Diabetes mellitus in patients with cirrhosis: clinical implications and management

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Abstract
Disorders of glucose metabolism, namely glucose intolerance and diabetes, are frequent in patients with chronic liver diseases. In patients with cirrhosis, diabetes can be either a classical type 2 diabetes mellitus or the so-called hepatogenous diabetes, i.e. a consequence of liver insufficiency and portal hypertension. This review article provides an overview of the possible pathophysiological mechanisms explaining diabetes in patients with cirrhosis. Cirrhosis is associated with portosystemic shunts as well as reduced hepatic mass, which can both impair insulin clearance by the liver, contributing to peripheral insulin resistance through insulin receptors down-regulation. Moreover, cirrhosis is associated with increased levels of advanced-glycation-end products and hypoxia-inducible-factors, which may play a role in the development of diabetes. This review also focuses on the clinical implications of diabetes in patients with cirrhosis. First, diabetes is an independent factor for poor prognosis in patients with cirrhosis. Specifically, diabetes is associated with the occurrence of major complications of cirrhosis, including ascites and renal dysfunction, hepatic encephalopathy and bacterial infections. Diabetes is also associated with an increased risk of hepatocellular carcinoma in patients with chronic liver diseases. Last, the management of patients with concurrent diabetes and liver disease is also addressed. Recent findings suggest a beneficial impact of metformin in patients with chronic liver diseases. Insulin is often required in patients with advanced cirrhosis. However, the favourable impact of controlling diabetes in patients with cirrhosis has not been demonstrated yet.

Keywords

Abbreviations
AGEs, advanced glycation-end products; CTGF, connective tissue growth factor; DPP-4, Dipeptyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HCC, hepatocellular carcinoma; HIF, hypoxia inducible factor; IGF1, insulin growth factor-1; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor.

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The liver plays a pivotal role in glucose homeostasis. It stores glycogen in the fed state and produces glucose through glycogenolysis and gluconeogenesis in the fasting state. There are close relationships between liver diseases and disorders of glucose metabolism. On the one hand, the risk of death from chronic liver diseases is increased in patients with type 2 diabetes mellitus (1–3). On the other hand, the presence of diabetes in patients with cirrhosis is an independent factor for poor survival, and is associated with the major complications of cirrhosis. The treatment of diabetes in patients with chronic liver diseases is complex, because of impaired liver and/or renal functions, and of the potential hepatotoxicity of oral hypoglycaemic agents. The aim of this review is to provide an update on the relationships between cirrhosis and diabetes. We will focus on recent advances in the pathophysiological mechanisms, diagnosis, clinical implications and therapeutic management of diabetes in patients with cirrhosis.

**Impact of diabetes on progression of liver fibrosis and cirrhosis development**

Epidemiological links between type 2 diabetes and cirrhosis

Type 2 diabetes is a risk factor for liver fibrosis development and progression. There is a strong relationship between the components of the insulin resistance syndrome and the stage of liver fibrosis (4, 5). Several independent groups observed in large cohorts of patients that type 2 diabetes is associated with a 2 to 2.5-fold increased risk of cirrhosis development, and of death from chronic liver diseases, mainly attributable to non-alcoholic fatty liver diseases (NAFLD) (1–3). Interestingly, the effect of diabetes on fibrosis has been found to be independent from other components of the metabolic syndrome (6). Furthermore, recent cohort studies in Taiwan showed that diabetes mellitus is an independent predictor of cirrhosis in patients with chronic hepatitis B and chronic hepatitis C (7, 8).

Pathophysiological mechanisms promoting liver fibrosis in patients with insulin resistance or type 2 diabetes

As a part of metabolic syndrome, type 2 diabetes can promote NAFLD. Patients with isolated steatosis generally have an excellent prognosis, while patients with non-alcoholic steatohepatitis (NASH) may develop fibrosis leading to cirrhosis and its complications (6). Pathophysiological mechanisms leading to NASH and NASH-related fibrosis have been recently reviewed in detail elsewhere (9). Moreover, diabetes likely contributes to fibrosis progression and cirrhosis independently from NAFLD by modulating several key processes implicated in fibrogenesis, which are detailed below.

