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REVIEW

Diabetes and cirrhosis: Current concepts on diagnosis and management

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Abstract

Type 2 diabetes mellitus is often associated with cirrhosis as comorbidities, acute illness, medications, and other conditions profoundly alter glucose metabolism. Both conditions are closely related in NAFLD, the leading cause of chronic liver disease, and given its rising burden worldwide, management of type 2 diabetes mellitus in cirrhosis will be an increasingly common dilemma. Having diabetes increases cirrhosis-related complications, including HCC as well as overall mortality. In the absence of effective treatments for cirrhosis, patients with type 2 diabetes mellitus should be systematically screened as early as possible for NAFLD-related fibrosis/cirrhosis using noninvasive tools, starting with a FIB-4 index followed by transient elastography, if available. In people with cirrhosis, an early diagnosis of diabetes is critical for an optimal management strategy (ie, nutritional goals, and glycemic targets). Diagnosis of diabetes may be missed if based on A1C in patients with cirrhosis and impaired liver function (Child-Pugh B–C) as anemia may turn the test unreliable. Clinicians must also become aware of their high risk of hypoglycemia, especially in decompensated cirrhosis where insulin is the only therapy. Care should be within multidisciplinary teams (nutritionists, obesity management teams, endocrinologists, hepatologists, and others) and take advantage of novel glucose-monitoring devices. Clinicians should become familiar with the safety and efficacy of diabetes medications for patients with advanced fibrosis and compensated cirrhosis. Management is conditioned by whether the patient has either compensated or decompensated cirrhosis. This review gives an update on the complex relationship between cirrhosis and type 2 diabetes mellitus, with a focus on its diagnosis and treatment, and highlights knowledge gaps and future directions.

INTRODUCTION

In patients with cirrhosis, type 2 diabetes mellitus (T2DM) occurs frequently, most commonly associated with NAFLD, the leading cause of chronic liver disease (CLD).[1] T2DM and cirrhosis account for 5 million and 1.2 million deaths worldwide each year, respectively.[2,3]

Diabetes is an independent factor of poor prognosis in patients with cirrhosis, associated with the occurrence of major complications such as ascites,

Abbreviations: cACLD, compensated advanced chronic liver disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CLD, chronic liver disease; CVD, cardiovascular disease; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; QOL, quality of life; T2DM, type 2 diabetes.

encephalopathy, and infections.[4] Conversely, the presence of cirrhosis may affect the diagnosis and management of T2DM. However, cirrhosis is often diagnosed at a late stage, that is when complications occur.[5] Early cirrhosis remains undiagnosed in most patients with T2DM because of low awareness regarding CLDs among general practitioners and the lack of a clear referral pathway between clinicians in primary care or diabetes clinics and liver specialists.[6] However, this is rapidly changing based on an increased awareness brought about by recent studies showing a high prevalence of NAFLD and advanced liver disease in people with obesity and T2DM in primary care and diabetes clinics,[7–10] combined with recent multidisciplinary consensus statements and clinical practice guidelines that have simplified the referral strategy.[11–13] Another challenge in the field is that the definitions of cirrhosis are highly heterogeneous through the literature because of limited data regarding liver function evaluation (preserved or not)[14] and of the recent introduction of noninvasive fibrosis tests to define early cirrhosis.[15,16] Finally, given the rising burden of NAFLD worldwide,[17] management of T2DM in patients with cirrhosis is likely to become an increasingly common issue in clinical practice.

In CLD, the progression of fibrosis is the main prognostic driver, with stages ranging from no or mild fibrosis (F0–F1) to significant (F2), advanced (F3) fibrosis, and ultimately cirrhosis (F4). The compensated advanced chronic liver disease (cACLD or F3–F4) concept has been introduced by the BAVENO VI consensus[18] to emphasize the continuity of disease severity over sharp distinction of stages in the course of CLD. As cirrhosis is a heterogeneous entity with a wide clinical spectrum, ranging from asymptomatic patients with normal liver function to end-stage liver disease with well-known complications (ascites, HE, gastrointestinal bleeding, and jaundice), it is important to clarify for the readers the definitions used in the present review. “Compensated” cirrhosis corresponds to patients who have never experienced complications and with normal liver function. “Decompensated” cirrhosis encompasses a broader clinical spectrum occurring through 2 distinct pathways: a non-acute (NAD) and an acute (AD) pathway.[19] NAD decompensation presents as slow development of ascites or mild grade 1 or 2 HE, or jaundice, not requiring hospitalization, whereas AD decompensation presents as grade 2 or 3 ascites, acute HE, gastrointestinal bleeding, and any type of acute bacterial infection in patients, who previously experienced decompensation.

The present review is aimed at providing an update on the relationships between cirrhosis and diabetes, with a focus on the diagnosis and management of diabetes in patients with cirrhosis.

EPIDEMIOLOGY AND IMPACT OF DIABETES IN PATIENTS WITH CIRRHOSIS

Prevalence and risk factors of diabetes in cirrhosis

A recent systematic review, based on 58 studies in 9705 patients with cirrhosis, reported an overall prevalence of diabetes of 30.7% (95% CI: 27.9–33.5).[20] Interestingly, the highest prevalence of diabetes was observed in patients with NAFLD (56%) and cryptogenic cirrhosis (51%) as compared with those with HCV (32%) or alcoholic cirrhosis (27%).[20] Factors associated with the presence of T2DM were age, overweight, and a family history of T2D.[21]

Prevalence and risk factors for cirrhosis in diabetes

The data on the prevalence of cirrhosis among patients with diabetes is limited and mainly based on NAFLD as the etiology. Among 248 patients with biopsy-proven NAFLD, a significantly higher prevalence of cirrhosis was observed in patients with diabetes (28%) compared with patients without diabetes (6%).[22] In a recent meta-analysis of 7 studies that included 439 patients with T2DM and biopsy-proven NAFLD, the prevalence of advanced fibrosis and cirrhosis was 17% (95% CI: 7.2–34.8).[1] Small sample cohorts and heterogeneity between studies have made it difficult to extrapolate these results to other populations. However, these findings are consistent with several recent reports that the prevalence of advanced fibrosis in patients with T2DM is ~15%–20%,[7,9,23–26] as recently reviewed.[27,28] It should be stressed that with the exception of one study,[7] liver biopsies were rarely performed to confirm the presence of advanced fibrosis. More recently, in a cohort of 713 outpatients with T2DM systematically screened for NAFLD referred to a hepatologist, of whom 330 underwent a liver biopsy, bridging fibrosis and cirrhosis were found in 28% and 10%, respectively, despite mild liver test abnormalities.[6] Liver lesions were independently associated with metabolic syndrome.

Liver-related complications and mortality

Diabetes is associated with the occurrence of major complications of cirrhosis, including ascites and renal dysfunction, HE and bacterial infections and higher mortality.[4] In a prospective community-based cohort of 63,275 patients in Singapore, diabetes was associated with an increased risk of cirrhosis-related mortality (HR: 2.80; 95% CI: 2.04–3.83), especially for nonviral hepatitis-related cirrhosis (HR: 3.06; 2.13–4.41).[29] Interestingly, in

a recent international cohort of 299 patients with biopsy-proven NASH[30] and compensated cirrhosis followed for a median of 5 years, having T2DM increased about twofold the risk of death (adjusted HR: 4.23; 95% CI: 1.93–9.29) and liver-related outcomes (adjusted HR: 2.03; 95% CI: 1.00–4.11), including HCC (adjusted HR: 5.42; 95% CI: 1.74–16.80). Thus, screening these patients for HCC using abdominal ultrasound every 6 months is particularly important.[31]

Cirrhosis is a key prognostic marker not only for liver-related outcomes[32] but also overall mortality.[33,34] The association of steatohepatitis with cancer offers a pathophysiological link for a long-time observation that diabetes is associated with a 2-fold higher risk of HCC and to extrahepatic cancers.[1,34–37] It has been suggested that patients with NAFLD cirrhosis have predominantly liver-related events whereas those with bridging fibrosis have predominantly nonhepatic cancers and vascular events.[32] In a recent multicenter prospective study where 1773 patients with NAFLD were followed for a median of 4 years, all-cause mortality increased with increasing fibrosis stages.[25] Compared with patients with stage F0 to F2, patients with stage F4 disease had higher all-cause mortality (HR: 3.9; 95% CI: 1.8–8.4) and liver-related mortality (HR: 12.7; 95% CI: 1.8–88.6). However, the incidence of cardiac events and nonhepatic cancers were similar across fibrosis stages. The low number of these outcomes, small sample size, and short duration of follow-up may have accounted for its discrepancy with the many reports suggesting an increased risk of cardiovascular disease (CVD) in people with NAFLD.[38,39]

CVD in patients with NAFLD and cirrhosis

The leading cause of death in patients with NAFLD is CVD, followed by extrahepatic malignancy (eg, colorectal cancer or breast cancer).[34,36,37] NAFLD has been linked not only to an increased risk of CVD but to arterial hypertension,[40] heart failure with preserved ejection fraction,[41] arterial stiffness and subclinical atherosclerosis,[42,43] atrial fibrillation and other cardiac arrhythmias,[44] and arterial stiffness and aortic valvular sclerosis.[40,45] People with NAFLD may also have more CVD given their ~2-fold higher risk of developing T2DM.[43,46] Advanced fibrosis (stage F3–F4), but not steatohepatitis, has been reported as a risk factor for CVD.[47] In a recent nationwide study from Sweden,[48] NAFLD was associated with a higher risk of nonfatal cardiovascular events but did not affect after CVD mortality risk. Patients diagnosed with NAFLD had a lower life expectancy than the general population.

Paradoxically, although patients with NAFLD usually have more atherogenic dyslipidemia associated with insulin resistance,[49] this appears to amend in more advanced liver disease with the development of cirrhosis (eg, with lower plasma VLDL, triglycerides, LDL particles and LDL-C, as well as small dense LDL-C).[50–52] In contrast, plasma HDL-C levels, as well as lipoprotein composition and function, have been reported to be significantly decreased in people with cirrhosis,[53,54] and be a predictor of future liver-related complications and of mortality, independent of the model for end-stage liver disease score (MELD).[54] Recent efforts suggest that lipidomic profiling may also have prognostic value in terms of survival in patients with acute decompensation from cirrhosis.[52] In summary, there are many causes for increased CVD in late stages of liver disease, but the specific contribution of changes in lipoprotein metabolism in their dynamic interaction between "protective" (ie, decreased atherogenic lipoprotein production in late cirrhosis) versus proatherogenic (ie, lower and dysfunctional HDL-C) remains incompletely understood.

