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Hepatogenous Diabetes: Knowledge, evidence, and skepticism

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Abstract

The diabetogenic potential of liver cirrhosis (LC) has been known for a long time, and the name "hepatogenous diabetes" (HD) was coined in 1906 to define the condition. Diabetes mellitus (DM) that develops as a consequence of LC is referred to as HD. In patients with LC, the prevalence rates of HD have been reported to vary from 21% to 57%. The pathophysiological basis of HD seems to involve insulin resistance (IR) and pancreatic β -cell dysfunction. The neurohormonal changes, endotoxemia, and chronic inflammation of LC initially create IR; however, the toxic effects eventually lead to β -cell dysfunction, which marks the transition from impaired glucose tolerance to HD. In addition, a number of factors, including sarcopenia, sarcopenic obesity, gut dysbiosis, and hyperammonemia, have recently been linked to impaired glucose metabolism in LC. DM is associated with complications and poor outcomes in patients with LC, although the individual impact of each type 2 DM and HD is unknown due to a lack of categorization of diabetes in most published research. In fact, there is much skepticism within scientific organizations over the recognition of HD as a separate disease and a consequence of LC. Currently, T2DM and HD are being treated in a similar manner although no standardized guidelines are available. The different pathophysiological basis of HD may have an impact on treatment options. This review article discusses the existence of HD as a distinct entity with high prevalence rates, a strong pathophysiological basis, clinical and therapeutic implications, as well as widespread skepticism and knowledge gaps.

Key Words: Cirrhosis; diabetes; hepatogenous diabetes; glucose intolerance; insulin resistance; metabolism

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Core Tip: Hepatogenous diabetes appears to be the most prevalent form of diabetes in patients with liver cirrhosis. It is linked to the pathophysiological alterations and severity of cirrhosis. However, it is still an underappreciated problem and is not recognized as a distinct entity by scientific organizations. This article discusses the current state of knowledge about hepatogenous diabetes, including evidence of its existence and clinical implications.

INTRODUCTION

The maintenance of glucose homeostasis necessitates a coordinated response of insulin secretion, hepatic and peripheral glucose uptake, and suppression of hepatic glucose synthesis. The same is achieved *via* a complex control process involving several tissues and inter-organ crosstalk, including the liver, pancreas, muscles, and adipose tissues, as well as a number of circulating factors^[1]. The liver plays a key role in glucose homeostasis by regulating multiple glucose metabolism pathways such as glycolysis, glycogenolysis, gluconeogenesis, and glycogenesis^[2-4]. Therefore, hepatic dysfunction is likely to have an impact on glucose metabolism. In fact, the association between liver cirrhosis (LC) and diabetes mellitus (DM) has been known for a long time^[5,6]. The prevalence of diabetes in patients with LC ranges from 20% to 70%, which is significantly higher than the 6.28% prevalence of type 2 DM (T2DM) in the general population^[7,8]. The wide range of reported prevalence rates appears to be due to heterogeneity in the studied population, stage of liver disease, and evaluation method(s).

In 1906, Naunyn first coined the term “hepatogenous diabetes” (HD) to describe DM caused by LC^[9]. In the subsequent years, the association between DM and LC was studied more thoroughly, with hyperinsulinemia, insulin resistance (IR), and pancreatic- β -cell dysfunctions being commonly reported^[10-14]. Although cirrhosis due alcohol, non-alcoholic fatty liver disease (NAFLD), hepatitis C viruses (HCV), and hemochromatosis has been deemed a diabetogenic condition, multiple studies have shown that diabetogenic potential of cirrhosis cuts across etiologies. Emerging evidences suggest that in patients with LC, a complex interplay between the liver, pancreas, skeletal muscles, gut, and adipose tissues is involved in the pathogenesis of impaired glucose tolerance (IGT) and HD^[7,9,15,16]. However, despite plethora of evidence, HD is still not regarded as a distinct disease or a recognized complication of LC^[7,17,18]. Such skepticism among scientific bodies appears to be paradoxical. The global acceptance of this term is important in order to spur more research in this area.