**Activation of hepatic stellate cells**

Hepatic stellate cells, the liver-specific pericytes, are localized in the space of Disse. In a chronically injured liver, hepatic stellate cells promote liver fibrosis through excessive extra-cellular matrix production and reduced extra-cellular matrix degradation (10). Glucose and insulin have profibrogenic properties on hepatic stellate cells. Indeed, incubation of hepatic stellate cells with high glucose or insulin levels leads to overexpression of the key profibrogenic gene connective tissue growth factor (CTGF) (11). Hyperglycaemia and oxidative stress contribute to the accumulation of advanced-glycation-end (AGE) products. Interestingly, functional receptors for AGE products are overexpressed in activated hepatic stellate cells (12). This up-regulation of receptors for AGE products suggests that insulin and hyperglycaemia may also activate hepatic stellate cells through the ligation of AGE products on their receptors.

**Inflammation**

Inflammation is a major player in the development of liver fibrosis. (13). The link between diabetes and inflammation is now well established and type 2 diabetes is viewed as an auto-inflammatory disease (14). Inflammation plays a crucial role in the pathogenesis of diabetes-related complications. For instance, inflammation and subsequent extracellular matrix expansion play a key role in the development and progression of diabetic nephropathy (15). Regarding the liver, indirect data suggest that systemic inflammation associated with insulin-resistance and diabetes might contribute to progression of liver fibrosis. In patients with hepatitis C, insulin resistance and diabetes are associated with liver fibrosis progression as well as with necroinflammatory activity (16, 17).

**Apoptosis**

Apoptosis is a type of cell death characterized by the fragmentation of the dying cell into membrane-bound fragments called apoptotic bodies. Apoptosis is a normal physiological process that plays a crucial role in maintaining tissue homeostasis. It is involved in the development, differentiation, and maintenance of the body. In liver disease, apoptosis is believed to regulate the balance between cell death and cell survival, thereby influencing the progression of liver fibrosis and cirrhosis. Understanding the mechanisms of apoptosis in liver disease can provide insights into the therapeutic strategies for the management of these conditions.
vesicles, called apoptotic bodies. Apoptosis is a key player in the progression of liver fibrosis (18). Engulfment of apoptotic bodies by hepatic stellate cells stimulates their fibrogenic activity and may be one mechanism by which hepatocyte apoptosis promotes fibrosis (19). Indirect data suggest that diabetes might promote fibrosis through apoptosis. First, the dysregulation of the insulin receptor pathway, associated with insulin resistance, promotes liver cell apoptosis (20). In patients with NASH, plasma cytokeratin 18 substrates, a biomarker of liver apoptosis, is associated with liver fibrosis (21, 22). However, the association between diabetes and apoptosis remains to be evaluated.

**Angiogenesis**

Angiogenesis consists in the formation of new vascular structures from pre-existing blood vessels. Excessive angiogenesis plays a major role in the pathophysiology of diabetic complications including nephropathy, retinopathy as well as macrovascular diseases (23). Interestingly, excessive angiogenesis plays a role in the pathophysiology of these diseases and promotes fibrosis through the activation of CTGF (24–26).

Pathological angiogenesis has also been described in chronic liver diseases, including NASH (27). First, it has been shown that leptin-mediated neovascularisation, coordinated by vascular endothelial growth factor (VEGF), plays an important role in the development of liver fibrosis in a rat model of NASH (28). More recently, the same group showed that CD34 expression, a marker of neovascularisation, was overexpressed in the liver of patients with NASH. Furthermore, there was a positive correlation between neovascularisation and insulin resistance as well as with liver fibrosis (29). Thus, this suggests that insulin resistance and diabetes, as in other tissues, promote liver fibrosis through angiogenesis. Yet, the impact of diabetes, outside the context of NASH, on excessive angiogenesis and subsequent liver fibrosis has not been evaluated.

**Hepatic sinusoidal capillarization**

Hepatic sinusoidal capillarization refers to the loss of endothelial cell fenestration, associated with the deposition of collagen and other extracellular matrix proteins in the space of Disse. This mechanism is implicated in the progression of liver fibrosis (30). The role of insulin signalling and of hyperglycaemia on sinusoidal endothelial cells and their impact on liver fibrogenesis has not been studied (31). Yet, the increase in extra-cellular matrix deposition in the space of Disse typically observed in liver biopsies from patients with diabetes suggests that hepatic sinusoidal capillarization may promote liver fibrosis in the diabetes setting (32–34).

**Impact of cirrhosis on glucose homeostasis**

In a normal individual, the liver plays a key role in maintaining glucose homeostasis. In patients with advanced cirrhosis, alterations in glucose metabolism, the so-called hepatogenous diabetes, have been described. Fig. 1 summarizes the potential mechanisms which might participate into the occurrence of hepatogenous diabetes mellitus in patients with cirrhosis.

