Hepatogenous Diabetes: An Underestimated Problem of Liver Cirrhosis

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Abstract

The prevalence of diabetes mellitus in cirrhotic patients is much higher than that in the general population. Two types of diabetes are usually seen in patients with cirrhosis: type 2 diabetes mellitus and hepatogenous diabetes (HD). The HD is an acquired condition which is believed to be caused by impaired insulin clearance and pancreatic β-cell dysfunction in cirrhotic patients. Increased levels of advanced glycation end products and hypoxia-inducible factors have been implicated in the pathogenesis of HD. Patients with HD typically present with normal fasting glucose, but abnormal response to an oral glucose tolerance test, which is required for the diagnosis. Because the level of glycated hemoglobin is often falsely low in patients with cirrhosis, it does not help in the early diagnosis of HD. HD is associated with an increased rate of complications of cirrhosis, decreased 5-year survival rate, and increased risk of hepatocellular carcinoma. The major complications of cirrhosis associated with HD include hepatic encephalopathy (HE), spontaneous bacterial peritonitis, sepsis, variceal hemorrhage, and renal dysfunction. Treatment of HD may be difficult as many antihyperglycemic therapies are associated with increased risk of complications in cirrhosis, particularly hypoglycemia. Biguanides, alpha-glucosidase inhibitors, and new medications such as dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter 2 inhibitors appear to be safe in patients with cirrhosis. Though insulin therapy is currently advocated, requirement of insulin is variable and is difficult to predict. The liver transplantation usually results in reversal of HD. This review article provides an overview of magnitude, patients’ characteristics, clinical implications, pathophysiological mechanisms, diagnosis, and management of HD.

Keywords: Cirrhosis, diabetes mellitus, hepatogenous diabetes, insulin resistance

Introduction

The liver has a major role in the control of glucose homeostasis in the body.[1] The association between chronic liver disease (CLD) and diabetes mellitus (DM) is known since long. Such association may be due to a common mechanism that leads to both diseases such as non-alcoholic fatty liver disease (NAFLD), hemochromatosis, autoimmune liver diseases, and chronic hepatitis C.[2,3] A 10-year follow-up study of Veteran Affairs cohort revealed 2-fold increased risk of CLD in the subjects with type 2 DM (T2DM) compared to those without T2DM, after adjusting the confounding variables.[4] However, more commonly, CLD per se can lead to diabetes as known as hepatogenous diabetes (HD).[5] The term HD was first used by Megyesi et al.[6] in the 60’s. This term did not get attention, as the entity was then poorly understood. Though, enough data now exist to support HD as a separate entity, it is still a neglected condition and surprisingly even American Diabetes Association does not recognize it. HD appears after the onset of liver disease in individuals without risk factors of T2DM such as high body mass index, hyperlipidemia, and previous or family history of DM.

Characteristics and Differential Prevalence of T2DM and HD in Cirrhosis

The prevalence of DM in cirrhotic subjects is higher than that in general population. The prevalence of DM in general population in India is estimated to be 6.1–16.6%,[7] whereas the reported prevalence rates of DM among cirrhotic patients across the world vary from 35 to 71% [Table 1]. Moreover, the prevalence rates of abnormal glucose regulation (AGR),
which includes increased fasting glucose (IFG), impaired glucose tolerance (IGT), and DM, are much higher among cirrhotic patients and vary from 58 to 96% [Table 1]. Such a high prevalence rate of AGR and DM in cirrhotic patients, compared to normal population, suggests that substantial number of cirrhotic with diabetes have HD. However, many studies have not clarified as to what proportions of cirrhotic patients with DM have true HD. The discrimination between T2DM and HD is frequently not possible especially when DM is overt [Table 2]. The onset of DM after development of cirrhosis usually indicates HD. However, considering both conditions having long and variable natural history of pathogenesis, using a cut-off such as “before or after” onset of cirrhosis could be impractical at times. HD should be suspected in non-obese patients without family history of DM, hypertension, or hyperlipidemia.[3] In a recent study, the ratios of postprandial plasma glucose to fasting plasma glucose (FPG), fasting plasma insulin, and insulin resistance (IR) were significantly higher in cirrhotic patients with HD as compared to those with T2DM.[9] The prevalence of retinopathy and cardiovascular disease are lower in HD patients compared to cirrhotic patients with T2DM.[10]

