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Pharmacokinetic and toxicological considerations for the treatment of diabetes in patients with liver disease

André J. Scheen

University of Liège, Center for Interdisciplinary Research on Medicines (CIRM),
Division of Diabetes, Nutrition and Metabolic Disorders
and Division of Clinical Pharmacology,
Department of Medicine, CHU Sart Tilman, University of Liège, Liège, Belgium

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Address for correspondence : Pr André J. SCHEEN
Department of Medicine
CHU Sart Tilman (B35)
B-4000 LIEGE 1
BELGIUM
Phone : 32-4-3667238
FAX : 32-4-3667068
Email : andre.scheen @ chu.ulg.ac.be

SUMMARY

Introduction : Patients with type 2 diabetes have an increased risk of chronic liver disease (CLD) such as non-alcoholic fatty liver disease and steatohepatitis and about one third of cirrhotic patients have diabetes. However, the use of several antidiabetic agents may be a concern in case of hepatic impairment (HI).

Area covered: An extensive literature search was performed to analyze the influence of HI on the pharmacokinetics (PK) of glucose-lowering agents and the potential consequences for clinical practice as far as the efficacy/safety balance of their use in diabetic patients with CLD.

Expert Opinion : Almost no PK studies have been published regarding metformin, sulfonylureas, thiazolidinediones and alpha-glucosidase inhibitors in patients with HI. Only mild changes in PK of glinides, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium glucose cotransporters type 2 (SGLT2) inhibitors were observed in dedicated PK studies in patients with various degrees of HI, presumably without major clinical relevance although large clinical experience is lacking. GLP-1 receptor agonists have a renal excretion rather than liver metabolism. Rare anecdotal case reports of hepatotoxicity have been described with various glucose-lowering agents contrasting with numerous reassuring data. Nevertheless, caution should be recommended, especially in patients with advanced cirrhosis, including with the use of metformin.

Key-words : Chronic liver disease – Cirrhosis – Glucose-lowering therapy – Hepatic impairment – Hepatotoxicity – Pharmacokinetics – Oral antidiabetic agent –Type 2 diabetes mellitus

1. Introduction

The liver is one of the principal organs involved in glucose metabolism. A link between diabetes and chronic liver disease (CLD) was first observed in the early half of the last century, and the complex and bi-directional relationship linking the liver and diabetes has recently gained intense new interest (Figure 1) [1, 2]. Type 2 diabetes mellitus (T2DM) favors non-alcoholic fatty liver disease (NAFLD), both steatosis and non-alcoholic steatohepatitis (NASH) [3] while alcoholic cirrhosis, chronic hepatitis C virus and hemochromatosis are frequently associated with diabetes [4]. Overall, about 30% of patients with cirrhosis have diabetes. Diabetes, which develops as a complication of cirrhosis, is known as "hepatogenous diabetes" [5]. An impaired response of the islet beta-cells of the pancreas and insulin resistance (both hepatic and muscular) are contributory factors to the development of diabetes in cirrhotic patients [6, 7]. Treatment of the diabetes is complex due to liver damage and potential hepatotoxicity of some oral hypoglycemic medications or drug-associated adverse events favored by CLD [8].

Differential use of antidiabetic drugs in patients with co-morbid disease constellations will help to reduce treatment related complications and might improve prognosis [9]. However, guidelines fail to give advice on the use of specific glucose-lowering medications in patients with co-morbidity and the literature is deficient in studies documenting antidiabetic drug use in patients with CLD. Whereas several recent articles focused on the use of glucose-lowering agents in patients with chronic kidney disease [10-12], only scarce review papers are available yet regarding the management of diabetic patients with CLD [13,14]. Furthermore, these papers focused on general management rather than on the specific use of glucose-lowering agents and the place of new medications such as dipeptidyl peptidase (DPP-4) inhibitors (also known as gliptins), sodium glucose cotransporters type 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists was almost not considered [13].

Managing diabetes in patients with CLD can be challenging because many antihyperglycemic therapies are contraindicated or must be used with caution for safety reasons [8]. Another interesting aspect concerns the use of insulin-sensitizing agents, well known compounds for the management of T2DM, in patients with NAFLD. Indeed, because insulin resistance seems to play a role in the development of NAFLD, the administration of insulin-sensitizing medications deserves much consideration in the management of patients with NAFLD, of course when T2DM is present but also in absence of diabetes [15, 16].

The aim of this review paper is to provide an updated analysis of the use of oral antidiabetic agents (OADs) and injectable agents in diabetic patients with CLD. After a brief description of how to assess liver function and evaluate the severity of hepatic impairment (HI), we will describe the PK characteristics as well as the safety profile of each glucose-lowering compound in patients with various degrees of CLD.

To identify relevant studies, an extensive literature search of MEDLINE was performed from 1970 to December 2013, with the names of the following pharmacological classes biguanides, sulfonylureas, meglitinides (glinides), alpha-glucosidase inhibitors, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, human insulin or insulin analogs combined with any of the following terms : “chronic liver disease”, “hepatic impairment” or “cirrhosis”. Each generic name - metformin, glibenclamide (glyburide), glimepiride, glipizide, gliclazide, gliquidone, repaglinide, nateglinide, acarbose, miglitol, voglibose, pioglitazone, rosiglitazone, sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, dapagliflozin, canagliflozin, empagliflozin, exenatide, liraglutide, lixisenatide - was also combined with each of the various terms corresponding to CLD. No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined.

2. Classification of liver impairment

Liver tests are commonly altered in patients with overweight/obesity and in patients with T2DM. The prevalence of NAFLD ranges 10-24% in the general population, reaching 60-95% and 28-55% in obese and diabetic patients, respectively [17]. Although the etiology of NAFLD is still unclear, several lines of evidences have indicated a pathogenic role of insulin resistance in this disorder [3, 17]. Chronic inflammation associated to NASH may lead to progressive fibrosis. Cirrhosis is the ultimate stage of HI, whose severity may vary from patient to patient, and the management of diabetes in those patients is most often difficult.

In hepatology, the Child-Pugh score, initially developed for selecting patients who may benefit from liver transplantation, is currently used to assess the overall prognosis of CLD, mainly cirrhosis [18]. In clinical pharmacology, it is used to score the severity of HI in order to guide the use of drugs in patients with CLD, although its limitations have been acknowledged [19]. The Child-Pugh score employs five clinical measures of liver disease : total bilirubin level, serum albumin concentration, prothrombin or international normalized ratio (INR) value, presence of ascitis and hepatic encephalopathy. Each measure is scored

from 1 to 3, with 3 indicating most severe derangement. CLD is classified into Child-Pugh class A-C, employing the added score from above : 5-6 (class A = mild HI), 7-9 (class B = moderate HI) and 10-15 (class C : severe HI). Such classification has been used in the various PK studies with glucose-lowering agents described below.

Noteworthy, hepatorenal syndrome is a distinctive complication of CLD and cirrhosis [20]. Therefore, renal function should be carefully monitored in all patients with cirrhosis and selection of antidiabetic pharmacotherapy should also take into account the possibility of associated renal impairment in such patients [10-12].

3. PK considerations

PK studies are recommended in subjects with impaired hepatic function if hepatic metabolism accounts for a substantial portion of the absorbed drug [19]. Numerous glucose-lowering drugs are excreted as parent drug or as active metabolite via the kidneys [12]. Nevertheless, HI may also interfere with the PK of various glucose-lowering medications. Considering the high prevalence of diabetes among patients with CLD and of hepatic disturbances among patients with T2DM, the analysis of PK changes of various glucose-lowering agents in patients with HI should deserve careful evaluation. Pharmacodynamic (PD) effects in this population may also be of interest, although rarely evaluated.