DEFINITION AND CHARACTERISTICS OF HD

DM that develops as a result of LC is referred to as HD^[19]. For HD to be diagnosed, DM must have occurred after the onset of cirrhosis. In practice, however, distinguishing HD from T2DM can be challenging, especially in early cirrhosis, because both DM and cirrhosis have a long, indolent, and clinically silent course, making it difficult to determine which condition appeared first. Furthermore, the association between diabetes and LC is bidirectional, as patients with T2DM can develop NAFLD which may progress to cirrhosis^[20]. Certain etiological agents of LC such as ethanol, NAFLD, HCV, and hemochromatosis, have a direct diabetogenic effect which can lead to DM even before onset of cirrhosis, posing a classification dilemma. Therefore, there is an unmet need to develop a consensus-based criteria for defining HD in LC patients in order to ensure consistency in future clinical research.

There are a number of soft indicators that can help distinguish HD from T2DM^[7,17-19]. Unlike T2DM, HD can occur in patients with LC who don't have metabolic risk factors including a high body mass index, hyperlipidemia, or a family history of diabetes. HD

patients frequently have normal fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) but abnormal oral glucose tolerance tests (OGTTs), whereas T2DM patients often have high FBG. In addition, the degree of hyperinsulinemia and IR is substantially higher in HD than in T2DM patients (Table1).

PATHOPHYSIOLOGY OF HD

The pathophysiology of HD is complex and poorly understood. This appears to be caused by two major factors: IR and pancreatic β -cell dysfunction [Figure 1]. The development of IR is triggered by neurohormonal changes, endotoxemia, and chronic inflammation of LC. The toxic effects eventually reach the pancreatic islets, causing β -cell dysfunction, which leads to the development of HD. Recently, roles of hepatokines, adipokines, gut dysbiosis, hyperammonemia, sarcopenia and myosteatosis have emerged in the pathogenesis of metabolic disturbances in LC, including IR and glucose intolerance [Figure 2]. Thus, the identification of mechanisms that connect multi-organ dysfunction might unravel a novel understanding of HD pathophysiology.

Hyperinsulinemia and IR

Several studies have confirmed hyperinsulinemia and IR in LC patients^[10-12,32]. Hyperinsulinemia appears to be caused primarily by two abnormalities: decreased hepatic extraction and portosystemic shunting of insulin. Hyperglucagonemia, due to insufficient hepatic metabolism, may also contribute to hyperinsulinemia^[33]. An augmented insulin secretion due to pancreatic islet hypertrophy may contribute to hyperinsulinemia before the development of significant β -cell dysfunction^[34]. Persistent hyperinsulinemia leads to IR as insulin receptors are downregulated over target cell membranes^[35]. Insulin sensitivity has been reported to be normalized when hyperinsulinemia is reduced^[36]. Many studies have found a link between clinically significant portal hypertension and elevated IR^[37,38], which could be due to the existence of a portosystemic shunt. In LC patients, hyperinsulinemia deteriorates after the placement of a trans jugular intrahepatic portosystemic shunt (TIPS)^[39]. In contrast,

balloon-occluded retrograde transvenous obliteration (BRTO) of portosystemic shunts has been shown to ameliorate hyperinsulinemia in portal hypertensive patients^[40].

Clamp studies of whole-body glucose utilization have shown that IR in patients with LC is due to reduction in nonoxidative glucose disposal, which includes glucose conversion to glycogen or fat, as well as anaerobic glycolysis^[41,42]. Since ²extrahepatic glucose metabolism accounts for majority (~ 85%) of total body glucose metabolism under glucose clamp condition, reduction in nonoxidative glucose disposal leads to significant IR at peripheral tissues^[43, 44]. Many other studies have consistently ²demonstrated that diminished insulin-dependent glucose transport into skeletal muscle and a reduction in glycogen synthesis are mainly responsible for the reduction in peripheral glucose turnover in patients with LC^[45,46]. On the other hand, there appears to be no significant hepatic IR in LC^[47]. Thus, skeletal muscle is the primary site of IR in patients with LC.