PATHOPHYSIOLOGY: INTERACTIONS BETWEEN DIABETES AND CIRRHOSIS

Impact of cirrhosis on glucose homeostasis

Patients with cirrhosis develop diabetes from defects in insulin action (eg, insulin resistance at the level of the liver, skeletal muscle, and adipose tissue) and in pancreatic β-cell function. Figure 1 summarizes the many factors at play that may lead to diabetes in people with cirrhosis. A full understanding of the impact of cirrhosis on glucose and lipid metabolism is clouded by the broad spectrum of what is defined as cirrhosis, often with heterogeneous populations in earlier versus more recent studies, and even within more contemporary reports. Early studies have highlighted the major role of insulin resistance associated with cirrhosis,[55–58] and although the etiology of cirrhosis played no apparent role, insulin resistance was often worse with the severity of the Child-Pugh score and in patients with diabetes compared with those with prediabetes. Muscle insulin resistance predominates in patients with prediabetes,[56] but as hepatic insulin resistance worsens it is associated with increased rates of hepatic glucose production and rising fasting and postprandial plasma glucose when diabetes is fully established.[59] Protein metabolism in response to insulin is not altered in patients with cirrhosis,[57] with normal insulin suppression of protein degradation and stimulation of protein synthesis, in a clear-cut dissociation between the effects of insulin on protein and glucose metabolism. In NAFLD, insulin resistance and lipotoxicity already play a central role in the development of steatohepatitis and possibly fibrosis,[60] although the pathways leading to cirrhosis remain poorly understood in humans. Factors at play that lead to abnormal glucose metabolism in people with cirrhosis (Figure 1) include chronic hyperinsulinemia,[56,59] which may cause downregulation of insulin signaling and decreased

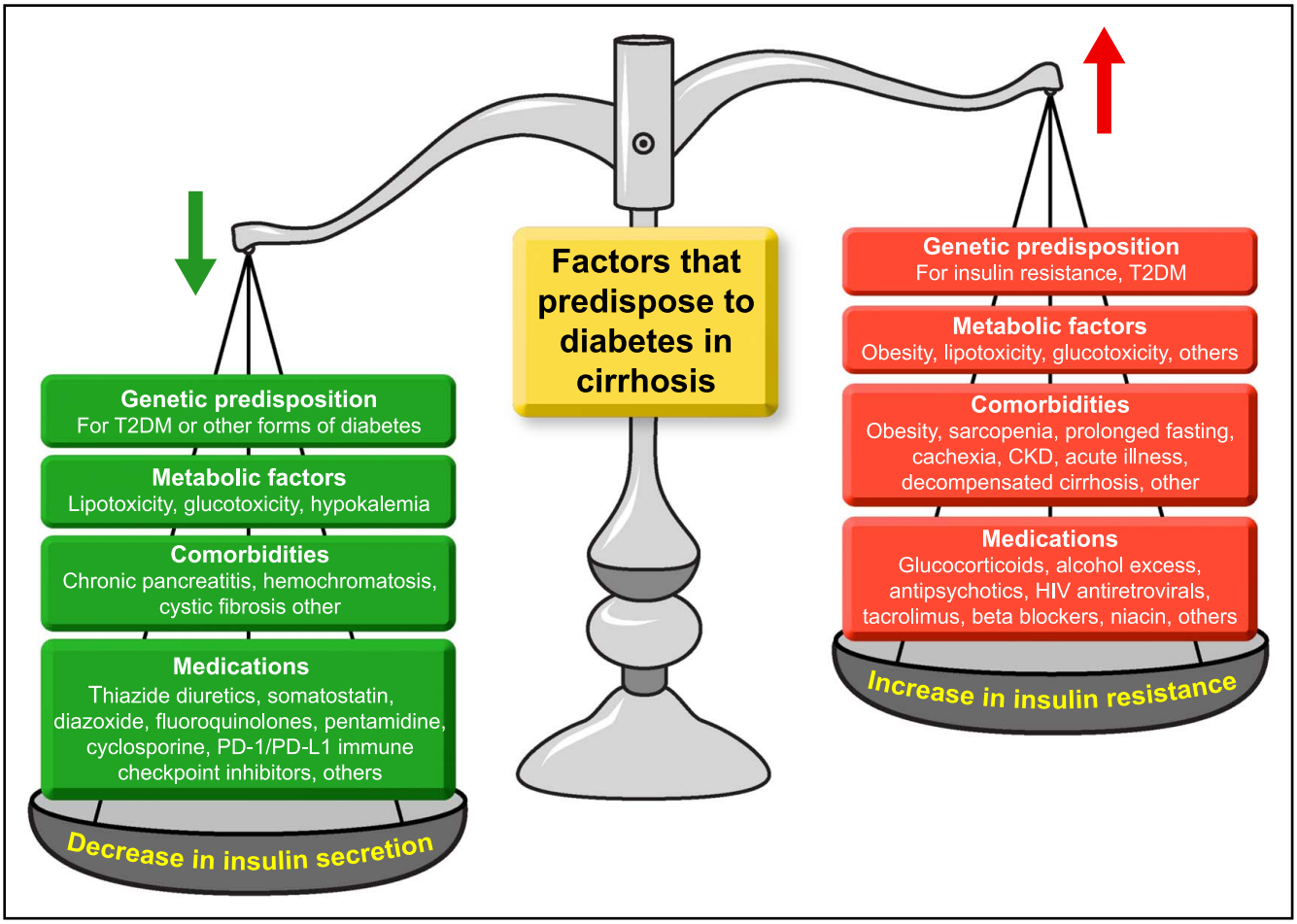

FIGURE 1 Factors that lead to type 2 diabetes mellitus (T2DM) in patients with cirrhosis.

tissue response to insulin, elevated plasma-free fatty acids and adipose tissue insulin resistance,[56] glucotoxicity that affects both insulin secretion and peripheral glucose metabolism,[55] intercurrent illnesses, and medications that may impair insulin secretion or worsen insulin resistance. More recent work has highlighted the role of impaired insulin secretion in the development of hyperglycemia in cirrhosis.[61] In the end, diabetes only develops when there is pancreatic β-cell failure, with hyperglycemia developing initially in the postprandial state (ie, impaired glucose tolerance). As in the early stages of T2DM without liver disease, diabetes associated with early-stage cirrhosis is often characterized by hyperinsulinemia due to insulin resistance and postprandial hyperglycemia as maintenance of normal glucose homeostasis is more difficult in the more dynamic postprandial state.[62] As insulin secretion declines over time, glucose homeostasis deteriorates further with not only postprandial but fasting hyperglycemia as well. Of note, restoration of normoglycemia in people with diabetes following liver transplantation depends fundamentally on their presurgical pancreatic insulin secretory reserve, and not so much on other factors such as age, body mass index, family history of diabetes, immunosuppressive drugs, or the pathogenesis of cirrhosis.[58]

CLD as a "cause" for diabetes, or "hepatogenous diabetes," has been proposed by some as a unique entity, when altered liver function in cirrhosis presents with hyperinsulinemia and often near-normal (or normal) fasting plasma glucose (FPG) or glycosylated hemoglobin (A1c), but an abnormal response to an oral glucose tolerance test (OGTT).[63,64] Hyperinsulinemia in cirrhosis was recognized already in early studies,[56] and now clearly established as secondary to the combined effect of severe insulin resistance and reduced peripheral tissue (largely muscle) insulin clearance. The role of steatohepatitis and fibrosis on hepatic and peripheral insulin clearance in NAFLD was carefully examined by Bril et al.[65] in 190 patients across a broad spectrum of liver disease, including patients without NAFLD (controls), simple steatosis, and biopsy-proven NASH with different stages of fibrosis. Compared with healthy controls, patients with steatohepatitis or simple steatosis had a similar reduction hepatic insulin clearance of ~30%. The reduction of hepatic insulin clearance was not associated with the severity of inflammation, ballooning, or fibrosis but rather with hepatic insulin resistance.[65]

However, those with severe steatohepatitis compared with those with simple steatosis had worse hyperinsulinemia, driven by a reduction in whole-body insulin (extrahepatic) clearance and more severe adipose tissue insulin resistance. These results align well with our current understanding of the pathophysiology of T2DM, where a combination of muscle and liver insulin resistance, together with inadequate compensatory pancreatic β-cell insulin secretion, fails to keep normal glucose homeostasis.[60] Postulating hepatogenous diabetes as a separate entity fails to recognize the many factors at play in CLD, including genetic predisposition, metabolic conditions, comorbidities and medications used in cirrhosis (Figure 1) that worsen insulin secretion and insulin resistance. Cirrhosis appears to simply "unmask" genetically determined, underlying abnormal pancreatic β-cell function to the point of overwhelming its capacity to compensate to the higher insulin demand. Therefore, the term "hepatogenous diabetes" should be abandoned as we understand better today the relationship between insulin resistance, lipotoxicity and NASH,[66] and the mechanisms underlying the development of T2DM and pancreatic β-cell failure.[60,62] Indeed, the American Diabetes Association (ADA) (and all other diabetes societies) does not recognize diabetes developing in the course of cirrhosis as an independent entity.[67]

Role of sarcopenia and myosteatosis

Ectopic fat accumulation in skeletal muscle (myosteatosis) and lipotoxicity play a key role in the development of insulin resistance and is closely associated with hepatic insulin resistance in individuals genetically predisposed to T2DM,[68] as well as in obesity, T2DM, and NAFLD.[66,69–71] It interrelates with sarcopenia, which is the loss of muscle mass and strength or performance in aging (primary sarcopenia), but that can also be associated with sedentary lifestyle, be disease-related such as in organ failure (heart, lung, liver, other), malignancy or endocrine disease, or associated with malnutrition (inadequate dietary intake of energy and/or protein, as with malabsorption, gastrointestinal disorders).[72] Usually insulin resistance and myosteatosis precede sarcopenia, but in the clinic it is difficult to separate the pathophysiological pathways and risk factors contributing to each of them. The strong interrelationship of sarcopenia and myosteatosis with NAFLD suggests that their presence is a disease modifier that leads to worse outcomes.[73] The detrimental effects of sarcopenia are magnified in obesity and T2DM. Skeletal muscle mass and function are key determinants of the whole-body insulin-mediated glucose metabolism and impact fatty liver oxidation. Insulin resistance, lipotoxicity, and accumulation of ectopic fat as observed in NAFLD affects both the liver and the skeletal muscle function.[66,74–76] Several studies have correlated myosteatosis with the severity of liver injury.[73] It is reported in more than half of patients with cirrhosis, and has been associated with reduced survival and increased risk of complications.[77] Data on the mechanisms by which excess lipid accumulates within the muscle in individuals with cirrhosis remains limited. In the setting of obesity, T2DM and insulin resistance, hyperammonemia, protein malnutrition, end-organ failure (eg, end-stage liver disease), endocrine diseases (eg, hypogonadism, growth hormone deficiency, other), and age-associated differentiation of muscle stem cells into adipocytes have all been also suggested as potential mechanisms contributing to myosteatosis.[77]

Mechanisms for the impact of diabetes on fibrosis progression to cirrhosis

There are common mechanisms of liver fibrogenesis that may lead to fibrosis progression in patients with NASH.[78] Activated hepatic stellate cells and portal myofibroblasts are prime effectors of liver fibrogenesis. They are characterized by increased proliferation, migration and contractility, and by a relative resistance to apoptosis. Activated cholangiocytes, which share common characteristics with fibrogenic progenitor cells, emerge with increasing hepatocyte lipoapoptosis and growth arrest. Apart from an upregulation of the synthesis and deposition of various extracellular matrix components, fibrolysis is compromised by an increased synthesis of TIMP-1 and a decreased production of fibrolytic matrix metalloproteinases, both by hepatic stellate cells/myofibrobasts and by KCs/macrophages.

Diabetes, through lipotoxicity and glucotoxicity among other multiple mechanisms, may contribute to fibrosis progression and cirrhosis independent of NAFLD by modulating several key processes implicated in fibrogenesis, including activation of hepatic stellate cells, inflammation, apoptosis, angiogenesis, and hepatic sinusoidal capillarization.[4,78]

Role of dysfunctional adipose tissue and lipotoxicity

Insulin resistance with overflow of fatty acids to the liver[79] and ectopic fat deposition have been a hallmark in the pathophysiology of NAFLD,[69] and is associated with increased cellular levels of toxic lipids such as diacylglycerols, ceramides, and long-chain fatty acyl-CoA,[80] which are also involved in multiple pathways altering insulin signaling and inflammation.[81,82] Lipotoxicity is also involved in the pathophysiology of T2DM.[60,68] Excess flow of FFA to the liver, muscle, and other tissues promotes mitochondrial dysfunction,[83] and in animal

models of NASH treatment with a GLP-1RA[84] or pioglitazone[85] decreases liver triglyceride content together with that of diacylglycerols and ceramides with a restoration of hepatic insulin sensitivity and mitochondrial function. Activation of inflammatory pathways with lipotoxicity promotes the activation of hepatic stellate cells[86,87] that can fuel the progression to NASH and development of cirrhosis.[60] In insulin-resistant states, adipose tissue is prone to release pro-inflammatory cytokines (eg, TNF-α, TGF-β, and IL-6),[88] while deficient in secreting anti-inflammatory adipokines, such as adiponectin.[89] Pro-inflammatory cytokines can directly damage the liver, or act indirectly, by increasing oxidative stress, hepatocellular damage, liver fibrosis, and tumor development.

