Managing Diabetes in Patients with Chronic Liver Disease

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Managing Diabetes in Patients with Chronic Liver Disease

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Abstract: Diabetes and chronic liver disease (CLD) are common long-term conditions in the developed and developing world. The 2 conditions often coexist, and there is evidence to suggest that diabetes can have a significant adverse effect on patients with CLD, leading to increased complications and premature mortality. While diabetes, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis (NASH) appear to have common origins related to obesity and insulin resistance, diabetes is also common among patients with alcoholic and viral CLD. In patients with NASH, improvement in metabolic indices appears to reduce the progression of CLD. It is not clear whether improving glycemic control in other forms of CLD leads to improved outcomes. Managing diabetes in patients with CLD can be challenging because many antihyperglycemic therapies are contraindicated or must be used with care. Metformin and pioglitazone may be useful in patients with NASH, but sulfonylureas and insulin must be used with caution, as hypoglycemia may be a problem. Insulin doses frequently need to be reduced in patients with CLD. Newer glycemic agents have not been widely used in patients with CLD, but bariatric surgery may lead to significant improvement in liver indices in patients with NASH. Management of patients with diabetes and CLD may be enhanced by using a multidisciplinary approach.

Keywords: diabetes; chronic liver disease; nonalcoholic steatohepatitis; cirrhosis; nonalcoholic fatty liver disease

Introduction

Diabetes is a prevalent long-term condition with a high societal and economic burden due to premature cardiovascular and microvascular morbidity and mortality. In the United Kingdom in 2010, > 2.7 million people had diabetes, and this number is predicted to increase to nearly 4 million people by 2025.⁴ Approximately 10% of health care expenditure in the United Kingdom is directly related to diabetes and its attendant complications, and approximately 15% of hospital inpatients have diabetes.⁵ Diagnosis of diabetes is associated with a life expectancy that is shortened by approximately 10 years.⁶ Diabetic complications are multisystem, placing an increasing burden on cardiovascular, renal, ophthalmological, podiatric, and vascular health care services. Approximately 90% of patients with diabetes have type 2 diabetes mellitus (T2DM).⁷

It is becoming increasingly recognized that diabetes is associated with chronic liver disease (CLD), particularly nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).⁸ Because CLD and diabetes are common conditions, they often coexist in the same patient, and may have a shared pathogenesis (Figure 1). This article examines the management of diabetes in patients with CLD.

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How Common is Diabetes in Patients with CLD?

Observational studies suggest an association between T2DM and CLD.\(^2\)\(^-\)\(^5\) A 10-year follow-up of the Veterans Affairs cohort, a large cohort of 173,643 patients with T2DM and 650,620 patients without T2DM, in whom CLD was excluded at the time of enrollment, showed a 2-fold increased risk of CLD in the patient cohort with T2DM compared with the patient cohort without T2DM, independent of alcohol intake, viral hepatitis, and demographic factors, although the presence of CLD was not verified biochemically or histologically.\(^2\) Approximately one-third of all patients with cirrhosis have T2DM.\(^1\) Much of this relationship may be explained by the common etiology of insulin resistance in patients with NASH,\(^4\) and T2DM is present in approximately 50% of patients diagnosed with NASH.\(^3\)\(^-\)\(^5\) Type 2 diabetes mellitus is, however, also more common in patients with other forms of CLD, such as hepatitis C virus (HCV)\(^3\)\(^,\)\(^6\) or hepatocellular carcinoma (HCC).\(^3\)\(^,\)\(^7\)