![Figure 1](https://example.com/fig1.png)

**Fig. 1.** Proposed pathophysiology of diabetes mellitus in patients with cirrhosis.
Decreased insulin clearance by the liver

In patients with cirrhosis, several structural changes can decrease the extraction of insulin by the liver, leading to increased systemic insulin levels. These structural modifications include: (a) a reduction in liver cell mass, which decreases the clearance of insulin (35) because insulin is metabolized and degraded mainly by parenchymal liver cells (36); (b) portosystemic venous collaterals, because of the decreased hepatic first-pass extraction, resulting in high levels of insulin. In patients with cirrhosis and surgical portocaval shunts, insulin levels in the hepatic veins are markedly increased, compared to patients without surgical shunts. By contrast, C-peptide levels do not differ between patients with cirrhosis and controls (37). This view is also supported by the fact that glucose control deteriorates and circulating insulin levels increase after transjugular intrahepatic portosystemic shunt placement in diabetic patients (38).

Subsequently, hyperinsulinaemia can lead to resistance to insulin through insulin receptor down-regulation. Indeed, hyperinsulinaemia induces a reduction in insulin receptor affinity, a reduction in the number of receptors exposed at the surface of the target cell and a diminution of the effectiveness of the insulin receptor as a transmitter of stimulatory signals (39).

Increased advanced-glycation-end products

Although hyperglycaemia fosters the AGES, AGEs could also induce insulin resistance and beta-cell injury prior to diabetes onset (40). Besides the kidney, the liver also seems to be involved in the removal of AGEs (41). In patients with cirrhosis without diabetes, plasma AGE levels are markedly elevated and correlate with the severity of the liver disease (42, 43). After liver transplantation, a clear decline in AGEs levels occurs (42). According to these findings, it can be speculated that in patients with cirrhosis, the accumulation of AGES, related to a reduced removal of AGES, may promote diabetes.

Hypoxia and hypoxia-inducible factors

Systemic hypoxia is observed in patients with advanced cirrhosis, and is related to the severity of the liver disease (44). The hypoxia-inducible factors (HIFs) are a family of transcriptional regulators that induce a homeostatic response to hypoxia in virtually all cells and tissues. HIFs have been implicated in the development of liver fibrosis in in vitro and murine models (45, 46). HIFs also play a key role in glucose metabolism, and are implicated in the development of diabetes mellitus (47). HIF, namely HIF-1α, is also important for pancreatic β-cell reserve. However, the mechanisms are complex. Indeed, in HIF-1 knock-out mice, pancreatic β-cell function is impaired (48). Mild increase in HIF-1α is beneficial for β-cell function and glucose tolerance. By contrast, very high levels of HIF-1, such as those observe in severe hypoxia are clearly deleterious for β-cell function (48). Thus, cirrhosis-related hypoxia might be hypothetized to promote the occurrence of hepatogenous diabetes mellitus.

A liver–pancreas axis

Glucose intolerance in cirrhosis results from peripheral insulin resistance and hyperinsulinemia. Interestingly, in patients with cirrhosis and overt diabetes, beta-cell secretion, in response to hyperglycaemia is significantly reduced, compared to patients with cirrhosis and normal glucose tolerance as well as those with glucose intolerance (49), suggesting that an altered secretion of insulin by beta cells may contribute to the development of overt diabetes (36). Recently, Yi and colleagues observed that a hormone named betatrophin, primarily expressed in the hepatocytes, induced β-cell proliferation and improved glucose tolerance in a murine model (50). However, recent data suggest that betatrophin levels might rather be associated with insulin resistance, rather than β-cell proliferation. Betatrophin levels were found to be increased in patients with type 2 diabetes compared to non-diabetic subjects (51–54). Furthermore, in a recent study including more than 1000 non-diabetic subjects, there was a strong correlation between betatrophin levels and HOMA-IR (54). Plasma betatrophin levels were significantly increased in patients with cirrhosis compared to healthy individuals. Betatrophin levels were also associated with liver disease severity. Moreover, betatrophin levels were significantly higher in patients with insulin resistance than in those without (55). These findings support a possible functional role of betatrophin in type 2 diabetes, where it could play a role in compensating for the increased insulin demand despite liver insufficiency.

