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Hypoglycemic Therapy in Chronic Hepatic Disease Literature Review

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Abstract

Chronic liver disease (CLD) refers to a structural and functional change of the liver, which modifies the pharmacokinetics of multiple drugs, including hypoglycemic agents. This alteration depends on the severity degree of the liver disease, clinical characteristics of the patient, and comorbidities presence such as kidney disease and drug biochemistry. Insulin is considered a safe therapeutic strategy in patients with CLD, however, for many oral hypoglycemic agents, its use and dose adjustment will depend on the Child-Pugh score, based on the risk of hypoglycemia in this type of patient.

Keywords

Cirrhosis, Hypoglycemic Agents, Pharmacokinetics (MeSH)

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1. Effects of Chronic Liver Disease on Pharmacokinetics

The structural and functional change of the liver in chronic liver disease (CLD) can generate hemodynamic and metabolic disorders that alter the pharmacokinetics of the drugs; this will depend on the characteristics of the patient (comorbidities, nutritional status), the severity of the CLD, and chemical characteristics of the drug [1] [2].

Multiple risk factors for adverse drug reactions are described in patients with CLD [3], such as:

- Decreased portal blood flow or increased resistance of the hepatic artery [4].
- Portosystemic shunt: avoids the liver's first-pass effect. Cardiotoxic drugs are not metabolized in the liver and cause changes in the heart rhythm [5] [6].
- Changes in cytochrome P450 activity [7].
- Cholestasis: serum drug levels may be increased due to inadequate bile secretion [3].
- Hypoalbuminemia: changes in fluid dynamics with retention in interstitial space [8]. In drugs with a high degree of albumin binding, it occurs with an increase of the plasma free level [9].
- Portal hypertension: Secondary complications such as ascites (change in volume of distribution), portal gastropathy (decreased absorption), and impaired renal blood flow (reduced renal clearance) [10].

2. Diabetes and Chronic Liver Disease

The liver is one of the main targets of insulin and counter-regulatory hormones, such as glucagon. A direct association between diabetes mellitus and the development of non-alcoholic fatty liver disease (NAFLD) was established, as shown in **Figure 1** [11]. The prevalence of diabetes mellitus in patients with NAFLD and non-alcoholic steatohepatitis (non-alcoholic steatohepatitis NASH) is very high, reporting figures of up to 22.51% and 43.63% respectively; compared to the general population with a prevalence of 8.5% [12]. As a result of type 2 diabetes mellitus is being considered one of the risk factors most strongly related to the progression from NAFLD to NASH and cirrhosis [13], increasing the probability of developing NASH 2 - 3 times to non-diabetic patients [14]. Studies based on liver histology find that a proportion of patients with type 2 diabetes mellitus exhibits NASH up to 80% and advanced fibrosis of 30% - 40% [15] [16] [17] [18].

3. Pathophysiology between Diabetes Mellitus and Chronic Liver Disease

Due to peripheral insulin resistance, the release of free fatty acids from adipose tissue increased [19], and so the absorption of fats by hepatocytes [20]. Initially, this accumulation of lipids in the liver works as a compensatory mechanism against lipotoxicity mediated by the increase in free fatty acids; however, as a consequence of the accumulation of intracellular triglycerides [21] the inflammatory

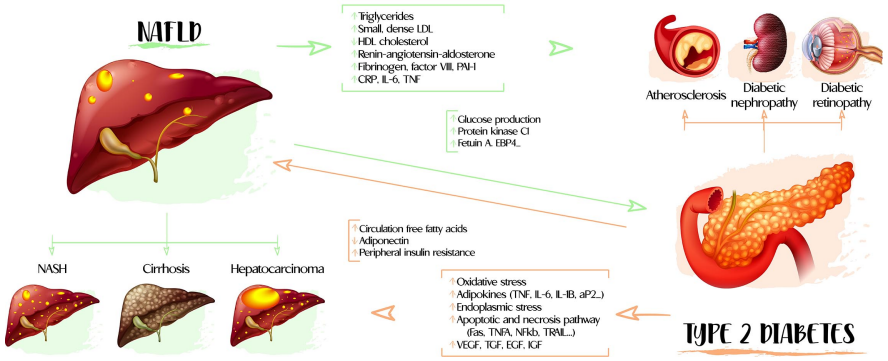

Figure 1. Pathophysiology of the connection between NAFLD, NASH and diabetes mellitus. Adapted from: Xia M-F, Bian H and Gao X (2019) NAFLD and Diabetes: Two Sides of the Same Coin? Rationale for Gene-Based Personalized NAFLD Treatment.

mediators MCP-1, IL-6, TNFα, IL-1β [22] are expressed, activating the Kupffer cells [22], which results in the death of the hepatocyte due to apoptosis and necrosis [23]. The hepatic influence of cholesterol, lysophosphatidylcholine, and other lipid substances perpetuate the inflammatory state and lead to the formation of fibrosis [24]. As a result, a continuum of liver damage progression is generated, passing from NAFLD to NASH, cirrhosis, and finally, hepatocarcinoma [11].

