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Position Statement

Management of diabetes mellitus in patients with cirrhosis: An overview and joint statement

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a frequent comorbidity in patients with cirrhosis that is projected to rise in prevalence due to the worldwide burden of obesity, insulin-resistance and non-alcoholic fatty liver disease. The management of T2DM in patients with cirrhosis is complex given the requirement for accurate adaptation according to the level of liver function impairment, with lack of summary of the little evidence available in the literature. Here, we summarise the data available with respect to the epidemiology and the impact of T2DM in patients with cirrhosis, as well as those on the management of T2DM in these patients. We provide guidance for the diagnosis of T2DM and the monitoring of glycaemic control in patients with cirrhosis, and for the management of nutrition and pharmacological treatments in relation to the level of liver dysfunction.

Abbreviations: ADA, American Diabetes Association; 2h-PG, 2-hour plasma glucose; AUC, area under the concentration-time curve; CGM, continuous glucose monitoring; C_{max}, maximum plasma concentration; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OGTT, oral glucose tolerance test; SGLT2i, sodium-glucose cotransporter 2 inhibitors; T2DM, type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) and liver cirrhosis are two frequent diseases accounting for 5 million and 1.2 million deaths worldwide each year, respectively [1,2]. T2DM is highly prevalent in patients with advanced liver disease, and likewise, advanced liver disease is present in a significant proportion of patients with T2DM [3,4]. This relationship can be explained by the fact that non-alcoholic fatty liver disease (NAFLD), which is considered the hepatic manifestation of the metabolic syndrome, is now the leading cause of chronic liver diseases [5]. In addition, NAFLD acts as a co-factor for fibrosis progression in other causes of chronic liver diseases, contributing thus to the development of cirrhosis. Recent projections estimate that NAFLD-related cirrhosis will increase by 64%–156% (depending on the country) by 2030 [6]. Therefore, it is anticipated that the management of diabetes in patients with cirrhosis will become an increasingly frequent clinical situation. Given the strong relationship between T2DM and cirrhosis, together the French Association for the Study of the Liver (AFEF) and the Francophone Diabetes Society (SFD) decided to establish a group of experts aimed at promoting research, education and patient care in the field of liver diseases and diabetes (**Table S1; see supplementary materials associated with this article on line**). The first work of this expert panel was to address T2DM management in the specific context of cirrhosis. The panel identified key relevant topics requiring focus with respect to T2DM management in patients with cirrhosis. Following, three–four experts were assigned to each topic to put forward guidance based on a literature review. All experts met on five occasions to discuss and approve the statement. The final manuscript was approved by all experts.

Definitions

Liver cirrhosis corresponds to a heterogeneous entity that encompasses different disease stages, ranging from asymptomatic patients with normal liver function to end-stage liver disease. Numerous terms and classifications are used to describe the different stages of cirrhosis, such as "compensated vs decompensated" cirrhosis, or "preserved versus altered" liver function. The well-known Child-Pugh score (**Table S2; see supplementary materials associated with this article on line**) stratifies cirrhosis into three classes (A, B, C) according to clinical signs of cirrhosis decompensation (ascites, encephalopathy) and liver function tests (bilirubin, albumin, prothrombin time). The complexity lies in the fact that the different terms used can correspond to different or overlapping situations. Therefore, to ensure the correct translation of the present statement for clinical practice, the experts first decided to agree on definitions and to recapitulate in a single table the different terms generally used by physicians. The experts agreed that patients with "compensated" and "Child-Pugh A" cirrhosis include two distinct patient profiles: those with preserved (i.e., normal) liver function and those with slightly impaired liver function (i.e., bilirubin higher than the upper limit of normal, prothrombin time below 80% or patients with a history of cirrhosis decompensation). Finally, four categories were established and lead to use of the following terms in the present manuscript: "preserved", "slightly impaired", "moderately impaired" and "severely impaired" liver function (Table 1). The term "impaired liver function" encompasses all "slightly impaired", "moderately impaired" and "severely impaired" liver function.

Epidemiology and impact of type 2 diabetes mellitus in patients with cirrhosis

The presence of liver cirrhosis is associated with significant impairment in glucose homeostasis [7]. The principal mechanism responsible for glucose abnormalities in patients with cirrhosis is a defect in glucose uptake that produces marked and sustained hyperglycaemia [8]. The reported prevalence of diabetes in patients with cirrhosis ranges from 14–71 % (Table 2) [9-16], depending on the aetiology, liver disease severity, as well as the methods used for the diagnosis of diabetes. In patients with cirrhosis, the main factors associated with the presence of T2DM are age, overweight and a family history of T2DM [11]. Recently, a systematic review on the prevalence of T2DM in patients with cirrhosis (58 studies including a total of 9705 patients) found an overall prevalence of 30.7% (95% confidence interval 27.9–33.5%) [3]. Interestingly, the highest prevalence of diabetes in this study was reported in patients with NAFLD (56%) and cryptogenic-cirrhosis (51%), compared to 32% in patients with hepatitis C infection or 27% in alcoholic cirrhosis [3]. On the other hand, the prevalence of cirrhosis among patients with diabetes has been primarily investigated in the context of NAFLD. An Australian retrospective study in 284 patients with biopsy-proven NAFLD found a prevalence of 28% for cirrhosis in patients with T2DM vs 6% in those without ($p < 0.001$) [17]. A recent meta-analysis in patients with T2DM and biopsy-proven NAFLD has estimated the overall prevalence of advanced fibrosis at 17% (95% CI: 7.2–34.8) [4]. However, the selection of patients with biopsy-proven NAFLD and attending diabetic clinics likely overestimated these rates of advanced fibrosis/cirrhosis. Finally, in a community-based cohort of 705 subjects with diabetes, the prevalence of cirrhosis defined by liver stiffness >13 kPa was estimated at 2.1% [18]. Daily alcohol intake and metabolic disorders were associated with increased liver stiffness.

Most clinical studies do not make the distinction between T2DM associated with cirrhosis and hepatogenous diabetes. Hepatogenous diabetes is considered a consequence of cirrhosis, implying that diabetes develops after cirrhosis onset (**Table S3; see supplementary materials associated with this article on line**). In a Mexican retrospective study with the aim of distinguishing between these two types of diabetes in 130 patients with cirrhosis, 40% of patients had diabetes and half had hepatogenous diabetes [9]. Patients in whom diabetes was identified before cirrhosis had a different clinical profile to those with hepatogenous diabetes. Indeed, patients with diabetes had a higher prevalence of cryptogenic cirrhosis, renal impairment, family history of diabetes and hypertriglyceridaemia when compared to those with hepatogenous diabetes. Patients with hepatogenous

Table 1
Definitions.

Liver function[a]		Child-Pughscore (points)	Severity of cirrhosis	History of complications of cirrhosis [b]	Clinical characteristics	Prothrombin time (%)	Bilirubin (μmol/l)
Preserved		A (5)	Compensated	No	0	80–100	<17
Impaired	Slightly impaired	A (6)	Compensated	Yes	0	50–80	17–35
	Moderately impaired	B (7–9)	Decompensated	Yes	Ascites	40–50	35–50
	Severely impaired	C (10–15)	Decompensated	Yes	Ascites and/or HE	<40	>50

HE, hepatic encephalopathy.
[a] Terms used throughout the manuscript.
[b] Ascites, jaundice, variceal bleeding, hepatorenal syndrome, encephalopathy.

Table 2
Prevalence of type 2 diabetes mellitus among patients with cirrhosis.