Role of glucotoxicity

Glucotoxicity is a concept first highlighted by Unger and Grundy in 1985,[90] that initially underscored the deleterious effect of chronic hyperglycemia on pancreatic β-cell insulin secretion. This concept has been more broadly extrapolated to the impairment of glucose uptake across a number of tissues and of overall glucose metabolism with increasing hyperglycemia. This has been studied extensively in T2DM,[60,91,92] and is closely associated with lipotoxicity, such that both contribute to worsen insulin resistance and insulin secretion. We refer the readers to in-depth reviews on how glucotoxicity and lipotoxicity synergize in CLD and in NAFLD to provide the pathophysiological basis for advanced fibrosis and cirrhosis.[69,82,93–95]

SCREENING FOR NAFLD FOR THE PREVENTION OF CIRRHOSIS

The prevalence of cirrhosis is expected to rise in the future with the continuous increase of the dual epidemics of obesity and T2DM. Both conditions promote the development of NAFLD, soon to be the most common cause of cirrhosis worldwide.[1,28] There have recently been "calls to action" for an early diagnosis of NAFLD and for screening all patients with T2DM, with multidisciplinary efforts for a more proactive approach in the primary care and diabetes clinic settings,[96–99] as well as from consensus statements.[11–13,100–103] In 2016, the EASL-EASD-EASO guidelines[100] recommended that persons with NAFLD be screened for diabetes. Vice versa, in patients with T2DM, the presence of NAFLD should be looked for irrespective of ALT levels given their high risk of fibrosis. A shift in strategy from case finding to universal screening is supported by recent studies from Europe,[25,26] Southeast Asia,[23,24] and in the US[7,9,104] that suggest that, using transient elastography or serum biomarkers, about 15%–20% of patients with T2DM may have advanced fibrosis (F3–F4) or cACLD. In that respect, liver stiffness, using VCTE, has been shown to have prognostic value in the context of cACLD and recommended as a surrogate of HVPG for detecting clinically significant portal hypertension and monitoring cirrhosis progression.[105]

A shift from case finding to universal screening is also supported by the availability of low-cost and widely available point-of-care tests, such as FIB-4, with high negative predictive value to rule out cirrhosis[106] and a strong predictor of future outcomes when elevated.[107,108] Moreover, a recent elegant study by Noureddin et al.[109] showed the cost-effectiveness of an approach based on ALT/AST and transient elastography when combined with a 1-year lifestyle intervention or pioglitazone treatment. Since 2019, the ADA has recommended that patients with T2DM (or prediabetes) and elevated ALT or fatty liver be evaluated for the presence of steatohepatitis and liver fibrosis and more recently incorporated FIB-4 as a valuable screening test.[101] With a rapid increase in the region's prevalence of diabetes, in 2020 the Latin American Association for the study of the liver (ALEH) practice guidance recommended screening for NASH and liver fibrosis in patients with T2DM.[102] Screening efforts in primary care have galvanized around clinical care pathways developed by multidisciplinary teams of experts from primary care, endocrinology, diabetes, obesity management, nutritionists, and hepatologists, aimed at identifying patients for referral to the specialist to avert future cirrhosis.[12,13,96,99–103,110] Recommendations supported screening with FIB-4 for all high-risk patients (ie, with obesity/metabolic syndrome, T2DM, elevated plasma aminotransferases, and/or steatosis), followed by transient elastography if the FIB-4 index suggested an intermediate to high risk of clinically significant fibrosis. These recommendations are in line with those recently proposed by the European Association for the Study of Liver Disease (EASL)[111] and by the first guidelines tailoring endocrinologists and primary care providers from the American Association of Clinical Endocrinologists (AACE).[11] Additional work-up, including commercially available biomarkers or imaging (ie, MRE, cT1, other), would be preferably performed by liver specialists depending on each clinical care setting.[11,16,111]

MANAGEMENT IN CLINICAL PRACTICE

Diagnosis of diabetes in patients with compensated cirrhosis

In patients with compensated cirrhosis the diagnosis of diabetes is similar to people without liver disease (Figure 2). As discussed earlier, an early diagnosis of T2DM is needed because it has prognostic implications[60,61] and gives an opportunity to optimize

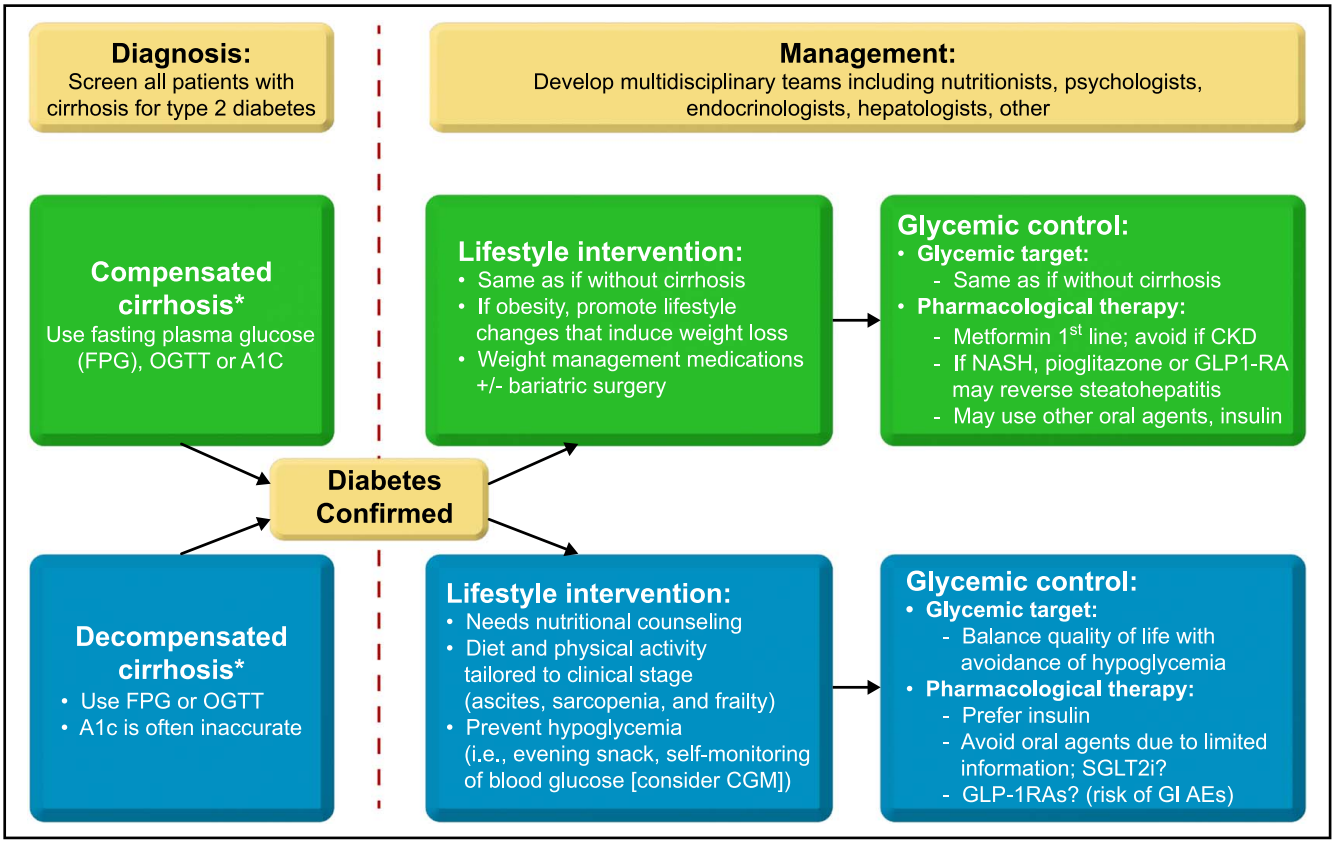

FIGURE 2 Diagnostic and management algorithm for patients with diabetes and cirrhosis. Abbreviations: CKD, chronic kidney disease; OGTT, oral glucose tolerance test.

diabetes care to reduce morbidity and mortality by preventing or delaying diabetes complications.[3,96] Irrespective of gender, ethnicity, or geographical location, studies across the globe suggest that patients having obesity and diabetes with compensated cirrhosis are on a path of more rapid disease progression (independent of the etiology) and the development of liver-related complications such as bleeding, encephalopathy, ascites, hospital readmissions, and HCC.[29,112–115]

The ADA classifies diabetes into the following categories [67]: (a) type 1 diabetes, due to autoimmune pancreatic β-cell destruction; (b) T2DM, from the progressive loss of pancreatic β-cell function most often in the background of IR. As such, what some authors have called as "hepatogenous" diabetes[63,64] would fall within this pathophysiological category, in instances with a "normal" HbA1c due to associated anemia from hyperesplensim, chronic kidney disease (CKD), or other comorbidities; (c) gestational diabetes mellitus, developing in the absence of prior diabetes; and (d) several widely accepted specific types of diabetes such as monogenic diabetes syndromes (ie, maturity-onset diabetes of the young or MODY), exocrine pancreas diseases (such as cystic fibrosis and chronic pancreatitis) and drug-induced diabetes (ie, from glucocorticoids and other medications, after organ transplantation or therapy for HIV/AIDS).

As discussed under the pathophysiology of the disease, patients with cirrhosis develop diabetes from a combination of insulin resistance and pancreatic β-cell dysfunction. The diagnosis of T2DM can be done in 4 ways[67]: (a) FPG $\geq$126 mg/dL or 7.0 mmol/L (fasting meaning no caloric intake for $\geq$8 h); (b) 2-hour PG $\geq$200 mg/dL (11.1 mmol/L) during an OGTT (75 g anhydrous glucose dissolved in water); (c) A1c $\geq$6.5% (48 mmol/mol) using a well-standardized assay; or (d) a random glucose $>$200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia or hyperglycemic crisis. The diagnosis of diabetes has its caveats as there may be discordance between OGTT and A1c, made worse when there is anemia due to hypersplenism, CKD, or a host of other comorbidities associated with cirrhosis.[67] Unless there is a clear clinical diagnosis, the ADA recommends confirming without delay the diagnosis by either repeating the initial test or with a different test. All tests have analytical variability. If discordance, the abnormal test should be repeated. Consideration should be given for an A1c assay interference, or that the FPG or 2-hour PG samples remained at room temperature and not centrifuged promptly, reducing their glucose concentration.[67] The diagnosis is made on the basis of the confirmed test. If results are near the normal cutoff, with no obvious symptoms, testing should be repeated in 3–6 months.

Diabetes will grow as a medical problem so clinicians must be alert in seeking its diagnosis in the primary care or liver clinics. In 2017, there were an estimated 451 million people with diabetes worldwide and it is expected to increase to 693 million by 2045, with about half of all people living with diabetes being yet undiagnosed.[116] In Africa, Asia, and South America, the incidence and prevalence of T2DM are increasing most rapidly.[116]

Diagnosis of diabetes in patients with decompensated cirrhosis

Moderate to severe anemia in decompensated cirrhosis with portal hypertension and hypersplenism, often with CKD and/or hepatorenal syndrome, makes the use of A1c inadequate as can lead to a falsely lower or "normal" value. It has been known for a long time that in cirrhosis there is a state of increased red blood cell turnover from hypersplenism.[117] Other typical conditions of elevated red blood cell turnover include hemolytic and other anemias, recent blood transfusion, glucose-6-phosphate dehydrogenase deficiency, agents that stimulate erythropoesis, and CKD. This can give a deceivingly "normal" A1c level that deserves further investigation. The ADA recommends that only blood glucose criteria should be used to diagnose diabetes in patients with conditions associated with increased red cell turnover.[67,101] In this clinical setting, an OGTT is considered the optimal test, although seldom performed in the clinical realm (Figure 2). Early studies proposed that an OGTT would allow to better predict the overall prognosis of patients with liver cirrhosis,[118,119] and even add to the prognostic value of the Child-Pugh score.[61] However, this awaits to be systematically tested. It could potentially be of value, as cirrhosis in people with diabetes has a worse prognosis, and optimal diabetes management could improve the quality of life (QOL) or long-term survival.