Viral Hepatitis

The US National Health and Nutrition Examination Survey suggests a 3-fold higher risk of diabetes in patients with chronic HCV.\(^6\)\(^,\)\(^8\) Other studies suggest an even greater risk. One study showed a 33% prevalence of diabetes in noncirrhotic patients with chronic HCV compared with a 5.6% prevalence in matched controls.\(^3\) This phenomenon may be due to chronic inflammation leading to insulin resistance,\(^10\) although studies measuring insulin resistance before and after viral clearance show that some, but not all, viral genotypes can increase insulin resistance, indicating that other, viral-specific factors must be involved.\(^11\) Additionally, the insulin resistance observed in these patients is an independent risk factor for development of steatosis and progression to fibrosis. In patients with HCV, progression to advanced fibrosis over 5 years occurs more frequently in patients with T2DM compared with patients without T2DM (13% vs 5%, respectively).\(^12\)\(^,\)\(^13\)

Alcohol

Alcoholic CLD is a significant risk factor for developing T2DM, and appears to be dose related, with the risk increasing to 2-fold in patients ingesting \(>270\) g of alcohol per week compared with those ingesting \(<120\) g per week.\(^14\) Acute alcohol ingestion produces a significant reduction in insulin-mediated glucose uptake.\(^15\) Alcohol has a high calorific content, and excess alcohol can lead to obesity and development of T2DM.
Hemochromatosis
Hereditary hemochromatosis is an autosomal dominant condition caused by a mutation of the HFE gene. It is characterized by iron accumulation in several organs, particularly in the liver and heart, but also the pancreas and other endocrine organs.16,17 Because infiltration of pancreatic islets is common, diabetes is observed in 50% to 85% of patients with symptomatic disease.16,17 Liver damage due to intrahepatic iron deposition is common in hemochromatosis; therefore, diabetes and liver damage often coexist in patients with this disorder. However, many patients with genetic hemochromatosis do not develop significant increases in iron storage.

HCC
Many studies suggest a higher risk of HCC in patients with T2DM compared with those without T2DM.7,18,19 This relationship may be related to the greater prevalence of NASH in patients with diabetes, but the presence of T2DM in patients with viral hepatitis also appears to increase the risk of HCC.7

Does the Diagnosis of Diabetes Influence Morbidity or Mortality Rates in Patients with CLD?
The effect of diabetes on the clinical outcome of CLD (ie, cirrhosis and HCC) has been evaluated in some studies.17,20–22 In cross-sectional retrospective studies in patients with cirrhosis of any etiology, diabetes is associated with an increased risk of complications, such as HCC and hepatic decompensation.17,20 A population-based study of > 7000 patients with T2DM from Verona, Italy showed the risk of death at 5 years from CLD to be 2.52 times greater than in the general population.21 Another study reports that the presence of diabetes is associated with more severe fibrosis in NASH.22

In patients with HCC, diabetes appears to increase morbidity and mortality rates.23,24 A study of HCC deaths in Edinburgh, Scotland showed a 2-fold increased risk of death from HCC in patients with diabetes compared with patients without diabetes.23 Similarly, in patients with hepatitis B or C infection or alcoholic CLD, the presence of diabetes increased the risk of HCC by 10-fold.24

Challenges in Management of Hyperglycemia in Patients with CLD
Effects of HCV on Diabetes Control
Type 2 diabetes mellitus is a common complication of HCV-related CLD. Clinical and experimental data suggest a direct role of HCV in the perturbation of glucose metabolism.26–28 There are good epidemiological data to suggest that patients with HCV have a greater risk for developing T2DM,26 and that HCV seems to increase the risk of incident T2DM in predisposed individuals.27 The association between HCV and T2DM is more evident in patients who are older, more overweight or obese, and in at-risk ethnic groups, such as African-Caribbeans or South Asians.28

The mechanism by which this increased risk of diabetes occurs is not clear, but may be related to increased insulin resistance in HCV-infected individuals, possibly due to a direct effect of the virus on insulin sensitivity.29 This effect may be associated with specific HCV sequences and/or subtypes, and shows some dose dependence, in that it may be correlated with HCV replication level.30 It has also been suggested that hyperproduction of proinflammatory cytokines in HCV infection leading to chronic inflammation may lead to glucose intolerance.31,32 Diabetes and insulin resistance are associated with a poorer response to antiviral therapy in patients with HCV;31 however, for patients with genotype 1 HCV, if a virological cure is attained, it appears to have beneficial effects on insulin sensitivity.32