Study	Year	Patients(*n*)	Design	Setting	Diagnostic criteria	Prevalence of T2DM (%)
Bianchi [13]	1994	354	Retrospective, prospective Single centre	Alcohol; decompensated cirrhosis	Overt glycosuria and postabsorptive glycaemia	98 (27.6%)
Zein [10]	2000	204	Retrospective Single centre	End-stage liver disease (chronic hepatitis C, alcohol) before liver transplantation	FPG	28 (13.7%)
Holstein [14]	2002	42	Prospective Single centre	56% Child-Pugh B and C alcoholic cirrhosis	FPG + OGTT	37 (71%)
Nishida [15]	2006	56	Prospective Single centre	Chronic hepatitis C; decompensated cirrhosis	FPG + OGTT	21 (38%)
Garcia-Compean [9]	2012	130	Retrospective Single centre	Alcohol and NASH-related cirrhosis; 50% compensated	FPG + OGTT	43 (40.7%)
Petit [11]	2014	1068	Prospective Multicentre	Alcohol, chronic hepatitis C or NASH-related cirrhosis; 52% compensated (35% with hepatocellular carcinoma)	FPG	412 (39.7%)
Marselli [12]	2016	300	Retrospective Single centre	End-stage liver disease (chronic hepatitis B or C, NAFLD) before liver transplantation	FPG + OGTT	105 (35%)
Vilar-Gomez [16]	2020	299	Retrospective International multicentre cohort	Biopsy-proven compensated NASH-related cirrhosis	FPG + HbA1c + anti-hyperglycaemic drugs	212 (71%)

T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

diabetes also seem to have a lower risk of diabetes complications, but this could be related to increased mortality due to liver disease-related complications [19].

Alternatively, patients with diabetes and cirrhosis could have pancreatic diabetes which is commonly misdiagnosed as T2DM [20]. A distinguishing feature is concurrent pancreatic exocrine insufficiency that could be diagnosed by performing faecal elastase 1 test. Chronic alcoholism is a well-known aetiologic factor associated with chronic pancreatitis and liver cirrhosis, and both diseases could be associated with diabetes mellitus. Even though the frequency of the association between alcoholic chronic pancreatitis and liver cirrhosis is low, it is important to rule out diabetes secondary to alcoholic pancreatitis in people with cirrhosis [21].

Cirrhotic patients with diabetes have a higher incidence of liver disease-related complications, including death, versus cirrhotic patients without diabetes. Several prospective and retrospective studies [13,15,16,22-27] have shown that survival was significantly lower in cirrhotic patients with diabetes compared to those without diabetes (Table 3). Most of these studies were performed in patients with either chronic hepatitis C infection or alcoholic cirrhosis, some of them being decompensated at baseline. For instance, in a prospective cohort of 250 patients with compensated chronic hepatitis C-related cirrhosis without known diabetes at baseline, overall mortality, liver transplantation, and hepatic decompensation events were significantly more frequent in patients with diabetes compared to those without. In this study, diabetes was assessed by the oral glucose tolerance test (OGTT) [24]. In a prospective community-based cohort of 63,275 subjects in Singapore, diabetes was associated with an increased risk of cirrhosis-related mortality, especially for cases with non-viral hepatitis-related cirrhosis [28]. In a very recent international cohort of 299 patients with Child-Pugh class A cirrhosis due to non-alcoholic steatohepatitis (NASH), T2DM increased the risk of death (adjusted hazard ratio: 4.23, 95% confidence interval: 1.93−9.29) during a median follow-up of five years. The presence of T2DM also increased the risk of liver-related outcomes (adjusted hazard ratio: 2.03, 95% confidence interval: 1.005−4.11), including hepatocellular carcinoma (HCC) (adjusted hazard ratio: 5.42; 95% confidence interval: 1.74−16.80) [16]. Thus, although glucose metabolism abnormalities are not included in the most widely used prognostic tools, including that of the Child-Pugh and MELD scoring systems (**Table S2; see supplementary materials associated with this article on line**), diabetes appears to be a major predictor of mortality in patients with cirrhosis.

1. **Diabetes is highly prevalent in patients with cirrhosis and is an independent risk factor for poor prognosis. Diabetes is associated with the occurrence of major complications of cirrhosis, including ascites, encephalopathy, renal dysfunction, bacterial infection and hepatocellular carcinoma. Therefore, patients with cirrhosis should be systematically screened for diabetes.**

Diagnosis of diabetes in patients with cirrhosis

Diabetes can be diagnosed based on plasma glucose criteria, either by fasting plasma glucose (FPG) or the 2-hour plasma glucose value during a 75-g OGTT (2h-PG), or based on glycated haemoglobin (HbA1c) criteria [20]. However, cirrhosis is associated with significant modifications in the sensitivity of these methods of diabetes diagnosis. An FPG cut-off value of 126 mg/dL is associated with weak performance for the diagnosis of diabetes in patients with cirrhosis. For example, Imano et al. analysed FPG and 2h-PG in 60 patients with compensated liver cirrhosis due to chronic hepatitis C [29]. They showed that 21% of patients with cirrhosis presenting with a normal FPG were classified as having diabetes according to the OGTT with increased 2h-PG [29]. Furthermore, the OGTT performed in 80 patients with cirrhosis and normal FPG in a Mexican study allowed for the identification of diabetes in 20.7% of patients [9]. In this light, Nishida et al. even proposed a reduction of the FPG level to 107 mg/dL for the diagnosis of diabetes in patients with cirrhosis [30].

HbA1c measurement is the gold standard for monitoring blood glycaemic control in diabetes. The American Diabetes Association (ADA) proposed using HbA1c values ≥6.5% (48 mmol/mol) for the diagnosis of diabetes [20]. In conditions associated with an altered correlation between HbA1c and glycaemia, such as sickle cell disease, pregnancy (second and third trimesters, and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, human immunodeficiency virus infection, haemodialysis, recent blood loss or transfusion, or erythropoietin therapy, the ADA suggests exclusive use of FPG criteria for diagnosing diabetes. It is also important to consider alcohol consumption which may decrease HbA1C level

Table 3
Impact of type 2 diabetes mellitus on long-term survival in patients with cirrhosis.

Study	Year	Patients(*n*)	Design	Setting	Follow-up	Survival in patients with diabetes vs without diabetes	*P* value
Bianchi [13]	1994	354	Retrospective, prospective Single centre	Alcohol; decompensated cirrhosis	37 months	64 vs 82%	0.005
Moreau [27]	2004	75	Prospective Single centre	Refractory ascites	2 years	18 vs 58%	0.0004
Nishida [15]	2006	56	Prospective Single centre	Chronic hepatitis C; decompensated cirrhosis	5 years	56 vs 92%	< 0.05
Jaquez-Quintana [26]	2011	110	Prospective Single centre	Alcohol and NASH; half compensated	2.5 years	48 vs 69%	< 0.05
Garcia-Compean [23]	2014	100	Prospective Single centre	Alcohol, NASH or hepatitis C-related cirrhosis; 47% compensated	5 years	32 vs 72%	0.02
Elkrief [22]	2014	348	Retrospective Single centre	Chronic hepatitis C; cirrhosis hospitalised for decompensation	4.5 years	24 vs 34%	0.03
Calzadilla-Bertot [24]	2016	250	Prospective Single centre	Chronic hepatitis C; compensated cirrhosis	4 years	82 vs 91%	0.04
Vilar-Gomez [16]	2020	299	Retrospective International multicentre cohort	Biopsy-proven compensated NASH-related cirrhosis	5 years	38 vs 81%	< 0.01

independently of blood glucose [31]. Although cirrhosis is not considered a pathological state requiring the avoidance of using HbA1c to diagnose diabetes [20], a retrospective study identified liver cirrhosis as a main medical condition that could potentially explain a decrease in HbA1c levels [32]. In this study, 58% of HbA1c values lower than the normal range were linked to liver cirrhosis. In addition, Lahousen et al. showed that 40% of patients with cirrhosis had HbA1c levels below the non-diabetic reference range [33]. The mean HbA1c values in patients with cirrhosis and with normal glycaemic control were significantly lower compared to healthy control individuals [34]. In the same way, it has been reported that HbA1c levels in patients with comorbid cirrhosis and T2DM were lower than those in patients with T2DM [30]. Interestingly, using continuous glucose monitoring (CGM), Addepally et al. identified 14% of patients with diabetes among a group of cirrhotic patients without prior diabetes diagnosis according to both OGTT and HbA1c results [35]. HbA1c level is directly proportional to glucose concentration, but also to the lifespan of red blood cells [36]. In cirrhosis, several factors can affect HbA1c levels, such as anaemia, hypersplenism, gastrointestinal bleeding or vitamin deficiency. Therefore, HbA1c is not a reliable marker for the diagnosis of diabetes in patients with cirrhosis and impaired liver function.