The diagnostic methods greatly influence the detection rates of HD in cirrhotic patients. In patients with cirrhosis the levels of FPG and glycated hemoglobin (HbA1c) may be falsely low.[11–13] In a study, the FPG levels were normal in 23% of the cirrhotic patients with overt diabetes.[13] However, postprandial blood glucose in these patients were >200 mg/L. Also, the HbA1c levels in cirrhotic patients frequently fall within normal range (4–6%).[12] The falsely low levels of HbA1c are believed to be due to shortened erythrocyte life span caused by hypersplenism in cirrhotic patients. Therefore, an oral glucose tolerance test (OGTT) is needed to detect the IGT or DM in patients with cirrhosis. Patients with normal FPG (and HbA1c) and abnormal OGTT likely to be those with HD, while in most subjects with increased FPG levels; diabetes is usually T2DM.

Using combination of tests, the prevalence of DM in patients with CLD were: 48.3% in study by Garcia-Compeán et al.[14], 71.1% in study by Holstein et al.[10], 59.6% in study by Grancini et al.[15], and 55.4% in study by Jeon et al.[16] The corresponding prevalence rates of AGR were much higher: 86.9%, 96.1%, 88.3%, and 86.7%, respectively. Garcia-Compeán et al.[14] reported that, out of 36 cirrhotic subjects with increased FPG levels, 69.4% had a pre-existing T2DM, whereas only 30.6% could fit into criterion for HD. Jeon et al.[16] using OGTT in 195 consecutive cirrhotic liver patients who had no history of DM found HD in 55.4%. About 62% of HD patients in this study had normal FPG level. The severity of liver disease also determines the prevalence of DM in cirrhotic patients.

| Table 1: Prevalence of abnormalities of glucose regulation among patients with cirrhosis |
| Study | n | Method | IFG or IGT* | DM | AGR (IFG, IGT, or DM) |
| Garcia-Compeán et al.[14] | 130 | FPG | 10.7% | 27.6% | 38.3% |
| Holstein et al.[10] | 52 | OGTT | 45.0% | 33.8% | 78.8% |
| Jeon et al.[16] | 28 | FPG + OGTT | 38.6% | 48.3% | 86.9% |
| Grancini et al.[15] | 206 | FPG + OGTT | 37.1% | 57.2% | 94.3% |
| Marselli et al.[17] | 30 | FPG + OGTT | 25.0% | 71.1% | 96.1% |
| Lunati et al.[9] | 84 | FPG + HbA1c | 47.7% | 32.0% | 79.7% |
| Tietge et al.[18] | 100 | FPG + HbA1c | 31.3% | 55.4% | 86.7% |

*IFG in case of increased FBG, and IGT whenever OGTT is used. FPG, fasting plasma glucose; IFG: Increased fasting glucose; IGT: Impaired glucose tolerance; DM: Diabetes mellitus; AGR: Abnormal glucose regulation; OGTT: Oral glucose tolerance test; HbA1c: Glycated hemoglobin

| Table 2: Differential characteristics of cirrhotic patients with Type 2 DM or HD |
| Parameters | Type 2 DM | HD |
| Onset | Before onset of CLD | After onset of CLD |
| Risk factors of DM* | More frequent | Less frequent |
| Serum insulin and HOMA-IR | Less frequent | Higher compared to Type 2 DM patients |
| Diabetes-related complications | More frequent | Less frequent |
| CLD-related complications | Less common | More common |
| Hypoglycaemia | Lower risk | Higher risk |
| Effect of liver transplantation | Persistence of DM | Reversal of DM |

