DIABETES MELLITUS, LIVER DISEASE AND ITS RELATED COMPLICATION OF DIABETES THERAPY- A REVIEW

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INTRODUCTION

Diabetes mellitus has been defined by American Diabetes Association Expert Committee in their 1997 recommendations as a group of metabolic diseases characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia is associated with long damage, dysfunction and failure of various organs especially the eyes, kidneys, nerves, liver, heart and blood vessels thus covering a wide range of heterogeneous disease incidences of diabetes are increasing at epidemic proportions. According to the estimates of the World Health Organization, there are more than 180 million people with diabetes worldwide and this number is likely to more than double by 2030 (1).

Two major types of diabetes mellitus are recognized. Type 1, previously known as juvenile diabetes, is the result of the body's failure to produce enough insulin. This type of diabetes is prevalent in 5% to 10% of the diabetic population and is generally diagnosed in children (2). Type 2 diabetes is a result of insulin resistance (a condition in which the body cannot properly use insulin). This type of diabetes is more prevalent and is generally diagnosed in adults.

In developing countries, the majority of people with diabetes are in 45 to 64 year range, similar to the finding reported previously. In contrast, the majority of people with diabetes in developed countries are > 64 years of age. 2030, it is estimated that the number of people with diabetes > 64 years of age will be > 682 million in developing countries and > 48 million in developed countries. India being one of the fastest developing country, and youth being force for it, which will be hampered at the most is not a good sign. Proper patient education and general awareness about the disease can help reducing the extent of this damage (3).

The prevalence of type 2 diabetes is showing is showing a rapid progression world wide. Type 2 diabetes currently affecting 5 % to 10 % of most population, has become the most frequently encountered metabolic disorder in the world. The global prevalence of type 2 diabetes will rise from 171 million in the year 2000 to 366 millions by the year 2030 and these figures are higher the earlier estimates **[181].**

DIABETES-ASSOCIATED COMPLICATIONS

Diabetes is associated with a number of clinical complications such as cardiopathy, nephropathy, and retinopathy. Many individuals are not even aware that they have diabetes until they are diagnosed with one of these complications. Unmanaged diabetes can lead to life-threatening complications such as heart disease, stroke, blindness, and kidney failure (2). Diabetes is the sixth leading cause of death in the U.S.

HEPATOTOXICITY IN THE DIABETIC POPULATION

Until now, the link between risk of hepatic failure and diabetic condition was unclear. Recently, a large prospective cohort study was performed to examine whether patients with type

2 diabetes are at an increased risk of developing acute liver failure (4). This study suggested that diabetic patients are twice as likely to suffer hepatic failure compared to normal patients. Another study of the same prospective cohort population indicated that diabetes is associated with increased risk of hepatocellular carcinoma and chronic liver diseases (5).

Hepatotoxicity did not receive as much attention as other prevalent complications (i.e., cardiopathy, retinopathy, nephropathy) until hepatotoxicity of antidiabetic drugs emerged as a common clinical complication. This article is an attempt to summarize the current understanding of hepatotoxicity of antidiabetic drugs.

ANATOMY AND PHYSIOLOGY OF LIVER:

The liver is located in the upper right-hand portion of the abdominal cavity, beneath the diaphragm and on top of the stomach, right kidney and intestines. The liver, a dark reddish-brown organ that weighs about 3 pounds, has multiple functions.

There are two distinct sources that supply blood to the liver:

- ✓ oxygenated blood flows in from the hepatic artery
- ✓ nutrient-rich blood flows in from the portal vein

The liver holds about one pint (13 percent) of the body's blood supply at any given moment. The liver consists of two main lobes, both of which are made up of thousands of lobules. These lobules are connected to small ducts that connect with larger ducts to ultimately form the hepatic duct. The hepatic duct transports the bile produced by the liver cells to the gallbladder and duodenum (the first part of the small intestine).

HEPATIC COMPLICATIONS IN DIABETES MELLITUS

Liver disease complication is one of the most common causes of morbidity and mortality in diabetic patients. The role of the liver in normal glucose homeostasis and variety of liver conditions associated with abnormal glucose homeostasis. This association may explain the pathogenesis of the liver disease or of the abnormal glucose homeostasis, or may be purely coincidental.

Liver Disease and Diabetes Mellitus

1. Liver disease occurring as a consequence of diabetes mellitus

- Glycogen deposition
- Steatosis and nonalcoholic steatohepatitis (NASH)
- Fibrosis and cirrhosis
- Biliary disease, cholelithiasis, cholecystitis
- Complications of therapy of diabetes (cholestatic and necroinflammatory)

2. Diabetes mellitus and abnormalities of glucose homeostasis occurring as a complication of liver disease

- Hepatitis
- Cirrhosis
- Hepatocellular carcinoma
- Fulminant hepatic failure
- Postorthotopic liver transplantation

3. Liver disease occurring coincidentally with diabetes mellitus and abnormalities of glucose homeostasis

- Hemochromatosis
- Glycogen storage diseases
- Autoimmunebiliary disease

The prevalence of type 1 diabetes in the United States is 0.26%. The prevalence of type 2 diabetes is far higher, 1–2% in Caucasian Americans and up to 40% in Pima Indians. According to the Centers for Disease Control and Prevention, hepatitis C alone chronically infects more than 1.8% of the American population, or more than 4 million people. It would not be unusual for these two diseases to occur by chance in the same person, which explains in part the apparent association between liver disease and diabetes mellitus.

The liver plays a central and crucial role in the regulation of carbohydrate metabolism. Its normal functioning is essential for the maintenance of blood glucose levels and of a continued supply to organs that require a glucose energy source. This central role for the liver in glucose homeostasis offers a clue to the pathogenesis of glucose intolerance in liver diseases but little insight into the mechanisms of liver disease in diabetes mellitus. This review will draw on sources in the literature that address both pathogenetic directions.