An OGTT could also be of value to identify patients with prediabetes, who also are at an increased risk for both microvascular and macrovascular disease.[120] Prediabetes is present long before the development of cirrhosis and likely contributes to poor outcomes in cirrhosis, but is often overlooked in patients with NAFLD. It is difficult to give a precise estimate of the prevalence of prediabetes (or diabetes) in patients with cirrhosis as other than in research studies; OGTTs are rarely performed in the outpatient setting.[121] Results vary depending on the diagnostic methodology used, population tested (compensated vs. decompensated cirrhosis), and clinical setting (secondary or tertiary medical centers), but is estimated to be ~15%–30%.[64] Nishida[63] reported on 12 studies in a total of 1747 patients with cirrhosis undergoing an OGTT, finding the prevalence of diabetes to be a 35% and that of impaired glucose tolerance to be 28%. The presence of impaired glucose tolerance is not only important as a risk factor for future diabetes and worse outcomes in cirrhosis, but is associated with a 2- to 3-fold higher risk of CVD.[122] CVD contributes significantly to the overall mortality of patients with cirrhosis.[39]

In a study in 118 patients with NAFLD systematically screened with an OGTT,[121] the prevalence of prediabetes was 3-fold higher ($p < 0.001$) compared with matched controls without NAFLD. One in 6 patients with NAFLD had undiagnosed diabetes. This is consistent with a recent meta-analysis that reported diabetes to be 2-fold higher in the setting of NAFLD.[46] Muscle and liver insulin sensitivity are usually impaired in patients with NAFLD with prediabetes providing the pathophysiological basis for their high risk of diabetes. It has been recently estimated that worldwide there are an estimated 374 million people with impaired glucose tolerance and is projected to increase ~50% by 2045, most living in low- and middle-income countries.[116] At least in part, the prevalence of diabetes increases in people with cirrhosis because insulin resistance becomes more severe with liver disease progression,[66,123] and may further deteriorate in association with acute illness and decompensations requiring hospitalization.[64,124]

In summary, many patients with cirrhosis have normal or near-normal FPG levels or A1c, so clinicians who rely only on the FPG or the gold-standard hemoglobin A1c levels may often overlook the presence of diabetes. In this situation, an OGTT is recommended, in particular should there be a family history of T2DM, central obesity or other features of the metabolic syndrome, or a history of in-hospital hyperglycemia (also known as "stress hyperglycemia"). A shorter and more practical 1-hour postprandial glucose or continuous glucose monitoring (CGM) may be novel approaches to test in the future for the diagnosis of diabetes in this population.[125,126]

Treatment of diabetes in patients with cirrhosis

Diabetes treatment goals and prevention of hypoglycemia

The degree of glycemic control for patients with diabetes should be individualized balancing QOL versus treatment intensity and potential side effects of treatment (ie, risk of hypoglycemia). Another factor to consider is life expectancy from the associated liver and diabetes complications. Shared physician-patient decision-making and the patient's social network must work together to set clear management goals. This is best achieved with the development of multidisciplinary groups that can satisfy the needs of these complex patients. Assessment of the nutritional and functional status is also important, even more in the setting of diabetes and decompensated cirrhosis (Figure 2).

Diabetes poses unique challenges to patients with cirrhosis. A major one is the greater risk of hypoglycemia of patients with cirrhosis. Hypoglycemia is defined as level 1 when the plasma glucose concentration is <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L), level 2 when the plasma glucose concentration is ≤54 mg/dL (3.0 mmol/L), and level 3 as a severe event characterized by altered mental and/or physical status requiring assistance for the treatment of hypoglycemia.[127] Figure 3 summarizes the many risk factors and mechanisms at play for hypoglycemia in patients with cirrhosis, including (a) chronic malnutrition and cachexia, in particular in decompensated cirrhosis; (b) decreased hepatocyte mass for gluconeogenesis, also associated with reduced glycogen stores (worsened by malnutrition in advanced cirrhosis stages); (c) sarcopenia, where a reduction in muscle mass limits the availability of lactate and key amino acids to support hepatic gluconeogenic pathways; (d) concomitant comorbidities, such as CHF, chronic pancreatitis with glucagon deficiency, and acute or CKD and hepatorenal syndrome. The presence of CKD predisposes to hypoglycemia as there is reduced renal clearance of insulin (ie, prolonging the action of both endogenous and exogenous insulin) and decreased clearance of hypoglycemic agents (ie, metformin, sulfonylureas); (e) advanced age, longstanding diabetes or ammonia buildup, all are associated with cognitive dysfunction and diminished alertness to warning symptoms of hypoglycemia; (f) liver-associated complications, such as volume overload and ascites, that alter liver and kidney function and the metabolism of oral antidiabetic and the clearance of insulin; (g) concomitant medications, such as beta blockers for portal (or systemic) hypertension or coronary artery disease, that mitigate adrenergic symptoms of hypoglycemia; and (h) diabetes itself with its associated complications, such as hypoglycemia unawareness or severe diabetic neuropathy, both known to be associated with severe hypoglycemia and increased mortality.[127] Needless to say, patients are often on multiple pharmacological agents that are metabolized by the hepatic CYP450 system, which combined with the many factors listed above creates the ideal conditions for severe hypoglycemia.

Clinicians should educate the patient about the risk factors described above (summarized in Figure 3) to develop strategies to prevent hypoglycemia, including self-monitoring of blood glucose levels and close monitoring of all medications, particularly when taking insulin. CGM is an important tool to assess the effectiveness and safety of treatment, but is underutilized in this population. Another often forgotten but valuable tool is educating the patient's healthcare providers in the emergency use of glucagon administration to treat severe hypoglycemia. Family

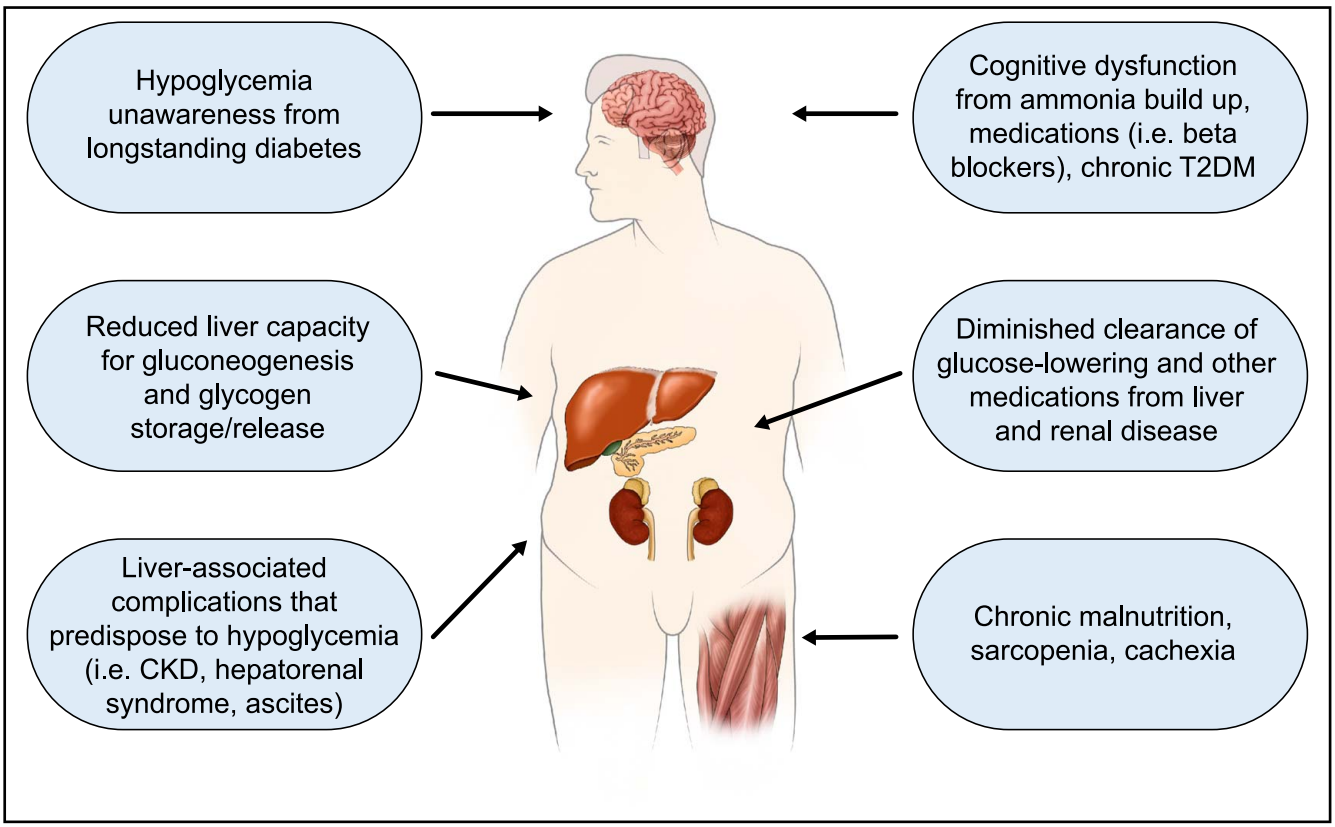

FIGURE 3 Mechanisms related to the development of hypoglycemia in patients with cirrhosis. Abbreviations: CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus.

TABLE 1 Efficacy and safety of diabetes medications in patients with liver disease

Diabetes medication	Primary mechanism(s) of glucose-lowering	Expected range of glucose-lowering[a]	Liver histological effects[b]	Use in compensated cirrhosis [Child-Pugh A (5–6)][c]	Use in decompensated cirrhosis [Child-Pugh B–C (≥7)]
Metformin	Insulin-sensitizer	0.8%–1.2%	No effect	Caution, monitor for CKD or hepatorenal syndrome	Avoid due to high risk of comorbid conditions and lactic acidosis
Sulfonylureas	↑ insulin secretion	0.8%–1.2%	Unknown	Caution given higher risk of hypoglycemia with cirrhosis	Avoid due to high risk of hypoglycemia
Pioglitazone	Insulin sensitizer	0.8%–1.2%	Improves steatohepatitis. May improve fibrosis and halt fibrosis progression	Limited data, use with caution	Avoid due to hepatic metabolism of pioglitazone. Risk for fluid retention
DPP-IV inhibitors	↑ insulin secretion, predominantly after meals	0.5%–0.7%	Unknown	Overall believed safe	Avoid due to limited data
SGLT2 inhibitors	↓ renal reabsorption of glucose. Cardiorenal benefits	0.7%–1.0%	Reduce steatosis	Overall safe	Avoid due to limited data
GLP-1RA	↑ insulin secretion, induction of satiety and weight loss. Cardiorenal benefits	0.8%–2.0%	Improves steatohepatitis. May improve fibrosis and halt fibrosis progression	Overall safe	Avoid due to gastrointestinal side effects
Insulin	Suppression of hepatic glucose production. Stimulation of muscle glucose uptake	Dose-dependent	Reduces steatosis	Adjust dosing carefully and monitor closely given risk of hypoglycemia	Carefully adjust dosing given very high risk of hypoglycemia

[a]Glucose-lowering range has a great variability depending on agent potency within class, duration of diabetes, patient clinical characteristics, and baseline A1c (greater effect if higher).
[b]The effects on liver histology have not been examined in paired-biopsy randomized controlled trials except for metformin, pioglitazone, and GLP-1RA. SGLT2 inhibitors reduce steatosis on imaging.
[c]Limited information overall in patients with cirrhosis, but most diabetes medications are considered safe in early stages (Child-Pugh A), but best avoided in B–C except for insulin.
Abbreviation: CKD, chronic kidney disease.

members, coworkers, and people taking care of patients with diabetes and cirrhosis should learn about emergency glucagon administration. Traditionally, glucagon has been given as an i.m. injection, but an intranasal formulation of glucagon is now available.[128] In summary, clinicians must be extremely thoughtful and set realistic targets for patients with cirrhosis and diabetes. It should be based on strong patient and healthcare team engagement, ideally within a multidisciplinary team that includes a nutritionist and an endocrinologist, shared agreement on treatment goals (ie, higher A1c targets may be needed to prevent hypoglycemia), and the utilization of a spectrum of novel tools to safely reach the glycemic target.

