

The treatment of diabetes mellitus of patients with chronic liver disease

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ABSTRACT

About 80% of patients with liver cirrhosis may have glucose metabolism disorders, 30% show overt diabetes mellitus (DM). Prospective studies have demonstrated that DM is associated with an increased risk of hepatic complications and death in patients with liver cirrhosis. DM might contribute to liver damage by promoting inflammation and fibrosis through an increase in mitochondrial oxidative stress mediated by adipokines. Based on the above mentioned the effective control of hyperglycemia may have a favorable impact on the evolution of these patients. However, only few therapeutic studies have evaluated the effectiveness and safety of antidiabetic drugs and the impact of the treatment of DM on morbidity and mortality in patients with liver cirrhosis. In addition, oral hypoglycemic agents and insulin may produce hypoglycemia and lactic acidosis, as most of these agents are metabolized by the liver. This review discusses the clinical implications of DM in patients with chronic liver disease. In addition the effectiveness and safety of old, but particularly the new antidiabetic drugs will be described based on pharmacokinetic studies and chronic administration to patients. Recent reports regarding the use of the SGLT2 inhibitors as well as the new incretin-based therapies such as injectable glucagon-like peptide-1 (GLP-1) receptor agonists and oral inhibitors of dipeptidylpeptidase-4 (DPP-4) will be discussed. The establishment of clear guidelines for the management of diabetes in patients with CLD is strongly required.

Key words. Insulin resistance. Liver cirrhosis. Insulin. Hypoglycemic drugs. Outcome.

INTRODUCTION

About 30% of patients with liver cirrhosis have overt diabetes mellitus (DM).¹ However, 80% with normal fasting blood glucose have impaired glucose tolerance (IGT) or DM by means of an oral glucose tolerance test (OGTT).²

There is a bidirectional relationship between DM and liver cirrhosis: hereditary type 2 DM is a risk factor for chronic liver disease (CLD).³⁻⁵ On the other hand, DM may occur as a complication of cirrhosis.

This type of diabetes is known as hepatogenous diabetes (HD).⁶

DM AND CIRRHOSIS

Retrospective studies have shown that DM is associated with an increased risk of hepatic complications and death in patients with liver cirrhosis.⁷⁻⁹ DM is associated with hepatic encephalopathy,¹⁰ portal hypertension and bleeding from esophageal varices in decompensated patients.¹¹ In a cohort of individuals with liver infection by HBV, those who developed de novo DM had higher risk of developing cirrhosis and hepatic complications.¹² In patients with chronic hepatitis C, DM was an independent predictor of hepatic complications such as ascites, spontaneous bacterial peritonitis, renal dysfunction and hepatocellular cancer.¹³

DM also has a negative impact on survival of cirrhotic patients. Nevertheless, few prospective studies have been published on this issue¹⁴⁻¹⁸ (Table 1). In a study with cirrhotic patients, cumulative

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Table 1. Prospective studies evaluating the impact of diabetes mellitus on survival of patients with liver cirrhosis.

Author	N	Design	Follow-up, years	Results
Bianchi, 1994 ⁹	382	Retro and prospective	5	DM, serum albumin, ascites, HE, serum bilirubin and platelets were predictors of death.
Holstein, 2002 ¹⁵	54	Prospective	5	Patients showing overt DM or abnormal OGTT had lower cumulated survival.
Nishida, 2006 ¹⁶	56	Prospective	5	Normal fasting blood glucose as inclusion criteria. Abnormal OGTT was associated with reduction of survival.
Jáquez-Quintana, 2011 ¹⁴	110	Prospective	3	Compensated cirrhosis. Patients with overt DM showed a reduction of cumulated survival.
Hagel, 2011 ¹⁸	78	Prospective	30 days	Decompensated cirrhosis. Abnormal OGTT associated to increase of 30-day mortality.
García-Compeán, 2014 ¹⁷	100	Prospective	5	Compensated cirrhosis. Those with abnormal OGTT had a reduction of survival.