3.1. Biguanides (metformin)

Metformin, a biguanide compound, is considered as the first-line drug for the treatment of T2DM [21]. Chemically, it is a hydrophilic base which exists at physiological pH as the cationic species. Consequently, its passive diffusion through cell membranes is very limited as well as liver metabolism. No metabolites or conjugates of metformin have been identified [22]. The absence of liver metabolism clearly differentiates the PK of metformin from that of other biguanides, such as phenformin (withdrawn from the market because of lactic acidosis). Metformin undergoes renal excretion. The elimination is prolonged in patients with renal impairment and correlates with creatinine clearance, even in patients with HI [23]. In contrast, liver impairment stricto sensu should not interfere with PK of metformin. However, no PK studies are available in patients with CLD. Recent experimental data in animals showed that metformin sinusoidal efflux from the liver is consistent with negligible biliary excretion and absence of enterohepatic cycling [24].

3.2. Sulfonylureas

Sulfonylureas remain largely used in the management of T2DM [25] and are currently positioned as second-line after failure of metformin monotherapy [21]. They are associated with a higher risk of severe hypoglycemia, compared with metformin and more recent glucose-lowering therapies [26], especially in the elderly population and in patients with renal or liver disease. Among the possible extra-pancreatic effects of sulfonylureas, a reduction of the hepatic extraction of insulin has been reported, which could contribute to increase peripheral insulin concentrations [25].

Due to hepatic metabolism and renal excretion of the parent drug and/or active metabolites, sulfonylureas are classically contraindicated in patients with liver or kidney disease [27]. However, PK data on sulfonylureas are very limited in cirrhotic patients.

3.2.1. Tolbutamide

The PK data after tolbutamide intravenous injection were compared in patients with cirrhosis (diagnosis made by clinical symptoms, liver function tests and laparoscopic examination, but without score of severity), in T2DM patients and in patients with renal impairment. The disappearance rate of tolbutamide from the blood was reduced in five of ten cases with cirrhosis. Prolonged half-lives (from about 4 hours in normal subjects to 7.8 to 11.2 hours) were measured in those subjects although no significant correlation was observed with the results of liver function tests. No severe renal impairment was noticed in these patients. Reduction in arterial glucose concentrations tended to be greater and more prolonged in some cirrhotic patients. However, such changes in arterial blood glucose were not attributable to the prolongation of half-life of tolbutamide [28]. In another study in 10 subjects with HI, hepatic dysfunction did not necessarily cause a prolongation in the rate of metabolism of tolbutamide, but there was an apparent prolongation of the half-life for metabolism of tolbutamide when renal function was impaired [29]. No similar study has been published regarding chlorpropamide. Nevertheless, these limited observations led to recommendation of cautious use of first-generation sulfonylureas in patients with CLD because of a potential high risk of hypoglycemia [13, 14].

3.2.2. Glibenclamide (glyburide)

Experimental results showed that human cytochrome P450 3A4 (CYP3A4) is the major enzyme involved in the in vitro metabolism of glibenclamide [30]. Glibenclamide is

inactivated by the liver to 4-trans-hydroxyglibenclamide and 3-cis-hydroxyglibenclamide. Elimination of the drug appears to be evenly divided between biliary and renal routes [31]. Glibenclamide should not be prescribed for patients with severe CLD [32], although no specific PK studies in patients with HI are available in the literature.

3.2.3. Glimepiride

Glimepiride has fewer and less severe adverse effects than glibenclamide. It is metabolized by CYP2C9 and its PK is mainly unaltered in patients with liver disease [33]. In 11 patients with CLD, the PK of glimepiride was similar to those of healthy volunteers [34]. Thus, whereas the PK characteristics of glimepiride are altered in T2DM subjects with renal disease [12], they may not be seriously affected in patients with CLD. However, data were obtained from patients with liver disease of unspecified severity and are, therefore, of limited clinical usefulness. Administration of glimepiride in diabetic patients with severe CLD is not recommended, as is the case for other sulfonylureas.

3.2.4. Glipizide

The PK properties, spectrum and severity of side effects and metabolism of glipizide are somewhat different from those of first-generation sulfonylureas or even glibenclamide [35]. The hepatic metabolism of glipizide involves CYP2C9 and to a lesser extent CYP2C19. There are no data on PK of glipizide in patients with CLD. However, a study showed that glipizide significantly increased the estimated hepatic uptake of insulin in cirrhotic patients but not in other patients without CLD [36]. In absence of clear-cut data, caution is recommended when considering the use of glipizide in patients with CLD.

3.2.1. Gliclazide

Gliclazide is metabolized by the liver to inactive metabolites, which are eliminated mainly in the urine (80%). CYP2C9 is the major contributor to gliclazide metabolic clearance, although CYP2C19 may also be involved in hydroxymethyl metabolite of gliclazide formation (the major metabolic pathway) [37]. There are no data on PK of gliclazide in patients with CLD. In absence of specific data, gliclazide should also be used with caution in patients with CLD.

3.2.5. Gliquidone

Gliquidone is metabolized in the liver and has no renal excretion, in contrast to other sulfonylureas. Because accumulation does not take place in patients with renal impairment, this sulfonylurea may be used in patients with stable chronic kidney disease [38]. Because of its specific hepatic metabolism, its use should not be recommended in patients with CLD and no data are available in this population.

3.3. Meglitinides (glinides)

Compared to sulfonylureas, glinides are characterized by shorter half-lives as well as by the absence of significant renal excretion [39, 40]. These compounds are exposed to drug-drug interactions via significant interferences on hepatic metabolism [41]. Despite they are metabolized in the liver, there are no large scale studies having assessed both the efficacy and safety of repaglinide and nateglinide in T2DM patients with CLD [39]. However, PK characteristics have been evaluated in patients with HI. The influence of HI on drug exposure and elimination appears to differ between repaglinide (significant interference) and nateglinide (only minimal change) (Table 1). The reason of this discrepancy remains speculative. However, the two meglitinide compounds are metabolized by different CYP isoforms, 2C8 for repaglinide [43] and 2C9 for nateglinide [40]. Furthermore, SLCO1B1 **(**organic anion-transporting polypeptide 1B1) polymorphism exerts different effects on the PK/PD of repaglinide (significant PK changes) and nateglinide (PK unaffected) [42]. The SLCO1B1*1B/*1B genotype is associated with reduced plasma concentrations of repaglinide, consistent with an enhanced hepatic uptake by OATP1B1, but has limited effects on the PK of nateglinide [43].

3.3.1. Repaglinide

Repaglinide is metabolized mainly in the liver and is eliminated rapidly via the biliary route [44]. Its PK may therefore be altered by hepatic dysfunction. An open, parallel-group study compared the PK and tolerability of a single 4 mg dose of repaglinide in healthy subjects and patients with CLD (Table 1). Values for area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) were significantly higher in CLD patients compared with healthy subjects. Values for time to reach C_{max} (t_{max}) did not differ between the groups, but terminal elimination half-life ($_{t1/2}$) was significantly prolonged in CLD patients compared with previously determined values in healthy subjects. The mean residence time

was prolonged in CLD patients compared to healthy subjects [5.9±4.4 versus 1.2±0.4 hours; geometric mean ratio or GMR : 4.7 (90% confidence interval or CI : 1.6-7.8); p=0.005]. AUC was inversely correlated with caffeine clearance in CLD patients but not in healthy subjects. Thus, repaglinide clearance is significantly reduced in patients with HI so that this glucose-lowering agent should be used with caution in patients with CLD and is contraindicated in diabetic patients with severe HI [45].