Screening for diabetes can be performed using glycated hemoglobin (HbA1c) level as a diagnostic test for T2DM, with a threshold for detection of diabetes of 6.5% (48 mmol/L).23 It should be noted, however, that CLD with hypersplenism may reduce red blood cell life, leading to a falsely lowered HbA1c level. Patients with risk factors for developing T2DM (eg, obesity, sedentary lifestyle, high-risk ethnic group, strong family history, previous gestational diabetes) should be advised to improve their diets and exercise more frequently in order to lose weight when starting antiviral therapy. Hepatitis C virus infection has also been reported to be associated with a greater incidence of developing type 1 diabetes mellitus (T1DM).34

Antiviral Therapy and T1DM
Antiviral therapy may have an adverse effect on glucose tolerance in patients with HCV, and may predispose to the development of hyperglycemia and T1DM.35–37 One study suggests an incidence of 2.6% in patients treated with pegylated interferon alpha,37 although this is a higher incidence than that seen in other studies. A greater incidence of autoimmune endocrine conditions appears to be associated with pegylated interferon alpha therapy, possibly due to its interaction with immune effector cells.38 Hepatologists should monitor patients on antiviral therapy carefully for signs and symptoms of developing diabetes or thyroid disease. Patients’ fasting plasma glucose
levels should be checked at baseline and within 3 to 6 months after starting or changing antiviral therapy.

**Use of Statins in Patients with CLD**

Hypercholesterolemia is a significant risk factor for diabetic macrovascular complications, and statin therapy is mandatory in patients with T2DM who are aged > 40 years, even with modestly elevated cholesterol levels. Some guidelines suggest using statin therapy in all patients with T2DM aged > 40 years, irrespective of their prevailing cholesterol levels. The beneficial effect of statins on reducing cardiovascular morbidity and mortality rates in patients with T2DM is highly significant. Withholding statins in patients with T2DM is not desirable, as their increased cardiovascular risk will not be mitigated. In patients with CLD, however, many physicians are concerned about the effect of statins on the liver.

However, it appears that the risk of significant liver damage from statins is extremely rare in clinical trials and in clinical practice.41,42 The reported risk of elevated transaminases at 3 times the upper limit of normal with statin therapy ranges from 0% to 1.8%, with atorvastatin having the lowest reported incidence and simvastatin the highest.42 In patients with CLD, there is no evidence of increased risk of deterioration in liver function with statin therapy.43,44 Thus, many hepatologists advocate their use, particularly in patients with NAFLD and NASH. There is some evidence to suggest that statins may improve outcomes in patients with NASH.45 Some studies suggest that statin use reduces the risk of HCC in patients with T2DM.46 Statins may also have a beneficial effect on viremia in patients with HCV.47 Overall, the evidence strongly suggests that the risk/benefit ratio for statins in patients with CLD is greatly in favor of therapy, and statins should not be withheld in patients with CLD.

**Hypoglycemia**

Hypoglycemia is common in patients with diabetes, and more common in those with good glycemic control. Hypoglycemia is a potentially greater issue in patients with diabetes and CLD. All patients with diabetes and CLD on oral hypoglycemic therapy or insulin must be counselled carefully about recognition and management of hypoglycemia. New guidelines on management of hypoglycemia are available in the United Kingdom.48