Table 1 summarizes currently available diabetes agents for the treatment of T2DM, including their safety and efficacy when used in patients with cirrhosis. Needless to say, patients with compensated cirrhosis can be more safely prescribed oral agents than those with decompensated disease. For patients with early, stable cirrhosis, and without anemia or severe comorbidities, the glycemic targets are the same as for patients without liver disease. The 2023 ADA guidelines establish as a general goal an A1C of $\leq$7.0% (53 mmol/mol) for adults if achieved without significant hypoglycemia.[127] The A1C indicates the average glycemia over approximately the past 3 months. A lower target ($\leq$6.5%) may be acceptable based on provider judgment and patient preference, and if it can be achieved safely without significant hypoglycemia or other adverse effects. Frequent reassessment and tailoring to changing clinical situations is needed. A less stringent A1C goals [such as $\leq$8.0% (64 mmol/mol)] may be appropriate for patients with limited life expectancy, or where the harms of treatment (ie, hypoglycemia-prone diabetes) are greater than expected benefits. The challenge is that the liver disease status may be at times difficult to define precisely. Acute decompensations or intercurrent illnesses add to the complexity of care. It should be noted that A1C does not provide a measure of glycemic variability or hypoglycemia, as is often observed in patients with cirrhosis with a history of longstanding T2DM or associated with chronic pancreatitis and severe insulin deficiency (eg, from alcohol abuse or other etiologies). In such patients, glycemic control is best determined by the combination of measuring A1C and self-monitoring of blood glucose (or use of a CGM).

For patients with decompensated diabetes and moderate to severe anemia, A1c is not useful (ie, A1c will appear as "normal" even with significant hyperglycemia) and should not be used to monitor therapy. Plasma fructosamine, a measure of the average plasma glucose concentration in the past ~3 weeks, may also underestimate the mean glucose level if liver synthetic function is impaired.[125] In such clinical setting, therapy is best guided by the use of preprandial (fasting) capillary plasma glucose (standard target: 80–130 mg/dL or 4.4–7.2 mmol/L) and the peak postprandial capillary plasma glucose (target: $\leq$180 mg/dL or 10.0 mmol/L)[127] together with self-monitoring of blood glucose or CGM.[125,126]

In the absence of long-term controlled studies, it remains unclear whether optimal achievement of diabetes glycemic targets may significantly impact the QOL or improve liver outcomes in CLD, something well established to be the case and to reduce diabetic microvascular complications in the general population with T2DM. The many mechanisms by which hyperglycemia may alter hepatocyte and stellate cell biology, discussed above, provides a plausible rationale to seek strict control of hyperglycemia. The limiting factor remains severe hypoglycemia. The availability of a number of new agents to treat diabetes that can be more safely prescribed to patients is encouraging,[127] although not tested in decompensated cirrhosis.[11] They have a lower chance of inducing hypoglycemia than with intensive insulin therapy, which combined with better means to continuously monitor glycemia in the outpatient setting (ie, CGMs) make this aspect of care worth testing in future controlled multicenter trials.

Diet, nutrition, and physical activity

Compensated cirrhosis. The importance of nutrition and exercise in cirrhosis is increasingly recognized. However, data regarding the specific management of overweight/obesity or malnutrition are very limited in patients with T2DM and cirrhosis. In those with compensated cirrhosis without malnutrition/sarcopenia, the same lifestyle modifications can be applied than in patients without cirrhosis. Alcohol abstinence is encouraged and a 7%–10% weight loss is the target of most lifestyle interventions associated with improvement of histology.[11,13,100–103,129] A Mediterranean diet without alcohol is the preferred diet with caloric restriction maintaining carbohydrate intake between 50% and 65% to avoid iatrogenic hypoglycemia. Protein intake should be carefully monitored to prevent sarcopenia (at least 1.2–1.5 g/kg/d).[129] As for physical activity, no clear-cut data is available regarding the best type of physical exercise (aerobic vs. anaerobic; endurance vs. resistance/strength training) or its duration in this population. Like in noncirrhotic patients, 150–200 min/wk of moderate intensity aerobic physical activities in 3–5 sessions are generally recommended.[11]

Decompensated cirrhosis. Protein energy malnutrition, sarcopenia, and physical inactivity are common in patients with decompensated cirrhosis and increases with impaired liver function.[130] Sarcopenia is an independent prognostic factor of mortality in decompensated cirrhosis and should therefore be assessed.[129] Sarcopenia may be masked by the coexistence of morbid obesity, which is most notable in patients with NAFLD. Sarcopenia and obesity have previously been viewed as separate entities on opposite ends of the spectrum.

However, sarcopenic obesity, defined as the combination of sarcopenia and obesity, is observed with increasing frequency in patients with cirrhosis, especially in those with NASH, because of the coexistence of T2DM as well as other features of the metabolic syndrome.[131] Patients with NAFLD and decompensated cirrhosis should undergo anthropometric measures (handgrip strength), dry body mass index, and measures of physical frailty (including muscle function, not just mass) to enable targeted early interventions. However, lifestyle interventions and physical activities may be challenging in patients with decompensated cirrhosis. First, poor nutritional status contraindicates hypocaloric diets. Second, ascites, edema, and fatigue frequently hamper physical exercise programs.[132] In patients with cirrhosis and malnutrition or sarcopenia, nutritional supplementation (oral, enteral, or parenteral) should be initiated by a multidisciplinary team.[130]

Bariatric surgery

Bariatric surgery is the most effective and durable weight-loss approach to treat obesity, improve T2DM control,[133] and reduce major cardiovascular events,[134] including in patients with NASH.[135] Paired biopsy studies before and after bariatric surgery have shown substantial improvements in liver histology, including decreased prevalence of NASH and fibrosis after 1 year[136] and 5 years of follow-up.[137] Survival benefit with bariatric surgery has been demonstrated in general patient populations, although data for improved transplant-free survival in cirrhosis are lacking.[138] Fibrosis regression may reduce the risk for complications from CLD, including HCC and mortality. However, long-term data evaluating the impact of weight loss–induced improvement in fibrosis and portal hypertension on liver-related morbidity and mortality are not currently available.

Although bariatric surgery is considered a safe procedure with low perioperative mortality rates, ranging between 0.03% and 0.2%, its safety for patients with cirrhosis is not well established.[139] The mortality risk of bariatric surgery in compensated cirrhosis has been suggested to be slightly higher than in patients without cirrhosis (0.9% vs. 0.3%, respectively), but significantly higher in decompensated cirrhosis (16.3%).[138] Several studies[140–142] have suggested that in well-compensated, carefully selected obese patients with cirrhosis, bariatric surgery is overall safe and is associated with only a slight increase in procedure risk. The higher mortality rate with compensated cirrhosis may be justified because of the potential benefits that weight loss could offer to these very ill patients, but this higher procedure risk needs to be acknowledged and discussed in a shared-decision process with potential candidates for surgery.[11,103,138]

Also, the presence of clinically significant portal hypertension should be evaluated before bariatric surgery in all patients with cirrhosis. There are several small series reporting feasibility of bariatric surgery among patients with clinically significant portal hypertension, with low rates of postoperative mortality or portal hypertension.[141,143,144] Despite relatively low rates of complications reported in these case series, performance of bariatric surgery on patients with evidence of clinically significant portal hypertension should be restricted to selected medical centers with experience and resources for managing complications. Clearly, further long-term, controlled studies are needed. Finally, there is no consensus on which bariatric modality is best suited for patients with cirrhosis.[138,145]

In summary, the risk-to-benefit ratio for bariatric surgery in individuals with cirrhosis is complex to determine and is hampered by a lack of randomized controlled trials. Future studies are needed to establish the type, safety, and efficacy of bariatric surgery in people with obesity and established cirrhosis. In experienced surgical centers, bariatric surgery in patients with compensated cirrhosis from NASH may be considered but only on a case-by-case basis. It is not recommended in patients with decompensated cirrhosis.[11,13,101,103] More studies are needed to assess the impact and risk-benefit ratio on diabetes and liver outcomes following bariatric surgery in patients with diabetes and cirrhosis.

Pharmacotherapy

The pharmacological approach should be divided between treating patients with diabetes with either compensated or decompensated cirrhosis. In the early stages of cirrhosis, management should not fundamentally differ from that of patients without CLD. In contrast, decompensated cirrhosis can become especially challenging when associated conditions complicate management, such as CKD or hepatorenal syndrome, CVD, CHF with reduced ejection fraction and edema, portal hypertension with frank ascites, and hypersplenism with anemia or recurrent SBP, and obesity-related comorbidities, among others. Careful decision-making will allow the clinician to navigate the changing circumstances. The A1c targets should be individualized based on associated complications, QOL, and life expectancy.

Diabetes medications should be used being fully aware of the pros/cons of each diabetes medication. Insulin has been the traditional approach to patients with decompensated cirrhosis. Oral agents should be used with caution due to the limitations imposed by end-stage liver disease on the metabolism of each agent. Each sulfonylurea is cleared differently, depending on the proportion metabolized by the hepatocyte CYP450 system (primarily CYP450:2C9 isoenzyme) or renally excreted. Long-acting sulfonylureas (with a half-life of 9–10 h) such as glyburide and glimepiride may pose a greater risk of hypoglycemia, especially if associated with CKD, as they are significantly

excreted by the kidney (50% and 60%, respectively).[146] In contrast, glipizide has a shorter half-life (2–5 h) and is primarily metabolized in the liver to inactive metabolites with less that 10% of the intact drug detected in the urine, making it potentially safer in patients with CLD, especially if CKD is present,[147] although this has not been systematically examined. Overall, the prescription of sulfonylureas has declined significantly in the US because of a greater risk of hypoglycemia compared with other antidiabetic agents, along with controversy from epidemiological studies suggesting an increase in major cardiovascular events and total mortality,[148] although not in all studies.[146] Glimepiride seems to be the safest among sulfonylureas from a cardiovascular perspective, being overall neutral regarding the risk of cardiovascular events.[148,149] However, given the many factors promoting hypoglycemia in people with cirrhosis (Figure 3), including decreased appetite and cachexia, clinical judgment is needed if prescribed, but in general sulfonylureas should be avoided.[150] Finally, when the eGFR < 60 mL/min/1.73 m^2 sulfonylurea use should be definitively discouraged as they may accumulate and add to their risk of inducing severe hypoglycemia.[147]

Decreased hepatic lactate clearance and the frequent risk of cardiorenal complications place patients with cirrhosis at an increased risk of metformin-associated lactic acidosis. The biguanide should be used with caution, or best avoided, in people with Child-Pugh class B cirrhosis and stage eGFR <60 mL/min/1.73 m^2,[151] while contraindicated in decompensated liver disease independent of renal function. Of note, some studies have shown improved outcomes of patients with NASH.[152–154] One retrospective analysis in patients with diabetes and compensated cirrhosis from NASH compared outcomes in 110 users of metformin (mean dose = ~1 g/d) versus 81 nonusers. Mean follow-up was ~7 years.[153] During this time, 28 patients developed HCC (metformin users: 7, nonusers: 21), and 52 died (metformin users: 7, nonusers: 24) or were transplanted (metformin users: 13, non-users: 13). The investigators concluded that long-term metformin use was associated with a reduction in the risk of all-cause mortality and HCC in this population. Of note, the mean dose of metformin of ~1 g per day used in the study was about 50% of the usual dose of 2 g per day prescribed in patients with T2DM in the general population. More recently, the same group studied an international cohort (from Australia, Cuba, Hong Kong, and Spain) of 212 patients with T2DM and Child-Pugh A cirrhosis reporting a significant reduction in the risk of death or liver transplantation, hepatic decompensation, and HCC.[154] Taken together, while we await future controlled trials to fully establish the benefit of metformin in people with cirrhosis, any potential benefit must be balanced with the risk of harm when prescribing the biguanide in this population.

