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Opinions

The treatment of diabetes in advanced liver disease: Change of a paradigm

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The treatment of type 2 diabetes (T2DM) has entered a new era in the past 15 years. After decades of stagnation, novel drugs, adding beneficial pleiotropic effects to their glucose lowering activity (Table 1), entered the market and totally replaced the old drugs in treatment diagrams proposed by international societies [1]. Also, the use of metformin as an initial treatment of hyperglycemia has been challenged following the evidence that gliflozins (sodium-glucose cotransporter-2 inhibitors – SGLT-2Is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) may reduce the risk of heart and kidney disease progression, the most common outcomes in patients with long-standing diabetes. A large network meta-analysis comparing the effects of 5-year T2DM treatment with these new classes versus any other intervention in randomized controlled trials (764 RCT, a total of 421,364 patients) confirmed the superiority of these drugs [2]. The risks of all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, kidney failure and hospital admission for heart failure were all reduced [2], with differences between GLP-1RAs and SGLT-2Is and in relation to *a priori* severity of cardiovascular risk. Changes in drug use are slowly being accepted in the community, despite clinical inertia and budget restriction [3].

These beneficial effects prompt to reconsider the treatment of T2DM also in patients with liver disease, a specific area of research where the risk of hepatotoxicity, drug-drug interaction, comorbidity and frailty commonly indicate the use of insulin as a preferred drug. The questions now are: 1) May we confidently use these drugs in the presence of advanced liver disease? 2) Do these beneficial effects also occur in patients with T2DM and cirrhosis? 3) Is there any evidence that these drugs may also improve – or reduce the progression of – the underlying liver disease?

As to the first question, all SGLT-2Is share similar pharmacokinetic characteristics. Following oral administration and rapid absorption, they undergo extensive hepatic metabolism via glucuronidation to inactive metabolites, which are finally excreted by the kidney. Their systemic exposure (C_{max} and AUC_{∞}) increases with the severity of hepatic disease, classified according to Child-Pugh score [4], but no signs of hepatotoxicity have ever been reported. Nonetheless, very few data are available, and review articles suggest caution for use in patients with advanced liver disease [5] and even more in the presence of combined liver and renal failure. No dose adjustment is suggested for patients up to Child-Pugh B class [6].

Incretin-based therapies include GLP-1RAs and the dipeptidyl-peptidase-4 inhibitors (DPP-4Is). Both classes are scarcely metabolized by the liver and are mostly excreted unchanged by the kidney [7], which regulates systemic exposure (with the notable exception of linagliptin). DPP-4Is are safe and do not induce hypoglycemia, but do not share the beneficial effects of GLP-1RAs on the cardiovascular and renal systems. Therefore, they are considered the second choice in the treatment algorithm. On the contrary, liraglutide and the long-acting weekly GLP-1RAs (exenatide LAR, dulaglutide and semaglutide) qualify as potential treatment also in the presence of liver disease [8], considering their safety and efficacy [9]. The only possible risk comes from the reported interaction of GLP-1RAs with beta-blocking agents for the prevention of recurrent bleeding [10], requiring further investigation.

As to the second question, there are no systematic data on cardiovascular and renal disease progression in specific cohorts with T2DM and liver disease, a group of patients largely identifiable as NASH-cirrhosis. The beneficial effects of GLP-1RAs and SGLT-2Is have been extensively reproduced in large cohorts of patients with T2DM, and most of them were expected to have non-alcoholic steatohepatitis

Abbreviations: AGI, alfa-glucosidase inhibitor; AUC, area under the curve; Cmax, maximum concentration; CKD, chronic kidney disease; CV, cardiovascular; GIP, glucose-dependent insulinotropic peptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; NASH, nonalcoholic steatohepatitis; RCT, randomized controlled trial; SGLT-2I, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus

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Table 1
Agents for diabetes treatment and their clinical effects. The last three classes have been added to the spectrum of available treatment in the past 15 years.