3.3.2. Nateglinide

The clinical PK of nateglinide, a rapidly-absorbed, short-acting insulinotropic agent, has been extensively reviewed [40]. No significant PK alterations occur in patients with mild HI. A single-dose, open-label, parallel-group study compared the PK of 120 mg doses of nateglinide in subjects with cirrhosis and matched healthy subjects. In both groups, plasma concentration peaked in a median of 0.5 hours, and mean $t_{1/2}$ values were comparable. However, exposure tended to be slightly increased (+ 30 % for AUC and + 37 % for C_{max}) (Table 1). Mean apparent total clearance and mean renal clearance of nateglinide were comparable in both groups. Mean protein-bound fractions were also equivalent. No statistically significant or clinically relevant alterations in PK parameters of nateglinide resulted from hepatic dysfunction; therefore, adjustment of nateglinide dosage is not required in subjects with mild to moderate cirrhosis [46]. No data are available in patients with severe HI.

Nateglinide was tested in a pilot 20-week study in diabetic patients with NASH who were randomly divided into two groups, 5 patients treated with nateglinide (90 mg before each meal, i.e. 270 mg/day) and 5 patients non-treated with nateglinide used as control group. Postprandial blood glucose, glycated hemoglobin (HbA_{1c}), a 75-g oral glucose tolerance test, liver function, abdominal ultrasound and computerized tomography imaging tests and liver histological findings were all improved after treatment with nateglinide. This medication was considered as useful and safe in the treatment of NASH in patients with T2DM [47].

3.3.3. Mitiglinide

Mitiglinide is another rapid-acting insulin secretion-stimulating agent, which is approved in Japan for the treatment of T2DM [48]. Uridine diphosphate glucuronosyltransferase (UGT) isoforms UGT1A3 and UGT2B7 were found to be catalytic enzymes in mitiglinide carboxyl-glucuronidation in human liver [49] No PK study was specifically performed with mitiglinide in patients with CLD.

3.4. Alpha-glucosidase inhibitors

3.4.1. Acarbose

Acarbose acts locally within the gastrointestinal tract and is characterized by a low systemic bioavailability [50]. Several results clearly documented the good tolerability and the absence of toxic effects of acarbose on liver, due to the lack of both intestinal absorption and hepatic metabolism of the drug at doses in the therapeutic range. Because of these characteristics, no PK studies are available with this compound in patients with CLD. However, several limited studies demonstrated the efficacy and safety of acarbose in diabetic patients with CLD [51], alcoholic cirrhosis [52], well-compensated non-alcoholic cirrhosis [53], and low-grade hepatic encephalopathy [54]. Acarbose has been also considered as a promising therapeutic strategy for the treatment of patients with NASH [55].

3.4.2. Miglitol and voglibose

Miglitol is systemically absorbed but is not metabolized, and is rapidly eliminated by renal excretion as unchanged drug [56]. Voglibose is another alpha-glucosidase inhibitor commercialized in Japan. Only a minimal amount of drug is absorbed in unchanged form. One study reported that voglibose was an effective therapy for NASH in a patient with insufficient dietary and exercise therapy [57].

3.5. Thiazolidinediones

Troglitazone was the first thiazolidinedione antidiabetic agent approved for clinical use in 1997 [58], but it was withdrawn from the market in 2000 due to serious idiosyncratic hepatocellular injury-type hepatotoxicity. Troglitazone contains the structure of a unique chroman ring of vitamin E, and this structure has the potential to undergo metabolic biotransformation to form quinone metabolites, phenoxy radical intermediate, and epoxide species [59]. Furthermore, troglitazone, unlike pioglitazone and rosiglitazone, induces the

cytochrome P450 isoform 3A4, which is partly responsible for its metabolism, and may be prone to drug interactions [60]. The involvement of reactive metabolites in the troglitazone cytotoxicity has been proposed but still remains controversial [59]. Nevertheless, because troglitazone was withdrawn from the market because of hepatotoxicity, concern emerged about the use of other compounds of this pharmacological class in patients with CLD [60].

3.5.1. Pioglitazone

Pioglitazone and its active metabolites are excreted via the liver rather than the kidneys. It is metabolised mainly by CYP2C8 and to a lesser extent by CYP3A4 in vitro [61]. No study published the PK of pioglitazone in patients with CLD but some limited information could be found in the Food and Drug Administration report [62]. Compared with normal controls, subjects with impaired hepatic function (Child-Pugh class B/C) have an approximate 45% reduction in pioglitazone mean peak concentrations but no change in the mean AUC values. In hepatic insufficiency, volume of distribution was increased, probably explaining why C_{max} was reduced [63].

In a proof-of-concept study, the administration of pioglitazone, acting as an insuli-sensitizer compound, led to metabolic and histologic improvement in subjects with NASH [64]. Further studies showed also favorable, although less convincing results, in NAFLD patients without diabetes [65]. Other findings suggest that long-term therapy with pioglitazone may be necessary to maintain improvements in disease activity in patients with NASH, although weight gain during treatment may ultimately limit its beneficial effects (see also section 4.5) [66].

3.5.2. Rosiglitazone

Rosiglitazone is mainly metabolized by CYP2C8 into inactive metabolites, and < 1% of the parent drug appears in the urine in unchanged form [67]. No published study investigated the PK of rosiglitazone in patients with CLD but some data are available in the FDA report [68]. Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh class B/C) compared to healthy subjects. As a result, unbound C_{max} and AUC_{∞} were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with CLD, compared to healthy

subjects. Therefore, caution is required in patient with moderate HI and the drug should not be prescribed in patients with severe HI.

In a study that compared the effects of rosiglitazone and metformin treatment, rosiglitazone but not metformin decreased liver fat, increased insulin clearance and augmented serum adiponectin concentrations (see also section 4.5) [69].

3.6. DPP-4 inhibitors

DPP-4 inhibitors (gliptins) are a new class of OADs belonging to the incretin-based glucose-lowering agents. By inhibiting the inactivation of endogenous GLP-1, they improve glucose control without inducing hypoglycemia (in contrast to sulfonylureas) and are weight-neutral [70]. Several molecules are already available, which are characterized by different PK properties [71, 72]. In contrast to previous glucose-lowering agents for which PK evaluation in patients with HI was almost absent (metformin, sulfonylureas) or scarce (repaglinide, nateglinide, glitazones), all five DPP-4 inhibitors already on the market were particularly well studied in patients with various degrees of HI as far as PK characteristics were concerned (Table 2). Furthermore, a recent intriguing paper suggests that DPP-4 may be a key player in CLD, a finding that may open new perspectives for the use of DPP-4 inhibitors in patients with CLD [73]. However, no clinical study with a chronic administration of a DPP-4 inhibitor in patients with CLD is available yet.

3.6.1. Sitagliptin

Sitagliptin is primarily excreted by renal elimination as unchanged drug, with only a small percentage (approximately 16%) undergoing hepatic metabolism. CYP3A4 has been shown to be the major cytochrome P450 isoenzyme responsible for the limited oxidative metabolism of sitagliptin, with some minor contribution from CYP2C8 [74]. The influence of moderate HI on the PK of sitagliptin should be minimal. In an open-label study, a single 100-mg oral dose of sitagliptin was administered to patients with moderate CLD (Child-Pugh's scores ranged from 7 to 9) and healthy control subjects [75]. The mean AUC_{∞} and C_{max} for sitagliptin were numerically, but not significantly, higher in patients with moderate HI compared with healthy matched control subjects (by 21% and 13%, respectively) (Table 2). These slight differences were not considered to be clinically meaningful. Furthermore, moderate HI had no statistically significant effect on the T_{max}, apparent terminal $t_{1/2}$ and renal

clearance of sitagliptin. Thus, moderate HI has no clinically meaningful effect on the PK of sitagliptin [75].

The efficacy and safety of sitagliptin therapy has been shown in patients with diabetes complicated by NAFLD [76-78], NASH [79] or CLD caused by hepatitis C virus [80]. However, it has been also reported that NAFLD adversely affects the glycemic control afforded by sitagliptin [81].