Among other pharmacological agents to treat diabetes, there is limited evidence about the safety and efficacy of agents tested in noncirrhotic NASH, such as DPP4 inhibitors, GLP-1RA, SGLT2 inhibitors, or pioglitazone.[11,155] However, safety is considered overall good, at least in compensated cirrhosis, with minimal risk of hypoglycemia compared with sulfonylureas or insulin. Another advantage is that pioglitazone, SGLT2 inhibitors, and GLP-1RA (except exenatide that is not recommended if eGFR <30 mL/min/1.73 m^2) are not cleared by the kidney and may be used in patients with CLD with or without CKD. While pioglitazone has been incorporated into clinical practice guidelines for the treatment of NASH without cirrhosis,[11,13,99,101,103,110] there is limited data with pioglitazone in patients with cirrhosis and it must be avoided in the presence of decompensated cirrhosis (the drug is metabolized mainly by CYPC28 and to a lesser extent by CYP3A4), preexisting heart failure, and/or lower extremity edema. However, pioglitazone seems to be overall safe from the limited data available in patients with cirrhosis.[156,157] Of interest, a recent study evaluating incident cirrhosis in adults aged ≥65 years suggested that pioglitazone use was associated with lower incidence of cirrhosis compared with DPP-4 inhibitors, SGLT2i or GLP-1RA,[158] but there is a lack of long-term controlled studies.

In addition to their well-established cardiorenal benefits and potential to improve steatohepatitis,[98,155] SGLT2 inhibitors may mitigate volume overload and improve outcomes in patients with advanced cirrhosis.[159] SGLT2 inhibition in the renal proximal tubule promotes both glycosuria and natriuresis, decreasing renin and angiotensin II secretion as well as salt and water retention. This may restore renal vascular tone (ie, arteriolar dilation and efferent constriction) and glomerular filtration, eventually ameliorating renal fibrosis. However, specific renal and hemodynamic benefits that improve overall survival in patients with cirrhosis need careful testing. SGLT2 inhibitors seem safe as rates of hepatic decompensation and mortality were comparable to that expected from epidemiological studies in a recent observational study in 78 patients with T2DM and predominantly compensated cirrhosis (50% with NASH) treated for an average ≥2 years.[160] In another observational study, investigators examined by propensity score-matched intention-to-treat analysis in 846 patients on metformin who subsequently received either SGLT2i or DPP-4 inhibitors.[161] Ascites was unchanged, but SGLT2i users had a reduced risk of death (adjusted HR: 0.33; 95% CI: 0.11–0.99; $p < 0.05$) compared with DPP-4 inhibitor users. Clearly long-term controlled studies are needed to assess the role of SGLT2i in cirrhosis. Finally, while the growing role of GLP-1RA for the management of NAFLD is evident from numerous controlled trials,[162] there is limited evidence for their use in people with cirrhosis. In a recent preliminary report in 71 patients with T2DM with NASH-related cirrhosis, although weekly semaglutide at 2.4 mg for 48 weeks significantly decreased body weight (~9 kg), plasma aminotransferases and A1c levels (−1.6%), it failed to improve steatohepatitis or fibrosis compared with

placebo.[163] However, treatment was well tolerated and safe, with adverse effects limited to mild-to-moderate gastrointestinal symptoms.

Insulin is extensively used in patients with cirrhosis but caution is needed as it is associated with a high risk of hypoglycemia by means of a number of mechanisms closely linked to end-stage liver disease (Figure 3), as discussed earlier. However, long-term studies examining whether its use improves liver outcomes or survival are lacking. Indeed, a recent study has suggested a deleterious effect and questioned the wisdom of using insulin in people with cirrhosis.[164] The investigators compared liver-related complications and cardiovascular events in people with T2DM and compensated liver cirrhosis followed for a mean of 5.8 years treated with insulin (n = 2047) and propensity score–matched non-users (n = 4094) from Taiwan's National Health Insurance Research Database. In addition to hypoglycemia being 3.3-fold greater in users versus nonusers of insulin, HRs of all-cause mortality, HCC, decompensated cirrhosis, hepatic failure, and major cardiovascular events were 18%–53% higher. These provocative findings call for long-term studies in patients with compensated liver cirrhosis to evaluate major outcomes with intensive insulin therapy, especially compared with oral agents or GLP-1RA. It also calls to assess the impact of optimal glycemic control and better prevention of hypoglycemia with improved glucose monitoring with newer devices on liver and cardiovascular outcomes. One should also keep in mind that although diabetes medications may have had a modest effect in reversing NASH-related cirrhosis, they may slow liver fibrosis progression and offer cardiovascular and renal benefit, which may improve patient's QOL and overall survival. Finally, vitamin E has been reported in a small, observational study to improve transplant-free survival and reduce hepatic decompensation in patients with NASH and advanced fibrosis.[165]

Statins are considered safe for patients with F2–F3 and Child A or B cirrhosis. A recent meta-analysis including 121,058 people with CLD reported significant benefit with statin treatment in those with cirrhosis, reducing both episodes of hepatic decompensation and overall mortality, by almost 50%.[166] In studies including patients with CLD without cirrhosis (n = 5), statin use was associated with a nonsignificant (but 58% lower) risk of developing cirrhosis or fibrosis progression. In addition, in a large retrospective cohort study of patients with newly diagnosed cirrhosis from the Veterans Health Administration, each cumulative year of statin exposure to statins was associated with an independent 8.0%–8.7% decrease of mortality of patients with cirrhosis of Child-Pugh classes A and B, but benefit did not extend to patients with Child-Pugh class C cirrhosis.[167] Data in patients with decompensated cirrhosis remains limited, but it is generally recommended that use in these patients should be avoided.

Monitoring diabetes in patients with cirrhosis

Compensated cirrhosis

Because patients with cirrhosis are prone to developing T2DM, all patients should be considered at risk and diabetes screening becomes a routine aspect of their care. In patients with compensated cirrhosis and diabetes, monitoring of hyperglycemia should be similar to those without cirrhosis as long as patients are not anemic. As reviewed, should anemia be present, testing by A1c becomes unreliable to assess glycemic control, so that plasma glucose, fructosamine (if preserved liver biosynthetic function),[67] or CGM[125,126] are better options to monitor control.

Decompensated cirrhosis

In this setting, most patients are anemic and the best tests for the diagnosis are based on the accurate measurement of plasma glucose, either fasting, or best during an OGTT, while monitoring relies heavily on self-monitoring of blood glucose and CGMs (Figure 2).[125,126] The use of CGMs has been modest in this population, but increasing with the greater access to this technology and the development of multidisciplinary teams involving endocrinologists. The medical team must individualize the target A1c for each patient taking into account the risk of hypoglycemia, QOL, comorbidities, and cirrhosis-associated complications.

CONCLUSION AND FUTURE DIRECTIONS

The prevalence of diabetes in patients with cirrhosis is high, and vice versa. NAFLD-related cirrhosis is common in patients with T2DM. In both settings the link between diabetes and cirrhosis remains today underestimated and inadequately managed by clinicians. Cirrhosis is obviously a major prognostic driver for liver-related outcomes and overall mortality in patients with diabetes and NAFLD. Risk factors for developing cirrhosis are related to obesity and lipotoxicity, insulin resistance, hyperglycemia, as well as comorbidities associated with metabolic syndrome, but the role of liver disease on diabetes complications requires further investigation. Thus, patients with diabetes should be systematically screened for NAFLD-related fibrosis and cirrhosis using noninvasive tools.[11,101,103] An early diagnosis would allow referral to a liver specialist to prevent cirrhosis-related complications. More work is needed in developing and fine-tuning effective clinical care pathways between primary care, diabetes, and liver specialists.

Multidisciplinary teams are needed to deliver optimal care and encourage lifestyle changes. While the impact

of lifestyle modification in liver disease is unquestionable, the optimal approach for patients with diabetes and cirrhosis still needs to be established in long-term randomized controlled trials. A greater use of structured weight loss programs, anti-obesity medications, and bariatric surgery should be encouraged. The ideal bariatric surgery approach in this setting also awaits carefully designed prospective studies. It also remains to be better explored if implementation of strict glycemic control using newer glucose-monitoring tools can modify the natural history of liver disease and prevent cirrhosis and its major complications. It may also matter how we achieve glycemic control. For instance, it may be of value to perform controlled trials comparing insulin to newer oral and injectable agents. Diabetes agents such as pioglitazone, SGLT2 inhibitors, GLP-1RA, and dual agonists GLP-1/GIP RA (tirzepatide) that improve steatohepatitis may slow fibrosis progression and should be investigated in prospective trials in people with T2DM and cirrhosis. Clearly, there is a need to address the many knowledge gaps with randomized controlled trials examining all aspects of care of patients with diabetes and cirrhosis to improve their QOL and long-term outcomes. Until then, clinicians should be proactive in the early diagnosis of liver fibrosis by screening all people with T2DM (ie, FIB-4) and intervene before the development of cirrhosis with multidisciplinary teams that encourage treatment of obesity with lifestyle changes (and anti-obesity agents when indicated) and of T2DM with medications of proven efficacy to reverse steatohepatitis and fibrosis progression in people with NASH.

CONFLICTS OF INTEREST

Laurent Castera consults for and is on the speakers' bureau for Echosens and Novo Nordisk. He consults for Madrigal, MSD, Pfizer, and Sagimet. Kenneth Cusi has received research support toward the University of Florida as principal investigator from Echosens, Inventiva, Novo Nordisk, Poxel, Labcorp, and Zydus. He consults for Aligos, Altimmune, Arrowhead, AstraZeneca, 89Bio, Boehringer Ingelheim, BMS, Covance, Lilly, Madrigal, Merck, Myovant, Novo Nordisk, Prosciento, Quest, Sagimet, Siemens, Sonic Incytes, and Terns.

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REFERENCES

1. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol. 2019;71:793–801.
2. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70:151–71.
3. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389:2239–51.
4. Elkrief L, Rautou PE, Sarin S, Valla D, Paradis V, Moreau R. Diabetes mellitus in patients with cirrhosis: clinical implications and management. Liver Int. 2016;36:936–48.
5. Gines P, Castera L, Lammert F, Graupera I, Serra-Burriel M, Allen AM, et al. Population screening for liver fibrosis: toward early diagnosis and intervention for chronic liver diseases. Hepatology. 2022;75:219–8.
6. Castera L, Laouenan C, Vallet-Pichard A, Vidal-Trecan T, Manchon P, Paradis V, et al. High prevalence of NASH and advanced fibrosis in type 2 diabetes: a prospective study in 330 outpatients undergoing liver biopsies for elevated ALT using a low threshold. Diabetes Care Published online April 12, 202310.2337/dc22-2048
7. Lomonaco R, Godinez Leiva E, Bril F, Shrestha S, Mansour L, Budd J, et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening. Diabetes Care. 2021;44:399–406.
8. Barb D, Repetto EM, Stokes ME, Shankar SS, Cusi K. Type 2 diabetes mellitus increases the risk of hepatic fibrosis in individuals with obesity and nonalcoholic fatty liver disease. Obesity (Silver Spring). 2021;29:1950–60.
9. Ciardullo S, Monti T, Perseghin G. High prevalence of advanced liver fibrosis assessed by transient elastography among U.S. adults with type 2 diabetes. Diabetes Care. 2021;44:519–25.
10. Harrison SA, Gawrieh S, Roberts K, Lisanti CJ, Schwope RB, Cebe KM, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. J Hepatol. 2021;75:284–91.
11. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract. 2022;28:528–62.
12. Kanwal F, Shubrook JH, Younossi Z, Natarajan Y, Bugianesi E, Rinella ME, et al. Preparing for the NASH epidemic: a call to action. Diabetes Care. 2021;44:2162–72.
13. Kanwal F, Shubrook JH, Adams LA, Pfotenhauer K, Wai-Sun Wong V, Wright E, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology. 2021;161:1657–69.
14. Boursier J, Anty R, Carette C, Cariou B, Castera L, Caussy C, et al. Management of diabetes mellitus in patients with cirrhosis: an overview and joint statement. Diabetes Metab. 2021;47:101272.
15. Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, et al. Noninvasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol. 2021;116:723–32.
16. Anstee QM, Castera L, Loomba R. Impact of non-invasive biomarkers on hepatology practice: past, present and future. J Hepatol. 2022;76:1362–78.
17. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol. 2018;69:896–904.
18. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.
19. D'Amico G, Bernardi M, Angeli P. Towards a new definition of decompensated cirrhosis. J Hepatol. 2022;76:202–7.