Agents	Favorable effects	Adverse effects
Metformin	• Modest control of glucose levels • Modest weight loss • Very low risk of hypoglycemia • Reduced risk of primary liver cancer	• Rare abdominal discomfort • Dose tapering and suspension in the presence of CKD grade 4-5 • Risk of lactic acidosis
Sulphonylureas and glinides	• Potent control of glucose levels • Intra-class difference in terms of renal or hepatic metabolism	• Risk of hypoglycemia • Increased CV risk • Weight gain • Low durability
Pioglitazone	• Moderate control of glucose levels • CV and cerebrovascular protection • Very low risk of hypoglycemia • Reduced progression of NASH fibrosis	• Weight gain • Heart failure risk
AGIs	• Modest post-prandial glucose control	• Abdominal discomfort • Low compliance
Insulin	• Maximum control of glucose levels	• Weight gain • High risk of hypoglycemia • Low compliance and high burden with intensive treatment
DPP-4Is	• Moderate control of glucose levels	• Negligible adverse events
GLP-1RAs	• Potent control of glucose levels (valid alternative to insulin treatment) • Reduced CV and renal disease progression • Important weight loss • Very low risk of hypoglycemia	• Nausea and abdominal discomfort (relatively high discontinuation rate) • Possible risk of weight loss-induced sarcopenia • Limited use in advanced CKD
SGLT-2Is	• Moderate control of glucose levels • Reduced risk of CV and renal disease progression • Prevention of heart failure • Modest weight loss • Very low risk of hypoglycemia • Long-term durability	• Polyuria causing low compliance • Risk of genital and urinary infections • Low effectiveness in advanced CKD

AGIs, alfa-glucosidase inhibitors; DPP-4Is, dipeptidyl-peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT-2Is, sodium-glucose cotransporter-2 inhibitors; CKD, chronic kidney disease, CV, cardiovascular; NASH, non-alcoholic steatohepatitis.

(NASH) superimposed to T2DM. Old studies identified liver failure or bleeding, not cardiovascular events, as most common cause of death in cirrhosis with T2DM [11], but the present epidemics of metabolic liver disease significantly increased the cardiovascular risk in the general population with advanced liver disease [12 13]. Although liver disease was not systematically considered an exclusion criterion in cardiovascular and renal outcome trials [14–23], probably very few enrolled patients might be classified as NASH-cirrhosis. This is a very novel area of research that should be extensively investigated in the future.

The third question is far more intriguing. GLP-1RAs have been extensively investigated as treatment for NASH, but the results are inconclusive. Liraglutide and semaglutide reduced steatosis and NASH [24], but failed to improve fibrosis [25 26]. Similar effects on steatosis and liver biomarkers were observed with dulaglutide [27] and tirzepatide, the dual GIP (glucose-dependent insulinotropic peptide)/GLP-1RA [28], and data on fibrosis are being investigated. SGLT-2Is similarly reduced steatosis [24], with no definite effect on fibrosis. For both classes, changes in steatosis and fibrosis biomarkers might stem from weight loss [29], favored by behavioral treatment [30]. Beneficial effects might also be achieved by high dose semaglutide and tirzepatide, causing 15% mean weight reduction [31 32], provided that the negative effects of weight loss-associated sarcopenia are adequately corrected [33]. A recent report compared the effectiveness of antidiabetic agents at reducing the risk of hepatic decompensation (hospitalization for ascites, bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, bleeding varices) in T2DM with cirrhosis (60% NASH-cirrhosis), based on a large US commercial claims dataset [9]. After accurate propensity-score matching, patients receiving GLP-1RAs experienced lower rates of decompensation compared with DPP-4Is or sulphonylureas (HR 0.68, 95%CI 0.53-0.88; and HR 0.64, 95%CI 0.48-0.84), respectively), whereas no differences were observed between the cohorts treated with GLP-1RAs and SGLT-2Is. A role of SGLT-2Is in decompensated cirrhosis is also being explored in adequately powered trials, following anecdotal reports of control of refractory ascites, hydrothorax and peripheral edema [34,35]. With the limits of possible bias inherent to observational studies, these drugs appear to be safe and effective for T2DM treatment in cirrhosis.

In conclusion, a large body of evidence is accumulating for a systematic use of novel antidiabetic drugs, namely GLP-1RAs and SGLT-2Is, also in subjects with cirrhosis, as well as in candidates for liver transplantation [36], a population at very high risk of cardiovascular and renal disease. These novel drugs might be effectively associated with metformin and/or pioglitazone. Metformin continuation in cirrhosis with T2DM, in the safe renal function area, improved survival [37] and also reduced the risk of primary liver cancer [38], whereas pioglitazone remains the only drug associated with reduced risk of NASH fibrosis [39].

Declaration of interest

None.

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