HE: hepatic encephalopathy. OGTT: oral glucose tolerance test.

survival at 2 years was significantly lower in diabetics. Serum creatinine and the Child-Pugh score were independent predictors of death.¹⁴ In another study with patients with normal fasting glycaemia subjected to OGTT, the 5-year survival rate was lower in patients with IGT or DM.¹⁵ Another study found that the cumulative 5-year survival rate of those with abnormal OGTT values or overt DM was significantly lower.¹⁶ Our group recently reported that abnormal OGTT was associated with a significant increase in mortality at 5 years. The OGTT and the Child-Pugh score were independent predictors of death, suggesting that there might be a synergistic effect between conditions.¹⁷

DM might induce liver damage by promoting inflammation and fibrosis through an increase in mitochondrial oxidative stress by the action of leptin, adiponectin, interleukin-6 and TNF- α , which are produced in chronically inflamed adipose tissue (adipositis).^{19,20} The production of these chemical mediators is stimulated by insulin resistance (RI). TGF β 1 and leptin activate stellate cells, inducing them to produce collagen leading to fibrosis.²¹⁻²³

Cirrhotic patients with DM frequently die of liver-related causes. Although low frequency of cardiovascular complications have been reported,^{9,14-17} two recent publications found that patients with chronic hepatitis C showed an increase of carotid intimal layer thickness, the number of carotid plaques and the extent of atherosclerosis compared with control subjects.²⁴⁻²⁷ In another study, the

prevalence of non-obstructive coronary artery disease was similar in cirrhotic and non-cirrhotic individuals and it was associated with traditional risk factors, particularly DM.²⁸

The impact of DM also extends to immunocompetence, and can increase the risk of severe infection, such as spontaneous bacterial peritonitis.²⁹ Cirrhotic patients with such infections exhibit liver failure and hepatorenal syndrome, and have a high hospital mortality.³⁰

TREATMENT OF DM IN PATIENTS WITH CHRONIC LIVER DISEASE

The effective control of hyperglycemia may reduce complications and mortality rate in patients with DM and chronic liver disease. Nevertheless, pharmacodynamic studies of antidiabetic drugs have been conducted irregularly in these patients.^{31,32} In addition, only few studies³³⁻³⁷ (Table 2) have evaluated the rate of control of hyperglycemia,^{33,34} the effectiveness of specific drugs,³⁵ the impact of treatment on morbidity and mortality^{36,37} and the safety of antidiabetic drugs.³³⁻³⁷ In one of such studies, effective glycemic control was achieved in only a small proportion of patients with HCV/HBV infection (34.2 and 23.5% respectively).³⁴ In another study, treatment was effective in only 28% of patients largely due to the toxicity of the drugs; however, of those who showed glycemic control, there was a significantly lower incidence of hepatic

Table 2. Studies evaluating the impact of antidiabetic therapy on outcomes of patients with diabetes mellitus and liver cirrhosis.

Author (year)	Design	N	Treatments, n	Length of treatment	Control of hyperglycemia	Impact on morbidity and mortality	Toxicity
Gentile, 2001 ³⁵	DBRT	100	Acarbose 52; Placebo: 48	28 weeks	Improvement of FPG and postprandial glycemia, Hb A1c and C-peptide	Non assessed	None
Kwon, 2005 ³⁴	Retrospective descriptive	434	Insulin: HCV: 48% and HBV: 66% OHGA: HCV: 35% and HBV: 22%	Mean of 20.5 months	34.2% in HCV and 23.5% en HBV	Control of glycemia was a predictor of survival in HCV patients	Non reported
Nkontchou, 2011 ³⁶	Observational prospective cohort study	100 with HCV cirrhosis	Metformin: 26; Diet/insulin/ other OHGA: 74	3.8 to 9.5 years	Non assessed	Metformin was associated with reduced incidence of HCC and liver-related death/transplantation	No case of lactic acidosis
Gundling, 2013 ³³	Observational retrospective	285	Insulin, diet and/or OHGA: 87. No treatment: 198	3 years	28.70%	Control of hyperglycemia associated with reduction of HE. No effect on other liver-related or CV complications	Hypoglycemia in 12.6% (use of insulin and Child-Pugh B and C)
Zhang, 2014 ³⁷	Observational retrospective	250	Metformin: 172; No treatment: 78	3.1 to 151 months	Non assessed	Metformin was associated with significant increase survival	No case of lactic acidosis

