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REVIEW

The Liver Disease-Related Hypoglycemia: An Overview of the Impact, Management Approaches, and Underlying Mechanisms

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Abstract

Hypoglycemia in liver disease is a clinically significant yet underrecognized complication that severely impacts patient health and quality of life. Growing evidence highlights the liver's central role in glucose homeostasis, with dysfunction leading to hypoglycemia through impaired gluconeogenesis, insulin/glucagon dysregulation, and malnutrition. This review compiles disease-specific mechanisms (e.g., cirrhosis vs. acute liver failure) and their clinical implications, revealing that hypoglycemia risk correlates with liver disease severity, comorbidities, and therapeutic regimens. While current strategies emphasize tailored nutrition, careful pharmacotherapy, and continuous glucose monitoring (CGM), critical gaps persist in early diagnosis and personalized management. This work provides clinicians with a practical framework for hypoglycemia risk stratification, integrating (1) liver disease stage-specific monitoring protocols, (2) malnutrition correction strategies, and (3) insulin dose adjustment guidelines to alleviate iatrogenic hypoglycemia. Future directions include validating a liver-specific CGM algorithm optimized for cirrhosis, developing targeted therapies, and conducting multicenter trials to evaluate structured hypoglycemia prevention protocols in advanced liver disease. By bridging mechanistic insights with actionable care pathways, this review aims to reduce hypoglycemia-related morbidity in this vulnerable population.

Key words: liver disease; hypoglycemia; mechanisms; impacts; management strategies

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Introduction

Epidemiological studies show an alarming trend that global incidence and mortality rates of liver diseases continue to increase annually. This increase is particularly evident in metabolic liver disorders, including non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease, which have emerged as a major public health concern worldwide (Li and Alazawi, 2020; Wahlang et al, 2018). The liver plays a crucial role in maintaining glucose homeostasis in the blood (Scoditti et al, 2024; Zhang et al, 2014). Approximately 30%–50% of patients with liver diseases have been proven to experience clinically significant hypoglycemia. A hospital-based study in Peshawar, Pakistan, reported that 48% of patients with cirrhosis developed hypoglycemia (Khan et al, 2024). Similarly, a study that included 218 patients with acute-on-chronic liver failure in China observed a hypoglycemia prevalence rate of 45.41% (Yang et al, 2023).

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Furthermore, a retrospective cohort study using the National Health Insurance System of South Korea reported that NAFLD is linked to a higher risk of severe hypoglycemia, with 2.3% of patients experiencing a severe hypoglycemic event during a median follow-up of 5.2 years (Lee et al, 2022). Among diabetic patients, hypoglycemia is associated with a decline in quality of life, increased fear and anxiety, reduced productivity, and higher healthcare costs (Fidler et al, 2011; Sendekie et al, 2023). Moreover, it is linked to a poor prognosis in individuals with liver diseases, and it serves as an early independent predictor of bacteremia in cirrhotic patients (Saiman and Mahmud, 2021). Additionally, higher mortality rates have been observed in liver disease patients with hypoglycemia (Hung et al, 2021; Yang et al, 2023). Therefore, promptly identifying and managing hypoglycemia is essential for efficient treatment in individuals with liver disease.

Hypoglycemia poses significant challenges for patients with liver disease, as the liver plays a crucial role in glucose metabolism, including its synthesis, storage, and release. The liver stores excess glucose after meals and releases it during fasting to maintain stable blood glucose levels (Jones, 2016). When liver function is compromised, vulnerability to hypoglycemia increases, leading to severe consequences, including confusion, coma, or even death (Yalçın et al, 2022).

Hypoglycemia in liver disease patients results from complex mechanisms involving multiple interrelated factors. Liver dysfunction disrupts glucose metabolism and synthesis (Jones, 2016), while insulin resistance impairs the pancreas's ability to regulate blood sugar levels effectively, increasing the risk of hypoglycemia (Rahman et al, 2021). Additionally, factors like malnutrition and metabolic disorders further elevate this risk. However, the precise mechanisms through which different liver disease types lead to hypoglycemia are yet to be completely explored.

