Hepatogenous Diabetes: A Comprehensive Overview

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ABSTRACT

Cirrhosis is the advanced stage of liver disease, marked by the presence of liver fibrosis. Cirrhosis serves as a risk factor for various metabolic conditions, including hypoglycemia and hyperglycemia. Although the pathophysiology remains unclear, hyperglycemia can occur due to the interaction of various factors, such as insulin resistance. The prevalence of both diabetes mellitus and cirrhosis is increasing, and their interaction influences each other's outcomes. Hepatogenous diabetes (HD) refers to diabetes mellitus that develops in patients with cirrhosis. HD is diagnosed using an oral glucose tolerance test, which typically reveals elevated postprandial blood glucose levels. The management of HD follows the same principles as diabetes mellitus treatment; however, pharmacological therapy should be individualized based on the patient's liver function to ensure optimal outcome. The objective of this review is to provide a comprehensive discussion of HD, encompassing its pathophysiology, clinical implications, diagnostic approaches, and management strategies.

Keywords: *Cirrhosis, Diabetes, Insulin Resistance*

ABSTRAK

Sirosis merupakan penyakit kronis yang ditandai dengan fibrosis hati. Kondisi sirosis merupakan faktor risiko berbagai kondisi metabolik, antara lain hipoglikemia maupun hiperglikemia. Waluapun patofisiologinya belum jelas namun hiperglikemia dapat terjadi akibat interaksi dari berbagai macam faktor, salah satunya resistensi insulin. Prevalensi DM maupun sirosis semakin meningkat dan kedua hal tersebut saling mempengaruhi keluaran yang terjadi. Hepatogenous diabetes (HD) merupakan diabetes melitus yang terjadi di pasien sirosis. Diagnosis HD dilakukan dengan pemeriksaan test toleransi glukosa oral dan akan ditmeukan peningkatan gula darah post prandial. Tatalaksana HD sama dengan tatalaksana DM namun pemberian obat farmakologi yang diberikan disesuaikan dengan fungsi hati pasien untuk mendapatkan hasil keluaran yang optimal. Tinjauan ini bertujuan untuk membahas mengenai HD secara komrehensif, meliputi patofisiologi, implikasi klinis, pendekatan diagnostif, dan strategi penatalaksanaan. (menjawab poin revisi)

Kata kunci: *Sirosis, diabetes melitus, resistensi insulin*

INTRODUCTION

Cirrhosis is a chronic liver condition marked by progressive fibrosis, leading to reduced liver function and severe complications affecting multiple organ systems. The liver is essential for maintaining glucose metabolism.[1] A common metabolic disorder in cirrhosis patients is hypoglycemia (especially during fasting) due to impaired gluconeogenesis and glycogenolysis. During glucose metabolism, hepatocytes take up glucose from the intestines by activating glucose transporters. Hepatocytes subsequently transform glucose into glycogen, which is stored in the liver as an energy reserve. Glycogen is broken down when the body fasts for 2-6 hours through glycogenolysis. If the body fasts longer than this, glycogen stores are often insufficient, and the liver will convert amino acids, lactic acid, and glycerol via gluconeogenesis into glucose.[2] Cirrhosis reduces the number of liver cells significantly, impairing the liver's ability to produce glucose through glycogenolysis and gluconeogenesis. Cirrhosis patients also tend to experience malnutrition. Portal hypertension can cause portosystemic shunts, reducing first-pass metabolism and decreasing excretion of anti-diabetic drugs, leading to higher blood drug concentration levels. These factors combined will increase the risk of hypoglycemia in cirrhosis patients, especially during fasting.[2,3]

A study conducted by Yen et al. in 2023 examined 18,209 DM patients with cirrhosis and 538,510 DM patients without cirrhosis. Over an average follow-up period of 3.7 years, the incidence of severe hypoglycemia was notably higher among cirrhosis patients compared to those without cirrhosis (0.53 vs. 0.14 per 1000 patient-years; HR 2.74; 95% CI 1.52–4.92). This finding remained significant after adjusting for potential confounders, including chronic kidney disease, age, sex, sulfonylurea use, the number of diabetes medications, insulin use, and other medications [2]