*High body mass index, hyperlipidemia, and previous or family history of DM. DM: Diabetes mellitus, HD: Hepatogenous diabetes, CLD: Chronic liver disease, HOMA-IR: Homeostatic model assessment-insulin resistance
In a study, DM was present in 20.5%, 56.1%, and 61.2% of Child-Pugh Class A, B, and C, respectively. Müller et al. reported 37% prevalence of DM among 108 cirrhotic patients at baseline. But, after 1-year and 4-year follow-up, the prevalence rates of DM increased by 4.4% and 21.2%, respectively. Thus, in patients with cirrhosis, a transition from IR and IGT to DM may indicate progression of liver disease from early to advanced stage. The etiologies are also an important risk factor for DM in cirrhosis. DM is more frequent among those with hepatitis C virus (HCV), alcoholic, and cryptogenic etiology. A large study on population at low risk of diabetes found that serological evidence of hepatitis B virus (HBV) and HCV infection was associated with prevalence of diabetes. A recent meta-analysis also established that patients with HBV infection are at higher risk of developing DM. Therefore, infection with HBV or HCV must be ruled out in patients with DM and liver disease. Iron overload in patients with hemochromatosis can lead to the development of both DM and liver disease. Therefore, screening for abnormal iron indices must be done in patients with concomitant DM and CLD.

Pathophysiology

The pathophysiology of HD is complex and is not precisely known. Multiple factors are responsible for the development of peripheral IR and β-cell dysfunction in cirrhotic patients.

Hyperinsulinemia

Reduction in liver cell mass and presence of portosystemic collaterals in cirrhotic patients result in decreased extraction of insulin by the liver, leading to systemic hyperinsulinemia. An exaggerated insulin secretion, which occurs lately in cirrhotic patients due to pancreatic islet hypertrophy, also contributes to hyperinsulinemia. Hyperinsulinemia can lead to IR through down-regulation of insulin receptors of target cells. Indeed, reduction in hyperinsulinemia has been found to normalize insulin sensitivity.

Disease-specific glucose intolerance

In NAFLD, IR is mediated by multiple mechanisms such as altered secretion of adipokines and pro-inflammatory cytokines, increased free fatty acid release, and the reduced incretin effect. Both direct and cytokine-mediated interference with insulin signalling such as inactivation or degradation of the insulin receptor and their downstream target contributes to HCV-mediated IR. HCV may impair β-cell function through auto-immune effect by molecular mimicry, as it shares structural homology with glutamic acid decarboxylase. DM in patients with alcoholic cirrhosis and hemochromatosis has been related to the simultaneous injury to hepatocytes and pancreatic β-cells caused by alcohol and iron, respectively.

Reduced incretin effects

The incretins play important roles in the maintenance of glycemic control. The two naturally occurring incretin hormones are glucose-dependent insulinotropic polypeptide and glucagon-like peptide (GLP-1). GLP-1 is a gut-derived incretin hormone that stimulates insulin secretion and suppresses glucagon secretion. These peptides are rapidly hydroyzied by dipeptidyl peptidase-4 (DPP-4). The inactivation of GLP-1 results in the development of IGT, DM, and hepatic steatosis. Serum DPP-4 activity and hepatic expression of DPP-4 are up-regulated in cirrhotic patients which reduce incretin effects.

Role of advanced glycation endproducts

Hyperglycemia cultivates the advanced glycation endproducts (AGEs), and the liver is the main catabolic site for these AGEs. In patients with cirrhosis, plasma levels of AGEs are markedly elevated and correlate with the severity of the liver disease. The AGEs are thought to induce IR and β-cell injury. A significant decline in the level of serum AGEs is seen after liver transplantation.

Role of hypoxia-inducible factors and betatrophin

Hypoxia is a common feature in patients with advanced cirrhosis. Hypoxia-inducible factors, a family of transcription factors that mediate tissue response to hypoxia, have been implicated in the development of β-cell dysfunction and DM. Recently, Yi et al. discovered that a hormone named betatrophin, primarily expressed in the hepatocytes, induced β-cell proliferation and improved glucose tolerance in a murine model. A recent study has found a strong correlation between betatrophin levels and IR, more so in non-diabetic subject. Thus, an abnormal hepato-pancreatic axis may be partly responsible for IR in cirrhotic patients.

Clinical implications

Substantial data suggest that DM in patients with cirrhosis is associated with decreased survival, higher rate of complications of liver cirrhosis, and increased risk of malignancy. However, the comparative data on the adverse impact of T2DM versus HD in cirrhotic patients are not available.