20. Lee WG, Wells CI, McCall JL, Murphy R, Plank LD. Prevalence of diabetes in liver cirrhosis: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2019;35:e3157.
21. Petit JM, Hamza S, Rollot F, Sigonney V, Crevisy E, Duvillard L, et al. Impact of liver disease severity and etiology on the occurrence of diabetes mellitus in patients with liver cirrhosis. Acta Diabetol. 2014;51:455–60.
22. Bertot LC, Jeffrey GP, de Boer B, MacQuillan G, Garas G, Chin J, et al. Diabetes impacts prediction of cirrhosis and prognosis by non-invasive fibrosis models in non-alcoholic fatty liver disease. Liver Int. 2018;38:1793–802.
23. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65:1359–68.
24. Lai LL, Wan Yusoff WNI, Vethakkan SR, Nik Mustapha NR, Mahadeva S, Chan WK. Screening for non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus using transient elastography. J Gastroenterol Hepatol. 2019;34:1396–403.
25. Roulot D, Roudot-Thoraval F, G NK, Kouacou N, Costes JL, Elourimi G, et al. Concomitant screening for liver fibrosis and steatosis in French type 2 diabetic patients using Fibroscan. Liver Int. 2017;37:1897–906.
26. Sporea I, Mare R, Popescu A, Nistorescu S, Baldea V, Sirli R, et al. Screening for liver fibrosis and steatosis in a large cohort of patients with type 2 diabetes using vibration controlled transient elastography and controlled attenuation parameter in a single-center real-life experience. J Clin Med. 2020;9:1032.
27. Isaacs S. Nonalcoholic fatty liver disease. Endocrinol Metab Clin North Am. 2023;52:149–64.
28. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol. 2022;10:284–96.
29. Goh GB, Pan A, Chow WC, Yuan JM, Koh WP. Association between diabetes mellitus and cirrhosis mortality: the Singapore Chinese Health Study. Liver Int. 2017;37:251–8.
30. Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med. 2021; 385:1559–69.
31. European Association for the Study of Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236.
32. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology. 2018;155:443–57.e417.
33. Taylor RS, Taylor RJ, Bayliss S, Hagstrom H, Nasr P, Schattenberg JM, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology. 2020; 158:1611–25.e1612.
34. Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. Gut. 2021;70:1375–82.
35. Doycheva I, Zhang T, Amjad W, Thuluvath PJ. Diabetes and hepatocellular carcinoma: incidence trends and impact of liver disease etiology. J Clin Exp Hepatol. 2020;10:296–303.
36. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397:2212–24.
37. Mantovani A, Petracca G, Beatrice G, Csermely A, Tilg H, Byrne CD, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. Gut. 2022;71:778–88.
38. Cusi K, Godinez Leiva E. Cardiovascular risk in patients with nonalcoholic fatty liver disease: looking at the liver to shield the heart. Curr Opin Lipidol. 2020;31:364–6.
39. Mantovani A, Csermely A, Petracca G, Beatrice G, Corey KE, Simon TG, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6:903–13.
40. Polyzos SA, Kechagias S, Tsochatzis EA. Review article: non-alcoholic fatty liver disease and cardiovascular diseases: associations and treatment considerations. Aliment Pharmacol Ther. 2021;54:1013–25.
41. Wijarnpreecha K, Aby ES, Ahmed A, Kim D. Evaluation and management of extrahepatic manifestations of nonalcoholic fatty liver disease. Clin Mol Hepatol. 2021;27:221–35.
42. Lee SB, Park GM, Lee JY, Lee BU, Park JH, Kim BG, et al. Association between non-alcoholic fatty liver disease and subclinical coronary atherosclerosis: an observational cohort study. J Hepatol. 2018;68:1018–24.
43. Morrison AE, Zaccardi F, Khunti K, Davies MJ. Causality between non-alcoholic fatty liver disease and risk of cardiovascular disease and type 2 diabetes: a meta-analysis with bias analysis. Liver Int. 2019;39:557–67.
44. Mantovani A, Dauriz M, Sandri D, Bonapace S, Zoppini G, Tilg H, et al. Association between non-alcoholic fatty liver disease and risk of atrial fibrillation in adult individuals: an updated meta-analysis. Liver Int. 2019;39:758–69.
45. Mantovani A, Pernigo M, Bergamini C, Bonapace S, Lipari P, Valbusa F, et al. Heart valve calcification in patients with type 2 diabetes and nonalcoholic fatty liver disease. Metabolism. 2015;64:879–87.
46. Mantovani A, Byrne CD, Bonora E, Targher G. Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. Diabetes Care. 2018;41:372–82.
47. Henson JB, Simon TG, Kaplan A, Osganian S, Masia R, Corey KE. Advanced fibrosis is associated with incident cardiovascular disease in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2020;51:728–36.
48. Shang Y, Nasr P, Widman L, Hagstrom H. Risk of cardiovascular disease and loss in life expectancy in NAFLD. Hepatology. 2022;76:1495–505.
49. Bril F, Sninsky JJ, Baca AM, Superko HR, Portillo Sanchez P, Biernacki D, et al. Hepatic steatosis and insulin resistance, but not steatohepatitis, promote atherogenic dyslipidemia in NAFLD. J Clin Endocrinol Metab. 2016;101:644–52.
50. Siddiqui MS, Fuchs M, Idowu MO, Luketic VA, Boyett S, Sargeant C, et al. Severity of nonalcoholic fatty liver disease and progression to cirrhosis are associated with atherogenic lipoprotein profile. Clin Gastroenterol Hepatol. 2015;13:1000–8.e1003.
51. Patel S, Siddiqui MB, Chandrakumaran A, Rodriguez VA, Faridnia M, Hernandez Roman J, et al. Progression to cirrhosis leads to improvement in atherogenic milieu. Dig Dis Sci. 2021; 66:263–72.
52. Clària J, Curto A, Moreau R, Colsch B, López-Vicario C, Lozano JJ, et al. Untargeted lipidomics uncovers lipid signatures that distinguish severe from moderate forms of acutely decompensated cirrhosis. J Hepatol. 2021;75:1116–27.
53. Trieb M, Horvath A, Birner-Gruenberger R, Spindelboeck W, Stadlbauer V, Taschler U, et al. Liver disease alters high-density lipoprotein composition, metabolism and function. Biochim Biophys Acta. 2016;1861:630–8.
54. Trieb M, Rainer F, Stadlbauer V, Douschan P, Horvath A, Binder L, et al. HDL-related biomarkers are robust predictors of survival in patients with chronic liver failure. J Hepatol. 2020;73: 113–20.
55. Petrides AS, DeFronzo RA. Glucose metabolism in cirrhosis: a review with some perspectives for the future. Diabetes Metab Rev. 1989;5:691–709.
56. Petrides AS, Groop LC, Riely CA, DeFronzo RA. Effect of physiologic hyperinsulinemia on glucose and lipid metabolism in cirrhosis. J Clin Invest. 1991;88:561–70.

57. Petrides AS, Luzi L, Reuben A, Riely C, DeFronzo RA. Effect of insulin and plasma amino acid concentration on leucine metabolism in cirrhosis. Hepatology. 1991;14:432–1.
58. Perseghin G, Mazzaferro V, Sereni LP, Regalia E, Benedini S, Bazzigaluppi E, et al. Contribution of reduced insulin sensitivity and secretion to the pathogenesis of hepatogenous diabetes: effect of liver transplantation. Hepatology. 2000;31:694–703.
59. Petrides AS, Vogt C, Schulze-Berge D, Matthews D, Strohmeyer G. Pathogenesis of glucose intolerance and diabetes mellitus in cirrhosis. Hepatology. 1994;19:616–27.
60. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. JHEP Rep. 2019;1:312–28.
61. Grancini V, Trombetta M, Lunati ME, Zimbalatti D, Boselli ML, Gatti S, et al. Contribution of β-cell dysfunction and insulin resistance to cirrhosis-associated diabetes: Role of severity of liver disease. J Hepatol. 2015;63:1484–90.
62. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773–95.
63. Nishida T. Diagnosis and clinical implications of diabetes in liver cirrhosis: a focus on the oral glucose tolerance test. J Endocr Soc. 2017;1:886–96.
64. Coman LI, Coman OA, Bădărău IA, Păunescu H, Ciocîrlan M. Association between liver cirrhosis and diabetes mellitus: a review on hepatic outcomes. J Clin Med. 2021;10:262.
65. Bril F, Lomonaco R, Orsak B, Ortiz-Lopez C, Webb A, Tio F, et al. Relationship between disease severity, hyperinsulinemia, and impaired insulin clearance in patients with nonalcoholic steatohepatitis. Hepatology. 2014;59:2178–87.
66. Lomonaco R, Bril F, Portillo-Sanchez P, Ortiz-Lopez C, Orsak B, Biernacki D, et al. Metabolic impact of nonalcoholic steatohepatitis in obese patients with type 2 diabetes. Diabetes Care. 2016;39:632–8.
67. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Classification and diagnosis of diabetes: standards of medical care in diabetes-2023. Diabetes Care. 2023;46(suppl 1):S19–40.
68. Cusi K. The role of adipose tissue and lipotoxicity in the pathogenesis of type 2 diabetes. Curr Diab Rep. 2010;10:306–15.
69. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology. 2012;142:711–25.e716.
70. Lomonaco R, Ortiz-Lopez C, Orsak B, Finch J, Webb A, Bril F, et al. Role of ethnicity in overweight and obese patients with nonalcoholic steatohepatitis. Hepatology. 2011;54:837–45.
71. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell. 2021;184:2537–64.
72. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–23.
73. Zambon Azevedo V, Silaghi CA, Maurel T, Silaghi H, Ratziu V, Pais R. Impact of sarcopenia on the severity of the liver damage in patients with non-alcoholic fatty liver disease. Front Nutr. 2021;8:774030.
74. Gastaldelli A, Cusi K, Pettiti M, Hardies J, Miyazaki Y, Berria R, et al. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. Gastroenterology. 2007;133:496–506.
75. Maximos M, Bril F, Portillo Sanchez P, Lomonaco R, Orsak B, Biernacki D, et al. The role of liver fat and insulin resistance as determinants of plasma aminotransferase elevation in nonalcoholic fatty liver disease. Hepatology. 2015;61:153–60.
76. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. JHEP Rep. 2019;1:312–28.
77. Ebadi M, Tsien C, Bhanji RA, Dunichand-Hoedl AR, Rider E, Motamedrad M, et al. Myosteatosis in cirrhosis: a review of diagnosis, pathophysiological mechanisms and potential interventions. Cells. 2022;11:1216.
78. Schuppan D, Surabattula R, Wang XY. Determinants of fibrosis progression and regression in NASH. J Hepatol. 2018;68:238–50.
79. Bazerbachi F, Haffar S, Wang Z, Cabezas J, Arias-Loste MT, Crespo J, et al. Range of normal liver stiffness and factors associated with increased stiffness measurements in apparently healthy individuals. Clin Gastroenterol Hepatol. 2019;17:54–64.e51.
80. Sunny NE, Bril F, Cusi K. Mitochondrial adaptation in nonalcoholic fatty liver disease: Novel mechanisms and treatment strategies. Trends Endocrinol Metab. 2017;28:250–60.
81. Summers SA. Ceramides: nutrient signals that drive hepatosteatosis. J Lipid Atheroscler. 2020;9:50–65.
82. Fromenty B, Roden M. Mitochondrial alterations in fatty liver diseases. J Hepatol. 2023;78:415–29.
83. Patterson RE, Kalavalapalli S, Williams CM, Nautiyal M, Mathew JT, Martinez J, et al. Lipotoxicity in steatohepatitis occurs despite an increase in tricarboxylic acid cycle activity. Am J Physiol Endocrinol Metab. 2016;310:E484–494.
84. Kalavalapalli S, Bril F, Guingab J, Vergara A, Garrett TJ, Sunny NE, et al. Impact of exenatide on mitochondrial lipid metabolism in mice with nonalcoholic steatohepatitis. J Endocrinol. 2019;241:293–305.
85. Kalavalapalli S, Bril F, Koelmel JP, Abdo K, Guingab J, Andrews P, et al. Pioglitazone improves hepatic mitochondrial function in a mouse model of nonalcoholic steatohepatitis. Am J Physiol Endocrinol Metab. 2018;315:E163–e173.
86. Bessone F, Razori MV, Roma MG. Molecular pathways of nonalcoholic fatty liver disease development and progression. Cell Mol Life Sci. 2019;76:99–128.
87. Dong J, Viswanathan S, Adami E, Singh BK, Chothani SP, Ng B, et al. Hepatocyte-specific IL11 cis-signaling drives lipotoxicity and underlies the transition from NAFLD to NASH. Nat Commun. 2021;12:66.
88. Huby T, Gautier EL. Immune cell-mediated features of nonalcoholic steatohepatitis. Nat Rev Immunol. 2022;22:429–3.
89. Straub LG, Scherer PE. Metabolic messengers: adiponectin. Nat Metab. 2019;1:334–9.
90. Unger RH, Grundy S. Hyperglycaemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. Diabetologia. 1985;28:119–21.
91. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care. 1990;13:610–30.
92. Lytrivi M, Castell AL, Poitout V, Cnop M. Recent insights into mechanisms of β-Cell lipo- and glucolipotoxicity in type 2 diabetes. J Mol Biol. 2020;432:1514–34.
93. Portillo P, Yavuz S, Bril F, Cusi K. Role of insulin resistance and diabetes in the pathogenesis and treatment of NAFLD. Curr Hepatol Reports. 2014;13:159–70.
94. Azzu V, Vacca M, Virtue S, Allison M, Vidal-Puig A. Adipose tissue-liver Cross talk in the control of whole-body metabolism: implications in nonalcoholic fatty liver disease. Gastroenterology. 2020;158:1899–912.
95. Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol. 2019;7:313–24.
96. Wong VWS, Zelber-Sagi S, Cusi K, Carrieri P, Wright E, Crespo J, Lazarus JV. Management of NAFLD in primary care settings. Liver Int Published online August 20, 202210.1111/liv.15404
97. Bril F, Cusi K. Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action. Diabetes Care. 2017;40:419–30.
98. Cusi K. Time to include nonalcoholic steatohepatitis in the management of patients with type 2 diabetes. Diabetes Care. 2020;43:275–9.

