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Contents

Irregular Volume 7 Number 8 August 31, 2019

EDITORIAL

REVIEW

MINIREVIEWS

Contents

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Volume 7 Number 8 August 31, 2019

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REVIEW

Antidiabetic agents in patients with hepatic impairment

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Abstract

Chronic liver disease (CLD) often coexists with type 2 diabetes mellitus, making diabetes management a challenge to the clinician. It is well known that liver is the major site of drug metabolism, and, therefore, its impairment affects hepatic metabolism of many antidiabetic agents. Furthermore, patients with CLD have serious comorbidities such as impaired renal function, hypoalbuminemia, lactic acidosis, hypoglycemia and malnutrition, making their treatment even more difficult. On the other hand, most of the antidiabetic agents, with the exception of insulin, need dosage titration due to alterations to their pharmacokinetics in patients with CLD. For well-established antidiabetic treatments, like metformin and sulfonylureas there are studies regarding their dosage chance in these patients. However, despite the growing problem of management of diabetes in patients with CLD the existing literature data, especially on newer antidiabetic agents, are limited and, furthermore, no direct guidelines exist. Therefore, in the present review article we try to summarize the existing literature data regarding management of diabetes in patients with CLD.

Key words: Hepatic impairment; Type 2 diabetes mellitus; Pharmacokinetics; Antidiabetic drugs

Core tip: Most of the antidiabetic agents, with the exception of insulin, need dosage titration due to alterations to their pharmacokinetics in patients with chronic liver disease (CLD). For well-established antidiabetic treatments, like metformin and sulfonylureas there are studies regarding their dosage chance in these patients. However, despite the growing problem of management of diabetes in patients with CLD the existing literature data, especially on newer antidiabetic agents, are limited and, furthermore, no direct guidelines exist. Therefore, in the present review article we try to summarize the existing literature data regarding management of diabetes in patients with CLD.

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INTRODUCTION

Liver is one of the principal organs in carbohydrate metabolism due to its important role in neoglucogenesis and glycogenolysis[1]. A link between type 2 diabetes mellitus (T2DM) and chronic liver disease (CLD) was observed for the first time before almost 100 years[1,2]. Since then it is well-known that diabetes and CLD often coexist. Even more, presence of CLD increases not only T2DM complications but it is recognized as a cause of premature mortality in patients with T2DM[3]. On the contrary, diabetes *per se* has been recognized as a risk factor for CLD and hepatocellular carcinoma (HCC). It is estimated that about 30%-60% of patients with cirrhosis have T2DM[4]. In another study, the prevalence of T2DM in patients with CLD was varied between 18%-71%[5]. On the other hand, glucose intolerance is present in the majority of patients with CLD[6]. It is obvious, that there is a two-side relationship between T2DM and CLD making the management of these patients a challenge to the clinicians.

Since liver is the major site of metabolism for most of the antidiabetic agents, management of T2DM in patients with CLD is still challenging for the reasons that are listed below. First of all, patients with CLD have serious comorbidities such as impaired renal function, hypoalbuminemia, lactic acidosis, hypoglycemia and malnutrition[7,8]. Secondly, patients with CLD are more prone to acute kidney injury leading to accumulation of either drugs or their metabolites resulting in various adverse events[9]. Finally, patients with CLD develop malnutrition as the liver plays a key role in carbohydrate, protein, lipid, vitamin, and mineral metabolism and energy balance[10,11].

Liver is the major site of drug metabolism, and its impairment affects hepatic metabolism of drugs[12]. On the other hand, hypoalbuminemia, a result of protein deficiency[13], can cause serious toxicity by highly protein bound drugs since their free plasma concentrations are increased in CLD. Furthermore, the potential hepatotoxicity of some oral antidiabetic agents (OADs) associated adverse events favored by CLD makes management of T2DM in patients with CLD even more complex[4].

Until now, only limited literature data are available yet regarding the management of T2DM in patients with CLD[3,8]. Therefore, the aim of the present review is to summarize the existing literature data on the use of OADs and injectable agents in T2DM patients with CLD.