There is no clear consensus on the exact definition or diagnostic strategies for hypoglycemia in liver disease patients. The current standard for diagnosing liver disease-related hypoglycemia is based on non-liver disease populations (Oki et al, 2018; Verma et al, 2025). Furthermore, the clinical manifestations of hypoglycemia may be obscured by concurrent hepatic pathology, leading to diagnostic delays. For example, symptoms such as fatigue and mental confusion in liver disease patients closely resemble hypoglycemic episodes, making differentiation challenging (Scheen, 2014; Swain and Jones, 2019). Management strategies for hypoglycemia usually include dietary adjustments, medication management, lifestyle intervention, and blood glucose monitoring (Castera and Cusi, 2023; Isaacs et al, 2021; Johansen et al, 2017). However, effective treatment strategies must be tailored, and current guidelines, particularly addressing hypoglycemia in liver disease, remain limited.

Given the significant challenges in diagnosing and treating hypoglycemia in liver disease patients, along with limited research on its underlying mechanisms, this review aims to systematically compile current evidence on pathophysiology, clinical consequences, and evidence-based management of liver disease-related hypoglycemia. By integrating mechanistic insights into practical therapeutic strategies, this review seeks to address critical knowledge gaps and provide clinicians with practical approaches to reduce hypoglycemia-related morbidity in high-risk populations.

Hypoglycemia in Liver Disease Patients: A Health Issue Not to be Ignored

Pathological Mechanisms of Liver Disease-Related Hypoglycemia

The Role of the Liver in Glucose Metabolism

The liver plays a crucial role in glucose metabolism by maintaining stable blood glucose levels through mechanisms such as glycogenesis, glycogenolysis, and gluconeogenesis. Hepatic miR-291b-3p has been proven to regulate lipids and glucose metabolism, targeting p65 to regulate phosphatase and tensin homolog deleted on chromosome ten (PTEN) expression and adenosine monophosphate-activated kinase alpha1 (AMPK alpha1) (Guo et al, 2017). As the main storage site for glucose, the liver stores and releases this vital energy source when needed, highlighting its importance in glucose metabolism (Gjorgjieva et al, 2019). Several key factors affect hepatic glucose modulation, including hormones such as insulin and glucagon, nutritional status, and metabolic disorders (Kalra et al, 2021). For example, during starvation, the liver compensates for diminished glucose availability by activating gluconeogenesis and glycogenolysis to meet the energy demands (Jones, 2016). Therefore, any disruption in the liver's metabolic activities can lead to hypoglycemia.

The Impact of Liver Dysfunction on Glycogen Storage

Liver dysfunction significantly affects its capability to store glycogen, increasing the risk of hypoglycemia. Conditions like liver cirrhosis and other liver disorders damage liver cells, reducing their ability to glycogen synthesis. The conversion between glycogen and glucose involves specific metabolic pathways for glycogen synthesis and breakdown. Therefore, deficiencies in the enzymes regulating these pathways can disrupt glucose metabolism, resulting in hypoglycemia, hepatomegaly, and various liver conditions, including glycogen storage diseases (GSD). The symptoms of these conditions vary depending on the location of the enzymatic defect and may involve skeletal and/or cardiac myopathy (Kanungo et al, 2018). Furthermore, liver inflammation and fibrosis can exacerbate metabolic dysfunction, disrupting both glycogen synthesis and degradation, further increasing the likelihood of hypoglycemic episodes. In chronic liver disease, extensive fibrotic changes lead to a substantial decline in glycogen reserves (Senadhi, 2011).

Dysregulation of Insulin and Glucagon in Liver Disease

Insulin and glucagon play crucial roles in regulating blood glucose levels. Insulin, produced by pancreatic β-cells, promotes glucose uptake by cells, consequently reducing blood sugar levels (Rahman et al, 2021). In glucose metabolism, insulin first stimulates its receptor, activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signalling pathway (Arabloei Sani et al, 2022; Crespo-Masip et al, 2022). The PI3K/AKT pathway is the key regulator of insulin signalling, modulating blood glucose uptake, metabolism, cell survival, proliferation, migration, and glycogen synthesis (Liu et al, 2015). Conversely, glucagon, released by pancreatic α-cells, stimulates the liver to convert glycogen into glucose, thereby

increasing blood glucose levels (Brown and Tzanakakis, 2023). Glucagon works by increasing the cyclic adenosine monophosphate (cAMP) levels, activating protein kinase A (PKA), and subsequently phosphorylating cAMP response element-binding protein (CREB). This mechanism induces the expression of crucial gluconeogenic genes, including glucose-6-phosphatase catalytic subunit (G6PC) and phosphoenolpyruvate carboxykinase-1 (PCK1) (Goldstein and Hager, 2018).