Pancreatic dysfunction

Despite reports of pancreatic islet cell proliferation in patients with LC, insulin-positive islet area was found to be considerably reduced^[34,48,49]. In comparison to the control and T2DM groups, Sakata *et al* found that patients with LC have lower insulin expression and higher expression of the pancreatic transcription factor PDX-1 in their islets^[49]. Studies on animal models of LC and portal hypertension have also found a decreased insulin secretion from the pancreatic islets despite hyperinsulinemia^[13,14]. In a recent study, pancreas in LC patients showed congestive changes on dynamic contrast enhanced ultrasound and histopathology. In addition, decreased insulin secretion was found to be associated with pancreatic congestive changes. Despite the islets' expansion, the fraction of insulin-positive region per islet decreased, and this was negatively correlated with thickness of pancreatic vein due to portal hypertension^[14]. These data indicate that even when glucose tolerance is impaired, pancreatic hyposecretion can occur in LC patients. The inability of the pancreatic β -cell to compensate for worsening IR appears signal the switch from IGT to HD. An improved β -cell function is also required for the regression of diabetes after liver transplantation (LT)^[50].

Chronic hyperglycemia can produce toxic damage to the pancreatic islets, resulting in β -cells' dysfunction^[51-53]. The accumulation of advanced glycation end products (AGEs), which are normally eliminated by the liver, accelerates this process by causing oxidative stress in β -cells. The systemic low-grade hypoxia generated by advanced LC contributes to the further deterioration of β -cells function^[54]. Increased expression of hypoxia-inducible factors (HIF, mainly HIF-1 α) has been reported in many liver diseases, including NAFLD and alcoholic liver disease^[55]. HIF-1 α is known to regulate cellular glucose uptake, glycolytic enzyme activity, and insulin sensitivity^[56,57]. Apart from directly affecting glucose metabolism, activation of HIF-1 in patients with LC can elicit an inflammatory response in β -cells, contributing to the development of overt DM^[58].

In patients with LC, a number of disease-specific mechanisms of β -cell dysfunction may be operating. Chronic alcohol use and hemochromatosis produce glucokinase downregulation and increased oxidative stress, resulting in increased β -cells apoptosis and decreased glucose-induced insulin production, respectively^[59,60]. The combination of chronic hyperglycemia and high free fatty acid levels in NAFLD causes glucolipotoxicity, leading to pancreatic β -cells injury^[61]. Chronic HCV infection, on the other hand, causes pancreatic islets injury by a combination of autoimmune-mediated and direct cytopathic processes^[62-64].

Reduced incretins effect

Incretins serve an important function in maintaining glucose homeostasis. Enteroendocrine cells produce two naturally occurring incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide, which regulate glycemic control by boosting insulin secretion and lowering glucagon secretion during postprandial period. Dipeptidyl peptidase 4 (DPP-4) is a membrane-associated peptidase that has a wide range of organ distribution and exhibits pleiotropic effects through its peptidase activity. DPP4 inactivates GLP-1, which leads to the development of IGT and DM^[65]. Cirrhotic patients had higher serum DPP-4 activity and hepatic DPP-

4 expression, which reduces incretin effects^[66]. Thus, decreased incretin effects could play a role in the development of HD.

Gut dysbiosis

The gut microbiota is involved in the host immunity, metabolism, and intestinal endocrine function^[67]. Patients with LC frequently have changes in the composition and function of the gut microbiota with associated damage to the gut barrier, bacterial translocation, and systemic inflammation^[68,69]. The translocation of gut-derived endotoxins (notably lipopolysaccharide, LPS), which activates toll-like receptors, is involved in the pathogenesis of IR^[70]. Metabolic endotoxemia mediated by LPS/CD14 system dysregulates inflammatory tone, leading to diabetes and adiposity^[70]. Dysbiosis of the gut has been associated with obesity, metabolic diseases, and DM^[71]. Gut dysbiosis also contributes to hyperammonemia in LC patients which has some role in the development of peripheral IR^[72]. The human gut microbiota produces a variety of compounds, including branched-chain amino acids, whose circulation levels are linked to the risk of IR and DM^[73]. The gut microbiome of CLD patients with sarcopenia was found to be pro-diabetogenic in a recent study, with a high abundance of gram-negative bacteria containing LPS on the one hand and a low Firmicutes/Bacteroidetes ratio on the other^[74]. Therefore, gut dysbiosis could play an important role in the pathogenesis of HD in advanced LC.