Diagnosis and clinical presentation of diabetes in patients with cirrhosis

In patients with cirrhosis, disorders of glucose metabolism range from mere glucose intolerance to overt diabetes. It is estimated that only 30% of the patients have normal glucose tolerance, 30–50% have impaired glucose tolerance and up to 30% have overt diabetes (56–59). This is much higher than in the general population, where the prevalence of glucose intolerance is around 15% and that of diabetes is 8% (60, 61).

The diagnosis of diabetes in patients with cirrhosis may not be easy. First, at early stage, fasting serum glucose levels is normal in 23% of the patients with overt diabetes (57). Indeed, such patients have normal fasting blood glucose, whereas post-prandial blood glucose is >200 mg/L (62). Thus, an oral glucose tolerance test is needed to detect the impairment of glucose metabolism.
Furthermore, discrimination between type 2 diabetes and hepatogenous diabetes is frequently not possible. Still, hepatogenous diabetes may have different clinical characteristics from type 2 diabetes. Among 50 patients with hepatogenous diabetes, only 16% of patients had a family history of diabetes. Only 8% had retinopathy. After a mean follow-up of 5 years, no cardiovascular deaths was reported, whereas 52% of the patients had died, mainly from complications of cirrhosis (56). This may be either related to the shorter duration of diabetes in patients with hepatogenous diabetes than in patients with type 2 diabetes or to the fact that mortality is mostly related to cirrhosis-related complications in these patients (63).

In patients with isolated hepatogenous diabetes, liver transplantation by itself can normalize glucose tolerance and insulin sensitivity (64), supporting the idea that diabetes was related to cirrhosis. However, post-transplantation diabetes remains a very common condition, as it is estimated that about 30% of liver transplant recipients have diabetes (65). Interestingly, in patients receiving a liver graft, pretransplantation diabetes, as well as advanced age, family history of diabetes, and maximum body mass index over 25 kg/m² (which are risk factors for type 2 diabetes), is associated with the development of post-transplantation diabetes (66). These data suggest that diabetes mellitus present at the time of liver transplantation was not only exclusively related to advanced liver disease but also to pre-existing metabolic abnormalities. The causes of liver disease also appear to be an important risk factor for the development of diabetes in patients with cirrhosis. Indeed, diabetes is more frequent in patients with hepatitis C-related cirrhosis (67, 68) or alcohol-related cirrhosis than in patients with biliary cirrhosis (69). However, cirrhosis remains independently associated with cirrhosis. Indeed, among patients with hepatitis C infection, diabetes is more frequently observed in patients with cirrhosis (24%) than in those without (6%) (70).

Measurement of glycated haemoglobin (HbA1c) does not accurately reflect glycaemic status in patients with cirrhosis. In patients without liver diseases, HbA1c is used for routine evaluation and the management of patients with diabetes. HbA1c concentration reflects the previous 2–3 months of glycaemic status and is well correlated with the development of diabetes-related complications (71, 72). Studies on small-sized series of patients indicate that HbA1c measurement is not accurate in patients with cirrhosis (73–75). Indeed, 40% of the non-diabetic patients with cirrhosis had HbA1c values below the normal range in a non-diabetic reference population (75, 76). Furthermore, patients with cirrhosis and concurrent diabetes also had HbA1c values in the non-diabetic reference, namely between 4 and 6% (76). Only a small proportion of patients with cirrhosis and diabetes had high HbA1c (76). Furthermore, patients with cirrhosis showed similar values of HbA1c compared to control patients, although fasting plasma glucose was higher in patients with cirrhosis (74). The reason why HbA1c measurement is not accurately reflecting glycaemic control in patients with cirrhosis remains unclear. Shortened erythrocyte life span, which is common in patients with cirrhosis and is known to cause low HbA1c values, could play a role independent of glycaemia. Fructosamine measurement reflects glycaemic status over a period of 2–4 weeks. Fructosamine level appears to be a more accurate tool than HbA1c for monitoring glycaemic control in patients with cirrhosis (75, 76).

