gallstones in patients with diabetes mellitus (99-101). This prevalence is higher in type 2 than in type 1 diabetes (102). Obesity is a strong cofactor (103), but diabetes alone is an independent risk factor with an odds ratio of 1.6 (104). The pathogenesis of cholelithiasis is not completely understood. Although the chemical composition of gallstones in patients with diabetes has not been carefully studied, it is generally believed that the gallstones are predominantly composed of cholesterol. Chemical composition studies of bile in patients with diabetes and age-matched controls, however, have failed to show lithogenic bile (105, 106).

Hypomotility due to autonomic neuropathy may lead to bile stasis with precipitation of gallstones. However, studies of gallbladder motility that used ultrasonography (107-114) and cholescintigraphy (107, 115-117) have yielded conflicting results (107, 115-117). Despite this, it is generally accepted that patients with diabetes have cholecytoparesis (116, 118). The pathogenesis of the cholecytoparesis remains speculative.

The treatment of gallstones in patients with diabetes is surgical. Recent studies have indicated that the rate of surgical complications is similar in patients with or without diabetes (119-121) and that prophylactic cholecystectomy does not increase life expectancy or quality of life (122).

TREATMENT OF DIABETES IN PATIENTS WITH LIVER DISEASE

Poor general health, altered nutritional status, and accompanying alcoholism may compromise treatment of diabetes in patients with liver disease. Furthermore, alcohol may interact with insulin and sulfonylureas to cause or exacerbate hypoglycemia (123, 124). No clinical trial to date has specifically targeted patients with diabetic liver disease.

Lifestyle Change

Weight loss, best achieved through caloric restriction, is an important component of diabetes management and may be especially important in obese patients with fatty liver disease. Foods with a low glycemic index may be especially important in patients with cirrhosis. These foods reduce the mean incremental blood glucose level during the day by approximately 40% in these patients (125). The possible benefits of dietary management in reducing chronic hyperinsulinemia warrant further consideration. Exercise improves peripheral insulin sensitivity (126), although not specifically in patients with diabetic liver disease.

In general, alcohol should be avoided in patients with liver disease and diabetes not only because of potential toxic effects on the liver but also because of its caloric content and potential interaction with sulfonylureas and insulin.

Pharmacologic Therapy and Hepatotoxicity Issues

Pharmacologic therapies in the treatment of type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, and meglitinides. Therapy in patients with liver disease may be compromised because of concerns about drug metabolism and hepatotoxicity. However, only patients with very severe liver disease have altered drug metabolism, and there is no evidence that patients with liver disease are predisposed to hepatotoxicity. It is recommended that therapy in patients with liver disease begin with a secretagogue, such as sulfonylureas, with rapid advancement to insulin if control is not achieved. Increasing evidence suggests that sensitizers (for example, thiazolidinediones or metformin) may be useful in patients with fatty liver disease.

Of the agents used to treat type 2 diabetes, the thiazolidinediones, α-glucosidase inhibitors, and sulfonylureas have been associated with hepatotoxicity. Table 1 summa-
rizes the hepatotoxicity of these drugs. A recent cohort study by Chan and colleagues (98) demonstrated that the incidence of acute liver failure was approximately 1 in 10,000 person-years of treatment for diabetes. The hazard ratio was highest for patients being treated with insulin (2.41 [CI, 0.98 to 5.94]). It was lower and nearly identical for sulfonylureas (1.44 [CI, 0.59 to 3.5]), metformin (1.32 [CI, 0.18 to 9.92]), and troglitazone (1.37 [CI, 0.49 to 3.78]). However, at the time there had been little exposure to troglitazone; this drug was subsequently withdrawn because of a high incidence of liver failure.

Insulin Secretagogues

Sulfonylureas are 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 (126). Prolonged hyperglycemia may be seen with long-acting sulfonylureas, such as glyburide, when used in patients with alcoholism (123).

The sulfonylureas, including chlorpropamide (137–139), glyburide (140–143), glipizide (144), and tolbutamide (145), are more commonly associated with hepatotoxicity than any other class of antihyperglycemic medications. The most common presentation is cholestasis.

Meglitinides

Repagliidine and nateglinide may be useful in patients in the early stages of diabetes in whom postprandial hyperglycemia is a specific problem. These drugs have less propensity to cause hyperglycemia than do sulfonylureas and have not been associated with hepatotoxicity.

Biguanides

The FDA warns against the use of metformin in patients with chronic liver disease and in persons who are alcohol binge drinkers because it may exacerbate lactic acidosis. It is unclear whether liver disease or alcohol is the predisposing factor. However, metformin has not been associated with hepatotoxicity. This drug may be particularly useful in obese patients, in whom it may cause mild weight loss (146). Two trials have studied metformin in patients with fatty liver disease, but the numbers are small and specific recommendations cannot be made at this time (42, 43).

α-Glucosidase Inhibitors

The α-glucosidase inhibitors are useful in patients with mild to moderate liver disease because they act directly on the gastrointestinal tract to decrease carbohydrate digestion, thereby decreasing postprandial hyperglycemia. Acarbose has been reported to cause mild transient elevations of ALT levels and, on rare occasions, severe liver disease (134–136). It is not recommended in patients with cirrhosis, although there is no evidence that such patients are at increased risk for hepatotoxicity. Miglitol, the other medication in this class, has not been associated with hepatotoxicity.