CLASSIFICATION OF LIVER IMPAIRMENT

The Child-Pugh score is currently used to assess the overall prognosis of CLD, mainly cirrhosis[14]. The Child-Pugh score is consisted of 5 clinical characteristics of liver disease: total bilirubin level, serum albumin concentration, prothrombin or international normalized ratio value, presence of ascitis and hepatic encephalopathy. Each measure is scored from 1 to 3, with 3 indicating most severe derangement. Patients are classified into 3 Child-Pugh classes (A-C): Child-Pugh A = 5-6 points, Child-Pugh B = 7-9 points, and Child-Pugh C = 10 or more points.

ANTIDIABETIC TREATMENT

Biguanides (metformin)

Metformin, a biguanide compound, is the first-line therapy for T2DM patients for almost half a century[15]. Its action is mediated by the inhibition of gluconeogenesis and glycogenolysis in hepatocytes[15]. Metformin undergoes renal excretion and is excreted unchanged by the kidneys[16].

One of the most life threating adverse events of metformin is lactic acidosis. However, it must be noticed that metformin might cause lactic acidosis in predisposed patients (with heart, renal and liver failure), a rather rare, however, adverse event of metformin therapy. In patients with CLD, there is an increased risk

of low oxygen tension due to concurrent pulmonary or heart disease making lactic acidosis easy to happen. Even more, patients with CLD are at increased risk for sepsis or hemorrhage[17] making them vulnerable to lactic acidosis since metformin inhibits mitochondrial respiration in the liver[18]. It must be mentioned that lactic acidosis is rather a rare side effect of metformin since the incidence of lactic acidosis is 0.03-0.5 cases/1000 patient-years in metformin-treated population[19].

According to the existing studies, metformin therapy is safe in T2DM patients with cirrhosis, and further prolong patient's survival time. A study in 22 T2DM cirrhotic patients showed that metformin therapy was related to overt hepatic encephalopathy. A possible pathogenetic mechanism proposed by authors was the inhibition of glutaminase activity[20]. Another study showed that metformin was related with reduced incidence of HCC and liver-related death/transplantation in T2DM patients with cirrhosis due to hepatitis C virus[21]. It is noteworthy that metformin therapy reduced the risk of death by 57% in T2DM patients with cirrhosis[22].

The only risk of metformin therapy in patients with CLD, as it is mentioned above, is lactic acidosis. Therefore, according to the ADA guidelines, it is recommend to avoid metformin therapy in patients with severe hepatic impairment (HI) or in binge drinkers due to high risk for lactic acidosis[15] (Table 1).

Sulfonylureas

Liver is the major site of biotransformation for sulfonylureas. Sulfonylureas are metabolized into active and inactive metabolites in the liver through hepatic oxidative enzymes (CYP P450s). Then, they are extensively bound to serum proteins and excreted through renal pathway. Therefore, protein binding of sulfonylureas may be reduced in patients with T2DM and CLD due to hypoalbuminemia resulting to increased drug plasma concentrations[23-25] Therefore, sulfonylurea therapy in patients with CLD and renal failure increases the risk for hypoglycemia[26] that is more pronounced in the presence of malnutrition, a common comorbidity in CLD patients[7], and diminished gluconeogenic capacity[27]. Furthermore, in patients with alcoholic liver disease alcohol-induced enzyme degradation of sulfonylureas decreases drug's effectiveness and further increases the risk of hypoglycemia[26].

There are only a few studies examined the effect of CLD on sulfonylurea metabolism. A study examined the effect of glipizide on hepatic uptake of insulin, showed that glipizide caused an increase in the estimated uptake of insulin in T2DM patients with cirrhosis, whereas a small decrease was observed in the control group[28].

Sulfonylureas therapy in patients with HI may be challenging since they are metabolized by the liver and excreted by the kidneys not only the parent drug but it's active metabolites as well. Glimepiride and gliclazide are contraindicated in severe HI[23-25]. According to the position statement of the ADA and EASD insulin secretagogues should be avoided in severe HI due to the risk of hypoglycemia[15] (Table 1).