### Prognostic impact of diabetes in patients with cirrhosis

#### Survival

The prognostic value of diabetes in cirrhosis has previously been investigated only in a limited number of studies on selected patients. Some studies included patients with advanced cirrhosis, whereas others included patients with well-compensated cirrhosis; most of these studies found that diabetes was associated with a lower survival (57–59, 63, 77–79) (Table 1). Recently, a French cohort study of 348 patients with hepatitis C-related cirrhosis admitted to hospital found that diabetes was associated with a shorter transplantation-free survival, independent of model for end-stage liver disease (MELD) score (Odds ratio 1.3). Diabetes markedly influenced the prognosis in patients with baseline MELD score <10. By contrast, diabetes had no impact on survival in patients with a baseline MELD score ≥10 (63). These findings suggest that the severity of liver disease masks the deleterious effect of diabetes and/or that

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Year</th>
<th>Patients</th>
<th>Type of study</th>
<th>Characteristics of the patients</th>
<th>Follow-up</th>
<th>Survival (diabetics vs. non diabetic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bianchi (77)</td>
<td>1984</td>
<td>382</td>
<td>Retrospective</td>
<td>Hospitalized</td>
<td>37 months</td>
<td>64 vs. 82% (P = 0.005)</td>
</tr>
<tr>
<td>Moreau (78)</td>
<td>2004</td>
<td>100</td>
<td>Prospective</td>
<td>Refractory ascites</td>
<td>2 years</td>
<td>18 vs. 58% (P = 0.0004)</td>
</tr>
<tr>
<td>Nishida (76)</td>
<td>2006</td>
<td>56</td>
<td>Prospective</td>
<td>Various aetologies</td>
<td>5 years</td>
<td>56 vs. 95% (P &lt; 0.05)</td>
</tr>
<tr>
<td>Sangiovanni (98)</td>
<td>2006</td>
<td>214</td>
<td>Retrospective</td>
<td>HCV compensated cirrhosis</td>
<td>17 years</td>
<td>No difference</td>
</tr>
<tr>
<td>Berman (96)</td>
<td>2011</td>
<td>447</td>
<td>Retrospective</td>
<td>Hospitalized</td>
<td>90 days</td>
<td>No difference</td>
</tr>
<tr>
<td>Quintana (97)</td>
<td>2011</td>
<td>110</td>
<td>Prospective</td>
<td>Compensated cirrhosis</td>
<td>2.5 years</td>
<td>69 vs. 48% (P &lt; 0.05)</td>
</tr>
<tr>
<td>Elkrief (82)</td>
<td>2014</td>
<td>348</td>
<td>Retrospective</td>
<td>Hospitalized HCV cirrhosis</td>
<td>4.5 years</td>
<td>24 vs. 34% (P = 0.03)</td>
</tr>
</tbody>
</table>
in patients with high MELD score, diabetes related to cirrhosis, and thus has no independent effect on survival.

**Hepatocellular carcinoma**

It is now well established that the risk of cancer is increased in patients with type 2 diabetes, including hepatocellular carcinoma (HCC) (80). In a meta-analysis of 28 prospective studies, pre-existing diabetes was significantly associated with an increased incidence of HCC (relative risk 1.87) and HCC-specific mortality (relative risk 1.88) (81). Yet, no practical recommendations can be suggested for patients with cirrhosis and diabetes. In patients with cirrhosis, compared to patients undergoing ultrasound surveillance every 6 months, three-month ultrasonographical examination did not improve either the rate of detection of small HCCs eligible for curative treatment or the overall survival rate compared to patients undergoing surveillance every 6 months (82).

**Ascites and renal dysfunction**

We recently reported that diabetes is associated with the development of ascites, independent of MELD score in patients with hepatitis C-related cirrhosis (63). Diabetes also seems to be associated with refractory ascites. Indeed, in a French prospective study of 100 patients with cirrhosis and refractory ascites, diabetes was more frequently observed in patients with Child Pugh class B than Child Pugh class C cirrhosis suggesting a role of diabetes independent from impaired liver function (59). These observations suggest a specific role of diabetes in the development of ascites. However, the involved mechanisms remain elusive. In patients with cirrhosis, ascites formation has been related to circulatory disturbances, renal dysfunction and sodium retention (83). Moreover, in patients with cirrhosis on the waiting list for liver transplantation, diabetic nephropathy is frequently observed when kidney biopsy is performed, and is predictive of the development of renal dysfunction after liver transplantation (84). In humans or animal models without cirrhosis, diabetes is associated with specific changes in the hepatic microcirculation, called ‘hepatic microangiopathy’ (or diabetic hepatosclerosis), characterized by non-zonal perisinusoidal deposition of collagen and basement membrane (33, 34, 85, 86) (Fig. 2). In patients with cirrhosis and concurrent diabetes, such lesions might participate into the formation of ascites. It is thus tempting to speculate that diabetes-associated microcirculatory changes in the liver and the kidneys could promote ascites and renal dysfunction (33). Supplemental Fig. S1 summarizes the mechanisms promoting ascites in patients with cirrhosis and diabetes.