DBRT: double blind randomized trial. FPG: fasting plasma glucose. OHGA: oral hypoglycemic agents. CV: cardiovascular.

encephalopathy.³³ These two studies demonstrate that satisfactory glycemic control in cirrhotic patients can be achieved in only one third of cases by using current therapeutic schemes possibly because of hepatotoxicity, hypoglycemia and lactic acidosis, as most of antidiabetic drugs are metabolized in the liver.³⁸

Changes in lifestyle and exercise

The recommendations of changes in diet and exercise regimens are empirical, as these measures have not been evaluated in patients with hepatic insufficiency. Although physical exercise improves insulin resistance, it may not be appropriate for patients with active liver disease, while restrictive diets may aggravate the protein-calorie malnutrition often found in these patients.⁴ Studies are needed to determine what changes in lifestyle could benefit these patients.

Pharmacotherapy

Most patients will require oral hypoglycemic agents and/or insulin to control hyperglycemia, especially in advanced stages of liver disease. Notwithstanding, most of these drugs are metabolized in the liver, so that monitoring of blood glucose levels during treatment should be strict.

Inhibitors of alpha-glucosidase: acarbose

These drugs inhibit α -glucosidases, which contribute to degradation of disaccharides in the intestine. It results in reduction in the absorption of carbohydrates and in the risk of postprandial hyperglycemia. Acarbose also reduces the clinical expression of DM in patients with IGT in 25% of cases; liver toxicity is low. Although there are no pharmacodynamic studies with acarbose in patients with hepatic insufficiency, its efficacy on hyperglycemia and its safety has been evaluated in patients with DM and CLD,³⁹ alcoholic cirrhosis⁴⁰ and mild hepatic encephalopathy.⁴¹ Its use was associated with a significant reduction of fasting and postprandial hyperglycemia, as well as HbA1c and C-peptide in diabetic patients with compensated cirrhosis.³⁵

Biguanides: metformin

Metformin is used to increase insulin sensitivity, and has beneficial effects on lipid metabolism. It is not metabolized in the liver and is excreted almost

unchanged by the kidney. It is not recommended in patients with liver cirrhosis by fear of inducing lactic acidosis.⁴² However, this complication was reported only in anecdotal cases, particularly with concomitant alcohol intake.⁴³

The use of this drug for the treatment of simple steatosis and NASH with or without DM has yielded conflicting results. In most studies, it is associated with a normalization of transaminases and, to a lesser extent, with histological and IR improvement.⁴⁴⁻⁴⁶

Metformin has been associated with a reduced risk of HCC.⁴⁷ Two recent studies have shown that this drug reduced incidence of liver complications and increased survival of patients with liver cirrhosis. In one study, a significant reduction in the incidence of hepatocellular carcinoma and liver complications was observed in patients with DM and HCV cirrhosis after treatment of an average period of 5.7 years.³⁶ In another study, the long-term survival of diabetic patients with liver cirrhosis who continued taking metformin was longer than the ones who stopped it. Reduction in mortality was also significant in patients with stages B and C of Child Pugh. No patient developed lactic acidosis during a follow up period of 26.8 months.³⁷ Although these studies did not report the glycemic effects, it is likely that better glycemic control was a contributor to reduced morbidity and mortality. The low incidence of lactic acidosis reported in these studies is encouraging, though caution should still be taken when considering its use in patients with advanced liver failure.