2. **In patients with cirrhosis and preserved liver function, the diagnosis of diabetes relies on the same tests (fasting plasma glucose, HbA1c) as used in patients without cirrhosis.**
3. **In patients with cirrhosis and impaired liver function or anaemia, HbA1c is not recommended due to the risk of underestimation leading to false negative results.**
4. **In patients with cirrhosis and impaired liver function, an oral glucose tolerance test (75g glucose) with a 2-hour plasma glucose value is recommended for the diagnosis of diabetes in addition to fasting plasma glucose.**

Glucose monitoring and the glycaemic target in patients with cirrhosis

How is glycaemic control monitored in patients with diabetes and cirrhosis?

Monitoring glycaemic control using HbA1c levels or fructosamine measurements in patients with cirrhosis has significant limitations. These limitations must be acknowledged to avoid misunderstanding of the results that can lead to inappropriate treatment decisions. In a recent study, Addepally et al. investigated the accuracy of HbA1c levels for monitoring glycaemic control in patients with cirrhosis compared to actual blood glucose level assessed by CGM over a 12-week period [35]. This study did not support HbA1c measurement as an accurate method for monitoring diabetes in patients with cirrhosis given the association between HbA1c and CGM values was altered in these patients and the relationship between HbA1c level and plasma glucose level was affected by the degree of liver dysfunction [35]. Using CGM, another study evaluated the glycaemic variability in patients with T2DM and with chronic hepatitis compared to patients with T2DM and cirrhosis Child-Pugh class A or B/C [37]. Although HbA1c levels were significantly lower in the Child-Pugh class B/C group than in the chronic hepatitis group, the mean blood glucose measured by CGM was significantly higher in patients with Child-Pugh class B/C cirrhosis [37]. These results confirm that HbA1c measurement must be used with caution for monitoring glycaemic control in patients with diabetes and cirrhosis, especially in the case of severe liver disease. Nadelson et al. compared measured HbA1c values with HbA1c levels estimated on the ADA calculator website in 200 patients with decompensated cirrhosis. The authors also concluded a discordance in HbA1c values in patients with decompensated cirrhosis [38]. Therefore, this study indicates that HbA1c levels are not a reliable predictor of glycaemic control in patients with decompensated cirrhosis, and especially not in those with severe anaemia [38].

Fructosamine is a biological marker of plasma glycaemic control that is less standardised and less frequently used than HbA1c. Patients with cirrhosis frequently have hypoalbuminaemia that is correlated with liver disease severity. Hypoalbuminaemia leads to impaired degradation of albumin which results in a significantly increased half-life of albumin in patients with cirrhosis. Increased albumin half-life is linked to an increase in plasma fructosamine concentration, as previously described by Trenti et al. [34]. This could explain the findings of Addepally et al. Here, the authors studied patients with diabetes and cirrhosis and found that the association between fructosamine and CGM glucose geometric means was even weaker than the aforementioned association observed between HbA1c and CGM glucose values [35]. Consequently, fructosamine cannot be a valuable alternative for monitoring glycaemic control in patients with advanced liver disease.

Checking fingerstick capillary blood glucose at different times of the day could be of particular interest in patients with cirrhosis [39]. Self-monitoring of blood glucose can be an alternative way to assess

glycaemic control in patients with decompensated cirrhosis or anaemia in whom HbA1c or fructosamine levels are unreliable. Cirrhosis is characterised by reduced hepatic glycogen content and patients with cirrhosis exhibit increased gluconeogenesis that can contribute to sarcopaenia [40]. Nocturnal hypoglycaemia, induced by some glucose-lowering drugs, also increases gluconeogenesis and could likewise contribute to sarcopaenia. This encourages the implementation of optimal glycaemic monitoring for the detection of hypoglycaemic events, which are common in patients with liver cirrhosis. Using CGM, nocturnal hypoglycaemia was identified in 20% of patients with HbA1c levels above 7.0% (53 mmol/mol) and in 34% of non-anaemic patients with HbA1c levels below 7.0% [37]. Temporary or permanent use of CGM systems are thus valuable for estimating glycaemic control and for detecting nocturnal hypoglycaemia in patients with cirrhosis, especially in patients treated with anti-hyperglycaemic drugs, such as insulin. Of note, a recent study investigated the performance of a flash glucose monitoring system and demonstrated the usability of this mode of glucose monitoring in patients with diabetes mellitus and liver cirrhosis [41]. Alcohol intake has been associated with a higher risk of hypoglycaemia in patients with T2DM treated with insulin [42] or sulphonylureas [43,44]. Therefore, hypoglycaemia should be closely monitored in these patients.

5. **HbA1c must be used with caution for monitoring glycaemic control in patients with cirrhosis and diabetes. HbA1c is an unreliable indicator of glycaemic control in patients with cirrhosis and anaemia and/or impaired liver function.**
6. **Fructosamine is an unreliable indicator of glycaemic control in patients with cirrhosis and hypoalbuminaemia.**
7. **Self-monitoring of capillary blood glucose appears to be a good alternative in patients with cirrhosis and moderately/severely impaired liver function. Continuous glucose monitoring can detect nocturnal hypoglycaemia in patients with cirrhosis, especially those treated with anti-hyperglycaemic drugs, such as sulphonylureas, glinides or insulin.**

What is the glycaemic target for patients with cirrhosis?

There is ample evidence, as described above, that diabetes has a negative impact on the survival of patients with cirrhosis [13,15,16,19,22-26]. Diabetes increases the incidence of liver-related complications in patients with cirrhosis. It seems thus important to adapt anti-hyperglycaemic therapies with the aim to prevent/avoid cirrhosis−related complications rather than classical diabetes-related complications. Considering the drawbacks of HbA1c evaluation, it would be better to use glycaemic targets adapted from self-monitoring of blood glucose in patients with cirrhosis and impaired liver function. In the case of preserved liver function, the current guidelines for T2DM management (personalised HbA1c targets, self-monitoring of blood glucose in patients treated with sulphonylureas, glinides or insulin) should be followed for glycaemic target achievement, similar to patients without cirrhosis [20,45]. In patients with cirrhosis and impaired liver function, prognosis is primarily driven by liver-related complications rather than diabetes complications [13,15,16,19,22-26]. In these patients, fasting (pre-meal) capillary blood glucose should be maintained between 100 and 200 mg/dL (5.5−11.0 mmol/l), especially in those who require insulin therapy (Table 4). Indeed, inappropriate up-titration of insulin doses might lead to increased risk of hypoglycaemia, especially in the late post-prandial state following rapid acting insulin administration.

8. **For patients with cirrhosis and preserved liver function, the current guidelines for T2DM management should be followed for glycaemic target achievement, similar to patients without cirrhosis.**
9. **In patients with cirrhosis and impaired liver function, prognosis is primarily driven by liver-related complications rather than diabetes complications.**
10. **In patients with cirrhosis and moderately/severely impaired liver function, glycaemic targets under insulin therapy should be adjusted to maintain pre-meal values between 100 and 200 mg/dL (5.5−11.0 mmol/l).**

Anti-hyperglycaemic treatment

Biguanides

Metformin has limited passive diffusion through the membranes of hepatocytes and does not undergo hepatic metabolism. Its elimination is essentially renal, and no metabolites or conjugates of this drug have been identified [46]. Liver impairment should not interfere with the pharmacokinetics of metformin, but no specific pharmacokinetic studies have been performed in patients with chronic liver disease [47]. Metformin does not appear to cause or exacerbate liver injury, in contrast it can be beneficial for patients with NAFLD [48]. Metformin-associated metabolic acidosis in patients with chronic liver disease is largely represented by case reports in the literature, with most patients presenting with cirrhosis and some degree of renal impairment [49].