The Role of the Liver in Glucose Homeostasis

An appreciation of the role of the liver in the regulation of carbohydrate homeostasis is essential to understanding the many physical and biochemical alterations that occur in the liver in the presence of diabetes and to understanding how liver disease may affect glucose metabolism. The liver uses glucose as a fuel and also has the ability to store it as glycogen and synthesize it from noncarbohydrate precursors (gluconeogenesis). Mann and Magath demonstrated that a total hepatectomy in a dog results in death within a few hours from hypoglycemic shock, (6, 7) underscoring the important role the liver plays in maintaining normoglycemia.

Glucose absorbed from the intestinal tract is transported via the portal vein to the liver. Although the absolute fate of this glucose is still controversial, some authors suggest that most of the absorbed glucose is retained by the liver so that the rise in peripheral glucose concentration

reflects only a minor component of postprandial absorbed glucose. Therefore, it is possible that the liver plays a more significant role than does peripheral tissue in the regulation of systemic blood glucose levels following a meal (8). Katz and associates, (9). however, suggest that most absorbed glucose is not taken up by the liver but is rather metabolized via glycolysis in the peripheral tissues.

Many cells in the body, including fat, liver, and muscle cells, have specific cell membrane insulin receptors, and insulin facilitates the uptake and utilization of glucose by these cells. Glucose rapidly equilibrates between the liver cytosol and the extracellular fluid. Transport into certain cells, such as resting muscle, is tightly regulated by insulin, whereas uptake into the nervous system is not insulin-dependent.

Glucose can be used as a fuel or stored in a macromolecular form as polymers: starch in plants and glycogen in animals. Glycogen storage is promoted by insulin, but the capacity within tissues is physically limited because it is a bulky molecule.

Insulin is formed from a precursor molecule, preproinsulin, which is then cleaved to proinsulin. Further maturation results in the conversion of proinsulin into insulin and a smaller peptide called C-peptide. A small amount of proinsulin enters the circulation. It has a half-life 3–4 times longer than that of insulin because it is not metabolized by the liver. However, proinsulin has <10% of the biological activity of insulin.

Insulin is metabolized by insulinase in the liver, kidney, and placenta. About 50% of insulin secreted by the pancreas is removed by first-pass extraction in the liver. Insulin promotes glycogen synthesis (glycogenesis) in the liver and inhibits its breakdown (glycogenolysis). It promotes protein, cholesterol, and triglyceride synthesis and stimulates formation of very-low-density lipoprotein cholesterol. It also inhibits hepatic gluconeogenesis, stimulates glycolysis, and inhibits ketogenesis. The liver is the primary target organ for glucagon action, where it promotes glycogenolysis, gluconeogenesis, and ketogenesis **(**10, 11).

Glucose that is taken up by a cell may be oxidized to form energy (glycolysis). It is oxidized to pyruvate in the cytosol, and electrons generated from this process are transferred to the mitochondria. Pyruvate generated by this Emden-Meyerhof pathway is oxidized to acetyl CoA in the mitochondria, which in turn undergoes further oxidation by the Krebs tricarboxylic acid cycle. Nearly 36 moles of high energy phosphate are generated from each molecule of glucose by aerobic glycolysis.

Should oxygen not be available, pyruvate is converted to lactate by the action of lactate dehydrogenase. Lactate is a potential fuel, or it may be converted back to glucose. The formation of glucose from lactate and various noncarbohydrate precursors is known as gluconeogenesis and occurs mainly in the liver and kidneys. The liver, kidney, intestine, and platelets contain the enzyme glucose-6-phosphatase, which produces glucose from glucose-6-phosphate and is the final step in the production of glucose via gluconeogenesis. This enzyme is absent in other tissues. Glucose that is metabolized peripherally may therefore be converted back to glucose or

to hepatic glycogen via gluconeogenesis with lactate as the primary substrate (12). This is known as the Cori cycle.

In type 2 diabetes, excessive hepatic glucose output contributes to the fasting hyperglycemia. Increased gluconeogenesis is the predominant mechanism responsible for this increased glucose output, while glycogenolysis has not been shown to be increased in patients with type 2 diabetes (13). Hyperglucagonemia has been shown to augment increased rates of hepatic glucose output, probably through enhanced gluconeogenesis.

Liver Disease Occurring as a Consequence of Diabetes Mellitus

1) Glycogen Deposition

Excess glycogen accumulation in the liver is seen in 80% of diabetic patients (14). Glycogen synthesis in the liver is impaired in diabetes due to defective activation of glycogen synthase. However, studies attesting to this were usually performed on animals with recently induced diabetes. In patients with chronic diabetes, glycogen accumulation is seen, and it is postulated that long-standing insulin deficiency may actually facilitate synthase activity. This and enhanced gluconeogenesis may account for the net accumulation of glycogen in diabetes(15).

The mechanism of cytoplasmic glycogen deposition is uncertain but is perhaps related to the large variations in glucose concentration and frequent insulin dosing. No correlation between hepatic glycogen content and fasting blood glucose levels has been demonstrated. There is also no demonstrable association between the type of diabetes or the fat content of the hepatocytes and the presence of glycogen. The mechanism for nuclear glycogen deposition is also unclear, with the stored glycogen resembling muscle glycogen more than hepatocyte cytoplasmic glycogen (16-18). Nuclear glycogen deposition was first described by Ehrlich in 1883 (19). It is postulated that glycogen is actually synthesized in the nucleus and has been found in 60–75% of diabetic patient (20, 21). Nuclear glycogen deposition is also seen in sepsis, tuberculosis, some patients with hepatitis (particularly autoimmune chronic hepatitis), Wilson's disease, and cirrhosis. The finding of glycogen nuclei in a patient with fatty liver is useful confirmatory evidence that the fatty liver is secondary to diabetes even if the glucose tolerance test is normal. However, Creutzfeldt and associates have reported the combination also in obese patients (22-24).