Insulin sensitizers: thiazolidinediones

These drugs improve insulin sensitivity in target organs, while the peroxisome proliferator-activated gamma receptor (PPAR γ) has selective agonist effects. The troglitazone induces cytochrome P450, leading to hepatotoxic reactive metabolites. Because of this noxious effect, it was taken off the market.⁴⁸

Pioglitazone is metabolized by the CYP2C81 and CYP3A4 system.⁴⁹ There are no pharmacodynamic studies evaluating the effects of this drug in patients with CLD, and it may induce increase of body weight. Pioglitazone combined with pegylated interferon and ribavirin has been used in patients with chronic HCV liver disease for increasing sustained viral response.^{50,51}

Pharmacodynamic features of rosiglitazone have been poorly studied in patients with liver cirrhosis.

Elimination is slow so it is recommended to take precautions in patients with severe liver impairment.⁵²

The administration of pioglitazone and rosiglitazone for the treatment of NAFLD (presumably without cirrhosis) with or without DM has yielded conflicting results. Both improve serum transaminase levels and IR though improvement of inflammation and hepatic fibrosis is inconsistent.⁵³⁻⁵⁵ Although both have low hepatotoxicity, in patients with serum transaminases 2.5 times above the upper limit of normal and compensated cirrhosis, they should be used with careful monitoring. If the enzymes increase or remain at the same level several days after introduction, the drug should be discontinued. Its use in patients with Child-Pugh stage C cirrhosis should be avoided.

Insulin secretagogues: sulfonylureas

They stimulate insulin secretion and are associated with a higher risk of severe hypoglycemia than metformin and other drugs in patients with advanced age and chronic liver or kidney disease.⁵⁶ They do not modify IR and their effect may be limited in alcoholic individuals due to damage of the beta cells of pancreatic islets.⁵⁷

Tolbutamide is not recommended in patients with liver disease since half-life increases over 50%.⁵⁸ Glibenclamide (glyburide) and gliclazide are metabolized in the liver and eliminated through bile and kidney. Their pharmacodynamic features have not been evaluated in patients with CLD. However, hepatotoxicity has been reported with glibenclamide^{59,60} and gliclazide.^{61,62} Therefore their use is not recommended in severe hepatic impairment.⁶³

Meglitinides

Repaglinide and nateglinide are the most used drugs. They stimulate the beta cells of the pancreas, regulating the output of potassium through specific ATP-dependent channels and stimulating an increase of intracellular calcium.⁶⁴ Both agents are metabolized in the liver. However, repaglinide is rapidly eliminated through the bile⁶⁵ and its rate of elimination is significantly reduced in patients with CLD; thus, it may induce hypoglycemia and it is contraindicated in patients with advanced liver insufficiency.⁶⁶ In contrast, the pharmacodynamics of nateglinide is not altered in patients with CLD and is thus expected to be safer.⁶⁷

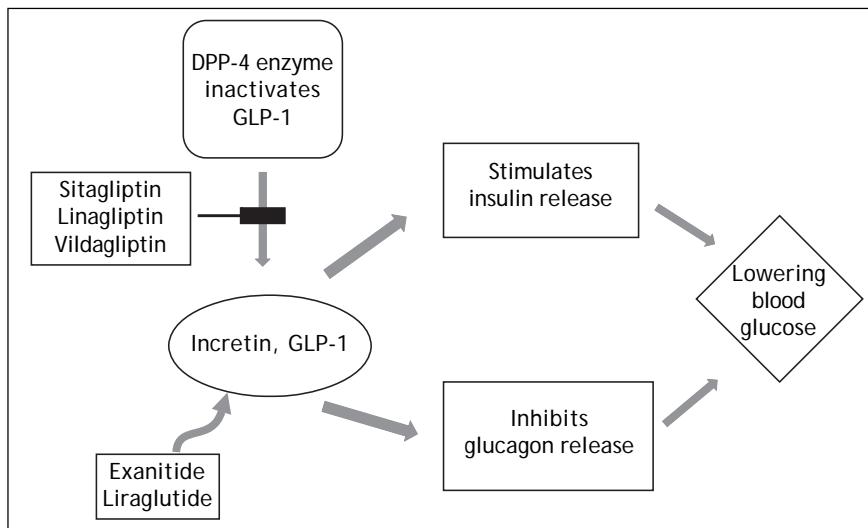


Figure 1. Mechanism of action of glucagon-like peptide-1 (GLP-1) receptor agonists and oral inhibitors of dipeptidylpeptidase-4 (DPP-4) (gliptins).