In a recent large nationwide case-control study, the use of metformin was associated with a decreased risk of HCC in patients with T2DM in a dose-dependent manner. Each incremental year increase in metformin use resulted in a 7% reduction in the risk of HCC (adjusted odds ratio: 0.93, $p < 0.0001$), even after adjusting for several confounding factors, including the presence of cirrhosis and different causes of chronic liver disease. The authors did not find any protective effect in the subset of patients with hepatitis B or C infection [50]. Another study comprised of matched cohorts of 21,900 ever-users and 21,900 never-users of metformin showed a hazard ratio of 0.76 (0.67−0.85), suggesting that metformin was associated with a reduced risk of HCC in a dose-response pattern [51]. Three studies have found a trend between lower all−cause mortality and metformin use in patients with T2DM and histologically confirmed cirrhosis [52-54]. A positive association between metformin use and survival was also reported in patients with cirrhosis due to NASH, but not in other causes, such as alcohol use or viral hepatitis infection [52]. A meta−analysis of ten studies showed a 50% reduction in HCC incidence due to metformin use in a total of 334,307 patients with

Table 4
Monitoring of glycaemic control in patients with cirrhosis and type 2 diabetes mellitus.

Liver function	Child-Pughscore (points)	Severityof cirrhosis	Assessment of glycaemic control	Glycaemic target
Preserved	A (5)	Compensated	HbA1c	Personalised HbA1c according to ADA and EASD guidelines **
Slightly impaired	A (6)		(self-monitoring of blood glucose*)	
Moderately impaired	B (7−9)	Decompensated	Self-monitoring of blood glucose	Under insulin therapy: pre-prandial plasma glucose between 100 and 200 mg/dl (5.5−11.0 mmol/l)
Severely impaired	C (10−15)			

Self-monitoring is based on capillary or interstitial glucose measurements.
* In patients treated with sulphonylureas, glinides or insulin.
** Target in patients without comorbidities: HbA1c < 7.0% (53 mmol/mol) without significant hypoglycaemia [20, 45].

T2DM, including 22,650 cases of HCC [55]. Compared to sulphonylureas or insulin treatment, metformin was associated with a significantly lower risk of HCC in both cirrhosis (odds ratio: 0.16, $p = 0.0006$) and control (odds ratio: 0.15; $p = 0.005$) groups [56]. In this study, poor glycaemic control in the cirrhosis group was associated with a significantly higher risk of HCC (odds ratio: 1.51, $p = 0.0005$). The observation that a protective effect of metformin was only reported in NASH-related cirrhosis could be due to the pleiotropic effects of metformin in cell proliferation and differentiation, apoptosis and inflammation, as well as glucose metabolism and lipid metabolism pathways [57]. A study conducted in patients with T2DM and biopsy-proven NASH with bridging fibrosis or compensated cirrhosis recruited 110 users and 81 never-users of metformin [58]. The primary endpoints were transplant-free survival, development of HCC or a first hepatic decompensation event. The ten-year cumulative incidence of HCC was significantly lower in metformin users compared to non-users (hazard ratio: 0.25; $p < 0.01$). The cumulative transplant−free survival rate at ten years was significantly lower in non−users (35%) than users (65%) of metformin, and the protective effect of metformin remained similar when adjusted for fibrosis severity, age and sex (hazard ratio: 0.47, $p = 0.010$). In another report, metformin use was found to be protective against hepatic encephalopathy in diabetic cirrhotic patients by a mechanism of inhibition of glutaminase activity in vitro [53].

In summary, epidemiological and clinical studies report that the use of metformin in patients with T2DM and cirrhosis is associated with an increased rate of survival, reduced all-cause mortality and a reduction in the risk of HCC development. It seems reasonable to discontinue metformin in patients with moderately/severely impaired liver function in order to avoid complications of lactic acidosis, and to consider patients with multiple comorbidities as patients at high risk of lactic acidosis [59].

11. **Metformin can be used in patients with cirrhosis and preserved/slightly impaired liver function. Dosage should be adapted to renal function.**
12. **Some studies suggest that metformin can reduce HCC occurrence in patients with cirrhosis.**
13. **Metformin should be discontinued in patients with cirrhosis and moderately/severely impaired liver function.**

Pioglitazone

Thiazolidinediones (pioglitazone and rosiglitazone) are insulin sensitizers, which are ligands for the peroxisome proliferator-activated receptor (PPAR)-γ transcription factor [60]. In many countries, pioglitazone remains the only drug of this class available for clinical use. In a meta-analysis, pioglitazone demonstrated its efficacy in the pharmacological management of NASH, with increased NASH resolution and improved liver fibrosis [61]. However, the clinical use of thiazolidinediones is limited by the occurrence of several adverse events, including body weight gain, congestive heart failure and bone fractures [60]. Pioglitazone is metabolised in the liver rather than the kidney, mainly by CYPC28 and to a lesser extent by CYP3A4 in vitro [62]. There have been no specific pharmacokinetic studies reporting on pioglitazone use in patients with impaired liver function or cirrhosis. However, a report from the United States Food and Drug Administration has stated that subjects with impaired liver function (Child-Pugh B/C) have a 45% reduction in pioglitazone mean peak concentrations without changes in mean area under the concentration-time curve (AUC) values compared to healthy subjects [47].

Among the randomised placebo-controlled trials performed on the evaluation of pioglitazone for the treatment of NASH, almost all patients included had no liver cirrhosis [63-67]. A post-marketing surveillance study was performed in Japan between December 1999 and March 2004. It included 25,000 patients with T2DM, among whom it can be assumed were also patients with cirrhosis, from 4093 institutions. There were no cases of hepatic failure reported, and 19 patients had liver reactions assessed as serious by the reporting physicians [68]. Very recently, a propensity score analysis performed in Taiwan's National Health Insurance Research Database cohort compared clinical outcomes between patients with T2DM and cirrhosis using or not using thiazolidinediones. In this study, use of thiazolidinediones was not associated with an increased risk of all-cause mortality, HCC, or decompensated cirrhosis. It is noteworthy that use of thiazolidinediones was found associated with a higher risk of cardiovascular events (coronary heart disease, stroke, heart failure), but this risk was mainly attributable to rosiglitazone, with pioglitazone having a neutral effect [69].

14. **Pioglitazone can be used in patients with cirrhosis and preserved/slightly impaired liver function, in countries where this drug is available for clinical practice.**
15. **Due to its side effects (fluid retention, heart failure), pioglitazone should be avoided in patients with cirrhosis and moderately/severely impaired liver function.**

Sulphonylureas and glinides

Sulphonylureas (second and third generation)

Sulphonylureas decrease blood glucose levels by stimulating insulin secretion in a glucose-independent manner. Thus, the inherent and major risk of sulphonylureas is severe hypoglycaemia, which is a life-threatening complication in patients with T2DM. While sulphonylureas have been used for over 40 years, studies on the pharmacodynamics and pharmacokinetics of sulphonylureas are lacking in patients with impaired liver function [47]. Sulphonylureas are metabolised in the liver into active and inactive metabolites via cytochrome P450 (CYP450) enzymes. Sulphonylureas are extensively bound to serum proteins and excreted mainly through the renal pathway. Protein binding of sulphonylureas can be reduced in hypoalbuminaemia, increasing plasma concentrations of unbound sulphonylureas and resulting in a higher risk of hypoglycaemia. Finally, patients with cirrhosis are often malnourished, with a reduced gluconeogenic capacity leading to an impaired counter-regulatory response to hypoglycaemia. Patients who do not abstain from alcohol should be very cautious when taking sulphonylureas, as alcohol intake increases the risk of hypoglycaemia in these patients by inhibiting hepatic gluconeogenesis.