The balance between insulin and glucagon is profoundly disrupted in patients with liver disease, resulting in significant glycemic instability. Impaired hepatic metabolic function reduces insulin clearance, leading to chronic hyperinsulinemia, and suppresses hepatic glucose production by inhibiting glycogenolysis and gluconeogenesis. Simultaneously, diminished glucagon clearance elevates systemic glucagon levels. However, despite hyperglucagonemia normally promotes glucose production, its effects are reduced due to insulin dominance and hepatic glucagon resistance. This resistance, caused by portal hypertension-induced dysfunction of glucagon receptor signalling, is particularly pronounced in cirrhosis. Furthermore, this dual hormonal dysregulation significantly increases the likelihood of hypoglycemia, particularly during fasting (Kalra et al, 2021).

Disease-Specific Regulatory Mechanisms

In patients with liver cirrhosis, insulin secretion is increased, insulin sensitivity is significantly reduced, and insulin clearance is disrupted (Letiexhe et al, 1993). Glucagon-like peptide-1 (GLP-1), a gut-derived incretin hormone, is pivotal in stimulating insulin secretion in response to glucose (Nouri-Vaskeh et al, 2023). Lower GLP-1 levels in cirrhotic patients (Nouri-Vaskeh et al, 2023) decrease insulin secretion, further exacerbating glucose metabolism disorders. Furthermore, liver cirrhotic patients exhibit elevated tumour necrosis factor-alpha (TNF-α) levels, a cytokine that plays a vital role in the development of insulin resistance. TNF-α, primarily produced by adipocytes and peripheral tissues, induces local inflammation by generating reactive oxygen species (ROS) and activating transcription pathways, ultimately impairing insulin signalling and leading to insulin resistance (Akash et al, 2018).

In liver cancer cells, Polycomb Repressive Complex 2 (PRC2)-mediated trimethylation of histone H3 lysine 27 downregulates the expression of fructose-1,6-bisphosphatase (FBP1), thereby inhibiting gluconeogenesis (Leithner, 2020). As a result, the liver's ability to generate glucose from non-carbohydrate precursors such as lactate, amino acids, and glycerol is substantially compromised, resulting in reduced glucose production and an increased risk of hypoglycemia. The mechanism underlying refractory hypoglycemia has been associated with tumour secretion of insulin-like growth factor 2 (IGF-2) (Daughaday, 2007). **Supplementary Fig. 1** presents the effects of liver disease on gluconeogenesis, glycogen metabolism, and insulin regulation.

The Impact of Liver Fibrosis on Hypoglycemia

Research has revealed that, compared to healthy rats, liver fibrotic rats exhibited a higher proportion of β-granules and fewer long glycogen chains. Addition-

ally, the activity of glycogen branching enzyme and glycogen phosphorylase was significantly reduced in the fibrotic rats. Transcriptome and proteomics analyses indicated mitochondrial dysfunction in fibrotic rats, which may lead to structural alterations in glycogen (Wan et al, 2022).

Incidence of Hypoglycemia in Liver Disease Patients

Occurrence of Hypoglycemia in Different Types of Liver Disease (Such as Hepatitis, Cirrhosis, Liver Cancer)

The frequency of hypoglycemia varies significantly among individuals with liver diseases, depending on the specific condition and its progression. Research indicates that patients with hepatitis generally have lower rates of hypoglycemia. However, it increases significantly as the disease progresses to cirrhosis or liver cancer. For example, a cross-sectional study observed that 48% of cirrhotic patients experienced hypoglycemia after a six-hour fasting period before an endoscopic examination, with its occurrence closely linked to disease duration and Child-Pugh classification (Khan et al, 2024). Additionally, individuals with type 2 diabetes and compensated cirrhosis demonstrated higher mortality rates and a greater prevalence of severe hypoglycemia than those without cirrhosis (Yen et al, 2022). In cases of chronic liver failure, hypoglycemia occurs in 45.41% of individuals, with cirrhosis and elevated Model for End-Stage Liver Disease (MELD) scores identified as major risk factors, whereas high fibrinogen levels appear to offer a protective effect (Yang et al, 2023).

In patients with hepatocellular carcinoma (HCC), hypoglycemia due to Non-islet cell tumour hypoglycemia (NICTH) occurs in 4%–27% of cases and is associated with a poor prognosis (Regino et al, 2020). Furthermore, a study involving 375 patients with NAFLD reported that 14.4% of cases experienced hypoglycemia three hours post a 75 g oral glucose tolerance test (OGTT), with this effect being particularly evident among those with early-stage liver fibrosis (Morio et al, 2017).