Meglitinides (glinides)

Glinides (nateglinide and repaglinide) have shorter half-lives than sulfonylureas and they do not have significant renal excretion[29,30]. They are extensively bound to serum albumin protein and are metabolized by oxidative biotransformation (CYP 450) and conjugation with glucuronic acid in the liver[31,32]. Repaglinide's metabolism is mainly affected by the presence of CLD while this is not the case for nateglinide.One possible explanation for this discrepancy is that repaglinide is metabolized by CYP isoform 2C8[33] and nateglinide by CYP isoform2C9[30].

Repaglinide clearance is significantly reduced in patients with HI and should be used with caution while in T2DM patients with severe HI the drug is contraindicated[34]. On the other hand, nateglinide pharmacokinetics (PK) is not affected in patients with HI and, therefore, no adjustment of nateglinide dosage is needed in patients with mild to moderate HI[35], There are no data available in patients with severe HI (Table 1).

Alpha-glucosidase inhibitors (Acarbose)

Acarbose acts locally within the gastrointestinal tract by inhibiting enzymes (glycoside hydrolases) needed to digest carbohydrates[36]. The lack of intestinal absorption and hepatic metabolism, makes acarbose a safe choice in CLD patients with a good tolerability and absence of toxic effects[38], well-compensated non-alcoholic cirrhosis[39], and low-grade hepatic encephalopathy[40]. However, there may be a possibility of hyperammonemia when acarbose is prescribed to T2DM patients with advanced HI[37]. The effect of acarbose in hepatic encephalopathy was studied in 107 cirrhotic patients with T2DM. Acarbose therapy was related with decreased ammonia blood levels. However, no change in biochemical parameters of liver function was observed at the end of the study[40]. The findings of another study with

Table 1 Use of antidiabetic agent according to the degree of hepatic impairment

Antidiabetic agent	Degree of hepatic impairment (HI)
Metformin	Avoid in severe HI
Sulfonylureas	
Glimepiride	Avoid in severe HI
Gliclazide	Avoid in severe HI
Glinides	
Repaglinide	Avoid in severe HI
Nateglinide	No adjustment of dosage in mild to moderate HI
Alpha-glucosidase inhibitors	
Acarbose	Well tolerated
Thiazolidinediones	
Pioglitazone	Safe in Child-Pugh Class A patients. Should be avoided in Class B and C patients
DPP-4 inhibitors	
Sitagliptin	Well tolerated
Vildagliptin	Well tolerated
Saxagliptin	Well tolerated
Alogliptin	Well tolerated
Linagliptin	Well tolerated
GLP-1 receptor agonists	
Exenatide	Well tolerated
Liraglutide	Well tolerated
Lixisenatide	Well tolerated
SGLT-2 inhibitors	
Canagliflozin	Safe in Child-Pugh Class A patients. Caution is needed in Class B patients. Should better be avoided in Class C patients
Dapagliflozin	Safe in Child-Pugh Class A patients. Caution is needed in Class B patients. Should better be avoided in Class C patients
Empagliflozin	Safe in Child-Pugh Class A patients. Caution is needed in Class B patients. Should better be avoided in Class C patients
Insulin	Safe in use

the use of acarbose showed that T2DM associated with HI might be safely and effectively treated with acarbose except for a small increase in ammonia blood levels. Therefore, acarbose treatment in T2DM patients with cirrhosis might increase the risk ofhyperammonemia[37]. According to the position statement of the ADA acarbose is safe, useful, and well tolerated in CLD patients[15,16] (Table 1).

Thiazolidinediones

Pioglitazone: Pioglitazone is the only drug available in the market of this class; it is extensively metabolized by hydroxylation and oxidation and it is metabolized mainly by CYP2C8[41]. It is excreted primarily as metabolites and their conjugates in bile and feces[41]. Hepatic safety of pioglitazone was evaluated in a large observational study in T2DM patients in Japan where no case of HI was reported and no alanine aminotransferase (ALT) abnormalities with pioglitazone therapy in different dosages[42].