**Treatment Options for Hyperglycemia in Patients with CLD**

Treatment of hyperglycemia in patients with diabetes is important to reduce the risk of microvascular disease; however, its effect on reducing macrovascular disease is more controversial.49 Metformin is now established as an important first-line drug in patients with T2DM, and has been shown to reduce morbidity and mortality rates in overweight patients with T2DM.47 Treatment of T2DM in patients with CLD, particularly cirrhosis, is complicated by the fact that many oral hypoglycemic agents may be contraindicated in patients with CLD. Because the risk of hypoglycemia may be enhanced, oral hypoglycemic therapy needs to be used with caution. Doses may need to be modified. In addition, nutrition can be an issue in patients with CLD, which may have an impact on the development of hypoglycemia. There are very few studies evaluating the role of antihyperglycemic therapies in patients with CLD. In particular, it is unclear whether improved glycemic control improves hepatic or other outcomes in such circumstances. There is, however, some evidence to suggest that some antihyperglycemic therapies might reduce the risk of progression in patients with NASH.50 Pioglitazone and metformin have been suggested as having a positive impact on liver outcomes,51 with evidence being strongest for pioglitazone. However, the effect on mortality rates in patients with CLD has not been established. Table 1 summarizes our recommendations on drug treatment for glycemia in patients with CLD.

**Diet and Lifestyle Changes**

As with all patients with T2DM, the cornerstones of therapy are diet and lifestyle changes. A healthy diet that is low in saturated fat, salt, and refined sugar, and high in complex carbohydrates, vegetables, fruits, and lean meat should be encouraged. At least 30 minutes of moderate-intensity exercise 3 times per week should also be encouraged. Cessation of cigarette smoking and alcohol consumption should be mandatory in all patients with T2DM and CLD. Modest weight loss can lead to improvements in liver indices in patients with CLD.51

**Metformin**

Metformin is first-line therapy for T2DM in patients with a body mass index > 25 kg/m². In patients with CLD, however, there may be an increased risk of developing lactic acidosis.52 The risk of lactic acidosis associated with metformin therapy appears to occur in patients with multiple comorbidities, such as renal, liver, and cardiac diseases, particularly when there is an acute deterioration.53 In the British National Formulary, it is recommended to “withdraw metformin if tissue hypoxia is likely.”54 In practice, this may not preclude metformin use in all circumstances of CLD. If a patient has stable CLD and few other comorbidities, metformin is likely to be reasonably safe, but the dose should be decreased to a maximum...
Table 1. Pharmacotherapy Recommendations for Patients with Diabetes and CLD

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Example</th>
<th>Mechanism of Action</th>
<th>Normal Dosage</th>
<th>Dosage Adjustment in Patients with CLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>Insulin sensitization leading to increased glucose uptake in muscle and reduced hepatic gluconeogenesis</td>
<td>500–3000 mg daily</td>
<td>Maximum dose, 1500 mg daily</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Gliclazide; glyburide; repaglinide</td>
<td>Stimulation of insulin release from pancreatic islet cells</td>
<td>80–320 mg daily; 2.5–20 mg daily; 4–16 mg daily</td>
<td>Dosage halved, especially if patient is not abstinent from alcohol</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>Acarbose</td>
<td>Inhibit disaccharidases to reduce glucose absorption in bowel</td>
<td>50–100 mg 3 times daily with meals</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Pioglitazone</td>
<td>Insulin sensitization via PPAR-γ agonist effect</td>
<td>15–45 mg daily</td>
<td>Maximum, 30 mg daily with careful monitoring of liver function</td>
</tr>
<tr>
<td>Insulin</td>
<td>Long acting, intermediate acting, mixed, and short acting</td>
<td>Replacement of insulin deficiency</td>
<td>Variable between patients</td>
<td>Reduction in dose by 25% in patients with CLD, with clear warnings about risk of hypoglycaemia</td>
</tr>
<tr>
<td>GLP-1 analog</td>
<td>Exenatide; liraglutide</td>
<td>GLP-1 stimulates insulin release and reduces appetite</td>
<td>10 μg twice daily; 0.6–1.8 mg daily</td>
<td>Little experience of use; hence, no dose recommendation. Use with caution.</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>Saxagliptin; linagliptin</td>
<td>Inhibit DPP-4 thereby elevating endogenous GLP-1</td>
<td>2.5–5 mg daily; 5 mg daily</td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>

Abbreviations: CLD, chronic liver disease; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PPAR-γ, peroxisome proliferator–activated receptor-γ.

of 1500 mg daily, and the drug should be withdrawn if liver or renal function is deteriorating, or in the setting of acute illness or decompensation.