Patients showing solely excessive glycogen deposition may exhibit hepatomegaly and liver enzyme abnormalities and may have abdominal pain and even nausea and vomiting and rarely ascites. All these abnormalities may improve with sustained glucose control (25).

2) Fatty Liver, Steatohepatitis

Fatty liver disease covers a range of conditions where there is a build-up of fat in the liver cells. The liver cells (hepatocytes) normally contain some fat and related fatty chemicals (triglycerides, fatty acids, etc). Excess fat is normally passed out of liver cells, into the

bloodstream, and then taken up and stored in fat cells (adipose cells) throughout the body. In fatty liver disease, excess fat builds up in liver cells. This is thought to happen if there is some problem or disruption in the normal processing of fat and related fatty chemicals in the liver cells. (Eating fatty food by itself is not a cause of fatty liver disease.)

Simple fatty liver also called 'hepatic steatosis. (In the US it is thought to occur in 1 in 4 adults.) Simple fatty liver is present when the fat content inside liver cells makes up more than 5-10% of the liver's weight. Simple fatty liver is not associated with serious damage or harm to the liver. It seems that the fat just builds up harmlessly in liver cells. It can occur for no apparent reason. However, most people with simple fatty liver have other conditions where fatty liver is a complication.

Hepatic fat accumulation is a well-recognized complication of diabetes with a reported frequency of 40–70%. Unfortunately, associated obesity is a frequently occurring confounding variable. Type 1 diabetes is not associated with fat accumulation if glycemia is well controlled, but type 2 diabetes may have a 70% correlation regardless of blood glucose control.

Fat is stored in the form of triglyceride and may be a manifestation of increased fat transport to the liver, enhanced hepatic fat synthesis, and decreased oxidation or removal of fat from the liver. The steatosis may be microvesicular or macrovesicular and may progress to fibrosis and cirrhosis. The degree of glycemic control does not correlate with the presence or absence of fat (26-31).The most common clinical presentation is hepatomegaly, and most patients have normal or only mildly abnormal transaminases and normal bilirubin.

CT scan and ultrasound are claimed to be sensitive tests for detecting hepatic fat accumulation. A negative ultrasound, however, does not exclude the presence of microscopic fatty infiltration (32). A liver biopsy is obviously the best method for detecting hepatic fat accumulation. It is unclear at this time whether a biopsy is always necessary in patients with suspected steatohepatitis. Biopsy probably should be performed when the diagnosis is unclear, although some authors suggest that it is necessary in all cases to confirm the diagnosis and assess the degree of fibrosis (33-34).

Excessive fat accumulation is seen in alcoholic liver disease, obesity, prolonged parenteral nutrition, protein malnutrition, jejunoileal bypass, and chronic illnesses complicated by impaired nutrition, such as ulcerative colitis and chronic pancreatitis. It can also occur as a result of hepatotoxins, such as carbon tetrachloride, and can be seen in association with abetalipoproteinemia, Weber-Christian disease, the HIV virus, cholesterol ester storage disease, and Wilson's disease, in addition to diabetes mellitus. A number of drugs, such as amiodarone, perhexilene, glucocorticoids, estrogens, and tamoxifen, may cause macrovesicular steatosis. The amount of fat frequently diminishes with improvement of the underlying condition.

Nonalcoholic steatohepatitis (NASH) is a variant of fatty liver in which fat in the hepatocytes is accompanied by lobular inflammation and steatonecrosis. The diagnosis can only be made in the absence of alcohol abuse or other causes of liver disease, particularly hepatitis C.

In patients with diabetes and steatohepatitis, Mallory bodies such as those seen in alcoholic liver disease may be seen. Nonalcoholic steatohepatitis has been associated most commonly with obese women with diabetes, but the disease is certainly not limited to patients with this clinical profile (35). There is certainly a higher prevalence in type 2 diabetic patients on insulin (36). The spectrum of clinical disease in fatty liver with steatohepatitis varies from the asymptomatic elevation of liver enzymes to severe liver disease with fibrosis and nodular regeneration. Patients with nonalcoholic steatohepatitis can develop progressive liver disease and complications to the point that they may need liver transplantation (37).

Nonalcoholic steatohepatitis should be considered as a cause for chronically elevated liver enzymes in asymptomatic diabetic patients particularly if they are obese and have hyperlipidemia (38, 39). In type 2 diabetic patients with or without obesity, up to 30% have fat with inflammation, 25% have associated fibrosis, and 1–8% has cirrhosis (40, 41).

The morphological pattern of diabetic steatohepatitis resembles that seen in alcoholic hepatitis. However, the histopathological changes in diabetes tend to be periportal (situated in zone I), while those in alcoholic hepatitis are predominantly pericentral (in zone III). It is not clear whether the diabetes is causally related to the steatohepatitis (42-43). In an animal model of type 1 diabetes, there is a high incidence of perisinusoidal hepatic fibrosis, while in humans perisinusoidal fibrosis often parallels with diabetic microangiopathy (44).

Gradual weight loss and good control of blood glucose levels is recommended for patients with steatohepatitis, since rapid weight loss may actually worsen NASH (45, 46). Weight loss >10% has been shown to be necessary for normalization of liver enzymes in patients who are significantly overweight (47). Ursodeoxycholic acid may be beneficial in reducing steatosis and may result in normalization of liver enzymes and improvement in histology without demonstrable impact on fibrosis (48-50).

