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Complications of Diabetes





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Diabetes and the Liver

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ABSTRACT

Liver disease is increasingly being recognized as a frequent accompaniment of diabetes. Nonalcoholic fatty liver disease is exceedingly common among individuals with type 2 diabetes mellitus (T2DM), and may progress to steatohepatitis or even cirrhosis. Diabetes has also been recognized as a risk factor for both hepatitis B and C. There is also an increased risk for diabetes among patients infected with hepatitis C. T2DM also confers an increased risk of hepatocellular carcinoma. Other hepatic manifestations of diabetes include diabetic hepatosclerosis and glycemic hepatopathy. Diabetes mellitus is also a common complication following liver transplant. In patients with advanced liver disease, selection of antidiabetic drugs should be done with caution on account of the increased risk of hypoglycemia.

INTRODUCTION

Diabetes affects 8% of the United States population (an estimated 25.8 million people).[1,2] As the seventh leading cause of death, accounting for approximately 17.2% of deaths in persons aged >25 years, diabetes is a major health problem in this country.[1-3] The disease affects multiple organ systems, including the cardiovascular, renal, and nervous systems; however, it is often unrealized that cirrhosis accounts for 4–12% of all diabetes related deaths.[1,4,5] Hepatic dysfunction in patients with diabetes ranges from fatty liver disease to cirrhosis and hepatocellular carcinoma. Diabetes is also associated with an increased risk of hepatitis B and C, as well

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as complications during pregnancy. This article will focus on the variety of liver diseases associated with both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) and includes a brief discussion on management of diabetic patients with liver disease.

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) is the most common liver problem in the Western world.[6] An estimated 20–33% of the adult population worldwide is affected, including 75% of obese adults.[6-8] The prevalence increases with age, and most patients with NAFLD have features of the metabolic syndrome.[9] NAFLD is present in over two-thirds of patients with unexplained abnormal liver tests.[6,10]

Nonalcoholic fatty liver disease is related to insulin resistance, not poor blood glucose control. Insulin resistance and hyperinsulinemia lead to fat accumulation in the liver. When hepatocytes take up free fatty acids, there is an increase in gene transcription of proinflammatory cytokines.[6,11,12] Cytokines activate inflammatory cells (such as the Kupffer cells in the liver) and a promote necrosis and apoptosis of hepatocytes.[6] Cytokines may also increase hepatic insulin resistance, contributing to the cycle.[6] Hepatic stellate cells are activated by hepatocyte injury and deposit scar tissue in the areas of cell damage. Hyperinsulinemia and hyperglycemia stimulate fibrogenic and connective tissue growth factor production by hepatic stellate cells.[7,13]

Nonalcoholic fatty liver disease progresses from simple steatosis, which generally carries a benign prognosis, to cirrhosis. Typically, 1–2% of patients with NAFLD will develop cirrhosis over 15–20 years.[6] In patients who develop cirrhosis, 25% will eventually develop hepatocellular carcinoma and 33% will die from their liver disease.[6] Predictors of progression to advanced liver disease include the following—age >45 years, BMI >30, diagnosis of T2DM (or elevated fasting blood glucose), and an AST/ALT ratio >1.0.[6,14] Some authors note that it is reasonable to perform a liver biopsy in patients with some or all of these risk factors to assess extent of disease.[6]

Patients with NAFLD have components of the metabolic syndrome, many of which are shared risk factors for cardiovascular disease (CVD).[15] In one study, 69.5% of patients with T2DM had NAFLD diagnosed by ultrasound. The patients with NAFLD had higher age and sex-adjusted prevalence of coronary (26.6% vs. 18.3%, p <0.001), cerebrovascular (20.0% vs. 13.3%, p <0.001) and peripheral vascular disease (15.4% vs. 10.0%, p <0.001) than patients without NAFLD.[9,15] These results were independent of known CVD risk factors, glycemic control, medications, and metabolic syndrome. Patients with NAFLD also have increased carotid intimal medial thickness and increased prevalence of atherosclerotic carotid plaques compared to patients without NAFLD.[15-18] The histologic severity of

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nonalcoholic steatohepatitis (NASH) correlates with the extent of carotid artery wall thickness.[15,19]