In addition to the threat of hypoglycemia, cirrhosis patients also have a higher risk of developing diabetes mellitus (DM) due to various mechanisms. Two types of diabetes can manifest in individuals with cirrhosis: type 2 diabetes mellitus (T2DM) and hepatogenous diabetes (HD). T2DM is a state where a patient already has diabetes and then develops cirrhosis, whereas HD emerges as a result of impaired pancreatic β-cell function and compromised insulin clearance in cirrhosis patients. Both T2DM and HD can exacerbate complications of cirrhosis, such as sepsis, esophageal variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and renal dysfunction.[4] This study aims to discuss HD comprehensively from its pathophysiology, clinical implications, diagnostic approaches, and management strategies.

EPIDEMIOLOGY

Cirrhosis is an end-stage of all chronic liver diseases, so all etiologies that can cause chronic liver inflammation can certainly cause cirrhosis. The prevalence of the most common etiologies varies depending on the geographical and demographic background. In Western countries, the most common etiology of cirrhosis is hepatitis C infection, followed by alcohol, hepatitis B, and Non-Alcoholic Fatty Liver Disease (NAFLD).[5] Meanwhile, data in Indonesia shows that hepatitis B remains the main cause of cirrhosis, followed by hepatitis C, which ranks second.[6] The prevalence of NAFLD also tends to increase considerably in Indonesia. A study by Bima et al reported that NAFLD can be found in 45% of patients with type 2 Diabetes Mellitus (DM) in Jakarta, and 25% of these patients have experienced moderate to severe fibrosis.[7]

The prevalence of diabetes mellitus, including T2DM and HD, among patients with cirrhosis is reported to be 20-70%, which is significantly higher than the approximately 6.28% prevalence in the general population.[8,9] A 2018 meta-analysis involving 9,705 patients reported an overall DM prevalence of 31% in individuals with cirrhosis. The highest proportion was observed in cirrhosis cases caused by non-alcoholic fatty liver disease (NAFLD) at 56%. In cirrhosis related to hepatitis C, the DM incidence was 32%, while in hepatitis B-related cirrhosis, it reached 27%.[10]

The increasing prevalence of diabetes mellitus (DM) in cirrhosis patients with worsening disease severity supports the role of cirrhosis in diabetes development. Data from one study showed that the prevalence of diabetes among patients with Child-Pugh A, B, and C cirrhosis was 20.5%, 56%, and 61%, respectively. Additionally, other findings indicate that diabetes prevalence increases with the duration of cirrhosis, particularly in patients experiencing progression in Child-Pugh classification and MELD scores. These findings suggest that the severity of chronic liver disease is associated with the onset of diabetes, independent of confounding factors such as family history of diabetes, age, or sex.[11]

PATHOPHYSIOLOGY

The pathophysiology of diabetes in cirrhosis is not fully understood. Current hypotheses suggest that the development of insulin resistance in cirrhosis involves various factors such as decreased insulin excretion in the liver, increased production of neurohormonal changes, endotoxemia, advanced glycation end products (AGEs), and chronic inflammation associated with cirrhosis. [1,11] The various mechanisms of HD are outlined below.

a. Insulin Resistance

The liver is the primary organ involved in clearing insulin from the blood. Damage to most of the liver parenchyma will affect the liver's ability to excrete insulin, leading to hyperinsulinemia. Portosystemic shunts prevent some insulin from passing through the liver. The influence of portosystemic shunts as a mechanism for insulin resistance is demonstrated by the rising incidence of diabetes mellitus with increasing portal vein pressure, which also increases the likelihood of portosystemic shunt formation. High blood insulin levels trigger the downregulation of insulin receptors, resulting in fewer receptors and reduced sensitivity to insulin stimulation. The end result of this process is insulin resistance, which leads to diabetes.[1]