Hyperammonemia

Hyperammonemia is a frequent abnormality in LC due to impaired hepatic detoxification to urea and bypass *via* portosystemic shunt. Hyperammonemia has been associated with IR for a long time^[75]. Hyperammonemia in LC is linked to enhanced myostatin expression in the skeletal muscle^[76]. Because myostatin is a negative regulator of muscle protein synthesis, a greater serum ammonia level can promote a rise in myostatin in skeletal muscle, leading to sarcopenia progression and its adverse consequences^[77,78]. Hyperammonemia is also associated with myosteatorsis which affects glucose transport and glycogen synthesis by downregulating muscle insulin

receptors^[79,80]. Thus, myostatin appears to have a role in cirrhosis-induced peripheral IR, as it causes sarcopenia and myosteatorsis.

Sarcopenia

Skeletal muscle is responsible for the majority of postprandial glucose consumption, making it an essential insulin target organ for glucose uptake and utilization^[81]. As a result, skeletal muscle loss might result in substantial IR^[81,82]. Sarcopenia, or the loss of skeletal muscle mass, quality, and strength, is common in LC patients and is linked to IR and DM^[83,84]. Sarcopenia in LC is caused by an imbalance in muscle protein turnover, which is influenced by a number of metabolic variables such as hyperammonemia, amino acid deficiency, hormone imbalance, gut dysbiosis, IR, and chronic inflammation^[81-84]. Sarcopenia and DM appear to have a bidirectional link. On the one hand, sarcopenia is common among DM patients; on the other hand, sarcopenia has been linked to an increased risk of DM^[85]. Sarcopenia is frequently accompanied by myosteatorsis, mitochondrial dysfunction, macrophage infiltration, and inflammatory cytokine release, all of which contribute to IR as well as lower glucose uptake and utilization^[83,84]. Previous studies have shown that skeletal muscles secrete a variety of cytokines, such as IL-6 and irisin, that regulate insulin sensitivity and promote metabolism^[86,87]. Thus, impairment of muscle secretory function due to sarcopenia may contribute to the development of DM in LC patients. Sarcopenic obesity, which affects up to 35% of patients waiting for a liver transplant, has a higher influence on metabolic profile than either condition alone^[88].

Hepatokines and Adipokines

Hepatokines and adipokines, proteins that regulate systemic metabolism and energy homeostasis, are secreted by the liver and adipose tissues, respectively^[89-91]. Crosstalk between hepatokines, adipokines, and myokines influences inflammation and fat metabolism in adipose and skeletal muscle, which can contribute to IR^[90,92,93]. Additionally, some hepatokines influence insulin secretion by the pancreas, which can independently affect peripheral tissue glucose uptake and metabolism. Hepatokines are known to contribute to the pathogenesis of metabolic syndrome, NAFLD, and

2DM^[90,92]. Furthermore, several hepatokines control pancreatic insulin secretion, which can affect glucose uptake and metabolism in peripheral tissues independently. Many hepatokines, including fetuin A, fetuin B, retinol-binding protein 4, and selenoprotein P, have been linked to the induction of metabolic dysfunction^[93]. Therefore, their significance in metabolic abnormalities of LC is worth investigating. Resistin is an adipokine that reduces insulin sensitivity in adipocytes, skeletal muscles, and hepatocytes. Serum resistin level has been found to be significantly elevated in patients with LC, which may contribute to IR ^[94].

CLINICAL IMPACT OF DM ON LC

The presence of DM (HD+T2DM) in patients with LC is associated with numerous complications and poor outcomes (Table 3). Because most studies have not stratified DM into HD and T2DM, the individual impact of HD cannot be ascertained^[16,18,95,96]. However, because HD is a direct complication of liver cirrhosis, it is likely to have a greater negative impact on prognosis of liver cirrhosis than T2DM.