Treatment of NAFLD is mainly directed at controlling and reducing features of the metabolic syndrome, including insulin resistance, hypertension, hyperlipidemia and obesity.[6] In a randomized, open label trial of nondiabetic patients with NAFLD, metformin was compared to both vitamin E and a weight reducing diet. Metformin reduced aminotransferases levels and significantly decreased fibrosis ($p = 0.012$) and liver fat ($p = 0.0004$).[6,20] In contrast, randomized control trials investigating treatment of NASH with vitamin C, vitamin E and ursodeoxycolic acid all showed no improvement in histologic fibrosis score compared to placebo.[21,22] Statins should be prescribed based on current recommendations. There is no evidence that presence of NAFLD increases the risk of hepatotoxicity from statins.[6,23] Liver transplant is an option for patients with decompensated cirrhosis or hepatocellular carcinoma; however, 50% of patients will have recurrence of NASH and fibrosis in 4 years.[6] T2DM or insulin resistance before and after transplant have been cited as a risk factor for recurrence of NASH.[6]

Given the high prevalence of NAFLD in patients with diabetes (up to 50%), as well as the potential for detrimental progression of this disease, early clinician awareness and patient education are paramount.[1] NAFLD or NASH should be suspected in any patient with concurrent diabetes mellitus (DM) and abnormal liver function tests.[1] The patient should be educated on the importance of diet and weight loss early after diagnosis.

HEPATIC DYSFUNCTION IN PREGNANT PATIENTS WITH DIABETES

Patients with diabetes who are pregnant deserve special mention regarding liver disease. As mentioned in the previous section discussing NAFLD, insulin resistance promotes fatty liver disease. Accordingly, there is a greater risk of NAFLD in gestational diabetes mellitus (GDM). One study found that the prevalence of NAFLD was greater in patients with previous GDM when compared to those without history of GDM (38% vs. 17%, $p = 0.001$).[24]

In addition to a greater risk for NAFLD, women with diabetes during pregnancy have a higher risk of hyperemesis gravidarum (HG), a syndrome of vomiting that results in ketonuria and at least a 5% weight loss from prepregnancy weight.[25-27] HG typically occurs between the 4th and 10th week of gestation, and pre-existing diabetes has been cited as a risk factor.[25,26] Liver dysfunction occurs in half of patients, with up to a 20-fold increase in aminotransferase levels.[25,27] Alanine aminotransferase (ALT) is typically greater than aspartate aminotransferase (AST).[28] HG alone is not a risk factor for poor outcomes, however preterm delivery and low fetal birth weight can result from significant maternal weight

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loss.[29,30] Treatment is often supportive, including antiemetics and intravenous fluids for cases of severe dehydration and intolerance to oral intake. Frequent, high carbohydrate meals have been cited as a potentially effective intervention as well.[31]

HEPATITIS B VIRUS AND DIABETES

Another association which warrants discussion is that of diabetes and the viral hepatidites. Diabetes is a well-established risk factor for both hepatitis B and C viruses. Reilly et al. discovered that after controlling for age, gender and race/ethnicity, adults with diabetes and no other Hepatitis B virus (HBV) risk behavior (i.e., injection drug use, male sex with a male or sex with multiple partners) aged 23 through 59 years with diabetes had 2.1 (95% CI = 1.6–2.8) times the odds of developing acute hepatitis B as those without diabetes.[32] When considering those persons aged 60 years or older, the odds were 1.5 (CI = 0.9–2.5) times as likely. This is corroborated by data from the National Health and Nutrition Examination Survey (NHANES) from the years 1999–2010, which indicated a 60% ($p < 0.001$) higher seroprevalence of antibody to hepatitis B core antigen among persons aged 18 years or older diagnosed with diabetes compared with those without diabetes.[33] Furthermore, Reilly also reported in a separate publication that the annual incidence of cases of acute HBV infection among adults with diabetes was 1.8 per 100,000 (CI = 1.5–2.2).[34]

The connection between HBV infection and those persons with diabetes has prompted research into the need for and cost-effectiveness of vaccinating diabetic patients against hepatitis B. Based on this research, the Advisory Committee on Immunization Practices (ACIP) recommends that all previously unvaccinated adults aged 19 through 59 years with diabetes (T1DM or T2DM) be vaccinated against hepatitis B as soon as possible after a diagnosis of diabetes is made (recommendation category A).[33] For adults aged 60 years or older, the data are less robust; therefore, the ACIP recommend that these patients can be vaccinated at the discretion of the treating clinician (recommendation category B).[33] When The Hepatitis Vaccines Work Group examined the cost-effectiveness of this strategy for vaccinating adults with diabetes, they found that by targeting adults aged 20 through 59 years, the intervention would prevent 4,271 HBV infections, 467 hospitalizations, 256 chronic cases, 33 cases of hepatocellular carcinoma, 13 liver transplants and 130 deaths. Vaccinating adults older than 60 years was not found to be cost-effective, as cost-effectiveness ratios rose with age at vaccination.[35]