**Insulin Secretagogues**
Insulin secretagogues (eg, gliclazide and repaglinide) are the second-line therapy for patients with T2DM, but may be used in patients with lower body mass indices, or in whom metformin is contraindicated or not tolerated. Because they are metabolized by the liver, their duration of action may be prolonged in patients with CLD. Therefore, they should be avoided or used with caution at low doses in patients with T2DM and CLD. Patients should be advised to be aware of signs of hypoglycaemia. Patients who are not abstinent from alcohol should also be cautious when taking sulfonylureas.

**Alpha-Glucosidase Inhibitors**
Alpha-glucosidase inhibitors reduce the absorption of glucose from the gut by blocking disaccharidases. This can result in a useful hypoglycemic effect and modest weight loss, but at the expense of gastrointestinal side effects (eg, bloating and flatulence). This class of drugs is not used extensively in many diabetes units, and experience with this agent in patients with CLD is limited. They have been used safely in patients with CLD in 1 clinical trial, although the risk of hyperammonemia was increased. In a randomized double-blind study involving 100 patients with compensated liver cirrhosis and insulin-treated diabetes, the control of postprandial and fasting blood glucose levels improved significantly with the use of acarbose. In another crossover placebo-controlled study involving patients with hepatic encephalopathy, acarbose produced a significant improvement in postprandial blood glucose level.

**Thiazolidinediones**
Thiazolidinediones are peroxisome proliferator–activated receptor-γ agonists that improve insulin sensitivity. They have come under much scrutiny in recent years due to adverse effects. Troglitazone was withdrawn from the market in 1997 due to an increased incidence of acute liver failure, which appeared to be an idiosyncratic reaction. Rosiglitazone has been withdrawn more recently due to an increased incidence of cardiovascular disease. The only remaining glitazone, pioglitazone, remains licensed for use in patients with T2DM in the United Kingdom and the United States. It may also have a specific role in patients with CLD and diabetes, particularly in patients with NAFLD and NASH, as a randomized study showed improvement in histological indices in patients with NASH who were treated with pioglitazone. Of importance, however, is the fact that deterioration in liver function has been reported with glitazones. As a result, careful liver function test monitoring is indicated in all patients commencing...
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pioglitazone therapy. The British National Formulary states that pioglitazone should be avoided in patients with hepatic impairment. Adverse effects of glitazones include weight gain (typically 3–5 kg), edema, exacerbation of heart failure (in which circumstance they are absolutely contraindicated), and possibly increased risk of postmenopausal fractures in women. More recently, a possible link with bladder cancer has been described.

Insulin

Insulin therapy is perhaps the safest and most effective antihyperglycemic therapy in patients with CLD, with the proviso that increased risk of hypoglycemia in such patients necessitates the need to take great care with doses of insulin, and the need for clear guidance on how to avoid and manage hypoglycemia. Insulin therapy usually starts with the addition of basal insulin to oral hypoglycemic therapy, with good evidence to suggest that adding insulin to metformin limits weight gain and insulin dose. In patients with CLD in whom oral hypoglycemic therapy is contraindicated, insulin alone as a twice-daily fixed mixture regimen or a basal-bolus regimen may be indicated. In patients with alcoholic CLD who are not abstinent from alcohol, great care should be exercised when using insulin therapy.

Bariatric Surgery

In severely obese patients with diabetes and CLD, bariatric surgery may be considered. Weight loss of up to 60% may occur, and cure of diabetes is also a possibility. There were early concerns about possible deleterious effects of rapid weight loss leading to increased liver inflammation, but this fear appears to be unfounded, and bariatric surgery appears to reduce steatosis, inflammation, and fibrosis in patients with established NASH.