Decreased survival

DM and IGT in cirrhotic patients are associated with lower survival rate. In a prospective study that included cirrhotic patients with DM (n = 21), IGT (n = 13), and normal glucose tolerance (NGT, n = 22), the cumulative survival rates at 5 years were 94.7%, 68.8%, and 56.6% for patients with NGT, IGT, and DM, respectively. Also, DM was among the most powerful independent negative predictors of survival. Another study reported that compensated cirrhotic patients with subclinical IGT had lower 5-year survival than those with NGT (31.7% vs 71.6%, P = 0.02). Holstein et al., in a prospective cohort study, which included 52 HD patients, reported that the majority death among 52% patients who died after a mean follow-up of 5.6 years were due to complications of the cirrhosis. There were no diabetes-associated or cardiovascular deaths. This may be because of accelerated liver failure in patients with HD, which might have curtailed the time in which diabetic complications could have developed.

Increased risk of cirrhotic complications

DM in cirrhosis is associated with HE, variceal hemorrhage, infection, spontaneous bacterial peritonitis, and renal
This may be because of the fact that DM causes gastrointestinal dysmotility, immune-suppression, intestinal bacterial overgrowth, and bacterial translocation. In a study, the severity of HE was greater in diabetic (35% mild, 60% severe) than in non-diabetic cirrhotic patients (58% mild, 20% severe), irrespective of the severity of liver disease.\(^{[42]}\) Jeon et al. documented that the presence of HD had a significant correlation with high Child-Pugh’s score, variceal hemorrhage, and hepatic venous pressure gradient \((P < 0.01)\) each. Postprandial hyperglycemia, in particular, had a significant relationship with variceal hemorrhage.\(^{[16]}\) DM has been found to be associated with renal insufficiency and decreased survival in patients with liver cirrhosis and hepatocellular carcinoma (HCC).\(^{[43]}\) A study, that included 348 patients with HCV-cirrhosis, found that baseline diabetes was independently associated with ascites \((P = 0.05)\), bacterial infections \((P = 0.001)\), and HE \((P < 0.001)\).\(^{[44]}\) DM in patients with liver cirrhosis itself is a risk factor for the development of diabetes after liver transplant.\(^{[45]}\)

**Increased risk of malignancy**

There is a strong association between DM and HCC. Yang et al.\(^{[46]}\) in a recent study, found that diabetes increases the risk of HCC in patients with non-HCV cirrhosis. In HCV cirrhosis patients who already have very high risk, diabetes may not increase the risk any further. Presence of glucose intolerance lowers the survival of male HCC patients.\(^{[47]}\) In a prospective study of large European-cohort \((n = 363,426)\), Schlesinger et al.\(^{[48]}\) found the incidence of bile tract cancer (BTC) and HCC in 204 and 176 cases during 8.5 years follow-up. Independent of body mass index, diabetes status was associated with higher risk of BTC and HCC \((1.77 (1.00-3.13)\) and \(2.17 (1.36-3.470)\).\(^{[48]}\)

**Treatment**

The management of diabetes in cirrhotic patients is challenging because of a lack of concrete guidelines, physio-pathological changes in the body due to cirrhosis, and alteration in pharmacokinetic properties of many oral hypoglycemic agents (OHA) rendering patients to increased risk of adverse events [Table 3].\(^{[49]}\) In non-cirrhotic patients with DM, a good glycemic control plays an important role in preventing or delaying diabetic complications. However, it is unclear as to whether a similar approach would result in improved outcome in cirrhotic patients with DM. Lifestyle modification, which include low-caloric diet and physical exercise, may not be appropriate in all cirrhotic patients with DM. A hypocaloric diet may aggravate increased liver function test and may lead to accumulation of drugs or its metabolites.

**OHA**

For patients with cirrhosis, an ideal OHA should have insignificant hepatic metabolism, low binding to plasma protein, non-hepatic route of elimination, relatively shorter half-life, and no risk of hypoglycemia or hepatotoxicity [Table 4].