Clinical Factors Affecting Hypoglycemia

Various key factors, such as age, play a crucial role in determining the risk of hypoglycemia among individuals with liver disease. Research indicates that older adults are more vulnerable to hypoglycemia due to age-related physiological declines (Anno et al, 2018). The severity of liver disease also impacts hypoglycemia risk, with individuals having both diabetes and liver cirrhosis experiencing hypoglycemic episodes 2.7 times more frequently than those without cirrhosis (Yen et al, 2022).

Additionally, comorbid conditions such as diabetes, renal insufficiency, obesity, and active infections increase the risk of hypoglycemia (Kaewput et al, 2020; Lee et al, 2022; Lv et al, 2020; Su et al, 2017). Medication use is another crucial factor, as patients receiving insulin or sulfonylureas encounter a substantially higher risk of hypoglycemia (Braet et al, 2020). Therefore, identifying and addressing these clinical factors is crucial for developing effective management strategies to reduce the frequency of hypoglycemia and its associated complications among liver disease patients.

Clinical Manifestations and Diagnosis

Typical Symptoms of Hypoglycemia

Hypoglycemia is a medical condition characterized by a drop in blood glucose levels below the normal range, commonly observed among diabetic individuals, particularly those receiving insulin or other glucose-lowering agents. Symptoms of hypoglycemia are divided into two main categories: autonomic and neuroglycopenic symptoms. Autonomic symptoms, caused by adrenaline release, include palpitations, excessive sweating, tremors, and anxiety. In contrast, neuroglycopenic symptoms occur due to insufficient glucose supply to the brain, resulting in dizziness, fatigue, confusion, and, in severe cases, coma (Adukauskiene and Blauzdyte, 2006).

In patients with liver disease, the presentation of hypoglycemia often overlaps with or is exacerbated by concurrent hepatic dysfunction. For instance, in individuals with hepatic encephalopathy (Frontera, 2014), hypoglycemia can trigger or worsen neurological symptoms such as asterixis (flapping tremor), disorientation, and impaired consciousness. These manifestations may either mimic or mask the primary neuroglycopenic effects, making diagnosis and management challenging. Additionally, patients with advanced liver failure may exhibit jaundice, coagulopathy, or ascites alongside hypoglycemic episodes (Rifaie and Saner, 2020), reflecting widespread metabolic dysregulation. In some patients, particularly among those experiencing recurrent episodes of hypoglycemia, a condition referred to as hypoglycemia unawareness may develop. This phenomenon is characterized by an inability to detect the early warning signs of hypoglycemia, despite the significant decrease in blood glucose levels. This reduced sensitivity substantially increases the risk of severe complications, highlighting the critical need for patients and caregivers to promptly recognize hypoglycemic symptoms to prevent adverse outcomes (Hölzen et al, 2024).

Diagnostic Criteria and Testing Methods

The identification of hypoglycemia is primarily based on "Whipple's triad", which comprises three principal elements: the presence of hypoglycemic symptoms, a blood glucose level below the normal range, and symptom resolution following glucose or carbohydrate intake (Kandaswamy et al, 2016). In healthy individuals, symptoms of hypoglycemia usually appear when blood glucose levels drop below 3.05 mmol/L (55.00 mg/dL). However, in cases with frequent hypoglycemic episodes, the threshold for symptom onset may be even lower. For diabetic patients, the American Diabetes Association defines hypoglycemia as a blood glucose level below 3.89 mmol/L (70 mg/dL) (ElSayed et al, 2023). Furthermore, diagnostic thresholds need to be stratified for liver disease patients. Those with concurrent diabetes should follow the American Diabetes Association's standard of $<$3.89 mmol/L (70 mg/dL), while non-diabetic patients with chronic or acute liver failure may exhibit pathological hypoglycemia at levels $<$2.8 mmol/L (50 mg/dL) due to impaired gluconeogenesis.

During acute liver failure, such as after paracetamol intoxication, gluconeogenesis can be severely impaired, resulting in elevated lactate levels ($>$20 mmol/L)

and significant hypoglycemia (<1 mmol/L) (Oldenbeuving et al, 2014). Notably, half of these patients experienced hypoglycemic episodes during hospitalization, underscoring hypoglycemia as an independent risk factor contributing to increased mortality within 90 days (Yang et al, 2023). For dynamic assessments, such as the 72-hour fasting test, the practical workflow involves inpatient monitoring with serial glucose measurements every 4–6 hours, along with insulin/C-peptide assays if the glucose falls below 3.0 mmol/L (Prieto-Saldarriaga et al, 2022). This test is primarily used for suspected insulinoma or unexplained non-diabetic hypoglycemia.