Impact on complications of LC

Many complications of LC, including hepatic encephalopathy (HE), variceal hemorrhage (VH), sepsis, and hepatocellular carcinoma (HCC) have been associated with DM. DM has been associated with an increased incidence and severity of HE in patients with LC. In a study, the proportion of patients with severe HE was found to be higher in diabetic than in nondiabetic patients (60% *vs* 20%, $P = 0.007$)^[97]. Jepsen *et al* reported that diabetic LC patients had a higher incidence of first-time overt HE in a year (26% *vs* 15.8%) as well as greater risk of HE progression > grade 2 (64% *vs* 42%), compared to non-diabetic LC^[98]. DM is an independent predictor of HE after TIPS in LC patients^[99,100]. Possible mechanisms by which DM can promote HE include induction of intestinal glutaminase, intestinal bacterial overgrowth, hyperammonemia, sepsis, and development of a chronic inflammatory state^[101–103].

Chronic hyperglycemia may induce splanchnic hyperemia in LC patients leading to an increased portal pressure and risk of VH^[22,104,105]. In a prospective study ($n = 194$), HD

(55.4%) was significantly associated with increased portal pressure and risk of VH^[104]. Yang *et al* also reported DM as an independent predictor of VH in LC patients (OR=2.99)^[105]. Wang *et al* have reported an increased risk of rebleeding following endoscopic variceal ligation in HD patients (44% vs 13.9% in 6 mo)^[22]. DM also increases the mortality risk following upper gastrointestinal bleeding in LC patients (OR 5.7)^[106]. DM increases the risk of bacterial infections in patients with LC^[107]. In a study on hospitalized LC patients ($n = 178$), the prevalence of bacterial infections was higher among diabetics than non-diabetic (85% vs 48%, $P < 0.0001$)^[108]. DM increases the risk of spontaneous bacterial peritonitis in LC (HR 1.51)^[109]. Furthermore, uncontrolled DM in LC has greater risk of bacterial infection, suggesting that glycemic control could be a modifiable target^[109,110]. DM is also a risk factor for HCC in LC patients. In a cohort study, DM increased the risk of HCC in patients with non-HCV cirrhosis (HR=2.1) but not in HCV-cirrhosis, who already have a very high risk of developing HCC^[111]. Takahashi *et al.* have reported that 2-hours post-glucose-challenge hyperglycemia was significant factor for HCC development in HCV-RNA-positive patients (HR 6.9)^[112].

Impact on outcome and LT

The survival rate in patients with LC is significantly reduced in presence of DM^[25,107,113,114]. Bianchi *et al* reported that 5-year survival of LC patients with or without DM was 41% and 56%, respectively, $P = 0.005$ ^[113]. In a prospective study on 100 compensated LC patients, 5-year cumulated survival rates were lower (31.7% vs 71.6%) in those with abnormal OGTT normal OGTT ($P = 0.02$)^[114]. In another prospective study, the cumulative 5-year survival was 94.7% in LC with normal glucose tolerance compared to 56.6% in those with DM on OGTT^[25]. In a recent French study, DM had a greater impact on survival in early stages of LC patients (MELD score <10), suggesting that the severity of liver disease can mask the deleterious effect of DM^[107]. In a longitudinal study, Holstein *et al* also found that all deaths in HD patients were due to complications related to LC rather than diabetes-related complications. This could be

because of advanced liver failure in HD patients which shortens the time for diabetes complications to emerge^[31].

The pre-transplant DM also has adverse impact on outcomes of liver transplantation. Tietge *et al* demonstrated that pre-liver transplant IGT or DM are the major risk factors for post-transplant diabetes^[115]. In a meta-analysis of 20 studies ($n = 4580$), impaired glucose metabolism was among the risk factors for new onset DM after LT^[116]. Post-LT DM is associated with increased risk of mortality and multiple morbid outcomes such as cardiovascular disease, infection, biliary complications, renal impairment, and graft rejection^[117-119].