4. Treatment for Diabetes in Patients with Chronic Liver Disease

Considering the pharmacokinetic alterations that hypoglycemic drugs can undergo in CLD, next will listed indications, contraindications, and dose adjustment of this group of patients.

4.1. Insulin

It is considered a safe treatment strategy in chronic liver disease. No dose adjustment is required regardless of cirrhosis severity [25] [26] [27]. Insulin requirements may vary. In patients with compensated cirrhosis, the requirements may be higher, since insulin resistance predominates in these, whereas in patients with decompensated cirrhosis, the hepatic insulin metabolism is severely impaired. Insulin should be used preferably with the hospitalized patient with close monitoring of blood glucose levels due to the risk of hypoglycemia [28].

4.2. Metformin

Metformin is the first-line therapy for patients with type 2 diabetes mellitus [29]. It does not undergo hepatic metabolism and is excreted unchanged by tubular secretion and glomerular filtration; however, chronic liver disease can be a risk factor to develop type B lactic acidosis [30]. The use of metformin has not been associated with the formation or exacerbation of liver injury, and may even be beneficial in patients with NAFLD, because a protective effect has been demonstrated for the development of hepatocarcinoma [31].

Due to case reports of type B lactic acidosis [32], the use of metformin exercise with caution on patients with moderate CLD and to avoid it on severe CLD patients. The Canadian Diabetes Association (CDA) recommends using clinical practice guidelines to avoid metformin in patients with hepatic failure [33] just as the American Diabetes Association (ADA) restricts the use of metformin in patients with severe liver disease [29].

It is suggested not to use metformin doses higher than 1500 mg per day in patients with chronic liver disease [30].

4.3. Sulfonylureas

Sulfonylureas (SU) are alternative treatments to metformin on patients with type 2 diabetes mellitus. The first-generation is currently in disuse. Those of the second generation (glyburide/glibenclamide, glipizide, gliclazide) and third-generation (glimepiride), are classified by the guide of the American Diabetes Association (ADA), as second-line treatments in well-selected patients: no comorbidities and low-risk hypoglycemia [29]. All metabolized in the liver [30], have high plasma protein binding and are excreted through the kidneys [34] [35] [36] [37]. Due to this, there is an increased risk of hypoglycemia due to a lack of inactivation of the SU.

Clinical practice guidelines recommend using SU with caution and at low doses in patients with Child-Pugh A and B class cirrhosis. Avoid its use in patients with Child-Pugh C [30].

4.4. Thiazolidinediones (TZD)

It is metabolized by hydroxylation and oxidation. Its excretion is through bile and feces. The main side effect associated with this group of drugs is peripheral edema. Pioglitazone could be beneficial in the setting of patients with NAFLD and NASH. Histological improvement and ALT and AST levels were showed in a clinical trial compared to placebo $P < 0.001$ [38].

It is recommended to avoid TZD use in patients with elevated transaminases (ALT > three times the upper limit of normal). Restrict the use of pioglitazone in patients with Child-Pugh B-C or peripheral edema [30].

4.5. Dipeptidyl Peptidase-IV Inhibitors (DPP-4 Inhibitors)

Sitagliptin and vildagliptin are excreted mostly through the kidneys or hydrolysis in multiple tissues without modification, respectively [39] [40]. For linagliptin, 80% of the administered dose is eliminated through enterohepatic recycling. Saxagliptin is metabolized mainly by hepatic cytochrome CYP3A4/5 and eliminated through the kidneys and the liver [39]. Compare with healthy controls, patients with a Child-Pugh score of 7 to 9 were included in a study to assess the pharmacokinetics of sitagliptin. An increase in the maximum serum concentration was found on patients with chronic liver disease, but it was not statistically significant [41]. Another case-control study evaluated the efficacy and safety of

sitagliptin on patients with diabetes and chronic liver disease secondary to infection with the hepatitis C virus (HCV). There were no significant changes in AST and ALT levels during the 48-week follow-up in the sitagliptin and control groups [42]. In a safety meta-analysis, consisting of 38 phase II and III clinical trials, patients treated with vildagliptin were found to have mild elevations in liver enzymes compared to controls. In two of the patients, a marked elevation of transaminases (ALT-AST > ten times the upper limit of normal) and bilirubins (>2 times ULN) was evident [43] [44]. Clinical practice guidelines recommend DPP-4 inhibitors be used safely in patients with Child-Pugh A class cirrhosis without a dose adjustment requirement (except for vildagliptin). In Child-Pugh B class patients, use with caution, and in Child-Pugh C class patients should be avoided [30].