Thiazolidinediones

Rosiglitazone and pioglitazone may be especially useful in patients with diabetes and fatty liver disease. Rosiglitazone has not only improved insulin sensitivity but also reduced hepatic fat content and decreased hepatocellular injury (52). Similar results have been reported with pioglitazone (48, 51, 147). In patients with type 2 diabetes, pioglitazone decreases hepatic fat, increases plasma adiponectin, and enhances hepatic and peripheral insulin sensitivity (148).

Both drugs cause mild transient increases in serum ALT levels. The FDA recommends monitoring ALT levels and not using these drugs in patients with liver disease. However, probably half the patients who have been treated with thiazolidinediones have underlying fatty liver disease. Furthermore, Lebovitz and colleagues (149) have recently demonstrated that the incidence of liver abnormalities is not increased in patients treated with rosiglitazone.

The risk for acute liver failure with rosiglitazone and

Table 1. Hepatotoxicity of Antihyperglycemic Medications*

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Medication</th>
<th>Clinical Presentation‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Rosiglitazone</td>
<td>68 cases of hepatitis or acute liver failure reported to FDA (127–130); ALT elevations &gt;3 times the ULN occur in 0.25% of cases; cholestasis (127); hepatocellular injury (128)</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>37 cases of hepatitis or acute liver failure reported to FDA of published (131–133); hepatocellular injury (132, 133); cholestasis (133)</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Hepatotoxicity in 4 cases, jaundice in 2 cases (136–136)</td>
</tr>
<tr>
<td></td>
<td>Miglitol</td>
<td>No association</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Chlorpropamide</td>
<td>Cholestasis (137–139)</td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td>Cholestatic injury (140); hepatocellular injury (granulomas on biopsy in 1 case, death from hepatic failure in 1 case) (141–143)</td>
</tr>
<tr>
<td></td>
<td>Glipizide</td>
<td>&quot;Toxic hepatitis&quot; (144)</td>
</tr>
<tr>
<td></td>
<td>Tolbutamide</td>
<td>Cholestasis (145)</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>Miglitol</td>
<td>No association</td>
</tr>
</tbody>
</table>

* ALT = alanine aminotransferase; FDA = U.S. Food and Drug Administration; ULN = upper limit of normal.
‡ Numbers in parentheses are reference citations.
Table 2. Incidence of Hepatitis and Acute Liver Failure with Antihyperglycemic Agents*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prescriptions $\times 10^6$, n</th>
<th>Hepatitis Cases per $10^6$ Prescriptions, n</th>
<th>Acute Liver Failure Cases per $10^6$ Prescriptions, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troglitazone</td>
<td>4.5</td>
<td>21.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>4.4</td>
<td>14.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>3.6</td>
<td>9.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Metformin</td>
<td>6.5</td>
<td>2.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Glyburide</td>
<td>3.6</td>
<td>4.1</td>
<td>0</td>
</tr>
</tbody>
</table>

* Data obtained from Zawadski et al. (150).
† Hepatitis is defined as alanine aminotransferase or aspartate aminotransferase level 3 or more times the upper limit of normal.
‡ Acute liver failure is defined as liver dysfunction leading to encephalopathy, liver transplantation, or death.

Pioglitazone is much lower than that with troglitazone (150) (Table 2). Sixty-eight cases of "hepatitis" or "acute liver failure" due to rosiglitazone have been reported to the FDA; however, many cases are confounded by concomitant medications and cardiovascular events (fluid retention and heart failure). Well-documented hepatotoxicity has been described in 4 published case reports (127-130). In the clinical trials, 1 patient experienced an 8-fold elevation of ALT level, which is considered the signal of hepatotoxicity. Pioglitazone has been associated with 37 cases of "hepatitis" or "acute liver failure"—either published or reported to the FDA (131-133). No patient experienced an 8-fold elevation of ALT level in clinical trials.

Insulin

Patients with diabetes and liver disease frequently require insulin treatment. Anecdotal data suggest that most patients require relatively high doses of insulin but that treatment poorly controls the disease. In patients who require high-carbohydrate diets and have resulting postprandial hyperglycemia, short-acting insulin analogues, such as lispro, may be particularly useful. Because of the results of the Veterans Study, there is concern that insulin may predispose to the development of cirrhosis (3). Despite this epidemiologic association, large long-term clinical trials have not demonstrated an increased incidence of cirrhosis. Furthermore, the need for metabolic control outweighs the risk for accelerating the course of the liver disease.

Discussion

Type 2 diabetes is associated with a wide spectrum of hepatobiliary diseases, including fatty liver disease, cirrhosis, acute liver failure, and hepatocellular carcinoma, as well as cholestasis. In addition, diabetes is strongly associated with hepatitis C. All classes of antihyperglycemic drugs, except the meglitinides and metformin, have been associated with rare reports of hepatotoxicity. The thiazolidinediones and metformin may have therapeutic benefit in nonalcoholic fatty liver disease. However, use of these drugs is compromised by the FDA recommendation to not use them in patients with liver disease. In population studies, insulin predisposes to the development of cirrhosis and hepatocellular carcinoma, but these disorders have not increased in clinical trials. In addition, patients with cirrhosis frequently need insulin treatment for metabolic control. In general, the presence of liver disease makes the treatment of diabetes complex, and additional research is needed to determine the best treatment strategies that may affect outcomes in these patients.

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