In a study, where the hepatic safety profile of pioglitazone (compared to glibenclamide) was examined in pioglitazone-treated patients, there was no case of hepatocellular injury in the pioglitazone group while and four cases were observed in the glibenclamide group. No case of hepatic dysfunction or HI was reported in the pioglitazone group[43]. However, in another study, the case-fatality rate of liver failure associated with rosiglitazone or pioglitazone was 81%, while only 14% of the patients recovered[44]. On the contrary, a large-scale study in Japan, in 24993 patients (28008 patient-years), no case of HI was found[42]. The above finding was confirmed in a retrospective data analysis of 1.12 patients with T2DM, where pioglitazone therapy was not associated with increased risk of HI or hepatitis compared to other OADs[45].

According to the position statement of the ADA in case of chirrosis or serum ALT level exceeding 2.5 times of upper normal limit (ULN), pioglitazone should be avoided[15]. Pioglitazone should be used with caution in CLD patients. It should be avoided in patients whose liver enzymes are > 3 times ULN range. Pioglitazone may be used in Child-Pugh Class A patients. However, it should be avoided in Class B and C patients[15] (Table 1).

DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin) belong to the incretin-based glucose-lowering agents[46]. Sitagliptin is primarily excreted by the kidney and only a small percentage of the drug undergoes hepatic metabolism (mainly through the CYP3A4 isoenzyme and less through CYP2C8 isoenzyme)[47]. Vildagliptin is metabolized *via* hydrolysis and its inactive metabolites show renal excretion[47]. Saxagliptin is metabolized in vivo to form an active metabolite, and both parent drug and metabolite are excreted primarily via the kidneys[48]. Saxagliptin is primarily metabolized by CYP3A4 and CYP3A5 isoforms and eliminated through renal and hepatic routes. Alogliptin is metabolized into M-I, an N-demethylated active metabolite *via* CYP2D6, and M-II, an N-acetylated inactive metabolite and it is excreted primarily *via* the kidneys[48,49]. In contrast to other DPP-4 inhibitors, approximately 80% of administered dose of linagliptin[50] is eliminated through enterohepatic recycling[48].

The safety of DPP-4 inhibitors in T2DM patients was examined in a systematic review and meta-analysis, whereas no adverse events of hepatotoxiticy were reported[51]. Regarding sitagliptin, a few cases of drug-induced hepatic injury[52] and of elevated hepatic enzymes[53] have been reported. However, the causal pathogenetic relationship is still unclear[54]. Despite the initial concern about a possible hepatotoxicity of vildagliptin a pooled analysis of 38 controlled trials showed that there in not any significant increase of liver enzymes with vildagliptin therapy[55]. The safety of vildagliptin was confirmed in another pooled analysis in clinical trials with duration more than two years[56]. Sitagliptin PK is not affected by moderate HI[57]. Similarly, vildagliptin PK is not affected in patients with mild, moderate or even severe HI[58].

According to the already conducted studies, there is no liver safety issues for saxagliptin[59]. In the placebo-controlled SAVOR-TIMI 53 cardiovascular outcome trial, no signal of liver toxicity was found in the saxagliptin group[60]. Saxagliptin PK is affected only in a small degree in patients with HI[61,62].

A meta-analysis of 8 placebo-controlled trials confirmed the hepatic safety of linagliptin[63]. In a study in patients with mild and moderate HI, linagliptin was well tolerated without any adverse events[64]. There is only one case report described a probable linagliptin-induced liver toxicity[65]. One study[64] reported that mild, moderate or severe HI did not affect linagliptin PK compared to normal hepatic function.

According to the already conducted studies, there is no concern for hepatoxicity for alogliptin[66]. The large cardiovascular outcome study EXAMINE showed no signal of hepatotoxicity in the alogliptin group[67]. There is only one observational study coming from Japan where hypoglycemic symptoms under alogliptin therapy were reported and associated with liver disease and alcohol consumption[68]. Finally, in patients with moderate HI alogliptin PK is not affected[69].

Summary of product characteristic of sitagliptin, saxagliptin, and linagliptin recommends no dosage adjustments in patients with CLD[70-72], while vildagliptin should not be used in patients with CLD, including patients with

ALT or aspartate aminotransferase (AST) > 3x the ULN[73]. Therefore, DPP-4 inhibitors may be used in Child-Pugh Class A patients while their use requires caution in Class B patients. On the contrary, DPP-4 inhibitors are not preferred in Class C patients (Table 1).

GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RA) (exenatide, liraglutide, lixisenatide and dulaglutide) belong to the incretin-based glucose-lowering agents and offer new opportunities for the management of T2DM[15]. Renal excretion is the main pathway for the elimination of exenatide. Liraglutide and dulaglutide are metabolized into their component amino acids by general protein catabolism pathways[74-76].

The existing literature data regarding the effect of GLP-1RAs therapy in patients with CLD is limited. Therefore, until nowadays, clinical experience with liraglutide, exenatide and lixisenatide in CLD patients is limited. However, since exenatide is primarly excreted by the kidney, blood concentrations of the drug are not affected in patients with HI[77]. Regarding liraglutide it seems that drug concentrations are not affected by HI[78].

According to the SPC of exenatide and lixisenatide no dosage adjustment is required regarding their administration to patients with HI, whereas for liraglutide the therapeutic experience in patients with CLD is limited. On the basis of available evidence, GLP-1RAs should be used with caution without dose modification in CLD patients. Drugs of this class can be administered to Child-Pugh Class A patients. However, GLP-1RAs should be avoided in Class B and C patients (Table 1).

SGLT-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) is a new class of antidiabetic agents acting through the inhibition of glucose reuptake in the kidney[79]. They undergo hepatic metabolism through glucuronidation, and small proportions of the parent drug are eliminated through renal route[79].

The safety of empagliflozin in patients with HI has been confirmed in a study investigating the effect of various degrees of HI on the PK of empagliflozin. In patients with HI empagliflozin PK was affected in a very small degree and, therefore, no dose adjustment of the drug is required in patients with HI[80]. The same pattern was observed in a canagliflozin trial, where the canagliflozin PK was not affected by the presence of mild or moderate HI. Therefore, no dose adjustment of canagliflozin is required for these patients[81]. Finally, a study on the PK and safety profile of dapagliflozin in patients with HI showed that systemic exposure to dapagliflozin was correlated with the degree of HI[82]. Therefore, dapagliflozin should be used with caution in these patients.

On the basis of available evidence, SGLT-2 inhibitors can be used with caution and lower doses should be considered during initiation of therapy in CLD patients. These agents are contraindicated in severe HI. The risk of dehydration and hypotension is associated with the use SGLT-2 inhibitors; hence, caution is required. Precisely, SGLT-2 inhibitors are safe in Child-Pugh Class A patients; however, they should be used with caution in Class B patients. Agents of this class should better be avoided in Class C patients (Table 1).

Insulin therapy

Liver is the major site of insulin metabolism. Almost half of the insulin produced by the pancreas is metabolized by the liver[83]. Hyperinsulinemia is a common finding in T2DM patients with cirrhosis, due to higher insulin secretion rate and reduced hepatic clearance. However, insulin requirement may vary in patients with CLD as a result of the reduced capacity for gluconeogenesis and hepatic breakdown of insulin. Therefore, daily dose requirements of exogenous administrated insulin can vary in a high degree and, therefore, is difficult to control blood glucose levels in these patients[7,16].

Insulin therapy is the safest and most effective therapy in patients with CLD. However, there is still the limitation of the increased risk of hypoglycemia[84]. Newer insulin analogs are preferred in CLD patients as their PK is unaltered and possesses low risk of hypoglycemia. However, it is suggested that frequent glucose monitoring and dose adjustments are required to minimize the risk of hypoglycemia or hyperglycemia in these patients[85-88]. The ADA guidelines highlight the importance of insulin therapy and suggest frequent dose adjustment and careful glucose monitoring in T2DM patients with CLD[15] (Table 1).

CONCLUSION

Management of T2DM in patients with CLD is still a challenge for the clinician. Most of the antidiabetic agents are either contradicted or need dosage titration due to alterations to their pharmacokinetics in patients with CLD. Insulin therapy seems to be the safest choice in patients with CLD. The existing literature data regarding the management of T2DM in patients with CLD are limited[89] and only small studies and meta-analyses exist showing the effect of CLD on PK of the OADs. However, the need for the development of guidelines for the management of T2DM in patients with CLD is growing following the high prevalence of HI that characterizes T2DM.

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