Glibenclamide is inactivated in the liver via CYP3A4 and elimination of the drug appears to be divided equally between biliary and renal routes [47,70,71]. Glimepiride is metabolised by CYP2C9, and it has been suggested in low-quality studies that its pharmacokinetics are unaltered in patients with chronic liver disease, with fewer and less severe adverse effects than glibenclamide [47,72]. Gliclazide is metabolised in the liver via CYP2C9 and CYP2C19 into inactive metabolites which are eliminated mainly in urine (80%) [73]. There are no data on the pharmacokinetics of gliclazide in patients with chronic liver disease. Glipizide is metabolised via CYP2C9 and to a lesser extent CYP2C19 [74]. Glipizide has the shortest half-life (2−4 h) amongst all sulphonylureas. It has been suggested that glipizide can be preferred in patients with impaired liver function [75], but adequate pharmacokinetic studies are lacking. Manufacturer prescribing information for all sulphonylureas suggests cautious use in patients at higher risk of hypoglycaemia, including with impaired liver function. The position statement from the ADA and the European Association for the Study of Diabetes (EASD) also recommends

avoiding sulphonylureas in severe liver disease due to the risk of hypoglycaemia [45].

Glinides

Glinides are glucose-independent insulin secretagogues that produce a rapid and short-lived insulin output. Compared to sulphonylureas, glinides (repaglinide and nateglinide) are characterised by a shorter half-life, as well as by the absence of significant renal excretion [76,77]. Glinides are completely metabolised by oxidative biotransformation (CYP450) and conjugation with glucuronic acid in the liver. Importantly, pharmacokinetics differs between repaglinide and nateglinide in patients with chronic liver disease [47].

The pharmacokinetics of a single 4 mg dose of repaglinide was assessed in an open-label, parallel-group study on both healthy individuals and patients with chronic liver disease [78]. Repaglinide clearance was significantly reduced in patients with impaired liver function. Rare case reports of either acute hepatotoxicity or cholestatic hepatitis have also been reported with repaglinide use [79,80]. In contrast to repaglinide, no major pharmacokinetic alterations of nateglinide have been reported in patients with mild to moderate hepatic insufficiency. Indeed, while T_{max} and mean $t_{1/2}$ values were comparable to healthy controls, exposure was slightly increased in patients with cirrhosis: +30% for AUC and +37% for maximum plasma concentration (C_{max}) [81]. However, no data are available in patients with severely impaired liver function [47].

It should be mentioned here that neither sulphonylureas nor glinides have demonstrated a cardiovascular benefit in patients with T2DM. They are not recommended as first- or even second-line therapy for diabetes management according to ADA/EASD guidelines [45] due to their associated risk of hypoglycaemia.

16. **Sulphonylureas and glinides can be used in patients with cirrhosis and preserved liver function. They should be avoided in patients with high risk of hypoglycaemia.**
17. **Sulphonylureas can be used with caution in patients with cirrhosis and slightly impaired liver function, but at lower doses to avoid hypoglycaemia.**
18. **Sulphonylureas are contraindicated in patients with cirrhosis and moderately/severely impaired liver function.**
19. **Repaglinide is contraindicated in patients with cirrhosis and impaired liver function.**
20. **Nateglinide can be used with caution in patients with cirrhosis and slightly/moderately impaired liver function, but at lower doses to avoid hypoglycaemia.**

DPP-4 inhibitors

DPPA-4 inhibitors are glucose-dependent insulin secretagogues. In contrast to sulphonylureas and glinides, they do not result in a risk of hypoglycaemia. Sitagliptin, primarily excreted by renal elimination, has shown similar pharmacodynamic parameters (AUC0-∞, Cmax, time to Cmax) in patients with cirrhosis and moderately impaired liver function compared to control subjects [82]. The AUC0-∞ of saxagliptin was 10% and 38% higher in patients with slightly and moderately impaired liver function, respectively, whereas the AUC0-∞ of its active catabolite (5-hydroxy saxagliptin) was decreased by 22% and 7% in the same patient groups, respectively [83]. Indeed, the increased exposure of the parent drug, saxagliptin, appears to be compensated by a decreased exposure to its active metabolite. Another study showed that the AUC0-∞ for linagliptin after a seven-day treatment showed no difference in patients with slightly and moderately impaired liver function compared to controls [84]. Likewise, in patients with moderately impaired liver function, the AUC0-∞ and the Cmax of alogliptin showed no differences from those in healthy individuals [85]. Finally, in patients with mild and moderately impaired liver function, the AUC0-∞ and Cmax for vildagliptin were slightly reduced compared to controls [86]. However, it should be noted that vildagliptin prescribing information stipulates that it should not be used in patients with impaired liver function, including patients with pre-treatment ALT or AST >3x the upper limit of normal.

21. **Vildagliptin should not be used in patients with cirrhosis and impaired liver function.**
22. **Sitagliptin, linagliptin, saxagliptin and alogliptin can be used in patients with cirrhosis and slightly/moderately impaired liver function.**
23. **DPP-4 inhibitors are not recommended in patients with cirrhosis and severely impaired liver function.**

SGLT2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a new class of drugs that reduce blood glucose levels by increasing urinary glucose excretion. In addition to their glucose-lowering effect with no risk of hypoglycaemia, SGLT2i offer cardiovascular and renal benefits [87]. SGLT2i are currently indicated in Europe and the United States as first- or second-line treatments of T2DM in patients with established cardiovascular disease, high/very high cardiovascular risk, chronic kidney disease or heart failure according to ADA/EASD guidelines [45]. Accumulated evidence from both pre-clinical studies and proof-of-concept clinical studies has suggested a potential beneficial effect of SGLT2i in NAFLD pathogenesis [88]. However, the impact of SGLT2i on liver histology remains to be determined.

Canagliflozin, dapagliflozin and empagliflozin are available on the market. SGLT2i undergo extensive hepatic metabolism mainly via glucuronidation, and small amounts of metabolite are eliminated through the renal route [89]. In a single dose pharmacokinetic study, systemic exposure to dapagliflozin in subjects with chronic liver disease was increased compared to healthy subjects, and the increase was correlated with the degree of liver function impairment [90]. This accumulation is further increased in the case of concomitant renal impairment and caution is recommended in this situation [47]. Similarly, exposure to empagliflozin progressively but modestly (< 2-fold) increased with the severity of liver function impairment [91]. While meta-analysis and review reports from large phase 2–3 trials have shown that SGLT2i do not cause hepatotoxicity, their long-term safety profile and efficacy have not been studied specifically in patients with cirrhosis. Some risks of dehydration and hypotension, as well as euglycaemic ketoacidosis (especially in patients with advanced T2DM under insulin therapy) are associated with SGLT2i use. Hence, caution is required.

24. **There are insufficient data on SGLT2 inhibitors in patients with cirrhosis. Pharmacological studies suggest increasing accumulation with decreasing liver function.**

Acarbose

Alpha-glucosidase inhibitors are competitive inhibitors of enzymes required for carbohydrate digestion, and specifically alpha-glucosidase enzymes in the brush border of the small intestines. Acarbose and miglitol, available in many countries, reduce HbA1c to a lesser extent (around -0.5%) vs other anti-hyperglycaemic drugs and primarily act on post-prandial hyperglycaemia [92]. Thus, it

should be kept in mind that the hypoglycaemic efficacy of alpha-glucosidase inhibitors is modest compared to other anti-hyperglycaemic therapies and they should not be first intention in the case of severely uncontrolled T2DM. In a large trial evaluating cardiovascular outcomes, acarbose did not reduce the risk of major adverse cardiovascular events [93].