**Biguanide**

Metformin, a biguanide, remains unmetabolized in the body, does not bind to plasma protein, has a short half-life (-5 hours), and is eliminated via kidney.\(^{[52]}\) Moreover, metformin has cardio-protective and anti-cancer effects. Metformin has been found to be associated with decreased risk of HCC \([HR 0.19]\) and liver-related death in cirrhotic patients with DM.\(^{[53]}\) Paradoxically, the majority of physicians are hesitant to recommend metformin in cirrhotic patients due to undue apprehension about an increased risk of lactic acidosis. However, systematic review and meta-analysis of 194 comparative trials has revealed no significant risk of lactic acidosis in metformin group compared to non-metformin group.\(^{[54]}\) Another study revealed that none of diabetic patients who continued metformin after diagnosis of cirrhosis \((n = 172)\) developed lactic acidosis. Moreover, the median survival among patients who received metformin was longer than those who discontinued metformin \((11.8 \text{ vs. } 5.6 \text{ years})\).\(^{[55]}\) Metformin is inexpensive and has low risk of hypoglycemia. Though, it may cause mild gastrointestinal disturbances after initiation, this too is unusual with extended release preparations. Thus, metformin appears to be reasonably safe in patients with cirrhosis, and the risk of metformin-induced lactic acidosis is extremely rare unless patients have concomitant renal dysfunction or hypoxemia.

**Table 3: Challenges in the management of DM in cirrhosis patients**

| Challenges in the management of DM in cirrhosis patients |
|--------------------------------------------------------|
| Patients with cirrhosis have alterations in hepatic blood flow, fluid distribution, protein, intestinal mucosal permeability, and bacteria flora. All these in turn affect absorption, distribution, bioavailability, metabolism, and elimination of drugs. |
| Drugs metabolized by cytochromes P450 enzyme system may be greatly altered. |
| Renal impairment can be present in patients with liver cirrhosis which may lead to accumulation of drugs or its metabolites. |
| Loss of hepatic mass and porto-systemic shunts causes reduced insulin clearance and increased risk of hypoglycemia. |
| Free plasma concentration of highly protein bound drugs would be increased due to hypoalbuminemia. |
| Liver plays major role in the lactate metabolism. In such conditions, use of certain drug like biguanides may precipitate lactic acidosis in presence of sepsis, hypotension, or renal dysfunction. |
| Certain oral hypoglycemic agents have been associated with hepatotoxicity. Requirement of insulin is variable and is difficult to predict. |
| Fasting plasma glucose and glycated hemoglobin are unreliable for monitoring glycemic control in cirrhotic patients. |
| Non-reversal of diabetes following liver transplantation in about one-third of patients due to persistent dysfunction of pancreatic \(\beta\)-cells. |
**Table 4: Characteristics of oral hypoglycaemic agents in relation to cirrhotic patients**

| Drug          | Effect                  | Plasma protein binding | Hepatic metabolism | Elimination route | Remarks                                                                 |
|---------------|-------------------------|------------------------|--------------------|-------------------|-------------------------------------------------------------------------|
| Biguanide     | Insulin sensitizer      | Negligible             | Insignificant      | Mainly renal      | Clinical experience in cirrhotic patients available                      |
|               |                         |                        |                    |                   | Evidence of survival benefit and protection from HCC in cirrhotic patients |
|               |                         |                        |                    |                   | Low risk of hypoglycemia                                                |
|               |                         |                        |                    |                   | High risk of hypoglycemia, hence not preferred in cirrhotic patients    |
|               |                         |                        |                    |                   | Caution during concomitant use of beta-blockers                         |
|               |                         |                        |                    |                   | No clinical experience in cirrhotic patients                             |
| SU            | Insulin secretion       | Highly bound           | Largely            | Mainly renal      | Limited clinical experience in cirrhotic patients                        |
|               |                         |                        |                    |                   | Has anti-fibrotic effects                                               |
|               |                         |                        |                    |                   | Weight gain may be problematic                                          |
| TZD           | PPARY-agonist           | Almost completely bound| Extensive          | Rosiglitazone and pioglitazone mainly eliminated via urine and bile | Favorable pharmacokinetic properties in cirrhotic patients               |
|               | True insulin sensitizer |                        |                    |                   | Clinical experience is limited                                          |
|               |                         |                        |                    |                   | Reduces lipids levels                                                   |
|               |                         |                        |                    |                   | Risk of nasopharyngitis                                                 |
| DPP-4 inhibitors | Inhibition of metabolism of GLP-1 | Low | Insignificant except in case of saxagliptin | Excreted via kidney, except linaagliptin which eliminates via faeces | Additional metabolic benefits                                           |
| AGI           | Delay absorption of carbohydrate | Negligible | Negligible | Mainly renal | Safe in cirrhotic patients as per clinical experience                   |
|               |                         |                        |                    |                   | Lowers blood ammonia level                                              |
|               |                         |                        |                    |                   | Beneficial in hepatic encephalopathy                                   |
|               |                         |                        |                    |                   | May cause pain abdomen, flatulence, and mild transaminases elevation   |
| SGLT2 inhibitors | Block glucose reabsorption in PRT | Mostly bound | Extensive hepatic metabolism to inactive metabolites | Low renal clearance as parent drug | Additional metabolic benefits                                           |
|               |                         |                        |                    |                   | Clinical experience is limited                                          |
|               |                         |                        |                    |                   | Risk of UTI, dyselektrolytemia, and dehydration                        |