3) Cirrhosis and Fibrosis

Cirrhosis of the liver is a chronic disease that causes cell destruction and fibrosis (scarring) of hepatic tissue. Fibrosis alters normal liver structure and vasculature, impairing blood and lymph flow and resulting in hepatic insufficiency and hypertension in the portal vein. Complications include hyponatremia, water retention, bleeding esophageal varices. Coagulopathy, spontaneous bacterial peritonitis, and hepatic encephalopathy. There is an increased incidence of cirrhosis in diabetic patients and, conversely, at least 80% of patients with cirrhosis have glucose intolerance (51-52). The reported prevalence of cirrhosis in diabetes varies widely.

Diabetes increases the risk of steatohepatitis, which can progress to cirrhosis. Obesity is a significant confounding variable in determining the prevalence of cirrhosis in diabetes. Even with normal glucose tolerance, obesity can cause steatohepatitis and cirrhosis. Likewise, the lack of a clear definition of diabetes in the past somewhat confounds these statistics.

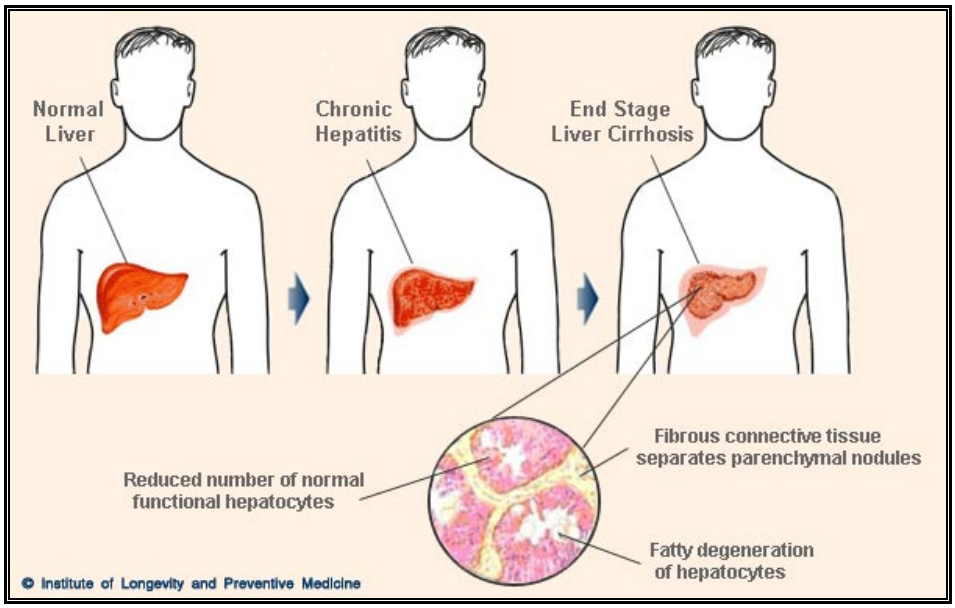

Figure 1 Cirrhosis is the end-stage of progressive liver fibrosis.

Cirrhosis is a potentially life-threatening condition that occurs when scarring damages the liver. This scarring replaces healthy tissue and prevents the liver from working normally. Cirrhosis usually develops after years of liver inflammation. When chronic diseases cause the liver to become permanently injured and scarred, the condition is called Cirrhosis. Cirrhosis harms the structure of the liver and blocks the flow of blood. The loss of normal liver tissue slows the processing of nutrients, hormones, drugs, and toxins by the liver. Also, the production of proteins and other substances made by the liver is suppressed. People with cirrhosis often have few symptoms at first. The person may experience fatigue, weakness, and exhaustion. Loss of appetite is usual, often with nausea and weight loss. As liver function declines, water may accumulate in the legs and the abdomen (ascites). A decrease in proteins needed for blood clotting makes it easy for the person to bruise, bleeding or infection. In the later stages of cirrhosis, jaundice (yellow skin) may occur, caused by the buildup of bile pigment that is passed by the liver into the intestines. The liver of a person with cirrhosis also has trouble removing toxins, which may build up in the blood. Drugs taken usually are filtered out by the liver, and this cleansing process also is slowed down by cirrhosis. People with cirrhosis often are very sensitive to medications and their side effects. The doctor often can diagnose cirrhosis from the patient's symptoms and from laboratory tests. During a physical exam, the doctor could notice a change in how your liver feels or how large it is. If the doctor suspects Cirrhosis, you will be given blood tests. The purpose of these tests is to find out if liver disease is present. In some cases, other tests that take pictures of the liver are performed such as the computerized axial tomography (CAT) scan, and ultrasound. The doctor may decide to confirm the diagnosis by putting a needle through the skin (biopsy) to take a sample of tissue from the liver. In some cases, cirrhosis is diagnosed during surgery when the doctor is able to see the entire liver.

Stellate cell activation is the central event in hepatic fibrosis. Activation consists of 2 major phases: (1) initiation (also called apreinflammatory stage) and (2) perpetuation (Figure 2). Initiation refers to early paracrine-mediated changes in gene expression and phenotype that render the cells responsive to other cytokines and stimuli. Perpetuation then results from the effects of these stimuli on maintaining the activated phenotype and generating fibrosis.