3.6.2. Vildagliptin

Vildagliptin is primarily metabolized via hydrolysis and the inactive metabolites are predominantly excreted by the kidneys [82]. An open-label, parallel-group study compared the PK of vildagliptin in patients with mild, moderate or severe CLD and in healthy subjects. All subjects received a single 100-mg oral dose of vildagliptin, and plasma concentrations of vildagliptin were measured up to 36 h post-dose. Exposure to vildagliptin (AUC_{∞} and C_{max}) decreased non-significantly by 20 and 30%, respectively, in patients with mild HI. Exposure to vildagliptin was also decreased non-significantly in patients with moderate HI, by 8 and 23 %, respectively. In patients with severe HI, C_{max} was 6% lower than that in healthy subjects, whereas AUC_{∞} was numerically increased by 22% (Table 2). Because there was no significant difference in exposure to vildagliptin in patients with mild, moderate or severe HI, the conclusion was that no dose adjustment of vildagliptin is necessary in patients with CLD [83].

3.6.3. Saxagliptin

Saxagliptin is metabolized in vivo to form an active metabolite (2-fold less potent than its parent molecule), and both parent drug and metabolite are excreted primarily via the kidneys [59, 72]. Saxagliptin is largely metabolized by CYP3A4 and CYP3A5 isoforms. The PK of saxagliptin and its pharmacologically active metabolite, 5-hydroxy saxagliptin, were compared in nondiabetic subjects with mild, moderate or severe CLD and in healthy adult subjects in an open-label, parallel-group, single-dose (10 mg saxagliptin) study. As compared with healthy subjects, the AUC_{∞} values for saxagliptin were 10%, 38% and 77% higher in subjects with mild, moderate or severe HI, respectively (Table 2). The corresponding values were 22%, 7% and 33% lower, respectively, for 5-hydroxy saxagliptin, compared with matched healthy subjects. Saxagliptin C_{max} values were 8% higher, 16 % higher and 6 % lower in patients with mild, moderate and severe HI, respectively, compared to controls

(corresponding values for 5-hydroxy saxagliptin : -17%, -16% and -59%, respectively). According to these results, i.e. increase of saxagliptin exposure compensated for by a corresponding decrease of the exposure to its active metabolite, no dose adjustment is recommended for patients with any degree of HI [84].

3.6.4. Linagliptin

In contrast to other DPP-4 inhibitors whose main route of elimination is the kidney [71, 72], the elimination of linagliptin is primarily non-renal [85]. Linagliptin undergoes enterohepatic cycling with a large majority (85%) of the absorbed dose eliminated in faeces via biliary excretion [72]. Therefore, a potential effect of HI on the PK of linagliptin may have important implications for dosing recommendations. This was the rationale for a multiple dose rather than a single dose study (as with other DPP-4 inhibitors described above) in patients with CLD.

An open label, parallel group, study enrolled patients with mild, moderate or severe CLD and healthy subjects to investigate whether HI affects linagliptin PK, PD and tolerability [86]. Primary endpoints were linagliptin exposure following 5 mg linagliptin once daily for 7 days in patients with mild and moderate HI vs. healthy subjects or after a single 5 mg dose for patients with severe HI vs. healthy subjects. In patients with mild and moderate HI, steady-state linagliptin exposure was slightly lower than in healthy subjects (Table 2). After a single dose, $AUC_{(0,24\ h)}$ in patients with severe HI was similar to that in healthy subjects and C_{max} tended to be lower (Table 2). Accumulation based on AUC or C_{max} and renal excretion of unchanged linagliptin (≤ 7%) were comparable across groups. Median plasma DPP-4 inhibition was similar in healthy subjects (91%), and patients with mild (90%) and moderate (89%) HI at steady-state trough concentrations, and in patients with severe HI 24 h after a single dose (84%). Thus, mild, moderate or severe HI did not result in any increase in linagliptin exposure after single and multiple dosing compared with normal hepatic function. The conclusion was that dose adjustment with linagliptin is not required in patients with HI [86].

3.6.5. Alogliptin

Alogliptin is metabolized into 2 identified minor metabolites: M-I, an N-demethylated active metabolite via CYP2D6, and M-II, an N-acetylated inactive metabolite. CYP3A4 may also be involved in the formation of other unidentified minor metabolites. Exposure to these 2

metabolites in plasma, relative to unchanged drug, are <1% and <6%, respectively. Metabolism represents only a small part of the elimination of alogliptin, which is mainly excreted through the kidneys [71, 72].

After a single oral administration of 25 mg alogliptin, no clinical significant differences in AUC and C_{max} exposure to the parent drug and its main metabolite M1 were observed in subjects with moderate HI (Child-Pugh 7-9) compared with healthy subjects. The elimination of both alogliptin and M1 was 2.5 hours longer in patients with moderate HI than in normal subjects. However, the magnitude of these increases was not considered clinically significant. Therefore, no dose adjustment is necessary for patients with mild to moderate HI (classes A and B) [87]. However, these data were reported only as an abstract so that caution is recommended. Subjects with severe HI were not evaluated [87].

3.7. SGLT2 inhibitors

SGLT2 inhibitors improve glycemic control in an insulin-independent fashion through inhibition of glucose reuptake in the kidney and offer a new option for the management of T2DM A recent review summarized the PK and toxicological characteristics of this novel pharmacological class [88].

3.7.1. Dapagliflozin

Dapagliflozin is the SGLT2 inhibitor with the most clinical data available to date [89] and its PK properties have been extensively described in a recent review [90]. Dapagliflozin elimination is primarily via glucuronidation to an inactive main metabolite, dapagliflozin 3-O-glucuronide. An open-label, parallel-group study compared the PK of a single 10-mg oral dose of dapagliflozin in patients with various degrees of HI and in healthy control subjects. In those with mild, moderate, or severe HI, dapagliflozin mean C_{max} values were 12% lower and 12% and 40% higher than healthy subjects, respectively. Mean dapagliflozin AUC_{∞} values were 3%, 36%, and 67% higher compared with healthy subjects, respectively (Table 3). These values were highly dependent on the calculated creatinine clearance of each group. Compared with healthy subjects, systemic exposure to dapagliflozin in subjects with CLD was correlated with the degree of HI. Due to the higher dapagliflozin exposures in patients with severe HI, the benefit:risk ratio should be individually assessed because the long-term safety profile and efficacy of dapagliflozin have

not been specifically studied in this population [91]. Caution should be even greater when HI is combined with some degree of renal impairment [90].

3.7.2. Canagliflozin

The PK and metabolism, the PD and the efficacy and safety of canagliflozin were recently reviewed [92]. One study (still unpublished) more specifically investigated the PK of canagliflozin in patients with CLD following administration of a single 300 mg dose of the drug. Relative to subjects with normal hepatic function, the geometric mean ratios for C_{max} and AUC_{∞} of canagliflozin were 107% and 110%, respectively, in subjects with Child-Pugh class A (mild HI) and 96% and 111%, respectively, in subjects with Child-Pugh class B (moderate HI) (Table 3). These differences are not considered to be clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) HI [93].

3.7.3. Empagliflozin

The PK/PD properties of empagliflozin have been recently reviewed [94]. The effect of HI on the PK of empagliflozin was investigated in an open-label, parallel-group study of subjects with mild, moderate, or severe HI and in matched controls with normal hepatic function who received a single dose of empagliflozin 50 mg [95]. Compared with subjects with normal hepatic function, exposure to empagliflozin (both C_{max} and AUC_{∞}) progressively increased with the severity of HI (Table 3) [95]. However, as the increase in empagliflozin exposure was less than two-fold in patients with impaired liver function, it was concluded that no dose adjustment of empagliflozin is required in these patients [95].