HCC: Hepatocellular carcinoma, SU: Sulfonylurea, TZD: Thiazolidinediones, PPAR: Peroxisome proliferator-activated receptor, DPP-4: Dipeptidyl peptidase-4, AGI: Alpha-glucosidase inhibitors, GLP: Glucagon-like peptide, SGLT2: Sodium-glucose cotransporter 2, PRT: Proximal renal tubule, UTI: Urinary tract infection

**Sulfonylureas (SU)**
Glyburide/glibenclamide, glipizide, gliclazide, and glimepiride are SUs belonging to second and third generation, respectively. The liver is the major site of metabolism for all SUs. SUs are extensively bound to serum proteins and excreted mainly through kidney.\(^{[56]}\) The risk of hypoglycemia is high with all SUs. This happens because of the stimulation of insulin secretion from the pancreatic \(\beta\)-cell, and reduced inactivation of SUs in liver, and enhanced free drug plasma concentrations due to hypoalbuminemia.\(^{[57]}\) Therefore, SUs should be better avoided in patients with cirrhosis; however, the ones with short half-life such as glipizide or glyburide may be used with caution.

**Meglitinides**
Repaglinide and nateglinide are the two currently available meglitinides for clinical use. No specific guidelines are available pertaining to meglitinides. However, meglitinides may be used as alternative to SUs, with a preference for nateglinide compared to repaglinide.

**Thiazolidinediones (TZD)**
TZDs improve insulin sensitivity through varied mechanisms. The first commercialized thiazolidinedione, troglitazone, was withdrawn from the market because of idiosyncratic hepatotoxicity.\(^{[58]}\) Pioglitazone is the only TZD available for clinical use in India. It is extensively metabolized in liver and is excreted via bile and feces. Pioglitazone has a good hepatic safety profile; however, no published study investigated the pharmacokinetic (PK) of pioglitazone in patients with CLD.\(^{[59]}\) The peroxisome proliferator-activated receptor-\(\gamma\) (PPAR\(\gamma\)) is the functioning receptor for TZD. Activation of PPAR\(\gamma\) inhibits collagen production from hepatic stellate cells. In a meta-analysis of eight RCT that included patients of NASH with advanced fibrosis (F3–F4), TZD was associated with improved fibrosis score (OR, 3.15).\(^{[60]}\) Also, TZD has negative impact on oxidative stress and pro-inflammatory cytokines. Though pioglitazone appears to be safe, the dose, in view of absence of evidence, should be kept on lower the side (maximum of 30 mg/day) in CLD patients, and liver function should be monitored periodically during treatment.