Liver Transplantation

Liver transplantation improves glucose tolerance and insulin sensitivity due to improvement in hepatic clearance and peripheral glucose disposal. Liver transplantation cures diabetes in approximately two-thirds of patients with cirrhosis and diabetes. In the remaining one-third, diabetes was not corrected because of reduced β-cell function. Pancreatic islet cell transplantation is a relatively new modality of therapy for patients with T1DM and erratic diabetes. It is restricted by the use of immunosuppressive therapy, but use of pancreatic islet cell transplantation in patients undergoing liver transplantation might be considered, as these patients would be prescribed immunosuppressive therapy anyway.

Newer Agents

Incretin mimetics (glucagon-like peptide-1 analogs) and dipeptidyl peptidase-4 inhibitors are new classes of antihyperglycemic agents. Incretin mimetics are administered subcutaneously and dipeptidyl peptidase-4 inhibitors orally. Both groups are effective in improving glycemic control in patients with diabetes, but with the added advantage of improving weight. Glucagon-like peptide-1 analogs (eg, exenatide, lixisenatide) are associated with significant weight loss (3–5 kg) and dipeptidyl peptidase-4 inhibitors (gliptins) are weight neutral. Some gliptins (eg, saxagliptin) can be used with caution in patients with hepatic impairment. It is suggested that NAFLD may attenuate the effect of sitagliptin on glycemic control. Glucagon-like peptide-1 analogs have not been used in patients with CLD, although animal studies suggest that they may reverse fat accumulation in fatty liver disease. At this stage, these drugs have not been extensively studied or used in patients with diabetes and CLD, although there are case reports of some improvement in patients with CLD.

Multidisciplinary Management of Patients with Diabetes and CLD

Patients with diabetes and CLD have higher morbidity and mortality rates compared with patients without diabetes. Their care may be enhanced by a multidisciplinary approach. Combined hepatology and diabetology clinics may be of benefit, as this may enable careful individualized discussion of the risks and benefits of various treatment modalities. In patients with NASH, improvement in metabolic indices appears to have an impact on progression of disease. Access to the wider multidisciplinary team (eg, dietitian, diabetes nurse specialist, or podiatrist) may be facilitated by such combined clinics, and is of particular importance in such patients because of how weight loss and increased physical exercise are of great benefit in reducing progression of CLD. A position statement on management of NAFLD and NASH has been published that suggests multidisciplinary approaches.

Figure 2. Key points about patients with CLD and diabetes.

- Diabetes and CLD frequently coexist.
- Diabetes is a risk factor for poorer outcome in patients with CLD and increases morbidity and mortality rates. However, there is no randomized trial evidence to suggest that improved metabolic indices affect outcomes.
- A number of antihyperglycemic therapies are contraindicated or must be used with caution in patients with CLD.
- Management of patients with diabetes and CLD may be improved by a multidisciplinary approach.

Abbreviation: CLD, chronic liver disease.
management of such patients. A combined clinic would also enable careful screening of such patients for diabetic and hepatic complications, such as micro- and macrovascular disease, and complications related to portal hypertension.

Summary

Diabetes is a frequent comorbidity in patients with CLD and appears to increase morbidity and mortality rates in patients with CLD (Figure 2). Therefore, it is important to recognize and manage. Such patients present a particular challenge in management because they have multiple comorbidities and the number of pharmacotherapeutic options is limited. There is good evidence to suggest that lifestyle changes (eg, increased exercise, improved diet, and alcohol cessation) are of great importance in reducing CLD progression. In addition, improvement in metabolic indices, such as glycemia and cholesterol, are also likely to improve outcomes. Early recognition and management of diabetes in patients with CLD is important, as is obtaining input from a variety of health care professionals. Because there is a significant evidence gap in our knowledge regarding the optimum management of patients with CLD and diabetes, this area requires further clinical and scientific research (Figure 3).

Conflict of Interest Statement

Roaid Khan, MBBS, MRCP and Tahseen A. Chowdhury, MD, FRCP disclose no conflicts of interest. Graham R. Foster, PhD, FRCP discloses conflicts of interest with Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen Pharmaceuticals, Inc., Merck and Co., Novartis, and Roche.

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