Monitoring blood glucose levels is essential for diagnosing hypoglycemia, primarily performed using fingertip blood glucose meters and continuous glucose monitors (CGM). Fingertip blood glucose meters are the preferred method due to their low cost and immediate results (Sempionatto et al, 2021). However, their accuracy in liver disease patients may be affected by peripheral hypoperfusion and anemia (Gonzalez-Casas et al, 2009). CGM technology offers real-time data on blood glucose fluctuations, enabling patients to better manage their blood sugar and prevent hypoglycemia (Ogawa et al, 2022). However, CGM reliability can be decreased in cases of severe edema, often seen in decompensated cirrhosis, and it requires calibration with venous blood. Laboratory tests are crucial for identifying the underlying causes of hypoglycemia by measuring insulin levels, C-peptide levels, and specific hormones, which help distinguish between types of hypoglycemia (Liu et al, 2023), such as those caused by insulinoma or medications.

Hypoglycemia in liver disease patients is mainly caused by insufficient glycogen reserve and decreased gluconeogenesis, especially in fasting, rather than abnormal insulin secretion. At this stage, the levels of insulin and C-peptide may be normal or low, but routine tests do not directly reflect the liver's impaired glucose metabolism. Therefore, these tests should be combined with liver function indicators, such as albumin and prothrombin time, as well as imaging examination.

For diabetic patients, assessing the risk of hypoglycemia includes self-monitoring blood glucose, maintaining detailed dietary records, and reviewing medication regimens. This information helps healthcare providers to devise personalized treatment plans to reduce hypoglycemia risk (Carlson et al, 2017). In contrast, assessing hypoglycemia in non-diabetic individuals can be more challenging, as it may arise from various endocrine dysfunctions or metabolic issues, requiring a comprehensive endocrine evaluation (Yukina et al, 2023). For hospitalized diabetic patients, especially those with liver impairment, CGM is recommended to promptly identify nocturnal hypoglycemia (McCall et al, 2023).

Complications of Hypoglycemia and Their Clinical Consequences

Failure to quickly identify and manage hypoglycemia can lead to severe health consequences, including seizures, irreversible brain injury, coma, and even death (Vannucci and Vannucci, 2001; Yalçın et al, 2022; Yen et al, 2022). In people with diabetes, repeated hypoglycemic episodes can adversely impact their quality of life and increase the risk of cardiovascular diseases (Echouffo-Tcheugui et al, 2022). Furthermore, hypoglycemia can cause long-term neurological damage, especially in infants and young children, potentially leading to cognitive deficits and develop-

mental delays (Yalçın et al, 2022). In patients with liver cirrhosis, hypoglycemia is a key prognostic indicator of 30-day mortality, particularly among those with pre-existing HCC (Hung et al, 2021). Moreover, it also serves as an early, independent predictor of bacteremia and mortality during hospitalization in cirrhotic individuals (Saiman and Mahmud, 2021). Hence, promptly identifying and managing hypoglycemic episodes is crucial for minimizing complications and enhancing patient outcomes.

Management Strategies for Hypoglycemia

Evaluation of Existing Treatment Methods

Management strategies for hypoglycemia should include dietary adjustments, pharmacological interventions, and patient education on recognizing symptoms. While these strategies are foundational, challenges in adherence, cost, and efficacy increase, particularly in patients with cirrhosis and additional comorbidities. Exercise and lifestyle changes, especially dietary modifications, are essential to ensure optimal nutritional health in individuals with chronic liver disease (Aller de la Fuente, 2022). Adopting a Mediterranean diet, where carbohydrates constitute 50%–65% of total caloric intake, can help prevent hypoglycemia (Castera and Cusi, 2023). It is also crucial to maintain postprandial glucose levels between 5.0–7.8 mmol/L (90–140 mg/dL) to avoid both hyperglycemia and hypoglycemia. Small, frequent meals with a balanced macronutrient distribution (40% carbohydrates, 30% protein, 30% fats) support hepatic function and glucose regulation (Quetglas-Llabrés et al, 2023). However, adherence to strict dietary regimens can be challenging due to cirrhosis-related symptoms like anorexia, early satiety, or hepatic encephalopathy. Additionally, cost-related barriers exist, as nutrient-dense foods (e.g., lean proteins and fresh produce) may be inaccessible to low-income individuals.