b. Pancreatic Beta Cell Dysfunction

Pancreatic damage and dysfunction occur as a result of cirrhosis. Liver is an important organ in removing AGEs. Cirrhosis causes the accumulation of AGEs, which damage pancreatic beta cells and reduce blood insulin production. Another factor thought to play a role in pancreatic beta cell damage is chronic hypoxia. Hypoxia causes the release of hypoxia-inducible factors-1 α (HIF-1α), leading to pancreatic beta cell destruction. In addition to these two factors, portal hypertension increases pressure in the veins that flow into the portal vein, including the pancreatic vein. This increased pressure causes congestion in the pancreas, which ultimately reduces insulin production. Furthermore, initial hyperglycemia due to this damage produces more AGEs that cannot be cleared by the liver, further damaging the beta cells and forming a positive feedback loop.[11]

c. Impaired Glucagon-like peptide-1 (GLP-1)

The intestine, as an organ adjacent to the liver, also contributes to the pathogenesis of hepatogenous diabetes. The intestine is known to produce at least two hormones that can increase GLP-1, glucose-dependent insulinotropic polypeptide, and the secretion of insulin. The hormone GLP-1 is regulated by its specific antagonist, dipeptidyl peptidase 4 (DPP-4), which undergoes metabolism in the liver. Liver damage has been shown to increase DPP-4 levels and effectiveness, thereby inhibiting GLP-1 action and triggering insulin resistance.[11,12]

d. Gut Microbiota Dysbiosis

Cirrhosis disrupts the composition of bacteria living in the gut. Cirrhosis also increases the family of gram-negative bacteria and reduces the ratio of Firmicutes/ Bacteroidetes, which is beneficial to the body. This condition results in the proliferation of harmful bacteria and elevated production of lipopolysaccharide endotoxins, which have been linked to the development of insulin resistance.[13]

e. Hyperammonemia

High ammonia levels are known to directly cause down-regulation of insulin receptors in muscle and cause myo-steatosis. Both processes contribute to increased insulin resistance. Ammonia that cannot be metabolized by the liver causes skeletal muscle to work harder to metabolize the existing ammonia, triggering a decrease in muscle mass. Skeletal muscle itself is the main target for postprandial glucose consumption. The loss of a large amount of muscle mass will lead to the loss of insulin receptors, which will trigger insulin resistance. Sarcopenia that occurs in cirrhosis patients can be caused by various factors such as hyperammonemia, hormonal disorders, malnutrition, and gut dysbiosis. Of all sarcopenia conditions, sarcopenia patients with obesity are the group that is most likely to experience insulin resistance among those with cirrhosis. Data from other countries shows that about 35% of cirrhosis patients awaiting transplantation suffer from this condition.[14]

f. Hepatokine Disorders

The liver also functions as a gland that produces hepatokines, a group of hormones similar to adipokines produced by adipose tissue, which play an important role in regulating systemic metabolism. Several types of hepatokine, such as fetuin A, fetuin B, retinol-binding protein 4, and selenoprotein P, are known to directly affect insulin secretion from the pancreas. Cirrhosis reduces the levels of these hormones, which may contribute to the development of insulin resistance. Unfortunately, research in this area is still limited in number, so the available data remains scarce.[11]

DIAGNOSIS

Hepatogenous diabetes (HD) is diagnosed when diabetes develops after the onset of liver disease. The criteria for diagnosing diabetes in cirrhosis patients are identical to those applied to individuals without cirrhosis. Laboratory tests indicate that patients with HD typically exhibit normal fasting glucose and HbA1c levels. The oral glucose tolerance test (OGTT) is the preferred diagnostic method for detecting diabetes in HD patients, as it often reveals normal fasting glucose levels but elevated postprandial blood sugar levels. This may be explained by the fact that cirrhosis patients can experience significant changes in haemoglobin levels due to reduced erythrocyte lifespan, splenomegaly, micronutrient deficiencies, and gastrointestinal bleeding. All these conditions render HbA1c an unreliable marker of DM. Similarly, in monitoring cirrhosis patients, the use of HbA1c often yields false-negative results, whereas postprandial blood sugar levels serve as a more reliable tool for monitoring therapy.[15]