HEPATITIS C VIRUS AND DIABETES

Similar to the association with hepatitis B infection, carrying a diagnosis of diabetes also confers a higher risk of acquiring hepatitis C. Allison et al. were one

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of the first groups to publish data on this link. They found that among patients with hepatitis C virus (HCV)-related cirrhosis, 50% had diabetes, in contrast to 9% of patients with cirrhosis unrelated to HCV. The group calculated an odds ratio for HCV by DM status of 10.0 (95% CI 3.4–29.3).[36] The relationship has since been corroborated by several other studies, including work done by Lecube and colleagues which identified a 3-fold increase in the prevalence of glucose abnormalities in HCV-positive patients with chronic hepatitis as opposed to HCV negative subjects (32% vs. 12%).[37] Similarly, in a systematic review and meta-analysis, White et al. found a significant risk for diabetes in HCV-infected cases in comparison to noninfected controls in both retrospective (adjusted OR = 1.68, 95% CI 1.15–2.2) and prospective studies (adjusted HR = 1.67, 95% CI 1.28–2.06).[38]

The pathophysiology behind this connection remains unclear, but appears related to insulin resistance both from fibrosis and/or cirrhosis which develops from chronic HCV, possibly enhanced from coexistent hepatic steatosis, as well as a direct cytopathic effect of the virus on insulin sensitivity.[39-41] Host factors such as weight gain, older age, family history, male gender and ethnicity may play a role,[39] though it has also been shown that HCV induces insulin resistance independently of body mass index or fibrosis stage.[40] This appears to be caused by overproduction of tumor necrosis factor (TNF), a cytokine which phosphorylates serine residues of insulin-receptor substrates 1 and 2 (IRS-1 and -2) and sets into motion a cascade of events which may ultimately block the transactivation of glucose transporter type 4 (GLUT-4) receptors.[40,41] This final step prevents the uptake of glucose by cells. Also, overproduction of TNF in patients with chronic hepatitis C has frequently been seen, and is correlated with higher fibrosis progression and impaired antiviral response to interferon alpha treatment.[40]

HEPATOCELLULAR CARCINOMA AND DIABETES MELLITUS

With regard to progression to frank hepatocellular carcinoma, T2DM has been shown to confer an increased risk for this as well.[42-44] Davila et al. conducted the first case-control study in the United States to evaluate this association. They showed that diabetes was linked to a 3-fold increase in the risk of hepatocellular carcinoma (HCC), even after adjusting for other HCC risk factors such as HBV, HCV, alcoholic liver disease and hemochromatosis.[43] Another Cohort study performed out of the Department of Veterans Affairs confirmed these findings, noting that the risk of HCC was doubled among men with diabetes, and this increase in risk was independent of alcoholic liver disease or viral hepatitis.[44] The above findings were supported in a meta-analysis which concluded that the association may be even stronger, up to a 4-fold increase in HCC risk when those persons with a prior history of diabetes are compared with nondiabetic individuals.[45]

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Similar to the mechanisms which promote the progression of fibrosis in patients with HCV; insulin resistance, hyperinsulinemia, increased TNF signaling pathways and alterations in cellular lipid metabolism have all been implicated in the emergence of HCC in diabetic patients.[39,46] HCC development related to hyperinsulinemia can be mediated through inflammation, cellular proliferation, inhibition of apoptosis and mutation of tumor suppressor genes.[45] Furthermore, insulin resistance is associated with lipid peroxidation, increased oxidative stress, and the generation of reactive oxygen species, which may also contribute to DNA mutation.[39,45,47]

The risk of developing carcinoma appears to increase as the duration of diabetes increases, as well as with specific diabetes medications. Hassan et al. found that use of sulfonylurea drugs was associated with a 7-fold increase in HCC risk compared to nonusers. Alternatively, medications such as biguanides and thiazolidinediones (TZDs) were associated with up to a 70% risk reduction of HCC when compared to those using insulin or sulfonylureas.[45] The risk reduction properties of metformin were highlighted in a comprehensive systematic review, which noted in observational studies that the risk of liver cancer was reduced in those taking metformin (OR 0.34; CI 0.19–0.60, p = 0.0003).[48] In the same analysis, metformin use was also associated with a significant reduction in the risk of colorectal, pancreatic, stomach and esophagus cancers.