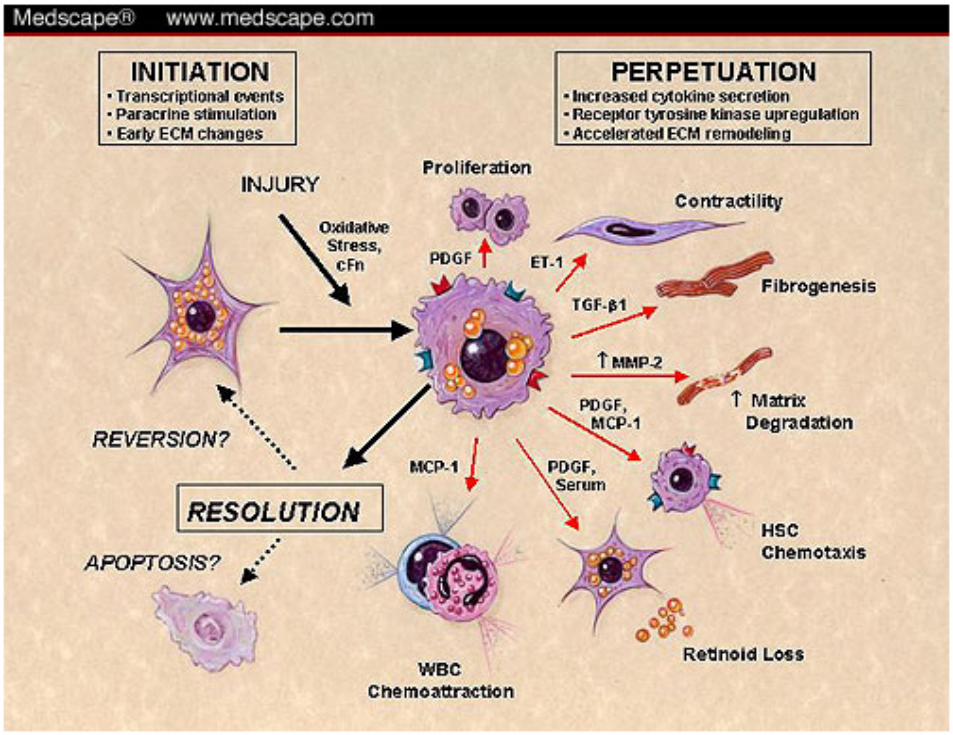

Figure 2. Phenotypic features of hepatic stellate cell activation during liver injury and resolution.

Following liver injury, hepatic stellate cells undergo "activation" which connotes a transition from quiescent vitamin A-rich cells into proliferative, fibrogenic, and contractile myofibroblasts. The major phenotypic changes after activation include proliferation, contractility, fibrogenesis, matrix degradation, chemotaxis, retinoid loss, and WBC chemoattraction. Key mediators underlying these effects are shown. The fate of activated stellate cells during resolution of liver injury is uncertain, but may include reversion to a quiescent phenotype and/or selective clearance by apoptosis.

4) Biliary Disease, Cholelithiasis, Cholecystitis

There is a reported increased incidence of cholelithiasis in diabetes mellitus, but obesity and hyperlipidemia may again be confounding variables. Several articles have reported a two- to threefold increased incidence of gallstones in diabetic patients, whereas others have failed to demonstrate a significant association (53-57). Gallbladder emptying abnormalities found in diabetic patients may predispose patients to cholelithiasis (58). Secretion of lithogenic bile by the liver in patients with type 2 diabetes probably predisposes them to forming gallstones, but this is

likely a result of concomitant obesity rather than a result of the diabetes itself (59). Increased biliary cholesterol saturation has not been demonstrated in insulin-dependent diabetic patients.

There is no indication in the literature that the natural history of gallstones is different in diabetic and nondiabetic individuals. The relative risk of mortality following acute cholecystitis is not significantly greater in diabetic patients than in the general population, and neither is the risk for serious complications. For that reason, prophylactic cholecystectomy cannot routinely be recommended for asymptomatic gallstones in patients with diabetes (60). Any increase in mortality may be attributed to underlying renal or vascular disease. Patients with diabetes have comparable survival outcomes from laparoscopic or open cholecystectomy (61).

Diabetes and Abnormalities of Glucose Homeostasis Occurring as a Complication of Liver Disease

1) Viral Hepatitis

There is no evidence in the literature that viral hepatitis has a worse prognosis in patients with diabetes. There is an increased prevalence of viral hepatitis in diabetes possibly due to an increased exposure to needles for the injection of insulin or for blood testing. Possible contamination of the platform in spring-loaded lancet devices may increase the risk of acquiring hepatitis B or C from these instruments. In 1996, hepatitis B outbreaks were noted in an Ohio nursing home and a New York hospital. Transmission was thought to be related to the use of spring-loaded devices for fingerstick glucose testing (62, 63).

Diabetes is far more prevalent in patients with hepatitis C than in patients with other forms of viral hepatitis. In a study by Grimbert and associates, 152 patients with hepatitis C and the same number with either hepatitis B or alcohol-induced liver disease were compared over the same period. Twenty-four percent of the patients with hepatitis C had diabetes compared with only 9% of the controls. The authors suggested a causative role of hepatitis C in the pathogenesis of diabetes (64).

Fraser and associates also found an association between chronic hepatitis C and the presence of impaired glucose control and reported that the prevalence of diabetes was much higher in hepatitis C than in the general population (65). One hundred adults with cirrhosis were evaluated in a retrospective study. Of the 34 patients with hepatitis C, 50% had diabetes mellitus, as opposed to 9% of the 66 patients with cirrhosis unrelated to hepatitis C. The association has been described also by others and was thought to be statistically significant (66-68).

Simo and associates also suggested that the hepatitis C virus may have a direct causative role in the development of diabetes. Most of their diabetic patients with hepatitis C had abnormal liver tests (69).

The association of diabetes with hepatitis C has also been investigated in post transplantation patients, and there is a reported higher incidence of diabetes in liver transplant

recipients with hepatitis C. This increased incidence appears to be significant, and the presence of the virus appears to be an independent risk factor (70).

Interferon therapy used to treat hepatitis B and C may induce hyperglycemia, result in the development of type 2 diabetes, and necessitate increased insulin requirements in patients with type 1 diabetes (71-74). Interferon therapy has resulted in the development of type 1 diabetes likely through the development of insulin autoantibodies (75-77). Fattovich and associates retrospectively studied 11,241 patients with chronic viral hepatitis who had undergone interferon therapy. However, only 10 patients developed de novo diabetes mellitus (78). Interferon therapy also reportedly led to severe hypertriglyceridemia in a diabetic patient (79).