MANAGEMENT

To date, there is no specific consensus exists for the management of HD. However, addressing the underlying liver disease remains crucial to improve liver function. Meanwhile, blood sugar management in these patients follows the management of T2DM, with adjustment according to their liver function. Lifestyle modifications are still important, such as a low-carbohydrate and low-fat diet and adequate aerobic exercise. Unfortunately, in patients with cirrhosis, malnutrition often hinders the dietary management of diabetes. In addition, ascites and reduced muscle mass often limit the patient's ability to perform physical activity. The next obstacle arises because most existing diabetes drugs are affected by liver function and can also exacerbate liver damage, while others carry an increased risk of hypoglycaemia, requiring cautious use.[1,10]

Metformin has long been recognized to be beneficial for metabolic disorders due to its ability to reduce insulin resistance and is not metabolized by the liver. Nevertheless, the use of metformin in patients with cirrhosis is not recommended due to the heightened risk of lactic acidosis. This assumption apparently cannot be proven empirically, considering that only a limited number of patients with metformin eventually experience lactic acidosis.[1,11,15,16] Conversely, the use of metformin in cirrhosis patients can provide additional benefits in preventing hepatocellular carcinoma. Several small studies have also demonstrated that metformin use in patients with cirrhosis improves survival and lowers the risk of complications. Metformin can generally be considered in cirrhosis patients without impaired renal function.[1] One existing review still provides a warning that metformin use should be considered for discontinuation in cases of decompensated cirrhosis.[15]

Another diabetes drug is a peroxisome proliferator-activated receptor (PPAR) gamma agonist class, such as thiazolidinedione (TZD). The advantage of this class of drugs in patients with cirrhosis is the low possibility of hypoglycemia, considering that they do not directly stimulate insulin production. Even so, TZDs are known to increase the risk of fluid retention, and in cirrhosis patients with ascites, this drug can complicate the management of ascites and edema. Moreover, this drug is also metabolized by the liver, and its use in cirrhosis patients is associated with an increased risk of mortality and liver cell carcinoma. Existing guidelines do not recommend using TZDs in decompensated cirrhosis patients, and their utilization in compensated cirrhosis must be considered carefully.[15]

Sulfonylureas are one of the most commonly used antidiabetic drugs. This class of drugs is metabolized by the liver into active components and will also be inactivated by the liver after some time. Active metabolites of sulfonylureas will also bind to albumin in plasma. In patients with cirrhosis, reduced liver function and impaired drug excretion, along with decreased blood albumin levels, result in elevated plasma levels of active drug metabolites. This process leads to a significant increase in the risk of hypoglycemia, especially in cirrhosis patients who are already predisposed to this condition. Current guidelines recommend discontinuing this class of drugs in patients with decompensated cirrhosis due to the high risk of hypoglycemia. In compensated cirrhosis, this drug can still be used with close monitoring.[1,15]

Other drugs, such as alpha-glycosidase inhibitors like acarbose, mainly work by inhibiting glucose absorption in the small intestine, thus playing a role in regulating postprandial glucose. This effect is relatively suitable for use in cirrhosis, considering that in cirrhosis, hyperglycemic disorders mainly arise in the postprandial state. Acarbose is metabolized in the intestine and can be used fairly safely in patients with cirrhosis, especially compensated cirrhosis. Even so, this drug generally exhibits a weak HbA1c-lowering profile and is often insufficient when used as

monotherapy. Several small studies have also reported an increased risk of hepatic encephalopathy with the use of acarbose.[1,15] To date, no specific studies have investigated the impact of acarbose use on cirrhosis-associated gut dysbiosis.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are oral antidiabetic medications that function by enhancing glucose excretion through urine. This drug almost never causes hypoglycemia, but all drugs in this class are metabolized by the liver. Current data reveal that plasma levels of SGLT-2 inhibitors increase significantly in patients with impaired liver function, making their use in cirrhosis patients has yet to be safely recommended.[15]

Drugs from the DPP-4 inhibitor class, such as sitagliptin and vildagliptin, work by helping to activate incretin, which serve to stimulate insulin production. So far, there have not been many studies that specifically discuss the use of this class of drugs in impaired liver function. However, several pharmacological studies have shown that the concentration of these drugs does not change much with impaired liver function. Nonetheless, due to limited available data, existing guidelines still cannot recommend the administration of this drug class in individuals with cirrhosis.