**Hepatic encephalopathy**

The association between diabetes and hepatic encephalopathy has been shown in several studies. In the first study, among 65 patients with hepatitis C-related cirrhosis, severe hepatic encephalopathy was more common, contrasting with a preserved liver function (87). In the second study, in 128 patients with cirrhosis, diabetes was associated with minimal hepatic encephalopathy (88). Furthermore, in a recent French cohort of 348 patients with hepatitis C-related cirrhosis, diabetes was associated with the presence of hepatic encephalopathy, independent of MELD score (63). The latter study included hospitalized patients, and only overt hepatic encephalopathy was taken into account.

Several mechanisms by which diabetes could theoretically promote hepatic encephalopathy have been investigated. First, diabetes could increase ammonia production by enhancing small intestine glutaminase type K. Indeed, metformin which reduces glutaminase activity in vitro has been shown to decrease the incidence of hepatic encephalopathy in patients with cirrhosis (89). Moreover, in a randomized control trial including more than 100 patients, the administration of an oral antidiabetic agent, acarbose, in patients with cirrhosis and concurrent diabetes significantly reduced ammonia blood levels, and improved psychometric tests for minimal hepatic encephalopathy (90). Second, the

![Fig. 2. Pathological lesions found in the liver of patients with diabetes. Haematoxylin–eosin staining: (A) Non-alcoholic steatohepatitis features include macrovesicular steatosis (star), hepatocyte ballooning (black arrow) and lobular inflammation (cross), (B) Metabolic cirrhosis: at the stage of cirrhosis, typical features of NAFLD may be lacking; Picrosirius coloration: (C) perisinusoidal fibrosis (star).](image-url)
inflammatory state associated with insulin resistance and type 2 diabetes (91) could act synergistically with cirrhosis and endotoxemia associated with encephalopathy (92). Third, intestine motility impairment has been described in diabetic patients as a part of autonomic neuropathy (93). It could promote small intestine bacterial overgrowth raising bacterial translocation, known to favour hepatic encephalopathy (94).

Bacterial infections

Diabetes mellitus and cirrhosis are two conditions that predispose to bacterial infections. Diabetes has been associated with increased rates of bacterial infections (95). This feature may be partially explained by a decreased T-cell-mediated immune response (96). Impaired neutrophil function has also been documented in diabetic patients (97). Bacterial infections are also more common in patients with cirrhosis than in the general population (98). They are also more severe since mortality is four-fold higher in infected patients with cirrhosis than in those without (99). The mechanisms of increased susceptibility to infections in cirrhosis are unclear. Functional alterations of monocytes and neutrophils have been observed. A role for deficiencies in C3 and C4 has also been suggested (100). The synergy of diabetes and cirrhosis to promote infections is supported by clinical evidence. In one cohort of 178 cirrhotic hospitalized patients (25% had diabetes), the prevalence of bacterial infections was more frequent in diabetic patients than in non-diabetic (85 vs. 48%, \( P < 0.0001 \)) (101). In our cohort of 348 hospitalized patients with HCV-related cirrhosis, diabetes was independently associated with bacterial infections development (63). Finally, in patients undergoing liver transplantation, those with diabetes are at higher risk for bacterial infections (102).

Management of diabetes in patients with cirrhosis

In patients with type 1 and type 2 diabetes, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) studies have demonstrated that poor glycaemic control (based on an HbA1c level above 7% for type 1 diabetes and 6.5% for type 2 diabetes) was directly associated with the development of diabetic micro- and macroangiopathy (71, 72). In patients with cirrhosis and diabetes, the risk of cirrhosis complications seems to be higher than the risk of diabetes complications. The impact of early diagnosis and treatment of diabetes on the clinical course of patients with cirrhosis and diabetes is unknown. However, it is tempting to speculate that it could be beneficial. As detailed below, recent data suggesting that metformin decreases the risk of HCC as well as the risk of hepatic encephalopathy are in favour of screening and treating diabetes in patients with cirrhosis.