The hepatitis B vaccine effectively induces protective antibodies in most patients with diabetes (80, 81). One study in children with type 1 diabetes concluded that children may not respond as well to the vaccination. This suggested that children should perhaps be vaccinated with four injections instead of three (82).

2) Cirrhosis

Individuals with cirrhosis have elevated insulin levels, perhaps indicating insulin resistance or reduced degradation of insulin by the cirrhotic liver. In the absence of peripheral insulin resistance, it is likely that patients with cirrhosis would become hypoglycemic.

The pathogenesis of the proposed insulin resistance is not known, although a receptor or postreceptor abnormality is postulated (83). Impaired insulin secretion from the pancreatic β-cells has been proposed as another cause for the hyperglycemia, (84) and glucose intolerance in patients with decompensate cirrhosis has been found to be associated with low insulin secretion (85). Potassium depletion, excess glucagon, growth hormone, cortisol, and increased fatty acid levels in blood, and reduced insulin receptors may account for the insulin resistance, but these are all unproved hypotheses.

Cirrhotic patients may develop fasting hypoglycemia by way of the "Insulin Autoimmune Syndrome" associated with the development of high levels of insulin autoantibodies even in the absence of hepatocellular carcinoma (86). Cirrhotic patients and patients with fulminant hepatic failure may have lower blood glucose concentrations than matched subjects, but significant hypoglycemia may be prevented by decreased utilization of glucose and an increased utilization of nonglucose fuels such as fat (87-89).

3) Hepatocellular Carcinoma

Hepatocellular carcinoma may be associated with the development of hypoglycemia. A proposed mechanism for the development of this hypoglycemia is the production of insulin-like growth factor-II (IGF-II) by hepatocellular carcinoma cells (HCC). Numerous case reports have discussed the development of this phenomenon.

IGF-II is a protein that functions as a partial insulin agonist (90). Diabetic patients who develop HCC may require progressively less insulin, not only due to the production of IGFs, but

also due to increased glucose utilization by insulin-sensitive tissue (91-94). A study by Adami and associates on a cohort of about 154,000 patients suggested that patients with diabetes are at increased risk for developing primary liver cancer (95). In a case-controlled study in Italy, it was again suggested that patients with diabetes may be at higher risk for hepatocellular carcinoma, although the reason why is unclear (96).

4) Fulminant Hepatic Failure

Fulminant hepatic failure may be complicated by hypoglycemia, and its development may portend a poor prognosis and increased mortality (97, 98). Such patients need to be closely observed, and most require glucose supplementation. Destruction of hepatocytes along with hyperinsulinism and inadequate storage of glucose in extrahepatic organs contributes to the hypoglycemia (99).

5) Liver Transplantation and Diabetes

The issue has been raised whether the presence of diabetes before or after liver transplantation influences the outcome. Carson and Hunt reported a 4–20% incidence of posttransplant diabetes following liver transplantation (100).

Trail and associates retrospectively investigated 497 patients who had received orthotropic liver transplants. Twenty-six patients (5.2%) had clinical evidence of diabetes 1 month after transplant. This did not influence graft survival, liver synthetic function, or number of rejection episodes during the first year. The investigators concluded that the presence of posttransplant diabetes did not significantly affect patient outcome in the first year (101).

Navasa and associates evaluated 102 patients who survived longer than 1 year after orthotopic liver transplantation. Fourteen had diabetes before transplantation, and all but one were alive 3 years later. Their reported incidence of posttransplant diabetes was 27% at 1 year, 9% at 2 years, and 7% at 3 years. Patients with posttransplant diabetes had a significantly higher mortality in the second postoperative year than did patients without this complication. This may be related to an increased use of immunosuppressive agents in those patients with rejection and thus a greater predisposition to diabetes (102).

Fk506, tacrolimus (Prograf), a potent immunosuppressive agent used in liver transplantation to prevent allograft rejection, may cause diabetes mellitus. Stopping the drug may result in restoration of normal glucose tolerance (103). Liver transplantation may be performed in patients with type 1 diabetes without any increased risk for graft or patient survival regardless of the underlying liver disease indication. Interestingly, in patients with renal transplants, both diabetes and hepatitis B were associated with less favorable outcomes (104).

Liver Disease Coincident With Diabetes and Abnormalities of Glucose Homeostasis

1) Hemochromatosis

Hemochromatosis is an autosomal recessive inherited condition characterized by an abnormally high absorption of iron from the small intestine and excessive accumulation of iron

in the liver and other tissues. Most patients (>80%) with the hemochromatosis (HFE) gene have one of the two described gene mutations, namely, the Cys282Tyr mutation, situated on the short arm of chromosome six. Patients with untreated hemochromatosis develop progressive liver disease, cirrhosis, and diabetes and are at high risk for developing hepatocellular carcinoma(105).

The term "bronze diabetes," coined by Hanot and Schachmann in 1886, refers to the association of diabetes with Hemochromatosis. About 75% of patients with hemochromatosis and established cirrhosis have diabetes. Patients with hemochromatosis and diabetes have a significantly reduced survival compared to hemochromatosis patients without diabetes (106).

Hemochromatosis is the most common single gene-inherited metabolic disease amongst Caucasians worldwide. The heterozygote frequency is about 10%; one in 250 people are homozygotes. Patients with hemochromatosis and diabetes have both impaired insulin secretion and increased insulin resistance (107). The likelihood of diabetes in patients with hemochromatosis increases as the liver iron concentration increases (108). Whether all diabetic patients should be screened for hemochromatosis has been considered. Turnbull and associates evaluated 727 patients in a diabetic clinic. Of those, 7.4% had elevated iron indices on initial screening, and in 3% these indices remained elevated on fasting blood specimens. However, only one had homozygous hereditary hemochromatosis, leading to their conclusion that routine screening for hemochromatosis in diabetic patients is probably not cost-effective(109). In contrast, patients with diabetes who have a family history of liver disease should probably be screened for hemochromatosis.