3.7.4. Ipragliflozin

Ipragliflozin, a SGLT2 inhibitor in clinical development, is primarily eliminated via conjugation by the liver as five pharmacologically inactive metabolites. In an open-label, single-dose, parallel-group study, eight subjects with moderate HI [Child-Pugh score 7-9] and eight healthy, matched controls received a single oral dose of 100-mg ipragliflozin to evaluate the effect of moderate HI on the PK of ipragliflozin and its metabolites. Only a trend for a mild increased exposure was observed in patients with moderate HI versus controls (Table 3). No changes in elimination $t_{1/2}$ and protein binding of ipragliflozin were observed in moderate HI subjects. Thus, moderate HI had no clinically relevant effects on the single-dose PK of ipragliflozin [96].

3.8. GLP-1 receptor agonists

When oral therapy is not sufficient to control blood glucose, injectable agents may be used. Besides insulin therapy, GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide) offer new opportunities for the management of T2DM [21]. A recent review describes the PK and safety aspects of the currently available GLP-1 receptor agonists [97].

3.8.1. Exenatide

The kidney appears to be the primary route of elimination and degradation of exenatide [98]. No PK studies have been done in patients with CLD; however, because exenatide is cleared primarily by the kidney, HI is not expected to affect blood levels and PD effects on glucose control.

3.8.2. Liraglutide

Liraglutide is metabolized in vitro by DPP-4 and neutral endopeptidase in a manner similar to that of native GLP-1, although at a much slower rate. The metabolite profiles suggest that both enzymes are also involved in the in vivo degradation of liraglutide. The lack of intact liraglutide excreted in urine and feces and the low levels of metabolites in plasma indicate that liraglutide is completely degraded within the body [99].

A parallel group, open label trial compared the PK of a single-dose (0.75 mg injected subcutaneously) of liraglutide in four groups of six subjects with healthy, mild, moderate and severe HI, respectively [100]. Exposure to liraglutide was not increased by HI. On the contrary, mean AUC_∞ was highest for healthy subjects and lowest for subjects with severe HI (severe/healthy: 0.56, with 90% CI 0.39, 0.81). C_{max} also tended to decrease with HI (severe/healthy: 0.71, with 90% CI 0.52, 0.97), but t_{max} was similar across groups (11.3-13.2 h). According to the authors, because the half-life of liraglutide was not affected by HI, the differences in the overall exposure (AUC_∞) of liraglutide might result primarily from differences in absorption of the drug from the subcutaneous depot rather than differences in its subsequent metabolism. Nevertheless, because the vast majority of liraglutide molecules are reversibly bound to plasma albumin, a decrease in albumin concentration as seen in patients with severe CLD may also result in an increased rate of metabolism of liraglutide by various enzymes. However, this PK effect, resulting in lower plasma levels, might be compensated for by a possible enhanced PD effect in the setting of reduced circulating

albumin concentrations that leads to an increased free fraction of liraglutide able to interact with GLP-1 receptors. Because of these diverse effects, data are not conclusive to suggest a dose increase of liraglutide. Thus, the results indicate that patients with T2DM and CLD can use standard treatment regimens of liraglutide. There is, however, currently limited clinical experience with liraglutide in patients with HI [100].

In a Japanese study, the effectiveness of liraglutide in NAFLD patients with T2DM was compared to sitagliptin and pioglitazone. Administration of liraglutide improved T2DM but also resulted in improvement of liver inflammation, alteration of liver fibrosis, and reduction of body weight and compared favorably with sitagliptin and pioglitazone [101]. In a case report, a patient who had suffered from T2DM and from concomitant cryptogenic cirrhosis was treated with liraglutide, obtaining an optimal metabolic control associated with an improved clinical condition for the cirrhosis [102]. Because of these preliminary promising results, LEAN ("Liraglutide Efficacy and Action in NASH"), a phase II, multicentre, double-blinded, placebo-controlled, randomized clinical trial, has been designed to investigate whether a 48-week treatment with 1.8 mg liraglutide will result in improvements in liver histology in patients with NASH [103]. The results are not available yet.

3.8.3. Lixisenatide

The elimination of lixisenatide is expected to follow that of endogenous peptides with renal filtration followed by tubular reabsorption and subsequent metabolic catabolism.

The influence of HI on lixisenatide PK has not been evaluated. No dose adjustment is needed in patients with HI as hepatic dysfunction is not expected to affect the PK of lixisenatide [104].

3.9. Other glucose-lowering agents

Some other glucose-lowering agents are only approved in the US : bile acid sequestrants (colesevelam), bromocriptine and pramlintide. Because these drugs are either not absorbed or not investigated in patients with CLD, they will not be considered in the present review.

3.10. Insulin and insulin analogs

To study the mechanisms of glucose intolerance and hyperinsulinism in cirrhosis, our group compared the plasma glucose, insulin, and C-peptide levels during a frequently

sampled intravenous glucose tolerance test in 9 compensated cirrhotic patients and 9 matched healthy volunteers. Cirrhosis was characterized by an important peripheral hyperinsulinism, resulting from both a higher insulin secretion rate and a markedly reduced insulin hepatic clearance [105]. Portosystemic/intrahepatic shunting may also play a role in some cirrhotic patients [6]. When exogenous insulin is necessary, the daily dose required to control blood glucose is difficult to predict because of the opposite influence of various factors. In patients with decompensated liver disease, the requirement may be decreased due to reduced capacity for gluconeogenesis, resulting in lower hepatic glucose output, and reduced hepatic breakdown of insulin. However, patients with impaired hepatic function may also have an increased need for insulin to compensate for insulin resistance [14].

Exogenous insulin uptake by the human cirrhotic liver was studied in 6 patients with Laennec's cirrhosis, and the result was compared with that found in 10 control patients with varying diseases affecting the biliary system. The fractional hepatic extraction of insulin was only 13±5% in cirrhotic patients and differed significantly from the fractional hepatic extraction found in controls (51±5%; $P<0.001$) [106].

Insulin therapy can be used at any stage of HI, although clinical studies are scarce in insulin-treated diabetic patients with CLD [13, 14]. In a small case series of four cirrhotic patients with T2DM and inadequate blood glucose control with conventional insulin therapy, initiation of continuous subcutaneous insulin infusion with a portable pump was beneficial in controlling blood glucose values [107]. There is no single study reporting extensive experience with insulin analogs in patients with CLD.

4. Toxicological considerations

Many patients with T2DM are treated by several medications, not only glucose-lowering agents, but also pharmacological compounds to manage comorbidities such as hypertension, dyslipidemia and cardiovascular diseases [108]. In case of the occurrence of hepatic disturbances in a patient with T2DM, and after exclusion of a viral or metabolic origin, it may not be easy to decide which drug might be responsible for hepatotoxicity. Furthermore, while some medications have predictable hepatotoxicity, many more have associated idiosyncratic reactions [109]. To our knowledge, there is no obvious information supporting a greater risk of severe hepatotoxicity in diabetic patients with mild liver disturbances (NAFLD) receiving any type of glucose-lowering agents.

4.1.Metformin

The use of metformin has been limited in many diabetic patients considered as at risk of complications, especially lactic acidosis [110]. Manufacturer prescribing information and some current literature caution against metformin use in patients with CLD [111]. This recommendation is interpreted variably by different prescribers, with some believing that the caution implies metformin can cause or worsen liver injury [112] and others rather believing that liver disease predisposes patients to developing lactic acidosis [113]. Metformin does not appear to cause or exacerbate liver injury and, indeed, may be beneficial in patients with NAFLD [17, 114]. NAFLD frequently presents with transaminase elevations (alanine aminotransferase or ALT) but should not be considered a contraindication to metformin use. The liver appears to be a key organ not only for the antidiabetic effect of metformin but also for the development of lactic acidosis [115]. Literature evidence of liver disease being implicated with metformin-associated metabolic acidosis is largely represented by case reports [113, 115]. Most such patients had cirrhosis, with some degree of renal impairment. For this reason, it seems reasonable to use metformin with caution in patients with moderate CLD and to avoid its use in patients with severe CLD (Table 4). Furthermore, identifying patients with cirrhosis and controlling renal function before initiating metformin seem prudent [111]. Any circumstance favoring dehydration should promote the interruption of metformin, especially in such fragile patients [113].