To overcome these challenges, culturally tailored meal plans, and ready-to-use nutritional supplements should be included in dietary plans, and dietitians consulted in multidisciplinary care teams to address individual-specific barriers, such as the need for texture modifications in patients with dysphagia. Patient education is crucial to ensure an understanding of risk factors, early warning signs, and treatment options for hypoglycemia (Nakhleh and Shehadeh, 2021). However, cognitive impairment in cirrhosis or encephalopathy can impede retention. Therefore, visual aids and caregiver-inclusive training programs should be used to enhance comprehension and facilitate effective implementation.

Additionally, establishing personalized blood glucose management targets is essential. The primary goal in treating hypoglycemia is to rapidly restore blood glucose levels to a safe range, thereby preventing neurological damage and reducing symptoms. For conscious individuals, the recommended treatment involves administering 15–20 grams of glucose orally, though any glucose-containing carbohydrate can be effective. Blood glucose levels should be evaluated after 15 minutes, and if hypoglycemia continues, treatment should be repeated; once blood glucose levels stabilize, consuming a meal is essential to avert recurrence (Quiroz-Aldave et al, 2024). In instances of severe hypoglycemia among diabetic patients, intra-

venous glucose administration is more effective than oral carbohydrate administration (Gilmore et al, 2022). Glucagon, acts as an emergency medication, swiftly elevating blood glucose levels in individuals who are unconscious or unable to consume glucose due to critical hypoglycemia (Isaacs et al, 2021).

The management of hypoglycemia generally entails increasing caloric consumption throughout the day, while patients are also advised to avoid alcohol and consider adjusting the dosage of hypoglycemic agents, such as insulin and sulfonylureas (Ahmed et al, 2023). In certain liver diseases, such as glycogen storage disorders, specific medications may be required to maintain normal blood glucose levels (Gümüş and Özen, 2023). For liver disease patients, novel formulations such as liquid-stable glucagon offer significant advantages over traditional injectable glucagon (Wilson and Castle, 2018), offering easier administration and longer shelf life. Furthermore, nasal glucagon is a practical alternative for patients with impaired dexterity or those at risk of aspiration due to hepatic encephalopathy (Borden et al, 2022).

Individual Differences in Treatment Response

Responses to hypoglycemia treatment can vary significantly among individuals due to factors such as age, sex, underlying health conditions, medication use, and metabolic profiles. Additionally, patients may respond differently to various treatments, such as oral carbohydrate administration and intravenous glucose infusion, complicating the development of personalized treatment strategies (Gilmore et al, 2022). A notable case involved a patient with hypoglycemia related to HCC caused by chronic hepatitis B virus infection. Despite multiple interventions, such as glucagon, steroids, octreotide, or embolization, the patient remained unresponsive and ultimately required home parenteral nutrition (Regino et al, 2020). Evidence indicates that insulin sensitivity, kidney function, and coexisting conditions like chronic liver disease or cardiovascular disorders significantly impact treatment efficacy. For instance, individuals with chronic liver disease experience an increased risk of hypoglycemia with insulin use, and treatment response tends to be more pronounced in this population (Chawla et al, 2023). Another example is a 62-year-old man with chronic fasting hypoglycemia caused by end-stage cirrhosis from hepatitis C. This patient presented altered consciousness and dizziness and was unresponsive to glucose supplementation, consistent with a Non-islet cell tumour hypoglycemia (NICTH). Given that the patient was not a candidate for surgical intervention or chemotherapy, prednisone was commenced, resulting in enhanced blood glucose homeostasis (Yu et al, 2020). Therefore, clinicians must consider individual patient differences when devising treatment plans to optimize hypoglycemia management.

The Impact of Comorbidities on Treatment

Comorbidities play a significant role in the management of hypoglycemia, particularly in patients with diabetes and cirrhosis. These patients experience many challenges, such as cognitive decline, an increased risk of hypoglycemia, altered drug metabolism, renal impairment, an elevated risk of lactic acidosis, and issues

related to malnutrition and sarcopenia (Puri and Kotwal, 2022). Several common antidiabetic medications may pose safety concerns or heighten hypoglycemia risk in patients with cirrhosis (Puri and Kotwal, 2022). Additionally, comorbidities such as chronic liver disease, chronic kidney disease, and cardiovascular disease can substantially change a patient's metabolic profile, thereby impacting both drug metabolism and the occurrence and management of hypoglycemia.