There is no clinical trial that specifically targeted patients with coexistent diabetes and cirrhosis. The ther-

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Table 2. Therapeutics options for treatment of diabetes mellitus in patients with cirrhosis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of action</th>
<th>Useful in type 2 DM</th>
<th>Useful in patients with cirrhosis and DM</th>
<th>Side-effects/risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low fat diet</td>
<td>Decrease liver and adipose fat</td>
<td>Very useful</td>
<td>Potentially useful</td>
<td>Malnutrition frequent in patients with cirrhosis</td>
</tr>
<tr>
<td>Physical exercise</td>
<td>Increase insulin sensitivity</td>
<td></td>
<td></td>
<td>Physical exercise may not be feasible in patients with advanced cirrhosis (edema, ascites)</td>
</tr>
<tr>
<td>Metformin</td>
<td>Increase insulin sensitivity</td>
<td>Very useful</td>
<td>Very useful</td>
<td>Contraindicated in patients with renal dysfunction</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Increase insulin sensitivity</td>
<td>Useful</td>
<td>No available data</td>
<td>Theoretical risk of lactic acidosis</td>
</tr>
<tr>
<td>Secretagogues</td>
<td>Increase endogenous production of insulin</td>
<td>Useful</td>
<td>Not useful</td>
<td>Reported hepatotoxicity</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td></td>
<td></td>
<td></td>
<td>Usefulness in patients with NASH has not been demonstrated</td>
</tr>
<tr>
<td>Glinides</td>
<td></td>
<td></td>
<td></td>
<td>Contraindicated in patients with advanced cirrhosis</td>
</tr>
<tr>
<td>Incretins</td>
<td>Increase insulin sensitivity</td>
<td>Very useful</td>
<td>No available data</td>
<td>Because of the risk of hypoglycaemia</td>
</tr>
<tr>
<td>GLP-1 receptor analogues</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Decrease carbohydrate absorption in the bowel</td>
<td>Useful</td>
<td>May be useful in patients with HE</td>
<td>Benign digestive side-effects</td>
</tr>
<tr>
<td>Insulin</td>
<td>Substitutive treatment</td>
<td>Often necessary</td>
<td>Often necessary</td>
<td></td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; NASH, non-alcoholic steatohepatitis; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; HE, hepatic encephalopathy.
Lifestyle interventions

The first-line therapy for type 2 diabetes consists of lifestyle changes, which includes hypocaloric diet and physical exercise. The goal of physical exercise is to increase peripheral insulin sensitivity. Unfortunately, in patients with cirrhosis, such therapies may be inappropriate or unfeasible. Indeed, up to 50 percent of cirrhotic patients have malnutrition (103), a contraindication to hypocaloric diet. Furthermore, ascites and edema hamper physical exercise.

Pharmacologic therapies

Pharmacologic options for the control of diabetes in patients with liver diseases are, for the most part, similar to patients without liver disease. Only patients with severe impaired liver function have altered drug metabolism. Regarding the risk of hepatotoxicity, while patients with liver disease are not predisposed to hepatotoxicity, the underlying liver disease may increase the severity of drug-induced liver injury (104).

Metformin

First-line therapy with metformin is theoretically appropriate in patients with cirrhosis because it decreases insulin resistance. Metformin has long been considered to be contraindicated in patients with advanced liver disease because of a theoretical increase in the risk of lactic acidosis (105). Yet, despite the widespread use of metformin, only rare patients with cirrhosis developed lactic acidosis, suggesting that metformin is safe in patients with cirrhosis without renal dysfunction (106–109) (Supplemental Table S1).

A growing number of observational studies suggest that metformin (relative to other glucose-lowering therapies) could be associated with a reduced risk of cancer or cancer mortality, including hepatocellular carcinoma (110, 111). Furthermore, Zhang et al. recently reported that continuation of metformin in patients with newly diagnosed cirrhosis is associated with a longer survival (112). In a recent cohort of 82 patients with cirrhosis and diabetes, the occurrence of hepatic encephalopathy was significantly lower in patients receiving metformin (5 vs. 41%) (89). An indication bias may limit the interpretation of observational studies, as metformin is most typically prescribed to patients with short duration of diabetes and without contraindicating factors (advanced age, liver or kidney disease) that also might impact the prognosis (113). However, these data suggest that metformin is the first-choice therapy for patients with cirrhosis and diabetes.