Finally, and interestingly, metformin therapy is associated with a reduced risk of hepatocellular carcinoma [116], especially in patients with hepatitis C virus [117], and seems to have a protective effect on hepatocellular carcinoma progression [118] and liver-related death or need for hepatic transplantation [119]. Further long-term, randomized controlled trials are needed to adequately assess the safety and efficacy of metformin therapy in patients with comorbid diabetes and chronic hepatitis C virus [117].

4.2.Sulfonylureas

Although the major risk associated with sulfonylureas is hypoglycemia and this risk is known to be increased in more fragile patients, no such observations were specifically described in patients with CLD in contrast to what has been reported in patients with chronic kidney disease [12]. Poor nutrition can be an issue in patients with CLD, which may have an impact on the development of hypoglycemia. Patients who are not abstinent from alcohol

should be very cautious when taking sulfonylureas, because alcohol increases the risk of hypoglycemia by inhibiting hepatic gluconeogenesis.

Drug-induced hepatotoxicity has been reported infrequently with various sulfonylureas used as glucose-lowering agents for the management of T2DM : chlorpropamide [120], tolazamide [121], glibenclamide (glyburide) [122-124], glimepiride [125], and gliclazide [126, 127].

4.3.Meglitinides (glinides)

As with sulfonylureas, rare case reports of hepatotoxicity associated with repaglinide have been reproted, either acute hepatotoxicity [128] or cholestatic hepatitis [129].

4.4.Alpha-glucosidase inhibitors

Acarbose has been used safely in patients with CLD in one clinical trial, although the risk of hyperammonemia was increased [51]. A case report described a patient with possible acarbose-induced hepatotoxicity and compared other reported cases from the literature [130]. Another case of hepatotoxicity has been reported with migitol [131] as well a case of hepatic necrosis with cholestasis associated with long-term voglibose administration [132].

4.5.Thiazolidinediones

Troglitazone was the first thiazolidinedione antidiabetic agent approved for clinical use, but it was rapidly withdrawn from the market due to serious idiosyncratic hepatotoxicity, as already discussed [59]. Clinical evidence supports the conclusion that rosiglitazone and pioglitazone do not share the hepatotoxic profile of troglitazone [60]. In a randomized, 3-year, double-blind, hepatic safety study in the US in which 2,097 patients with T2DM received either pioglitazone or glibenclamide (glyburide), the hepatic safety profile of pioglitazone was similar to that of glibenclamide in long-term use in patients with poorly controlled T2DM [133].No evidence of hepatotoxic effects was observed in studies that involved 5,006 patients taking rosiglitazone as monotherapy or combination therapy for 5,508 person-years [134]. All together, these findings suggest that the idiosyncratic liver toxicity observed with troglitazone is unlikely to be a thiazolidinedione or a PPAR-gamma agonist class effect [60]. On the

contrary, poorly controlled patients with T2DM may have moderate elevations of serum ALT (reflecting NAFLD) that will decrease with improved glycemic control during treatment with pioglitazone or rosiglitazone. These results are in agreement with the favorable effects of glitazones initially reported in patients with NAFLD [64, 65], although less convincing results were reported afterwards. These positive results may be at least partly explained by the glitazone-induced increase in adiponectin, which exerts an important metabolic role at the level of the liver and seems critical to reverse insulin resistance and improve liver histology in NASH patients [135]. It has been suggested that thiazolidinediones may in the future be increasingly used in patients with NASH [136]. However, so far there is no proof that any oral antidiabetic agent helps patients with NASH by a direct hepatic effect in the long run.

Two randomized placebo-controlled trials investigated the effects of pioglitazone in patients with insulin resistance and hepatitis C treated with peginterferon-alpha-2b and ribarivin and reported contrasted results. In patients with chronic hepatitis C genotype 4, a combination of pioglitazone, peginterferon-alpha-2b and ribavirin increased virological response and decreased insulin resistance, compared with patients not receiving pioglitazone, without an increase in adverse events [137]. However, in another study in patients with insulin resistance and chronic hepatitis C genotype 1, treatment with pioglitazone before and during treatment with peginterferon alpha-2a plus ribavirin improved several indices of glycemic control, but did not improve virologic response rates compared with peginterferon alpha-2a plus ribavirin alone [138].

According to the official labeling, pioglitazone should not be prescribed to patients suffering from liver disease or in case of an increase in alanine aminotransferase (ALT) enzyme 2.5 times above the limit. If liver enzymes increase and continue to stay high (2.5 times the upper limit of normal) after administration of pioglitazone, it is usually an obvious sign of liver damage. If the ALT test shows that the enzyme level is 3 times higher than the norm, the reanalysis should be undergone as quickly as possible. In case the second test reveals the same high level of enzymes, pioglitazone should be immediately discontinued.

4.6.DPP-4 inhibitors

The overall safety profile of DPP-4 inhibitors is generally good, even if some concern about possible exocrine pancreatic alterations have been reported [139]. Especially, no hepatotoxicity has been reported in large clinical trials. This has been shown in a pooled

analysis of 25 clinical studies and 14,611 patients (n = 7,726 : sitagliptin group; n = 6,885 : non-exposed group) for sitagliptin [140] and in a similar pooled analysis of 38 studies with vildagliptin (> 7000 subject-years of exposure to vildagliptin 50 mg bid and > 6500 subject-years of exposure to all comparators). For mild hepatic enzyme elevations with and without elevated bilirubin levels, the odds ratio for vildagliptin 50 mg bid were 1.24 (95% CI: [0.80, 1.93]) and 1.19 (95% CI: [0.29, 4.90]), respectively. The exposure-adjusted incidences of markedly elevated hepatic enzymes and for enzyme elevations with bilirubin ≥2 times the upper limit of normal with vildagliptin were similar or lower than those in the all comparator group. For hepatic-related adverse events, the odds ratio for vildagliptin was 0.87 (95% CI: [0.64, 1.19]) [141]. These data were confirmed in another pooled analysis showing that vildagliptin was overall well tolerated in clinical trials of up to >2 years in duration [142]. Reassuring hepatic safety data have also been reported with saxagliptin [143] and linagliptin [144]. In a systematic review and meta-analysis about the longer term safety of DPP-4 inhibitors in patients with T2DM, hepatotoxicity was not considered as a concern [139]. Nevertheless, a few cases of drug-induced hepatic injury associated with sitagliptin [145] or of elevated hepatic enzymes potentially associated with sitagliptin [146] have been reported. The causal relationship remains, however, uncertain because of the complex medical history of many case reports.

In the only study where a DPP-4 inhibitor (5 mg linagliptin) was administered once daily for 7 days in patients with mild and moderate HI, the DPP-4 inhibitor was well tolerated [86].

4.7.SGLT-2 inhibitors

Available data from large phase II-III trials showed that dapagliflozin [147], canagliflozin [148] and empagliflozin [94] do not cause hepatotoxicity. No case reports describing alterations of liver tests with SGLT-2 inhibitors have been reported so far.

4.8.GLP-1 receptor agonists

An interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials examined the metabolic effects of 2 years of exenatide treatment in patients with T2DM. Patients with normal baseline ALT had no significant ALT

change. However, patients with elevated ALT at baseline had a slight but significant reduction of ALT from baseline and 39% achieved normal ALT by week 104 [149]. A trial was specifically designed to investigate the effects of exenatide on liver biochemistry, liver histology and lipid metabolism in patients with NAFLD (ClinicalTrials.gov Identifier: NCT00529204), but the results are not available yet. Individual patient data meta-analysis of the LEAD program showed that a 26-week therapy with liraglutide 1.8 mg is safe, well tolerated and improves liver enzymes in patients with T2DM. This effect appears to be mediated by its favorable action on weight loss and glycemic control [150]. No such specific analysis has been performed yet with lixisenatide, but no liver safety concern has been reported with this new GLP-1 receptor agonist [151].