**Alpha-glucosidase inhibitors (AGI)**
AGIs available for the treatment of patients with DM are: voglibose, acarbose, and miglitol. AGIs are metabolized within the gastrointestinal tract.\(^{[61]}\) Due to a low systemic bioavailability and lack of hepatic metabolism, AGIs appear to be safe, useful, and well tolerated in CLD patients.\(^{[62,63]}\) AGI causes delayed carbohydrate digestion and absorption, with reduction of postprandial hyperglycemia. Because carbohydrate absorption is only delayed, and is not incomplete,
there are no nutritional caloric losses. Also, acarbose stimulates the gut peristalsis and proliferation of the saccarolytic bacteria which result in the reduction of blood ammonia levels. In a randomized controlled trial, acarbose significantly decreased blood ammonia levels, FPG, PPG, and improved encephalopathy scores compared with placebo \( (P < 0.01) \). However, acarbose may cause mild transient transaminitis requiring monitoring of liver function tests.\cite{64} Miglitol is not metabolized by liver; therefore, no influence of hepatic function on the kinetics of miglitol can be expected. Voglibose is more potent and better tolerated as compared to acarbose or miglitol. Rare cases of hepatitis with severe cholestasis attributed to voglibose hypersensitivity have been reported.\cite{65}

**DPP-4 inhibitors**

DPP-4 inhibitors are the therapeutic approaches for increasing incretin action. The currently available DPP-4 inhibitors are sitagliptin, saxagliptin, vilaglaptin, linagliptin, and alogliptin. Their PK characteristics in patients with different degrees of hepatic insufficiency (HI) are better known as compared to older OHAs \cite{66,67} \[ Table 4 \]. However, no clinical study with a long-term administration of a DPP-4 inhibitor in patients with CLD is yet available. In a case–control study, sitagliptin was found to be effective and safe for the treatment of T2DM in HCV-related CLD patients.\cite{69} PK study of vilaglaptin and linagliptin revealed no significant difference in drug exposure in patients with mild, moderate, or severe HI compared to healthy controls. Thus, dose adjustment with vilaglaptin or linagliptin is not required in patients with HI. On the other hand, saxagliptin is primarily metabolized in liver and thus requires dose adjustment in presence of HI.\cite{70}

**Sodium-glucose co-transporter 2 (SGLT2) inhibitors**

Canagliflozin, dapagliflozin, and empagliflozin are SGLT2 inhibitors currently available in India. SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2.\cite{71,72} In addition to robust glucose control, SGLT2 inhibitors have multiple non-glycemic benefits that include weight loss and reduction of high blood pressure, dyslipidemia, and hyperuricemia. The PK characteristics of SGLT2 inhibitors are similar and are not significantly affected by HI.\cite{73,74} Studies have found none of SGLT2 inhibitors to be hepatotoxic. Thus, SGLT-2 inhibitors can be used in CLD patients. The adverse events of SGLT2 inhibitors are due to their effect of increasing urinary glucose excretion and osmotic diuresis.

**Insulin**

Insulin therapy is believed to be the safest and most effective therapy in patients with CLD. It is frequently prescribed in patients with cirrhosis, although clinical studies are scant in the literature. Study has found no clinically significant impact of HI on PKs of insulin aspart.\cite{75} Insulin requirement may vary in patients with cirrhosis and is difficult to predict. It may be decreased due to reduced capacity for gluconeogenesis and reduced hepatic clearance of insulin; however, it may become higher to compensate for IR.\cite{76} Furthermore, beta-blockers, which are commonly used for portal hypertension, may make hypoglycemic episodes less symptomatic, leading to more worsening of mental state. A close monitoring of blood glucose levels is required during the initiation of insulin therapy in cirrhotic patients.

In conclusions, though enough data exist to support the fact that liver disease per se can lead to diabetes, HD is still a neglected condition. There is a need to separate HD from type-2 DM. HD appears to constitute a significant proportion of DM in cirrhotic patients. Differentiating HD from type-2 DM is often difficult, and an OGTT is required for its diagnosis. HD is associated with increased risk of cirrhotic complications, including HCC. Treatment of HD is not well defined. Because India falls in the intermediate endemicity zone of HBV infection which is an important cause of CLD, HBV vaccination might be an important step towards diabetes prevention. Additional works are needed to gain a better understanding of disease process and treatment of this condition.

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**Conflicts of interest**

There are no conflicts of interest.

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