DIABETIC MICROANGIOPATHY

Microangiopathy is the pattern of injury responsible for diabetic nephropathy, retinopathy and peripheral vascular disease.[49,50] It is a result of hyperglycemia which leads to increased glycation of proteins. Advanced glycation end products harm endothelial cells, resulting in thickening of the capillary wall and basement membrane. This mechanism is different from the inflammation and resultant hepatocyte injury, i.e. characteristic of NAFLD and nonalcoholic steatohepatitis.[51]

Diabetic hepatosclerosis (DHS) is the term used to describe microangiopathy in the liver. DHS is an uncommon pattern of liver disease first described in 2006 in patients with T1DM and insulin-dependent T2DM.[51] The term describes the histologic finding of hepatic perisinusoidal fibrosis not associated with NAFLD or steatohepatitis.[25] DHS is characterized by dense perisinusoidal fibrosis, basement membrane formation and hepatic hyaline arteriolosclerosis.[49,51] The formation of basement membrane is pathologic since it is normally absent in hepatic sinusoids. Chronic injury promotes deposition of fibronectin, collagen and laminin, all of which are components of basement membrane secreted by hepatic stellate cells and endothelial cells.[52,53] Hepatic stellate cells are activated by hepatocyte injury, however in DHS, there is no evidence of hepatocyte injury, such that basement membrane deposition in the sinusoids is thought to be secondary to endothelial cell damage.[49] Unlike cirrhosis and the NAFLD/NASH spectrum, there is

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no development of nodules in DHS since no hepatocyte injury or hepatocyte hyperplasia occurs.[51]

Patients with DHS often have severe microvascular disease in other organs, including nephropathy, retinopathy and neuropathy.[49,51] In an autopsy review of 254 patients with DM, 12% had histological evidence of DHS. The presence of renal microangiopathy was significantly higher in patients with DHS (89% vs. 47%) compared to age, gender and race matched diabetic patients with similar disease duration.[54] Despite the relationship to other organ damage, the clinical significance of DHS is unknown.[51,54] DHS has been described as a clinically "dormant" disease since there is no evidence of hepatic architectural changes; however, the long-term effects of this entity are still unknown.[51,54] For example, deposition of collagen in the perisinusoidal space may be the cause of elevated alkaline phosphatase in patients with DHS, which has been reported to be as high as 83%. In contrast, aminotransferase levels are more commonly elevated in patients with NAFLD.[51] The clinical implications of this sinusoidal "congestion" are still unknown, and DHS is certainly a rich area of research that deserves further investigation.

GLYCOGENIC HEPATOPATHY

Glycogenic hepatopathy (GH) is the hepatic response to ketosis and poorly controlled T1DM. It is a distinct entity from previously mentioned NAFLD and NASH, both of which are the hepatic response to T2DM and obesity.[55] GH is characterized by glycogen deposition in hepatocytes and is precipitated by poor glucose control. Fluctuations in blood glucose and insulin levels directly impair the balance of hepatic glycogenesis and glycogenolysis.[55-57] GH is precipitated when hyperglycemia is treated with insulin.[1] Hepatocytes turn the excess glucose into stored glycogen. Though not proven, it has been hypothesized that the hepatic glycogen phosphorylase enzyme may be inhibited during periods of poor glycemic control.[58]

Histologically, GH has characteristics that overlap with inherited glycogen storage diseases.[5] The biopsy findings of GH are drastically different from steatohepatitis. Unlikely steatosis, glycogenosis does not promote inflammation, such that inflammation is minimal in GH and fibrosis is absent.[56,59] Biopsy specimens in GH demonstrate glycogen deposition in hepatocyte cytoplasm and nuclei. The cells are subsequently pale staining and swollen on H&E (hemotoxylin and eosin) stain.[5] Hepatic architecture is well preserved.[59]

Patients with GH typically present with abdominal pain, early satiety, nausea and vomiting.[2,5] Hepatomegaly is usually present on examination.[59] Rarely, patients will have ascites, which is thought to be secondary to sinusoidal compression from glycogen-laden hepatocytes.[56,59] Laboratory values show elevated blood glucose levels, ketoacidosis and elevated glycosylated hemoglobin (all indicative of overall

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poor glycemic control). Hepatic synthetic function usually remains normal. Alkaline phosphatase is typically mildly elevated. Varying elevations of serum liver function tests (LFTs) have been reported in GH, and transaminitis likely represents leakage from cell injury rather than hepatocyte necrosis.[59] The extent of LFT elevation does not correlate with the severity of glycogen deposition.