4.9.Insulin and insulin analogs

Insulin can be used in patients with all stages of CLD and does not exert hepatotoxic effects. However, the dose of insulin required in cirrhotic patients for optimal glucose control without hypoglycemia should be carefully adjusted upon an individual basis and blood glucose monitoring.

5. Conclusion

The increasing prevalence of patients with T2DM and CLD, especially among obese individuals, requires appropriate selection and dosing of glucose-lowering agents (Table 4). Old antidiabetic drugs (metformin, sulfonylureas) were poorly investigated in patients with HI so that their use is classically contraindicated in patients with moderate to severe HI because of a possible higher risk of lactic acidosis (with metformin) and of hypoglycemia (with sulfonylureas). Glitazones were also poorly studied in this population after the withdrawal of troglitazone because of hepatotoxicity and should be used with caution even if pioglitazone and rosiglitazone are not hepatotoxic. Better PK data have been published specifically in patients with various degrees of HI with glinides, DPP-4 inhibitors and SGLT-2 inhibitors and overall the results were almost reassuring, with some limited PK changes probably without clinical relevance in most cases. A benefit/risk balance should be considered when prescribing a glucose-lowering medication in diabetic patients with CLD. Whereas NAFLD is generally improved by the use of glucose-lowering agents, via a better glucose control especially when insulin resistance is reduced, the problem of controlling effectively and safely blood glucose

becomes more crucial in patients with advanced cirrhosis.

EXPERT OPINION SECTION

Type 2 diabetes mellitus (T2DM) and chronic liver disease (CLD) are common long-term conditions in our modern society and the two conditions often coexist. There are strong arguments to support a bidirectional relationship : diabetes predisposes to liver disease and conversely liver disease predisposes to diabetes ("hepatogenous diabetes"). Furthermore, there is evidence to suggest that diabetes can have a significant adverse effect on patients with CLD, leading to increased complications and premature mortality. While type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), steatosis and nonalcoholic steatohepatitis (NASH), appears to have common origins related to abdominal obesity and insulin resistance, diabetes is also common among patients with alcoholic and viral CLD.
In patients with NAFLD and NASH, improvement in metabolic indices, with lifestyle changes but also via pharmacological approaches, appears to reduce the progression of CLD. Interestingly this effect seems more favorable with insulin-sensitizing agents than with strategies increasing insulin concentrations, although more recent studies with thiazolidinediones were more disappointing than initially reported observations. However, it is not clear whether improving glycemic control in other more advanced forms of CLD, especially cirrhosis, also leads to improved clinical outcomes and overall prognosis.

Managing diabetes in patients with CLD can be challenging because many glucose-lowering therapies are contraindicated or must be used with care. However, such precautions generally result from the fear of complications (as lactic acidosis with metformin and hypoglycemia with sulfonylureas) rather than from well-documented observations from controlled clinical studies. Indeed, only a paucity of data are available in the literature regarding the PK characteristics, the efficacy and the safety of commonly prescribed glucose-lowering agents such as metformin, sulfonylureas, alpha-glucosidase inhibitors (acarbose) and thiazolidinediones (pioglitazone and rosiglitazone) in diabetic patients with CLD. A few case reports have been published about a possible hepatotoxicity of some of these compounds but the causal relationship remains doubtful in most instances. Metformin may be useful in patients with NAFLD (detected by mild to moderate increases in transaminase liver enzymes), and even might reduce the progression to and the severity of hepatocellular carcinoma. However, in case of advanced cirrhosis, caution is recommended, especially

because the possibility of associated renal impairment and reduced tissue perfusion that could favor lactic acidosis. Pioglitazone, a well-known insulin sensitizer, has been shown to have the capacity to reduce fatty liver, at least in some studies, but its use in more advanced stages of CLD is not documented.

Sulfonylureas and insulin must be used with caution in patients with advanced CLD, as hypoglycemia may be a concern. In diabetic patients with moderate to severe stages of cirrhosis, it is probably prudent not to use sulfonylureas, and insulin doses must be carefully adjusted according to results of blood glucose monitoring in those patients. Glinides may represent an alternative to sulfonylureas, with a preference for nateglinide compared to repaglinide.

Newer antihyperglycemic agents have not been widely used in diabetic patients with CLD. Nevertheless, the recent literature offers more detailed specific PK studies with these medications in patients with various degrees of HI than the scarce data (if any) available with older compounds. No clinically relevant increase in systematic exposure to DPP-4 inhibitors (gliptins) has been reported so that no dose reduction is recommended in patients with HI, including with linagliptin whose specific hepatic metabolism is well known. This contrasts with the reduction of the daily dose according to the glomerular filtration rate in patients with chronic kidney disease (for sitagliptin, vildagliptin, saxagliptin and alogliptin, characterizd by renal elimination). Another advantage of DPP-4 inhibitors compared to sulfonylureas is the very limited risk of hypoglycemia. Similar favorable PK results were reported with GLP-1 receptor agonists, especially liraglutide, in patients with various degrees of HI, and liraglutide has been also shown to improve liver prognosis of patients with NAFLD. No signs of hepatotoxicity have been reported so far with incretin-based therapies, contrasting with some concern and controversy regarding exocrine pancreas.

Only limited data have been published regarding the use of SGLT2 inhibitors in diabetic patients with CLD. Available PK data suggested an increase in exposure to dapagliflozin, canagliflozin and empagliflozin in patients with mild to severe HI. Because the increase was less than two-fold, no dose reduction is recommended. However, caution is necessary in absence of larger clinical studies in such a fragile population with advanced CLD.

Finally, since CLD patients are commonly treated with multiple-drugs, the drug-drug interactions in diabetic patients with CLD are important considerations in selecting the most appropriate glucose-lowering medications.

In conclusion, the management of patients with diabetes and CLD represents a challenge for the clinician. Clinical success may be enhanced by selecting the most appropriate glucose-lowering medications and using a multidisciplinary approach if necessary.

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Article highlights

- Diabetes predisposes to chronic liver disease (CLD), especially non-alcoholic fatty liver disease that may progress to non-alcoholic steatohepatitis and cirrhosis.
- CLD, especially cirrhosis, predisposes to diabetes, which may require specific therapy for appropriate glucose control.
- Besides kidneys, liver contributes to the elimination of several glucose-lowering agents and CLD may render more difficult the management of diabetes.
- Overall, the influence of CLD on PK/PD of glucose-lowering agents is less well documented in the literature than the influence of chronic kidney disease.
- Almost no specific PK studies with classical antidiabetic agents (metformin, sulfonylureas, glitazones, alpha-glucosidase inhibitors) have been published in subjects with hepatic impairment (HI).
- Metformin, which is not metabolized but excreted unchanged by the kidneys, can be used in patients with HI and may exert various favourable effects.

- Caution is recommended with the use of sulfonylureas in absence of well-documented studies in patients with CLD and because of a potential higher risk of hypoglycemia.
- Specific PK studies in patients with HI showed no clinically relevant changes in exposure to DPP-4 inhibitors and liraglutide, arguing for no need of dose adjustment (in contrast to the reduction recommended in case of renal impairment).
- Specific PK studies in patients with HI have been performed with SGLT2 inhibitors. Only limited increase in overall exposure was observed, presumably without clinical relevance.
- Considering the increasing prevalence of patients combining CLD or HI and diabetes, there is a crucial need for more clinical studies to evaluate the efficacy/safety balance of the various available glucose-lowering strategies in this special population.