SKEPTICISM ABOUT HD

Ever since Naunyn first coined the term "hepatogenous diabetes" in 1906, there has been a lot of research on this subject, especially in the 1970s and 1980s, but the momentum faded little bit and the term HD began to lose its recognition and appeal. To date, the most scientific bodies, such as the American Diabetes Association (ADA) and the American Association for the Study of Liver Disease (AASLD), do not recognize HD as a distinct entity. As a result, HD is underestimated by most medical fraternity belonging to gastroenterology and endocrinology departments. There are no consensus-based diagnostic criteria or therapeutic guidelines for HD. Such skepticism does not appear to be justified. A strong link between LC and diabetes, several evidences of impaired glucose metabolism in LC patients, and a number of characteristics that distinguish HD from T2DM, all point to HD being a separate disease (Table 1). In addition, a number of factors have recently been identified as playing a role in the pathogenesis of impaired glucose metabolism in LC, including sarcopenia, sarcopenic obesity, gut dysbiosis, hyperammonemia, and hepato-adipokines. We believe that the time has arrived for scientific bodies to acknowledge HD as a distinct entity. This will pave the road and create doors for a large number of researchers to work on this topic in greater depth.

THERAPEUTIC CONSIDERATION

There are no standardized guidelines for managing diabetes in LC patients. Currently, T2DM and HD are being treated in a similar manner^[7,20,50,96]. In general, insulin is recommended for LC at all stages, while many oral hypoglycemic agents (OHA) are being used in LC up to Child-Pugh class B. A number of pathophysiological changes caused by LC, such as changes in the hepatic blood flow, fluid balance, hypoalbuminemia, and gut dysbiosis, might impact the bioavailability, distribution, and metabolism of antidiabetic medicines, posing a risk to patients. As a result, the majority of current OHA are considered unsafe for LC in Child-Pugh class-C, the stage which has the highest frequency of HD. Because the pathophysiology of T2DM and HD differs, the therapeutic approach should differ accordingly. However, because the pathophysiology of T2DM and HD differs, the therapeutic approach may need to be adjusted. Several pathophysiological changes produced by cirrhosis, such as degree of hepatic dysfunction, large portosystemic shunt, sarcopenia, gut dysbiosis, and hyperammonemia, all of which have an indirect impact on HD, could influence treatment choices, including drug selection (Table 4).

General measures

A moderate caloric restriction may be recommended for HD patients, particularly those who are overweight or obese. However, because of sarcopenia and sarcopenic obesity, it is important to maintain a sufficient protein intake to avoid muscle loss. Physical exercise may aid in the preservation and restoration of muscle function and mass while also improving IR. Physical exercise has also been shown to improve the HVPG and nutritional status in LC patients^[120,121]. Because HD is a direct complication of LC and is associated with severity of cirrhosis, improving hepatic dysfunction and portal hypertension should be one of the important goals of HD treatment. Etiology-specific therapy (for HCV, hepatitis B, autoimmune hepatitis, *etc.*) and non-selective β -blocker to control portal hypertension may play a role in preventing, delaying, or attuning HD in LC patients. In a recent prospective study of 96 acute-on-chronic liver failure patients, 51 (53.1%) of whom had new-onset diabetes, most likely HD, the glycemic

indices improved in one-third of patients following improvement of their liver function without taking anti-hyperglycemic medication^[122].

OHA

Among the OHAs that can be considered for HD patients are metformin, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI) and sodium glucose co-transporter-2 (SGLT2) inhibitors^[7,20,50,96]. Glycemic targets for HD patients should be set based on postprandial glucose levels rather than HbA1c or FBG. Metformin can be an important therapeutic agent for HD, because it is free of hepatic metabolism, plasma protein binding, and hypoglycemia risk, as well as having other benefits like cardio protection and a lower risk of HCC and HE^[123–125]. However, metformin should be avoided if there is concurrent renal impairment with an eGFR of less than 45 mL/min/1.73 m² due to the significant risk of lactic acidosis^[50]. Upregulation of DPP-4 expression in LC patients contributes to the development IR^[66]. Therefore, incretin-based antidiabetic agents, like GLP-1 receptor agonists (Liraglutide) and DPP-4 inhibitors can be an important agent for HD. They are generally safe in LC patients, increase muscle mass, and pose little risk of hypoglycemia or weight gain^[126,127]. Recently, a group of investigators from Taiwan have raised safety concerns about use of metformin and DPP4 inhibitors in LC^[128,129]. From analysis of Taiwan's National Health Insurance Research Database, investigators found that metformin use (>1000 mg/d) in patients with compensated LC patients was associated with higher risks of mortality and decompensation^[128]. Similarly, DPP-4 inhibitor was found to be associated with higher risks of hepatic decompensation and failure in another study^[129]. These results should be viewed with caution, as the findings need to be validated in prospective studies. In a recent study, sulfonylureas (SU) was found to be associated with lower risks of all-cause mortality and major cardiovascular events in LC patients with diabetes^[130]. However, SU should be better avoided in HD patients because of a high risk of hypoglycemia. HD patients are already at high risk of hypoglycemia due to poor