Alpha-glucosidase inhibitors are exclusively metabolised within the gastrointestinal tract with low systemic bioavailability. Although there are no pharmacokinetic or pharmacodynamic studies specifically dedicated to alpha-glucosidase inhibitors, clinical trials have demonstrated that acarbose can be safely and effectively used in patients with diabetes and chronic liver disease, alcoholic cirrhosis, well-compensated non-alcoholic cirrhosis and low-grade hepatic encephalopathy [94-97]. However, some cases of hyperammonaemia have been reported in patients with advanced liver cirrhosis [47].

25. **Acarbose is safe in patients with cirrhosis and slightly/moderately impaired liver function.**
26. **Acarbose should be avoided in patients with cirrhosis and severely impaired liver function due to an insufficient benefit-risk ratio.**
27. **Acarbose should be avoided in patients with cirrhosis and severely uncontrolled diabetes given its insufficient hypoglycaemic efficacy.**

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) decrease blood glucose by stimulating insulin secretion and decreasing glucagon secretion in a glucose-dependent manner, thus avoiding the risk of hypoglycaemia. GLP-1 RAs also significantly reduce body weight by increasing satiety at the level of the central nervous system. Some GLP-1 RAs (liraglutide, dulaglutide, semaglutide) reduce major cardiovascular events and they are recommended as second-line therapy in patients with T2D and high atherosclerotic cardiovascular disease risk [45]. Note that GLP-1 RAs are contra-indicated in patients with a history of chronic pancreatitis.

Hepatic metabolism is not the main pathway for the elimination of GLP-1 RAs; exenatide is primarily eliminated by the kidney, whereas liraglutide and dulaglutide are totally degraded within the body via the action of DPP-4. Treatment with GLP-1 RAs is often associated with improvement in serum aminotransferase levels (and hepatic steatosis), making them potential treatments for NAFLD [98,99]. There are no pharmacokinetic studies on exenatide (either short- or long-acting) or lixisenatide in patients with impaired liver function found in the literature. A pharmacokinetic study performed with a single 0.75 mg dose of liraglutide in patients with slightly, moderately and severely impaired liver function did not show increased exposure to liraglutide [100]. Although the liraglutide development programme did not show any hepatotoxicity, clinical experience with liraglutide in patients with impaired liver function was limited. In a pharmacokinetic study, systemic exposure to dulaglutide was decreased by 23%, 33% and 21% for slightly, moderately and severely impaired liver function, respectively, compared to subjects with normal liver function [101]. A pharmacokinetic study was performed with semaglutide in 19 patients with normal liver function, eight patients with slightly impaired liver function, ten patients with moderately impaired liver function and seven with severely impaired liver function [102]. In this work, the pharmacokinetic parameters for semaglutide (AUC0-∞ and Cmax) showed no difference between the four groups. Since licensure, there have been no published case reports of semaglutide-induced hepatotoxicity.

28. **Due to lack of data, exenatide and lixisenatide should not be used in patients with cirrhosis and impaired liver function.**
29. **Liraglutide, dulaglutide and semaglutide can be used in patients with cirrhosis and preserved/slightly impaired liver function.**
30. **Due to lack of data, liraglutide, dulaglutide and semaglutide should be used with caution in patients with cirrhosis and moderately impaired liver function, especially in those at risk of malnutrition.**
31. **GLP-1 receptor agonists are not recommended in patients with cirrhosis and severely impaired liver function.**
32. **Nutritional evaluation is recommended in patients with cirrhosis before and a few weeks after GLP-1 receptor agonist initiation due to the risk of gastrointestinal disorders and malnutrition; this treatment should be discontinued in the event of severe gastrointestinal side effects.**

Insulin

The major site of insulin metabolism is the liver, with close to 40−50% of endogenous insulin produced by the pancreas being metabolised by the liver. Morphological and functional liver changes are associated with several disturbances in the metabolic clearance of insulin in patients with chronic liver disease, and changes in liver function can also affect the glucose-lowering effects of insulin. In patients with decompensated liver disease, insulin requirement can be decreased due to a reduced gluconeogenic capacity. However, patients with impaired liver function can also require high insulin doses due to insulin resistance [47], hyperglucagonaemia [103] and decreased hepatic clearance of portal glucose [104]. Therefore, trying to optimise glucose control, both in the fasting and post-prandial periods, is a real challenge in patients with T2DM and impaired liver function due to cirrhosis. These specific conditions can lead patients and physicians to up-titrate the insulin doses inappropriately, resulting in an increased risk of hypoglycaemia, particularly during the late post-prandial period. In summary, to minimise the incidence of hypoglycaemia in patients with cirrhosis who require insulin therapy, glycaemic targets must be personalised, and insulin doses (especially those of rapid acting insulins) must be carefully adjusted on an individual basis according to regular blood glucose monitoring.

Clinical studies with short-acting insulins

A study assessed insulin aspart metabolism in healthy subjects and non-diabetic patients with varying degrees of liver function [105]. All the subjects received a 0.06 unit/kg subcutaneous dose of insulin aspart followed by a standardised meal immediately after injection. There was no correlation between any of the pharmacokinetic variables analysed and the degree of liver impairment. In patients with T2DM and compensated chronic liver disease (Child-Pugh A−B), CGM for 12 weeks in a cross-over protocol was used to compare insulin lispro to regular human insulin [106]. At the end of each treatment period, a one-week CGM session was performed followed by a standard meal test with 12 units of regular human insulin (30 min before each meal) or bolus insulin lispro (5 min before each meal). As expected, insulin peaked higher and earlier with lispro, and glucose excursions and delta AUC were significantly lower after lispro. However, these pharmacokinetic variables were not affected by the degree of liver function impairment. The use of continuous subcutaneous insulin infusion using an insulin pump was also studied in patients with uncontrolled T2DM and cirrhosis. The authors noted a reduction in daily insulin doses without incidents, including severe hypoglycaemia, diabetic ketoacidosis or weight gain [107]. In summary, impaired liver function or chronic liver disease do

not influence the pharmacokinetics of lispro and aspart. There are no data are available regarding glulisine, faster aspart or ultra-rapid lispro.

Clinical studies with long-acting insulins

Patients with severely impaired liver function show a lower bioavailability of insulin determir compared to healthy controls [47]. Insulin detemir is considered as hepatoselective; it binds to albumin and is thus unable to pass through the capillary endothelial cell barrier to reach peripheral adipocytes, whereas the albumin-detemir complex can freely pass through liver sinusoids. This allows detemir to exert a greater effect on hepatocytes than in peripheral tissues. Hypothetically, the efficacy of this hepatoselective insulin could be reduced in cirrhosis via reduced hepatic exposure to insulin (due to increased insulin clearance or portosystemic shunting) or from direct liver parenchymal cell damage, finally leading to hyperglycaemia. This fact was highlighted in a recent paper reporting two different clinical cases of patients treated by detemir for whom insulin detemir appeared less efficacious [108]. In contrast, Kupcova et al. examined the single-dose (0.4 unit/kg) pharmacokinetics of insulin degludec in patients with different degrees of liver impairment (normal liver function, Child-Pugh scores A–C) compared to controls. There were no differences reported in pharmacokinetic variables (AUC, C_{max} and apparent clearance of insulin measured at 120 h post-dose) for subjects with impaired liver function compared to patients with preserved liver function [109]. The effects of impaired liver function on insulin glargine (U-100 and U-300) pharmacokinetics and pharmacodynamics have not been studied.

In summary, insulin therapy is one of the safest and most efficient agents for the treatment of diabetes in patients with cirrhosis and is thus often considered as first-line therapy in the case of moderately to severely impaired liver function. However, the recommendations are to monitor glucose and to adjust insulin doses regularly to limit the risk of hypo- and hyperglycaemia. The newer short- and long-acting insulins should be preferred over the older insulins in patients with cirrhosis because their pharmacokinetic properties are not altered despite impaired liver function [14].