The GLP-1 receptor agonist class of drugs, such as liraglutide and semaglutide, also work by stimulating insulin secretion through the incretin pathway, like DPP-4 inhibitors. However, this drug is known to be metabolized by the liver, and because its use is relatively new, empirical data on its effects in patients with impaired liver function have not been explored further. It should also be noted that GLP-1 receptor antagonists also frequently cause gastrointestinal side effects and promote weight loss, which can aggravate existing malnutrition in cirrhosis patients.[1,15]

As mentioned above, the liver is the main organ involved in clearing insulin from the body. As a result, exogenous insulin therapy in cirrhosis patients must also consider the possibility of increased plasma insulin levels due to liver disorders. Cirrhosis patients also have an increased risk of hypoglycemia, so the use of insulin will certainly worsen this condition. However, some patients often require a higher insulin dose due to insulin resistance in cirrhosis. Therefore, close monitoring of blood glucose becomes very important when administering insulin to cirrhosis patients. The hepatotoxic effect of insulin preparations itself seems to be quite low from existing studies, both rapid-acting insulin such as lispro and glulisine, and long-acting insulin, such as detemir or glargine. Existing recommendations state that insulin is one of the safest therapies to use in patients with cirrhosis as long as blood sugar targets are adjusted to individual circumstances and close monitoring is carried out by patients and their families. It should be noted that cirrhosis patients often have ascites and malnutrition, resulting in thinning of the subcutaneous fat in the abdomen, which is commonly used for insulin injection in non-cirrhosis patients. In this condition, the injection angle should be adjusted, or an alternative therapy other than injection should be considered.[1,11,15] **Table 1** provides a summary of medications for HD**.**

Table 1. Medications for Diabetes and Their Modes of Action

Drug	Mechanism of action	Benefit	Limitation
Metformin	Decrease insulin resistance	Not metabolized by the liver; increases survival rate and decreases complication risk	Can not be used in a cirrhotic patient with kidney problems; not recommended in decompensated cirrhosis
PPAR-gamma-agonits (eg.thiazolidinedione)	Increase insulin sensitivity	Low risk of hypoglycemia	Not recommended in decompensated cirrhosis and patients with ascites
Sulfonilurea	Stimulate insulin production	High risk of hypoglycemia	Not recommended in decompensated cirrhosis; close monitoring in compensated cirrhosis patients
Alpha-glucosidase inhibitor	Inhibit glucose absorption in the intestine	Reduce postprandial blood glucose	Increased the risk of hepatic encephalopathy
Inhibitor-SGLT2	Increase glucose excretion in urine	Unable to cause hypoglycemia	Has not been recommended in cirrhotic patients
DPP-IV-inhibitor	Activate incretin, thereby stimulating insulin production	Low risk of hypoglycemia	Can be used in cirrhotic patients
GLP-1 reseptor agonis	Increase insulin secretion through the incretin activation pathway	Low risk of hypoglycemia	No consensus for use in liver disease
Insulin	Supplementation of endogenous insulin	Effective in controlling blood sugar	Close monitoring to avoid hypoglycemia

CONCLUSION

The effect of cirrhosis on glucose metabolism is intricate. While it heightens the risk of hypoglycemia, it also contributes to hyperglycemia and insulin resistance through multiple pathophysiological mechanisms. Accurate diagnosis and appropriate management are crucial and should be tailored based on the patient's specific condition.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

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AUTHOR CONTRIBUTION

Ignatius Bima Prasetya conceived the study idea and designed the review framework as well as the initial draft. Sharon Sandra contributed to data analysis and drafting of the manuscript. Both authors participated equally in the interpretation of results, critical revision, and final approval of the submitted version.

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DATA AVAILABILITY

No new data were generated or analyzed in this study. Data sharing is therefore not applicable.

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