Excessive iron accumulation in conditions other than hemochromatosis, such as dyserythropoietic disorders, may also be associated with diabetes. The pancreatic β-cell may recover to varying degrees when the excess iron is removed in conditions associated with iron overload (110-111). but rarely will phlebotomy therapy restore normal glucoe tolerance.

2) Glycogen Storage Disease

Absence of glucose-6-phosphatase or other enzymes necessary for glycogen degradation, as occurs in a variety of glycogen storage diseases, would prevent the use of stored glycogen to maintain the blood glucose concentration in the fasting state. An infant so affected may require carbohydrate feedings every 2–3 hours to prevent possible brain damage. Glycogen content in the livers of most of these affected patients is excessive. The most common form is type 1 glycogenesis, characterized by a deficiency of the enzyme glucose-6-phosphatase. It is inherited in an autosomal recessive fashion (112).

3) Autoimmune Biliary Disease

Type 1 diabetes may be one of the manifestations of the autoimmune polyglandular syndrome. Primary biliary cirrhosis (PBC) has been reported in a patient with this syndrome, raising the possibility that PBC may be an associated autoimmune manifestation of this condition (113). Primary sclerosing cholangitis (PSC), which involves to varying degrees the intrahepatic

and extra hepatic biliary tree and which may progress to cirrhosis, can also involve the pancreatic duct and result in chronic inflammatory pancreatic changes. The pancreatic changes may be severe enough to cause functional changes and may result in glucose intolerance (114).

It is also postulated that ulcerative colitis, sclerosing cholangitis, and diabetes may occur in the same patient as part of a generalized genetically determined autoimmune disease influenced by HLA genotype. Glucose intolerance may be higher in patients with PSC than in patients with other liver disease (115-117).

EXCESS RISK OF PRIMARY LIVER CANCER IN PATIENTS WITH DIABETES MELLITUS

Chronic infection with hepatitis B virus, alcohol consumption, and cirrhosis of the liver are recognized risk factors for primary liver cancer. A few, but not all, studies have suggested that diabetes mellitus also increases risk for this cancer.

Chronic infection with hepatitis B virus is a dominant cause of primary liver cancer in developing countries, but risk factors for this cancer in Western populations are poorly understood, although alcohol consumption and cirrhosis play some role (118). A few (two-six) but not all (one) case-control and cross-sectional studies of liver cancer have suggested an association with diabetes mellitus, although cohort studies (119, 120) have been inconclusive because of their limited size.

Chance is an unlikely explanation for our findings because of the high statistical significance of the results. Differential misclassification of outcome, with more complete ascertainment of liver cancer in diabetic patients, is also an unlikely explanation because liver cancer rarely escapes medical attention, difficulties in differential diagnosis should influence those with and without diabetes equally, the excess risk persisted after the exclusion of cases diagnosed first at autopsy, and notification to the Swedish Cancer Registry is close to 100% complete (121).

Several mechanisms may explain the association between diabetes and primary liver cancer. Increased cell proliferation is probably important in the development of at least some human cancers (122, 123) and may contribute to the excess risk for hepatocellular cancer in patients with chronic hepatitis B virus infection, alcoholic liver disease, and liver cirrhosis (124, 125). Patients with non-insulin-dependent diabetes mellitus are characterized by insulin resistance, compensatory hyperinsulinemia, and increased growth factor production (126, 127). Hence, liver cells are directly exposed via the portal circulation to high levels of insulin produced by the pancreas. Furthermore, the onset of clinical diabetes is preceded by years of chronic hyperinsulinemia, with an elevated proportion of proinsulin and split products of proinsulin, molecules with some homology to IGF-1 (128). Insulin or its precursors have been shown to interact with liver cells and to stimulate mitogenesis or carcinogenesis (129-131). The slightly higher risk among men than among women is paralleled by higher plasma insulin concentrations in men than in women (132, 133). In addition, diabetes has been associated with an increased

risk for chronic liver disease, including cirrhosis and fatty liver, particularly among obese patients (134, 135). Liver cancer occurs excessively in patients with cirrhosis that is associated with hepatitis B or C virus infection and with heavy consumption of alcohol.

COMPLICATIONS OF DIABETES THERAPY

Many therapeutic drugs target both fasting and postprandial hyperglycemia and other metabolic parameters involved in the diabetes-associated complications. These drugs are directed towards increasing insulin secretion, decreasing insulin resistance, and increasing insulin penetration into the cells. Antidiabetic drugs with reported cases of hepatotoxicity include sulfonylureas, alpha-glucosidase inhibitors, biguanides, and thiazolidinediones.

Class	Drug (Trade Name)
Sulfonylureas	**First-generation**
	Chlorpropamide (Diabinese)
	Tolazamide (Tolinase)
	Tolbutamide (Orinase)
	Second-generation
	Glimepiride (Amaryl)
	Glipizide (Glucotrol)
	Glyburide (Diabeta)
Alpha-Glucosidase Inhibitors	Acarbose (Precose)
Biguanides	Metformin (Fortamet)
Thiazolidinediones (TZDs)	Pioglitazone (Actos)
	Rosiglitazone (Avandia)
	Troglitazone (Rezulin)

Table 1 Antidiabetic Agent with Reported Hepatotoxicity.