Incretin-based therapies

Incretin-based therapies comprise injectable glucagon-like peptide-1 (GLP-1) receptor agonists and oral inhibitors of dipeptidylpeptidase-4 (DPP-4)(gliptins).

GLP-1 receptor agonists such as exenatide and liraglutide, mimic the effect of incretin and glucagon-like peptide 1 (GLP-1) (Figure 1). They stimulate insulin secretion and inhibit the release of glucagon by the beta and alpha cells of the Langerhans islets of the pancreas, thereby reducing postprandial plasma glucose levels.⁶⁸ They also reduce gastric emptying time and body weight.

Inhibitors of DPP-4, such as sitagliptin, vildagliptin and linagliptin, inhibit DPP-4, resulting in an increase of incretin and GLP-1 secretion (Figure 1), leading to an improvement in plasma glucose control without inducing hypoglycemia or increasing the body weight.⁶⁹

Both types of drugs are barely metabolized in the liver and are excreted unchanged by the kidney;⁷⁰ thus, they seem to be safe in cirrhotic patients.⁷¹ Unlike the old antidiabetic drugs, their pharmacodynamic characteristics have been assessed in patients with varying degrees of hepatic impairment and their safety has been assessed in studies comprising large number of individuals. Inhibitors of DPP-4 showed only minimal pharmacokinetic changes in patients with varying degrees of hepatic impairment.⁷⁰

Among agonists of GLP-1 receptors, only liraglutide has been studied in patients with CLD.⁷² No increase in liver enzymes was observed with this drug alone or combined with other agents; it was well tolerated over a period of two years.

Unlike sitagliptin and vildagliptin, linagliptin is excreted in bile (enterohepatic). Notwithstanding, in pharmacokinetic studies, patients with moderate or severe hepatic impairment showed no increase of drug exposure after administration of multiple doses of linagliptin, compared to normal controls; thus, no dose adjustment is required.⁷⁰

The effectiveness of liraglutide combined with sitagliptin or pioglitazone has been assessed in patients with NAFLD and DM. Liraglutide improved DM parameters and reduced inflammation, liver fibrosis and body weight.⁷³

Recently, long-acting GLP-1 receptor agonists have been developed. There are, at present, several once weekly GLP-1 receptor agonists available in the market: exenatide long-acting release (LAR), albiglutide, dulaglutide and semaglutide.^{74,75} Head-to-head clinical trials data suggest that long-acting GLP-1 receptor agonists produce superior glycemic control when compared with their shortacting counterparts (exenatide and liraglutide). Furthermore, they are generally well tolerated, with no hepatotoxicity in patients without liver disease.⁷⁶ Unfortunately there is no experience in chronic administration in patients with chronic liver disease, particularly those with severe dysfunction.

Based on the above discussed, patients with liver disease and DM may be benefited with incretin-based therapies due to their low liver toxicity and wide tolerance. However, no study of long term effectiveness and safety has been published to date. They seem to be well tolerated in patients with mild and moderate liver function impairment, though they should be cautiously administered in patients with advanced liver disease.^{77,78}

SGLT2 inhibitors

Selective renal sodium glucose co-transporter 2 (SGLT2) inhibitors improve glycemic control in an insulin-independent fashion through inhibition of glucose reuptake in the kidney.⁷⁹ The most used drugs from this group are: dapagliflozin, canagliflozin and empagliflozin.