For example, patients with cardiovascular disease may encounter additional challenges in recognizing and managing hypoglycemia due to potential medication interactions and physiological changes (Chen et al, 2023). Consequently, a holistic strategy to address hypoglycemia is crucial, integrating the patient's comorbidities to develop a safer and more effective treatment plan. A multidisciplinary team, including hepatologists, endocrinologists, and dietitians, plays a critical role in achieving this balance. A holistic, collaborative approach is critical to balance glycemic control with comorbidity management. Regular interdisciplinary collaboration ensures that treatment plans remain adaptable, optimizing glycemic control while addressing concurrent liver, renal, and cardiovascular conditions to minimize hypoglycemia risk.

The Importance of Monitoring and Follow-Up

Regular monitoring and follow-up are essential for patient safety and improving hypoglycemia treatment. Research shows that about 8% of individuals with cirrhosis may experience asymptomatic hypoglycemia, which can lead to irreversible neurological damage (Yen et al, 2022). This highlights the significance of regular blood glucose assessments. In diabetic patients with decompensated cirrhosis, impaired hepatic insulin metabolism can reduce insulin requirements, underscoring the critical need for careful blood glucose monitoring (Gangopadhyay and Singh, 2017; Yen et al, 2022). Additionally, the reduced hepatic functional reserve may result in inaccurately low glycosylated hemoglobin (HbA1c) levels. Therefore, continuous glucose monitoring systems (CGMS) offer a valuable tool for accurately assessing glycemic control and detecting both postprandial hyperglycemia and nocturnal hypoglycemia (Ogawa et al, 2022). For individuals with concurrent diabetes and cirrhosis, frequent capillary blood glucose detections, including nighttime and early morning evaluation, are recommended, as up to 20% of patients with HbA1c levels below 7% may still encounter nocturnal hypoglycemia (Boursier et al, 2021).

Additionally, follow-up should not be limited only to glucose level monitoring, it must include a comprehensive assessment of the patient's overall health status, including weight, nutritional habits, and physical activity, as these factors significantly affect blood glucose regulation (Sanchez-Rangel et al, 2022). Implementing a structured follow-up strategy enables healthcare practitioners to improve patient self-management, enhance adherence to treatment protocols and reduce the risk of hypoglycemia (Quinn et al, 2011). **Supplementary Table 1** shows the structured follow-up strategy for monitoring hypoglycemia in patients with liver disease.

Future Research Directions and Prospects

Role of Multidisciplinary Collaboration

Interdisciplinary collaboration plays a vital role in hypoglycemia management. Healthcare professionals from various specialities, including endocrinology, nutrition, and nursing, work collectively to assess the patient's condition and devise personalized treatment plans. Evidence shows that effective interdisciplinary teamwork enhances patient outcomes, decreases hospital stays, and reduces complication rates (Royani et al, 2024). This strategy is especially crucial for those with liver cirrhosis and diabetes who experience an increased risk of hypoglycemia, particularly in cases of decompensated cirrhosis. In such scenarios, coordinated care involving nutritionists, specialists in obesity management, endocrinologists, and hepatologists is essential to enhance treatment efficacy and patient satisfaction (Castera and Cusi, 2023). Therefore, establishing a strong interdisciplinary framework is essential for enhancing the quality and effectiveness of hypoglycemia management. Future research should focus on establishing standardized frameworks to define team roles, communication approaches, and measurable outcomes for multidisciplinary care.

Key Areas and Challenges in Future Research on Liver Disease-Related Hypoglycemia

Despite substantial advancements in understanding hypoglycemia in liver diseases, many challenges and key research priorities remain unexplored. A growing trend in contemporary medicine is the formulation of personalized treatment approaches, particularly for managing liver disorders in diabetic patients. The variability among patients with liver diseases complicates the underlying mechanisms of hypoglycemia, necessitating further studies on disease-specific mechanisms. Future studies should investigate the distinct pathophysiology of hypoglycemia in conditions like non-alcoholic steatohepatitis (NASH), alcoholic liver disease, and viral hepatitis, with a focus on gluconeogenic enzyme dysregulation.