1) SULFONYLUREAS

Sulfonylureas have been used as first-line oral ant hyperglycemic agents for type 2 diabetes since 1954. First-generation sulfonylureas include tolbutamide (Orinase), tolazamide (Tolinase), and chlorpropamide (Diabinese). Chlorpropamide and tolbutamide are well recognized as causes of hepatotoxicity. However, there have been only three reported cases of hepatic injury caused by a third oral hypoglycemic agent, tolazamide (136). With the arrival of second-generation sulfonylureas, first-generation sulfonylureas are rarely used. Second-generation sulfonylureas include glipizide (Glucotrol), glyburide (DiaBeta, Micronase, Glynase), and glimepiride (Amaryl). Drug-induced hepatotoxicity has been reported infrequently with second-generation sulfonylureas. For glimepiride, a second-generation sulfonylurea, there have

been no reports of hepatotoxicity in English literature; however, hepatotoxicity has been reported in French literature (137, 138).

The sulfonylurea glyburide (Micronase, Glynase, and Diabeta) is excreted in bile and urine in a 50/50 ratio. The sulfonylurea glipizide (Glucotrol, Glucotrol XL) is metabolized mainly by the liver, and, in theory, hepatic disease may result in increased blood levels. There is a rare association between the use of oral hypoglycemics and hepatic injury, but sulfonylureas can cause chronic hepatitis with necroinflammatory changes (139). Granulomatous changes can also be seen. They are described as having a well-circumscribed cellular infiltrate comprised of acidophilic histiocytes and eosinophils surrounding necrotic hepatocytes. The mechanism of liver injury is not known.

Chlorpropamide appears to be the most hepatotoxic of these drugs, with cholestatic hepatitis occurring in 0.5% of people on the drug. Jaundice develops over 2–5 weeks and resolves in virtually all patients when the drug is stopped. Hepatic disease is very rare with tolbutamide (Orinase and generics), and tolazamide (Tolinase and generics). Although very uncommon, acetohexamide and glyburide can cause acute hepatocellular necrosis, and fatalities have been reported. At least two cases of granulomatous hepatitis thought secondary to glyburide have been reported in the literature (140).

2) ALPHA-GLUCOSIDASE INHIBITORS

The glucosidase inhibitors are useful adjunctive therapies for type 2 diabetes. The prototype of this class is acarbose (Precose). Because acarbose is minimally absorbed in unchanged form after oral administration, the drug is widely believed to be safe, with only flatulence as a commonly reported complaint. However, cases of severe hepatotoxicity have been reported (141-143). Although acarbose-induced hepatotoxicity appears to be uncommon, diabetic patients receiving long-term acarbose therapy should be closely monitored for this adverse effect.

3) BIGUANIDES

Metformin hydrochloride is widely used for the treatment of type 2 diabetes. A serious but rare side effect, lactic acidosis, is caused because of its interference with mitochondrial oxidative processes (144). Metformin (Fortamet, Glucophage, Riomet) hepatotoxicity has rarely been reported, with two cases of acute hepatitis and one of bland cholestasis (145-146). A well-documented case of acute hepatitis caused by an idiosyncratic adverse reaction to metformin or to one of its metabolites, has also been reported.

4) THIAZOLIDINEDIONES

Thiazolidinediones (TZDs, also known as *glitazones*) are insulin sensitizers now widely used for the treatment of type 2 diabetes. Three TZDs have been used in clinical practice: troglitazone, pioglitazone, and rosiglitazone.

Troglitazone: Troglitazone (Rezulin), a peroxisome proliferators–activated receptor gamma agonist that enhances insulin sensitivity, was approved for the treatment of type 2 diabetes in 1997. It was an effective antidiabetic drug with a fundamentally new mechanism of action. However, within a year after its widespread use, individual cases of liver injury and failure were reported (147-150). The mounting evidence for the idiosyncratic hepatotoxicity of troglitazone in the following years led to its withdrawal from the market in 2000. Since then, a considerable effort has been made to elucidate the mechanism of troglitazone-induced hepatotoxicity. A number of hypotheses were brought forward to explain troglitazone-induced cell injury, including the formation and accumulation of toxic metabolites, mitochondrial dysfunction and oxidant stress, inhibition of the bile salt transporter and bile acid toxicity, and the induction of apoptosis (148).

Pioglitazone and Rosiglitazone: After the withdrawal of troglitazone due to hepatotoxicity, only pioglitazone (Actos) and rosiglitazone (Avandia) can be used for the treatment of patients with type 2 diabetes. Fortunately, these two newer drugs in the TZD class have a much larger margin of safety for liver toxicity. Very rare reports of liver toxicity, usually milder and reversible, have been seen with these drugs. Very few case reports have implicated it as a cause of hepatocellular injury and granulomatous hepatitis (151-153). Severe cholestatic hepatitis caused by rosiglitazone (8 mg/day) was reported in a 56-year-old female patient who had a history of receiving troglitazone treatment; it is indicated that rosiglitazone is not always a safe alternative in patients who had liver injury due to troglitazone (154). Pioglitazone-induced hepatocellular-cholestatic liver injury in a 49-year-old patient with diabetes who was on this drug for six months. Liver enzyme values returned to normal six weeks after the patient discontinued pioglitazone therapy (155).

In conclusion, while pharmacovigilance for hepatotoxicity is probably still warranted, the practitioner and patient can be fairly confident that these drugs are safe from a liver standpoint. Finally, recent work would suggest that these agents may prove useful to reduce hepatic fat in patients with nonalcoholic steatohepatitis and may possibly protect against adverse metabolic consequences and the ultimate development of cirrhosis in patients with fatty livers.

Pioglitazone and rosiglitazone are used either as monotherapy or in combination with metformin, sulfonylureas, or glinides. The combination of TZDs with insulin is also appealing, as it allows improvement of glycemic control while decreasing the daily insulin requirement. Insulin dosage has to be adjusted regularly to avoid hypoglycemic episodes. Recently, a prospective, open-labeled, nonrandomized study was conducted to assess safety and efficacy of rosiglitazone and insulin treatment in combination with poorly controlled insulin-treated patients with type 2 diabetes (156). It was concluded that the rosiglitazone plus insulin combination is safe and effective in this population. However, further studies are warranted.

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