33. **Insulin can be used in any patient with cirrhosis regardless of the level of liver function impairment.**
34. **Insulin titration needs to be monitored regularly in patients with cirrhosis to reduce the risk of hypoglycaemia.**
35. **The recommended insulin regimen in patients with cirrhosis comprises basal insulin alone or combined with prandial insulin.**
36. **For prandial insulin, fast-acting insulin analogues have unaltered pharmacokinetic properties in patients with cirrhosis and should therefore be preferred to regular rapid insulin in order to reduce the risk of hypoglycaemia.**

Management of obesity, malnutrition and sarcopaenia in patients with cirrhosis and type 2 diabetes mellitus

Very few studies have been conducted specifically in patients with T2DM and cirrhosis (particularly in patients with a cirrhotic NASH) regarding the management of overweight/obesity or malnutrition (used here with the significance of “undernutrition”).

Management of obesity in patients with cirrhosis and preserved liver function without malnutrition or sarcopaenia

In patients with cirrhosis who are overweight/obese, without malnutrition, not sarcopaenic and with preserved liver function, a management supporting weight loss can be proposed.

Lifestyle modifications. Like what is proposed for patients with NASH, caloric restriction maintaining carbohydrate intake between 50-65% to avoid iatrogenic hypoglycaemia could be set up. Protein intake should be carefully monitored to prevent sarcopaenia (at least 1.2-1.5 g/kg/d). The objective could be to progressively achieve 5-10% loss of total body weight [110]. A Mediterranean diet is recommended without any alcoholic beverages [111,112]. Multidisciplinary management is recommended, combined with physical activity adapted to the patient's capacities, starting with moderate intensity, and sustained in the long term [113].

Pharmacological approaches. The use of orlistat is not contraindicated in patients with cirrhosis, however the effects of orlistat on the natural evolution of liver pathology remain to be specified. The efficacy and tolerance of other treatments remain to be evaluated [114].

Bariatric procedures. Bariatric surgery is an effective treatment for NASH [115]. A French clinical trial is underway to evaluate its use in patients with advanced liver fibrosis (NCT03472157). Preliminary data indicate promising results among hyper-selected patients (Child-Pugh score A5, without portal hypertension proven by invasive portal pressure measurement) [116]. A new and interesting approach is bariatric endoscopy. Intragastric balloons do not seem to be contraindicated in the absence of endoscopic signs of severe portal hypertension. However, the specific long-term effects on the natural evolution of disease remain to be clarified in high-quality studies [117]. The efficacy and tolerability of other procedures of bariatric endoscopy seem promising but so far unevaluated [118].

37. **In patients with cirrhosis and preserved liver function, the same non-pharmacological approaches (personalised diet and physical activity) as for those in patients without cirrhosis could be recommended for reducing overweight/obesity and to control diabetes. Adequate protein intake (at least 1.2-1.5g protein per kg ideal body weight/day) should be maintained to achieve weight loss without compromising lean mass.**
38. **In patients with cirrhosis and preserved liver function and without portal hypertension, bariatric procedures (surgery and the emerging bariatric endoscopy) seem promising but further studies are needed. Such procedures for highly selected patients require an expert multidisciplinary team.**

Diagnosis of malnutrition in patients with cirrhosis

The major challenge in patients with cirrhosis is screening for malnutrition or sarcopaenia (loss of skeletal muscle mass and strength). Sarcopaenia can be seen even in overweight or obese patients ("sarcopaenic obesity"). Several works have reported an increased prevalence of sarcopaenia in overweight or obese patients with NASH [119,120]. Most patients with moderately/severely liver function, and some with preserved/slightly impaired liver function, suffer from or are at risk of malnutrition. The prevalence of malnutrition in patients with cirrhosis and hospitalised or awaiting liver transplantation is close to 50%. It is recommended for malnutrition to be systematically screened and evaluated at each consultation and hospitalisation, and to be documented in patients’ files (Fig. 1). The current assessment of the prognosis of patients with cirrhosis using the Child-Pugh and MELD scores is incomplete and should also consider nutritional status. The frailty often associated with malnutrition in patients with cirrhosis can be assessed by simple tests in clinical practice, such as the Liver Frailty Index (online calculator available at https://liverfrailtyindex.ucsf.edu/). This test improves the prediction of mortality in patients with cirrhosis, independently of Child-Pugh and MELD scores [121].

In the absence of specific diagnostic criteria, classical malnutrition screening and diagnostic tests can be used in patients with cirrhosis. These tests include recent involuntary weight loss, body mass index

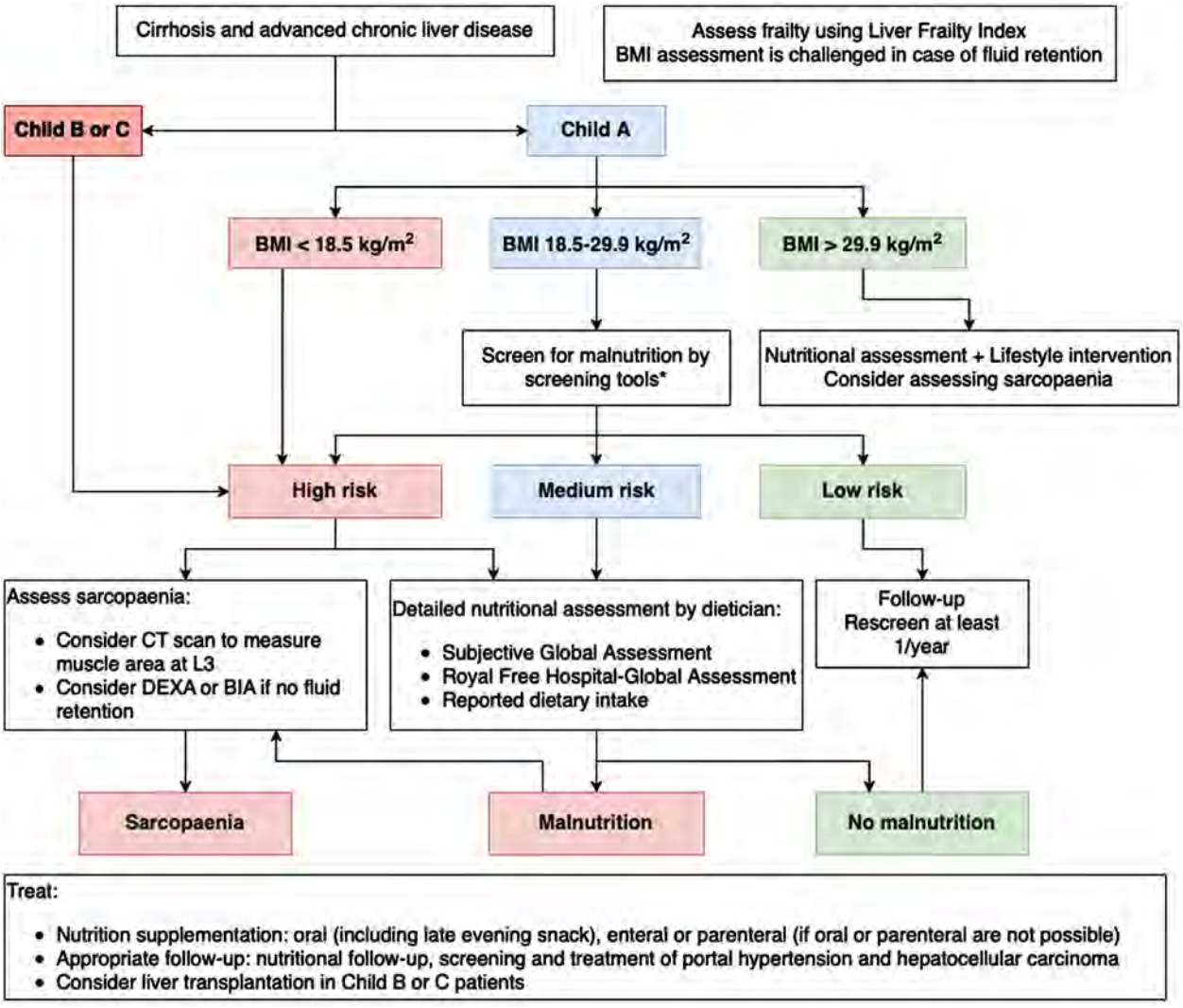

Fig. 1. Nutritional screening and assessment in patients with cirrhosis.
Adapted from EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019;70:172–193.
BMI: body mass index; CT: computed tomographic; DEXA: dual–energy X–ray absorptiometry; BIA: bioelectrical impedance analysis.
*Best screening tools (such as mid-arm muscle circumference and grip test) and their optimal thresholds must be validated.