SGLT2 inhibitors reduce plasma glucose levels by inducing glucosuria and osmotic diuresis. They should be carefully administered to patients with risks of hypovolemia (older age, cardiovascular diseases, treatment with diuretics, liver cirrhosis with circulatory dysfunction). They are contraindicated in patients with renal impairment manifested by hypercreatininemia and reduction of glomerular filtration rate. Undesirable side effects are based on their mechanism of action: renal failure, arterial hypotension, urinary tract candidiasis, body weight reduction and hyperkalemia.⁸⁰

Dapagliflozin is the SGLT2 inhibitor with the most clinical data available to date. This drug is eliminated primarily by glucuronidation. In pharmacokinetic studies, patients with moderate and severe hepatic impairment had higher systemic exposure to the drug than healthy subjects. Exposure was highly dependent on the calculated creatinine clearance. Although these differences were not clinically significant, the decision of administering dapagliflozin to cirrhotic patients should be individually assessed because the long-term safety profile and efficacy have not been specifically studied in this population.⁸¹ Caution should be even greater when hepatic dysfunction is combined with renal impairment. Pharmacokinetic studies with canagliflozin and empagliflozin also showed an increased drug systemic exposure in patients with impaired liver function. These drugs are well tolerated and reported hepatotoxicity is low in patients with mild and moderate liver function impairment. Nevertheless, there are no experience in chronic administration of these drugs in patients with severely impaired liver function (Child C group) so they might not be recommended in these patients.^{82,83}

Insulin

About 60% of diabetic patients with liver cirrhosis require insulin administration.^{33,34} However, long term efficacy and safety of insulin in large number of patients with liver cirrhosis have not been studied. Insulin requirements can be high in patients with compensated cirrhosis, whereas they

can be low in decompensated patients due to a reduction in hepatic clearance and gluconeogenesis.⁸⁴ Because of this, it is recommended that the administration of insulin in patients with cirrhosis should start with close monitoring due to the risk of hypoglycemia.⁸⁵

The pharmacokinetic of short-acting insulin analogues such as insulin lispro, aspart and glulisine is not significantly altered as a result of hepatic dysfunction; thus, these agents are useful for controlling postprandial hyperglycemia.⁸⁶ Insulin degludec has an ultra-long lasting effect and a stable pharmacokinetic profile. It shows no differences with respect to drug absorption or clearance in cirrhotic patients. No serious adverse effects, such as hypoglycemia, have been observed when using this kind of insulin in patients with cirrhosis.⁸⁷

Liver transplantation

Liver transplantation quickly normalizes glucose tolerance and insulin sensitivity in hepatogenous diabetes. This effect is due to an improvement in hepatic clearance and peripheral disposal of glucose in response to a correction of chronic hyperinsulinemia.^{88,89} However, liver transplantation cures DM only in 67% of cases. In 33% of cases, diabetes is not cured in cirrhotic patients due to the persistence of a reduction in the functioning of beta cells of the pancreas caused by an injury due to alcohol.⁹⁰ In the other side, a study comprised of a cohort of 85,194 liver transplant recipients showed that the presence of type 2 DM in recipients or donors was associated with an increased risk of adverse post-transplant outcomes.⁹¹

PERSPECTIVES

In the last decade, progresses in research regarding diabetes mellitus in liver cirrhosis have been achieved. Nevertheless, future studies should define some aspects:

- The efficacy and safety of incretin-based therapies.
- The impact of early treatment of IGT and DM (detected by OGTT) on incidence of complications and survival.
- Whether the control of hyperglycemia reduces the incidence of cardiovascular complications and mortality; and
- Finally, effective and safe therapeutic regimens for DM of cirrhotic patients should be designed in consensus of experts.

There are an increasing number of patients with liver disease and DM as a result of the global epidemic of obesity and NAFLD. Thus, hepatologists should have a basic knowledge of the use of antidiabetic drugs. At the same time, endocrinologists must recognize liver disease as a potential complication of type-2 diabetes and metabolic syndrome as well as the clinical implications of hepatogenous diabetes. Both specialists working together will make possible to optimize therapeutic outcomes of these patients.

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