Figure 1 : Illustration of the two-way relationship between diabetes and chronic liver disease. T2DM : type 2 diabetes mellitus. NAFLD : non-alcoholic fatty liver disease (steatosis). NASH : non alcoholic steatohepatitis.

Table 1 : PK characteristics of repaglinide and nateglinide in healthy subjects and patients with chronic liver disease (CLD).

	Healthy subjects	CLD patients	GMR (90% CI)	P value
Repaglinide [45] Single dose : 4 mg		(Child-Pugh : 7 to < 11 points)		
N	12	12		
AUC (ng.h/ml)	91.6 ± 67.0	368.9 ± 233.4	4.34 (2.29-8.23)	< 0.001
C_{max} (ng/ml)	46.7 ± 24.3	105.4 ± 31.6	2.46 (1.68-3.62)	< 0.001
T_{max} (h)	0.8 (0.5-1.1)	0.8 (0.5-1.0)	NA	NS
$T_{1/2}$ (h)	0.8 ± 0.2	3.3 ± 2.3	NA	< 0.001
Nateglinide [46] Single dose : 120 mg		(Child-Pugh : ≥5 to ≤11 points)		
N	8	8	1.30 (0.93-1.61)	0.20
AUC (ng.h/ml)	14,170 ± 2060	18,470 ± 7510	1.37 (0.70-2.05)	0.54
C_{max} (ng/ml)	5620 ± 1310	7700 ± 4890	NA	NS
T_{max} (h)	0.5 (0.5-2.0)	0.5 (0.5-0.75)	NA	NS
$T_{1/2}$ (h)	2.91 ± 1.84	2.62 ± 1.42		

Results are expressed as mean ± SD (except for T_{max} : median, range) and by geometric mean ratio (GMR) CLD/healthy subjects function (90% confidence intervals). NA : data not available. NS : not statistically significant. C_{max} : maximum plasma concentration. AUC : area under the concentration-time curve. T_{max} : time to reach C_{max}. $T_{1/2}$: terminal elimination half-life.

Table 2 : Drug exposure of DPP-4 inhibitors in subjects with various degrees of chronic liver disease (CLD) (according to Child-Pugh staging) compared with subjects with normal liver function.

	Reference	Exposure	Mild CLD GMR (90% CI)	Moderate CLD GMR (90% CI)	Severe CLD GMR (90% CI)
Sitagliptin (single dose of 100 mg)	Migoya et al 2009 [75]	C_{max} AUC_{∞}	NA NA	1.13 (0.91-1.42) 1.21 (1.01-1.46)	NA NA
Vildagliptin (single dose of 100 mg)	He et al 2007 [83]	C_{max} AUC_{∞}	0.70 (0.46- 1.05) 0.80 (0.60-1.06)	0.77 (0.51- 1.17) 0.92 (0.69-1.23)	0.94 (0.59-1.49) 1.22 (0.89-1.68)
Saxagliptin (single dose of 10 mg)	Boulton et al 2011 [84]	C_{max} AUC_{∞}	1.077 (0.763, 1.519) 1.097 (0.828, 1.453)	1.016 (0.720, 1.432) 1.383 (1.044, 1.832)	0.941 (0.667, 1.328) 1.767 (1.334, 2.341)
5-hydroxy-saxagliptin (active metabolite)		C_{max} AUC_{∞}	0.83 (NA) 0.78 (NA)	0.84 (NA) 0.93 (NA)	0.41 (NA) 0.67 (NA)
Linagliptin (5 mg once daily for 7 days) (*)	Graefe-Mody et al 2012 [86]	C_{max} AUC_{t}	64.4 (43.2-96.0) 75.5 (61.6-92.5)	92.3 (62.8- 135.6) 85.5 (70.2- 104.2)	77.0 (44.9-132.3) 100.4 (75.0- 134.3)
Alogliptin (single dose of 25 mg)	Karim et al 2007 [87]	C_{max} AUC_{∞}	NA NA	92 (NA, NS) 90 (NA, NS)	NA NA

Results are expressed as % changes versus subjects with normal liver function or as geometric mean ratio (GMR) CLD/healthy subjects function (90% confidence intervals). NA : data not available. NS : not statistically significant. C_{max} : maximum plasma concentration. AUC_{∞} : area under the concentration-time curve from zero to infinity (*) : Single dose of 5 mg in patients with severe HI.

Table 3 : Drug exposure of SGLT-2 inhibitors in subjects with various degrees of chronic liver disease (CLD) (according to Child-Pugh staging) compared with subjects with normal liver function.

	Reference	Exposure	Mild CLD GMR (90% CI)	Moderate CLD GMR (90% CI)	Severe CLD GMR (90% CI)
Dapagliflozin (single dose of 10 mg)	Kasicha-yanula et al 2011 [91]	C_{max} AUC_{∞}	88 (NA) 103 (75-143) (*)	112 (NA) 136 (101-187) (*)	140 (NA) 167 (124-232) (*)
Canagliflozin (single dose of 300 mg)	Janssen Pharma-ceuticals Inc [93]	C_{max} AUC_{∞}	107% 110%	96% 111%	NA NA
Empagliflozin (single dose of 50 mg)	Macha et al 2013 [95]	C_{max} AUC_{∞}	103.8 (82.3–131.0) 123.2 (98.9-153.4)	123.3 (97.7–155.6) 147.0 (118.0-183.0)	148.4 (117.7–187.2) 174.7 (140.3-217.5)
Ipragliflozin (single dose of 100 mg)	Zhang et al 2013 [96]	C_{max} AUC_{∞}	NA NA	127 (93-173) 125 (94-166)	NA NA

Results are expressed as % changes versus subjects with normal liver function or as geometric mean ratio (GMR) CLD/healthy subjects function (90% confidence intervals). NA : data not available. C_{max} : maximum plasma concentration. AUC_{∞} : area under the concentration-time curve from zero to infinity. (*) : 90% CI derived from data shown graphically.

Table 4 : Clinical practice recommendations regarding the use of glucose-lowering agents in diabetic patients with various degrees of hepatic impairment (HI). Please note that the reported experience with any of these pharmacological classes is very limited and the absence of official guidelines; therefore caution and careful clinical supervision are recommended in all diabetic patients with HI, especially when moderate or severe.

Medications	Mild HI	Moderate HI	Severe HI	Feared adverse event
Biguanides - Metformin	Yes (*)	Caution	No use	Lactic acidosis (***)
Sulfonylureas - Glibenclamide (glyburide), glimepiride, glipizide, gliclazide, gliquidone	Yes	Caution	No use	Hypoglycemia
Glinides - Repaglinide, nateglinide	Yes	Caution	No use	Hypoglycemia
Alpha-glucosidase inhibitors - Acarbose, miglitol, voglibose	Yes	Probably yes	Probably yes	Hyperamonemia
Thiazolidinediones - Pioglitazone, rosiglitazone	Yes (**)	Caution (check liver enzymes)	No use	Hepatotoxicity (?)
DPP-4 inhibitors - Sitagliptin, vildagliptin,		Probably		Unknown (but no

saxagliptin, linagliptin, alogliptin	Yes	yes	Caution	clinical experience)
SGLT2 inhibitors - Dapagliflozin, canagliflozin, empagliflozin	Yes	Caution	No use	Unknown (but no clinical experience)
GLP-1 receptor agonists - Exenatide, liraglutide, lixisenatide	Yes	Probably yes	Caution or no use	Unknown (but no clinical experience)
Insulin & insulin analogs	Yes	Yes	Yes with caution	Hypoglycemia

(*) Favorable effects on NAFLD (steatosis and NASH) and possible protective effects against hepatocelluar carcinoma

(**) Favorable effects on NAFLD (steatosis and NASH) and liver inflammation

(***) Caution, check also the renal function

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