4.6. Sodium-Glucose 2 (iSGLT2) Co-Transporter Inhibitors

The pharmacokinetics of SGLT2 inhibitors (Canagliflozin, Dapagliflozin, and Empagliflozin) are similar. They have a long half-life, which allows the administration once a day. Its metabolism is hepatic, and it is excreted by the kidneys [45]. The serum concentration of canagliflozin is not affected in patients with chronic liver disease [46]. Dapagliflozin decreases its maximum serum concentration in patients with CLD, even in mild forms [47].

In a safety meta-analysis with all SGLT2 inhibitors composed of phase II and III clinical trials, no hepatotoxicity mediated by these drugs was observed [48] [49] [50]. The current recommendation is to safely use iSGLT2 in patients with Child-Pugh A class liver cirrhosis, administer with caution in Child-Pugh B class patients and restrict them in Child-Pugh C class patients. Patients with a high risk of dehydration and arterial hypotension should be closely monitored. [30].

4.7. GLP1 Analogues

Renal mechanisms predominantly eliminate exenatide. Liraglutide and dulaglutide are broken down by protein catabolism. Nevertheless, liver metabolism is not an important route of elimination for these drugs. There are no clinical trials of exenatide pharmacokinetics in CLD [30]. However, reductions in ALT levels have been demonstrated in patients using said GLP1 analog [51].

The serum concentration of Liraglutide decreases in patients with CHD; however, this is not a negative outcome in clinical outcomes. In contrast, the use of Liraglutide improved diabetes mellitus and decreased inflammation and liver fibrosis and promoted bodyweight reduction [52].

All GLP1 analogs can be used in patients with Child-Pugh A class liver cirrhosis without dose adjustment requirement. In Child-Pugh B class patients, they should be used with caution, and in the case of Child-Pugh C class patients, their administration is not recommended [30].

5. Conclusions

Despite the accumulation of recent information regarding the negative impact of

diabetes mellitus on the survival of cirrhotic patients, to date, very few therapeutic studies have been published with the aim of knowing which are the most appropriate treatment regimens for diabetes and, above all, to find out what is the impact of treatment on patient survival. Furthermore, treatment of the patient with cirrhosis is difficult due to the following: 1) around half of the patients have malnutrition; 2) when DM is diagnosed, the patient has advanced liver failure; 3) the majority of oral hypoglycemic drugs and insulin are metabolized in the liver; 4) these patients frequently have hypoglycemic episodes; 5) adherence to treatment is possibly low, particularly in alcoholics, and 6) persistence of alcohol intake [53].

The initial treatment of patients with mild to moderate hyperglycemia and compensated liver disease could be a change in lifestyle, since at this stage insulin resistance is a predominant factor. However, these therapeutic measures can be compromised by very restrictive diets that could aggravate the state of malnutrition. Exercise, which improves insulin resistance, is not appropriate in patients with active liver disease [54]. In advanced stages of CLD, when diabetes mellitus manifests clinically, the use of oral hypoglycemic agents may be necessary. However, most of these drugs are metabolized in the liver, so monitoring of blood glucose levels during treatment should be close to avoid hypoglycemia [55].

Metformin is the first-line drug in type 2 diabetes mellitus since it decreases insulin resistance. However, this drug is relatively contraindicated in patients with advanced liver failure and in those who continue alcohol intake due to the risk of type B lactic acidosis.

All are metabolized in the liver, have high plasma protein binding and are excreted via the kidneys. Due to the increased risk of hypoglycemia due to lack of inactivation of the SU, clinical practice guidelines recommend: use the SU with caution and at low doses in patients with liver cirrhosis class CHILD PUGH A and B. Avoid its use in patients with CHILD PUGH C.

Thiazolidinediones can be especially helpful as they increase insulin sensitivity. Apparently safer, rosiglitazone and pioglitazone are not recommended if there is evidence of active liver disease or if ALT levels are above 3 times the normal value.

Finally, liver transplantation quickly normalizes glucose tolerance and insulin sensitivity. This effect is thought to be due to improved hepatic clearance and peripheral glucose disposition. This last effect could be secondary to a correction of chronic hyperinsulinemia. However, liver transplantation cures hepatogenic only in 67% of cases. Diabetes was not corrected in 33% due to the persistence of reduced pancreatic beta cell function [56].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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