Thiazolidindiones

Thiazolidinediones are insulin-sensitizing peroxisome proliferator-activated receptor (PPAR) gamma agonists that do not increase insulin secretion directly or cause hypoglycaemia when used alone. Thus, thiazolidinediones may be particularly useful in patients with diabetes and chronic liver diseases. However, troglitazone and rosiglitazone have been withdrawn from the market because of their potential hepatotoxicity.
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toxic effect and the risk of congestive heart failure respectively. Pioglitazone is still currently available. In patients with NASH, the usefulness of thiazolidinediones is debated (114). A meta-analysis of four randomized controlled trials found that thiazolidinediones significantly improve steatosis and liver inflammation, but not fibrosis (115). Patients with cirrhosis were excluded from these trials.

Insulin secretagogues

Insulin secretagogues include sulphonylureas and glinides. They trigger insulin release by the pancreatic beta cells. Thus, in patients with cirrhosis, they may not be the first-choice option, as they do not modify insulin sensitivity. Moreover, patients with cirrhosis, especially those with alcohol-related cirrhosis, may have pancreatic beta-islets cell damage. Most importantly, there is an increased risk of hypoglycaemia with these therapies. Thus, secretagogues are not recommended in patients with high risk of hypoglycaemia (105).

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (acarbose) could be useful in patients with cirrhosis, since they reduce carbohydrate absorption in the bowel, which would decrease the risk of postprandial hyperglycaemia. Indeed, patients with cirrhosis and diabetes frequently have normal plasma fasting glucose and abnormal oral glucose tolerance test (56, 57). In a randomized, double-blind study including 100 patients with compensated cirrhosis and insulin-treated diabetes, the control of postprandial and fasting blood glucose levels improved significantly with the use of acarbose (116). In another crossover placebo-controlled study involving patients with hepatic encephalopathy, there was a significant improvement in postprandial blood glucose level in patients treated with acarbose (90).

Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 is a gut-derived incretin hormone that stimulates insulin and suppresses glucagon secretion, inhibits gastric emptying and reduces appetite and food intake. Therapeutic approaches for enhancing incretin action include DDP-4 inhibitors and GLP-1 analogues. These classes of therapeutic agents for type 2 diabetes were developed in the past 10 years and have proven to be effective glucose lowering agents. In addition, GLP-1 analogues promote (moderate) weight loss (117). So far, preclinical studies have found that incretins can improve hepatic steatosis (118). Although some effects could be because of an overall improvement in metabolic parameters, there are data to support improvements independent from weight loss, as well as direct effect on the hepatocyte. However, the safety and the usefulness of incretins in patients with cirrhosis need further investigations.

Insulin

Despite the potential interest of oral antidiabetic agents, insulin therapy is frequently prescribed in patients with cirrhosis, especially in those with advanced cirrhosis. Among 348 patients with hepatitis C-related cirrhosis, 62% were on insulin therapy (63).

Importantly, caution must be made regarding the dosage of insulin therapy. Indeed, insulin requirements in patients with cirrhosis may vary depending on the severity of cirrhosis. In patients with compensated cirrhosis, insulin requirement may be important because insulin resistance predominates. In patients with decompensated cirrhosis, the hepatic metabolism of insulin is reduced, which decreases the needs for insulin. Therefore, hospitalization might be safe for the initiation of insulin therapy, by allowing for close monitoring of blood glucose levels, to reduce the risk of hypoglycaemia.

Non selective beta-blockers are widely used in patients with cirrhosis for prophylaxis of variceal bleeding (119). With regard to diabetic patients under insulin treatment, beta-blockers may make hypoglycaemic episodes less symptomatic, leading to more profound alteration in mental state to develop without warning symptoms. Moreover, hypoglycaemia can be precipitated by beta-adrenergic response because β2-adrenoceptors normally stimulate glycogenolysis and pancreatic release of glucagon. However, a study comparing subjects with diabetes receiving or not beta-blockers found that beta-blockers did not increase the number or the severity of hypoglycaemic episodes (120). Thus, beta-blockers are not contraindicated in patients with cirrhosis treated with insulin.

Conclusion

Diabetes mellitus is observed in up to 30% of patients with cirrhosis. Diabetes can be either an underlying type 2 diabetes mellitus or the consequence of alterations directly related to an impaired liver function. Diabetes mellitus is associated with a poor prognosis in patients with cirrhosis, mainly because of an increased risk of cirrhosis complications. Thus, screening for diabetes mellitus should be proposed to all patients with cirrhosis. Although it is tempting to speculate that controlling diabetes may have a beneficial effect, further controlled studies are needed to evaluate the effect of diabetes control on the development of complications of cirrhosis.

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