glycogen storage and reduced gluconeogenesis capacity. Due to hypoglycemia, stringent glycemic control should not be attempted in HD patients.

In obese HD patients, metformin, SGLT2i, and GLP-1 agonists can be preferred because they tend to promote weight loss. When sarcopenia is severe, metformin, GLP-1 agonist (Liraglutide), and DPP-4 inhibitors are preferable^[123]. SUs and SGLT2 inhibitors may increase the risk of sarcopenia^[131,132]. Metformin or AGI, both of which have a positive effect on blood ammonia levels and the risk of HE, should be considered in hyperammonemic HD patients. Metformin effect is mediated partially by inhibition of glutaminase activity in enterocytes, while AGI (acarbose) stimulates the gut peristalsis and proliferation of the saccharolytic bacteria^[133,134]. If there is a large portosystemic shunt in such patients, shunt occlusion using BRTO may be considered. Alteration of gut dysbiosis using probiotics is another option that requires investigation.

Insulin

Insulin therapy is considered to be the safest and most effective for patients with LC, and it is currently the sole option available for LC patients of Child-Pugh class C. However, there are many concerns about the use of insulin in HD patients who have a higher degree of hyperinsulinemia and IR than LC patients with T2DM. The insulin requirements in such patients might vary greatly, making it difficult to maintain glycemic control without increasing the risk of hypoglycemia. Insulin use has also been associated with HCC in LC patients^[134]. Hence, it should be avoided in patients who are at high risk of developing HCC, such as those with dysplastic liver nodules and elevated serum alpha fetoprotein levels. In a recent study, insulin use in LC patients with diabetes was found to be associated with increased risks of hypoglycemia, cardiovascular events, liver-related complications, and mortality compared to insulin nonusers^[135]. Given these considerations, insulin cannot be regarded an optimal anti-diabetic treatment for LC patients, and the search for a better alternative should be prioritized.

LT

Finally, HD should be reversible after LT because it is caused by LC. There have been reports of HD reversibility with LT, however this does not occur in all patients^[136]. In one study, DM regressed in 63.9% of patients after LT, while DM never regressed in 36% of patients after two years of follow-up. The reversibility of HD appears to be determined by the level of pre-LT pancreatic β -cell injury and its improvement after LT. Grancini *et al* found that improved β -cell function plays a major role in favoring diabetes regression following LT, in the presence of a sustained improvement of IR^[50]. With progression of LC, progressive accumulation of toxic materials (AGEs, HIF, *etc.*) may lead to severe non-repairable β -cells injury, making the chances of HD reversibility less likely. The diabetogenic potential of immunosuppressive therapies could also be one of the reasons behind non-reversibility of diabetes following LT.

CONCLUSION

In conclusion, the evidence suggests that patients with LC can have two forms of diabetes: T2DM and HD, with HD appearing to be the predominant type. HD is a direct complication of LC since it is strongly linked to the pathophysiological alterations and severity of LC. However, HD is still an underappreciated problem that isn't even recognized as a separate entity by scientific organizations. To maintain consistency in clinical research, future directions will first require recognition of HD as a distinct entity, followed by the creation of a consensus definition for HD. Understanding the complex pathophysiology of LC leading to HD, including changes in the liver-multiorgan cross-talk, will also be critical for providing evidence-based management recommendations.

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