Glycogenic hepatopathy in T1DM is under recognized by clinicians. It is much less common than NAFLD and cannot be clinically distinguished from NASH or NAFLD.[59,60] Ultrasound cannot differentiate steatosis in NAFLD from glycogenosis.[56,59] The distinction requires liver biopsy, and there is currently no consensus on need for biopsy in all diabetic patients with elevated LFTs and hepatomegaly.[57] Recognizing GH is important since the condition is reversible with improved glycemic control. This reversibility is in contrast to conditions known to lead to hepatic fibrosis (such as NAFLD). It takes approximately 2–14 weeks of good glycemic control to see reversal of GH, including decreased transaminase levels, resolution of hepatomegaly and normal ultrasound findings.[57,59] GH represents yet another important reason to strive for glycemic control in patients with T1DM. With greater clinician awareness of this rare condition, hepatic injury can be prevented and reversed.

DIABETES IN LIVER TRANSPLANT RECIPIENTS

As discussed previously, end-stage liver disease is frequently associated with diabetes. Impaired glucose metabolism is also a common complication after treatment with liver transplantation, with a mean reported incidence varying between 7% and 31%. This is largely due to immunosuppressive medications required to prevent organ rejection, though family history of diabetes, age >45 years, glucose intolerance prior to transplant, and central obesity may factor in as well.[61] Whether patients who have pre-existing DM or who develop DM post-transplant have worse outcomes than their counterparts without DM has been a topic of interest. One group compared transplant recipients who developed post-transplant diabetes mellitus (PTDM) with age and sex-matched controls that did not. They found that the duration and cost of hospitalization, re-transplant rate, graft survival and patient survival at 1, 3 and 5 years were similar among both groups.[62] However, they also found that the PTDM patients had higher rates of acute rejection, major and minor infections, and cardiac, neurologic, and neuropsychiatric complications than those without DM. This is corroborated by several other studies which noted PTDM to be linked to higher incidence of acute rejection and mortality rate,[61] as well as graft loss due to chronic rejection and late-onset hepatic artery thrombosis.[63] Furthermore, Johnston et al. reported that CVD is one of the most common causes of death in liver recipients (two-and-a-half times the cardiovascular mortality and three times the ischemic events of a matched population); for which diabetes is a well-established risk factor.[64]

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ROLE OF LIVER DISEASE IN SELECTION OF ANTIDIABETIC PHARMACOTHERAPY IN TYPE 2 DIABETES MELLITUS

Treatment of patients with T2DM and liver dysfunction is challenging as many oral hypoglycemic agents are contraindicated due to the increased risk for hypoglycemia. In this instance, insulin therapy may be the safest and most effective route, with careful attention to dosage. Glinides must be used with caution in liver dysfunction as they are mostly cleared through the liver, and sulfonylureas must be closely monitored as well, and are considered contraindicated in advanced liver failure by expert opinion.[65] Metformin rarely causes hepatotoxic side effects, but the risk for lactic acidosis is increased in those with liver dysfunction, especially if there is an acute deterioration.[65-67] Data regarding the use of GLP-1 agonists and DPP-4 inhibitors in patients with liver disease are currently lacking. It appears patients with moderate liver dysfunction can tolerate sitagliptin or exenatide.[67-69] Vildagliptin is contraindicated in hepatic dysfunction as it has been shown to cause transaminase elevation in high doses.[67] The TZD, troglitazone, was removed from the market in the United Kingdom and the United States due to a rare but severe hepatic injury. Hepatotoxicity does not appear to occur with rosiglitazone and pioglitazone; in fact, treatment with TZDs has been shown to cause a significant decline in the serum AST and ALT levels in NASH patients.[70] Similarly, GLP-1 agonists and SGLT-2 inhibitors have shown early efficacy in NASH, and also have beneficial cardiovascular and renal effects.[71]

CONCLUSION

Diabetes is a disease with wide ranging effects and systemic consequences. The liver is subject to damage, injury and concomitant disease in patients with diabetes. Special attention must be given to patients with diabetes and liver disease, particularly in regards to pregnancy. There are many therapeutic options for management of patients with diabetes, but in patients with liver damage, safety of medications must be considered, and options may be more limited.

Editor's Comment

Liver disease is one of the "nonconventional" complications of diabetes. The link between T2DM and nonalcoholic liver disease has received wide attention. The authors discuss the pathophysiology, diagnosis and management of NAFLD as well as other less common hepatic manifestations of diabetes, which may have a bearing of the management and prognosis of diabetes.

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