Additionally, the association between hypoglycemia and liver fibrosis progression, particularly the role of hepatic stellate cell activation, requires urgent exploration. Addressing these gaps could contribute to the development of individualized treatment approaches tailored to each patient's unique requirements. Furthermore, the complex interaction between liver disease and hypoglycemia warrants more extensive research, especially concerning the association between insulin resistance and hepatic metabolism (Senoymak and Ozkan, 2020). Research should also prioritize special populations, including pediatric patients with glycogen storage disorders (e.g., circadian hypoglycemia patterns), elderly individuals with cirrhosis and cognitive impairment, and those with coexisting liver disease and diabetes, where portal hypertension impacts drug absorption.

A crucial area for future research is the early identification of effective intervening approaches for hypoglycemia to reduce its negative effects on patients (Wang et al, 2024). Technology-driven innovations should be prioritized, such as optimizing CGM accuracy in cirrhotic patients with ascites and developing liver-specific CGM algorithms. Additionally, novel therapeutic formulations, like transdermal

glucagon patches and oral glucose nanoformulations, help address malabsorption challenges in advanced liver disease. In pharmaceutical formulation development, there is an urgent demand for innovative solutions. For example, early glucagon formulations introduced in the 1960s were mainly used in emergencies due to their inadequate long-term stability, leading to limited confidence in their clinical application. However, recent innovations like nasal powder glucagon and liquid-stable glucagon have substantially enhanced usability and accessibility, resulting in broader adoption in hypoglycemia treatment (Isaacs et al, 2021).

Lon protease-1 (LONP1) has emerged as a promising mediator in energy and glucose metabolism, particularly in addressing gluconeogenesis dysfunction linked with acute liver failure (ACLF). Current research indicates that LONP1 may enhance liver recovery and support gluconeogenesis functions, making it a potential therapeutic target for individuals with ACLF (Wu et al, 2024). Finally, large-scale multicenter studies with long-term follow-up are essential to evaluate the cost-effectiveness of multidisciplinary care models and establish evidence-based guidelines for managing hypoglycemia in cirrhosis.

Conclusion

Hypoglycemia in liver disease is a critical yet underrecognized issue that significantly influences patient safety and quality of life. This review compiles evidence demonstrating that hypoglycemia risk varies based on the type of liver disease (e.g., cirrhosis, acute liver failure) and patient-specific factors, with underlying mechanisms involving disrupted gluconeogenesis, insulin/glucagon dysregulation, and malnutrition. Notably, hypoglycemia not only reflects hepatic dysfunction but also exacerbates liver injury through oxidative stress and inflammatory cascades, creating a detrimental feedback loop. This study underscores the need for tailored, multidisciplinary management integrating glycemic monitoring, nutritional support, and cautious pharmacotherapy.

Future research must focus on three key areas: (1) validating liver-specific glucose monitoring technologies, such as CGM algorithm optimized for cirrhosis; (2) elucidating the molecular links between fibrosis progression and susceptibility to hypoglycemia; (3) developing targeted therapies, such as LONP1 agonists, to restore gluconeogenesis.

Furthermore, multicenter trials assessing long-term outcomes of structured hypoglycemia protocols are needed to translate mechanistic insights into clinical practice. By linking pathophysiological understanding with practical care strategies, this work aims to inform safer, individualized approaches for a vulnerable population often excluded from standard diabetes guidelines.

Key Points

- Liver dysfunction disrupts glucose homeostasis through impaired gluconeogenesis, insulin resistance, and reduced glycogen storage, with cirrhosis and hepatocellular carcinoma posing a substantial hypoglycemia risk due to disease-specific mechanisms such as hyperammonemia-driven PEPCK suppression and tumour-induced Warburg effect.
- Hypoglycemia in liver disease is associated with poor prognosis, directly contributing to cognitive decline, cardiovascular morbidity, and mortality, while recurrent episodes accelerate hepatic injury via oxidative stress and inflammatory cascades, creating a detrimental feedback loop.
- Diagnosis should follow Whipple's triad, but in liver disease, continuous glucose monitoring and malnutrition assessment are critical tools due to the potential asymptomatic presentations and inaccuracies in HbA1c. Management needs personalized nutrition, cautious insulin titration, and multidisciplinary coordinated care among hepatologists, endocrinologists, and dietitians.
- Future research must focus on developing liver-specific glucose monitoring technologies, targeted therapies to restore gluconeogenesis (e.g., LONP1 agonists), and multicenter trials to evaluate stage-specific hypoglycemia protocols while elucidating fibrosis-dependent metabolic changes leading to glucose dysregulation.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

LXS, YGW and MDK conceived and collaborated on the work. LXS drafted the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2025.0028.

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