<18.5 kg/m^2 or quantified reduction in muscle mass and/or function assessed by dynamometer, walking speed, computed tomography assessing the psoas muscle surface area in L3, impedance analysis or dual-energy X-ray absorptiometry (DEXA) [120,122]. However, these tests remain invalidated in patients with cirrhosis and T2DM. Criteria based on weight, body mass index and serum albumin can be applied in the case of preserved liver function (Fig. 1). Such criteria are much more difficult to interpret in case of impaired liver function, especially due to hypoalbuminaemia and/or fluid variations related to ascites or oedema [120]. Subjective Global Assessment is rarely used in routine practice because of its length and complexity, but is used in clinical research [112]. For routine practice, mid-arm muscle circumference and grip strength appear to be the best parameters for nutritional assessment and frailty in patients with cirrhosis.

39. **Malnutrition is common in patients with cirrhosis and increases with impaired liver function. Sarcopaenia is an independent prognostic factor of mortality in this population and should therefore be assessed.**
40. **There is neither a specific definition for malnutrition nor specific diagnostic tools for sarcopaenia in patients with cirrhosis and diabetes. Diagnosis of malnutrition may be difficult in patients with cirrhosis and impaired liver function because of fluid variations (ascites, oedema) or in the case of sarcopaenic obesity.**

Mid-arm muscle circumference and grip test show convincing results for sarcopaenia screening. Reported dietary intake, frailty scales and global assessment tools can be used to complete evaluation. Computed tomography assessing the psoas muscle area in L3 seems the most relevant test for confirming sarcopaenia. However, further validation of these tools in the specific population of patients with cirrhosis and diabetes is needed.

Nutritional management of patients with cirrhosis and malnutrition or sarcopaenia

Recommendations for the management of patients with cirrhosis, diabetes and malnutrition or sarcopenia are similar to those for patients suffering from malnutrition in general (**Table S4; see**

Table 5
Summary of the indications for anti-hyperglycaemic treatments in patients with cirrhosis.

Anti-hyperglycaemic treatment	Preserved liver function	Impaired liver function		
		Slightly	Moderately	Severely
Metformin	Yes	Yes	Contra-indicated	Contra-indicated
Pioglitazone	Yes	Yes	Contra-indicated	Contra-indicated
Sulphonylureas	Yes	With caution	Contra-indicated	Contra-indicated
Glinides (nateglinide)	Yes	With caution	With caution	No data
Glinides (repaglinide)	Yes	Contra-indicated	Contra-indicated	Contra-indicated
DPP-4 inhibitors [a]	Yes	Yes	Yes	Contra-indicated
SGLT2 inhibitors	No data	No data	No data	No data
Acarbose	Yes	Yes	Yes	Contra-indicated
GLP-1 receptor agonists [b]	Yes	Yes	With caution	Contra-indicated
Insulin	Yes	Yes	Yes	Yes

[a] Excepted for vildagliptin which is contra-indicated in patients with impaired liver function.
[b] Excepted for exenatide and lixisenatide which are contra-indicated in patients with impaired liver function.

supplementary materials associated with this article on line) [111,112,120]. In case of sarcopaenic obesity, sarcopaenia management is the priority. Nutritional care should be multidisciplinary and developed after assessment of nutritional status, protein-energy requirements, ingesta and digestive system functionality, with individualised nutritional goals. Physical activity is recommended. Protein intakes should not be decreased in cases of hepatic encephalopathy. Fasting periods should be limited and the consumption of 3–5 food intakes and a "late evening snack" is recommended [123]. Micronutrient and branched-chain amino-acid supplementation can be systematic [124].

Oral nutritional supplements can be proposed for achieving caloric objectives, favouring high energy density or non-liquid forms. There are currently no studies available on the value of sweetened forms of oral nutritional supplements in these patients. Enteral nutrition must be initiated in case of contraindication or insufficiency of oral nutrition. A flexible silicone enteral feeding tube (10 French gauge) is preferable. The presence of oesophageal varices is not a contraindication for enteral nutrition [112, 123]. The usual prophylactic measures for avoiding the occurrence of digestive haemorrhage due to portal hypertension should be applied. Hyper-caloric enteral nutrition mixtures are preferred. Parenteral nutrition should only be used in case of a non-functioning digestive tract, administered through a central venous catheter. Its prescription must be limited in time or forwarded to an expert centre in case of duration >3 months. It must be systematically associated with an infusion of vitamins and trace elements. Mixtures with the highest concentration of macronutrients are preferred.

Table 6
Unsolved issues in the management of type 2 diabetes mellitus in patients with cirrhosis.

- Best modality for the diagnosis of diabetes with respect to liver function status
- Frequency of diabetes screening with oral glucose tolerance test in patients with cirrhosis
- Clinical relevance of continuous glucose monitoring for diabetes management in patients with cirrhosis
- Impact of glycaemic control on liver-related prognosis
- Anti-hyperglycaemic drug class effect on the natural history of cirrhosis
- Potential benefit of metformin in the prevention of hepatocellular carcinoma
- Benefit/risk ratio of metformin in patients with moderately impaired liver function
- Efficacy and safety of GLP-1 RAs and SGLT2 inhibitors in patients with diabetes and cirrhosis with impaired liver function
- Reliable methods for the screening and diagnosis of sarcopaenia or malnutrition in patients with cirrhosis and T2DM

Regarding insulin therapy, the preference in the case of enteral nutrition is subcutaneous insulin with one injection Neutral Protamine Hagedorn (NPH) or insulin premix per enteral nutrition bag, depending on the duration of the nutrition bag. In case of parenteral nutrition, rapid insulin should be injected directly into the parenteral nutrition bag to reduce the risk of hypoglycaemia as much as possible. Glycaemic targets during artificial nutrition should be adapted to the patient's condition. A blood glucose level between 1.5–2.0 g/l is acceptable [125].

41. **In patients with cirrhosis and malnutrition or sarcopaenia, nutritional supplementation should be initiated. The strategy of nutritional supplementation (oral, enteral or parenteral) should follow the same rules as for patients without cirrhosis.**

Nocturnal fasting can be reduced by a "late evening snack" to promote protein synthesis and reduce the state of accelerated starvation.

Regular follow-up of blood glucose and insulin titration is recommended to avoid hyper/hypoglycaemia.

Conclusion

T2DM is difficult to manage in patients with cirrhosis and this complex clinical situation will become increasingly frequent with the rising burden of NAFLD. Minimal information is available in the literature with respect to how to diagnose T2DM, how to monitor glycaemic control (Table 4) and which treatments can be used in patients with cirrhosis (Table 5). T2DM can be managed in patients with cirrhosis and preserved liver function in the same way as in non-cirrhotic patients according to ADA and EASD guidelines. On the other hand, data regarding T2DM management in patients with cirrhosis and impaired liver function remain sparse. Several issues remain unsolved in this field and further studies are needed to address these unmet needs (Table 6).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2021.101272.

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