99. Younossi Z, Alkhouri N, Cusi K, Issacs S, Kanwal F, Noureddine M, et al. A practical use of noninvasive tests in clinical practice to identify high-risk patients with nonalcoholic steatohepatitis. Alimentary Pharmacology & Therapeutics. 2023;57:304–12.
100. European Association of the Study of Liver. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64:1388–402.
101. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Comprehensive medical evaluation and assessment of comorbidities: Standards of care in diabetes-2023. Diabetes Care. 2023;46(suppl 1):S49–67.
102. Arab JP, Dirchwolf M, Álvares-da-Silva MR, Barrera F, Benítez C, Castellanos-Fernandez M, et al. Latin American Association for the study of the liver (ALEH) practice guidance for the diagnosis and treatment of non-alcoholic fatty liver disease. Ann Hepatol. 2020;19:674–90.
103. Rinella M, Neuschwander-Tetri B, Siddiqui MS, Abdelmalek M, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77:1797–835.
104. Portillo-Sanchez P, Bril F, Maximos M, Lomonaco R, Biernacki D, Orsak B, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. J Clin Endocrinol Metab. 2015;100:2231–38.
105. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C. Baveno VII—renewing consensus in portal hypertension. J Hepatol. 2022;76:959–74.
106. Mózes FE, Lee JA, Selvaraj EA, Jayaswal ANA, Trauner M, Boursier J, et al. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. Gut. 2022;71:1006–9.
107. Unalp-Arida A, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. Hepatology. 2017;66:84–95.
108. Hagström H, Talbäck M, Andreasson A, Walldius G, Hammar N. Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease. J Hepatol. 2020;73:1023–9.
109. Noureddin M, Jones C, Alkhouri N, Gomez EV, Dieterich DT, Rinella ME. Screening for nonalcoholic fatty liver disease in persons with type 2 diabetes in the United States is cost-effective: a comprehensive cost-utility analysis. Gastroenterology. 2020;159:1985–7.e1984.
110. Belfort-DeAguiar R, Lomonaco R, Cusi K. Approach to the patient with nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2023;108:483–95.
111. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;75:659–89.
112. Hsiang JC, Gane EJ, Bai WW, Gerred SJ. Type 2 diabetes: a risk factor for liver mortality and complications in hepatitis B cirrhosis patients. J Gastroenterol Hepatol. 2015;30: 591–9.
113. Liu TL, Trogdon J, Weinberger M, Fried B, Barritt AST. Diabetes is associated with clinical decompensation events in patients with cirrhosis. Dig Dis Sci. 2016;61:3335–45.
114. Chung W, Promrat K, Wands J. Clinical implications, diagnosis, and management of diabetes in patients with chronic liver diseases. World J Hepatol. 2020;12:533–7.
115. Ahn SB, Powell EE, Russell A, Hartel G, Irvine KM, Moser C, et al. Type 2 diabetes: a risk factor for hospital readmissions and mortality in Australian patients with cirrhosis. Hepatol Commun. 2020;4:1279–92.
116. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clini Pract. 2018;138:271–81.
117. Subhiyah BW, al-Hindawi AY. Red cell survival and splenic accumulation of radiochromium in liver cirrhosis with splenomegaly. Br J Haematol. 1967;13:773–8.
118. Imano E, Nishida T, Shibata M, Kanda T. Significance of oral glucose tolerance test for the diagnosis of diabetes mellitus in patients with liver cirrhosis. Intern Med. 1999;38:918.
119. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Haruna Y, Imano E, et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. Am J Gastroenterol. 2006;101:70–5.
120. Edwards CM, Cusi K. Prediabetes: a worldwide epidemic. Endocrinol Metab Clin North Am. 2016;45:751–64.
121. Ortiz-Lopez C, Lomonaco R, Orsak B, Finch J, Chang Z, Kochunov VG, et al. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). Diabetes Care. 2012;35:873–8.
122. Gujral UP, Jagannathan R, He S, Huang M, Staimez LR, Wei J, et al. Association between varying cut-points of intermediate hyperglycemia and risk of mortality, cardiovascular events and chronic kidney disease: a systematic review and meta-analysis. BMJ Open Diabetes Res Care. 2021;9:e001776.
123. Park SK, Seo MH, Shin HC, Ryoo JH. Clinical availability of nonalcoholic fatty liver disease as an early predictor of type 2 diabetes mellitus in Korean men: 5-year prospective cohort study. Hepatology. 2013;57:1378–83.
124. Labenz C, Nagel M, Kremer WM, Hilscher M, Schilling CA, Toenges G, et al. Association between diabetes mellitus and hepatic encephalopathy in patients with cirrhosis. Aliment Pharmacol Ther. 2020;52:527–36.
125. Bergman M, Abdul-Ghani M, DeFronzo RA, Manco M, Sesti G, Fiorentino TV, et al. Review of methods for detecting glycemic disorders. Diabetes Res Clin Pract. 2020;165:108233.
126. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Diabetes technology: Standards of medical care in diabetes-2022. Diabetes Care. 2023;46(suppl 1):S111–27.
127. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Glycemic targets: Standards of care in diabetes-2023. Diabetes Care. 2023;46(suppl 1S. 97–110.
128. Singh-Franco D, Moreau C, Levin AD, Rosa D, Johnson M. Efficacy and usability of intranasal glucagon for the management of hypoglycemia in patients with diabetes: a systematic review. Clin Ther. 2020;42:e177–208.
129. European Association of the Study of Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol. 2019;70:172–93.
130. Bunchorntavakul C, Reddy KR. Review article: malnutrition/sarcopenia and frailty in patients with cirrhosis. Aliment Pharmacol Ther. 2020;51:64–77.
131. El Sherif O, Dhaliwal A, Newsome PN, Armstrong MJ. Sarcopenia in nonalcoholic fatty liver disease: new challenges for clinical practice. Expert Rev Gastroenterol Hepatol. 2020;14: 197–205.
132. Garcia-Pagan JC, Francoz C, Montagnese S, Senzolo M, Mookerjee RP. Management of the major complications of cirrhosis: Beyond guidelines. J Hepatol. 2021;75(suppl 1):S135–46.
133. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med. 2017; 376:641–51.
134. Aminian A, Zajichek A, Arterburn DE, Wolski KE, Brethauer SA, Schauer PR, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. JAMA. 2019;322:1271–82.
135. Aminian A, Al-Kurd A, Wilson R, Bena J, Fayazzadeh H, Singh T, et al. Association of bariatric surgery with major adverse liver and cardiovascular outcomes in patients with biopsy-proven nonalcoholic steatohepatitis. JAMA. 2021;326:2031–42.
136. Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, et al. Bariatric surgery reduces features of

nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology. 2015;149:379–88; quiz e315–76.
137. Lassailly G, Caiazzo R, Ntandja-Wandji LC, Gnemmi V, Baud G, Verkindt H, et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of fibrosis. Gastroenterology. 2020;159:1290–301.e1295.
138. Patton H, Heimbach J, McCullough A. AGA Clinical Practice Update on bariatric surgery in cirrhosis: expert review. Clin Gastroenterol Hepatol. 2021;19:436–5.
139. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and risks of bariatric surgery in adults: a review. JAMA. 2020; 324:879–87.
140. Rebibo L, Gerin O, Verhaeghe P, Dhahri A, Cosse C, Regimbeau JM. Laparoscopic sleeve gastrectomy in patients with NASH-related cirrhosis: a case-matched study. Surg Obes Relat Dis. 2014;10:405–10; quiz 565.
141. Pestana L, Swain J, Dierkhising R, Kendrick ML, Kamath PS, Watt KD. Bariatric surgery in patients with cirrhosis with and without portal hypertension: a single-center experience. Mayo Clin Proc. 2015;90:209–15.
142. Wolter S, Dupree A, Coelius C, El Gammal A, Kluwe J, Sauer N, et al. Influence of liver disease on perioperative outcome after bariatric surgery in a Northern German Cohort. Obes Surg. 2017;27:90–5.
143. Hanipah ZN, Punchai S, McCullough A, Dasarathy S, Brethauer SA, Aminian A, et al. Bariatric surgery in patients with cirrhosis and portal hypertension. Obes Surg. 2018;28: 3431–8.
144. Minambres I, Rubio MA, de Hollanda A, Breton I, Vilarrasa N, Pellitero S, et al. Outcomes of bariatric surgery in patients with cirrhosis. Obes Surg. 2019;29:585–92.
145. Goh GB, Schauer PR, McCullough AJ. Considerations for bariatric surgery in patients with cirrhosis. World J Gastroenterol. 2018;24:3112–9.
146. Douros A, Yin H, Yu OHY, Filion KB, Azoulay L, Suissa S. Pharmacologic differences of sulfonylureas and the risk of adverse cardiovascular and hypoglycemic events. Diabetes Care. 2017;40:1506–3.
147. Hahr AJ, Molitch ME. Management of diabetes mellitus in patients with CKD: core curriculum 2022. Am J Kidney Dis. 2022;79:728–36.
148. Huang HK, Yeh JI. Comparison of mortality and cardiovascular event risk associated with various insulin secretagogues: a nationwide real-world analysis. Diabetes Res Clin Pract. 2019; 152:103–10.
149. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: The CAROLINA randomized clinical trial. JAMA. 2019;322:1155–66.
150. Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2016; 164:740–51.
151. Yip TC, Chan RNC, Wong VW, Tse YK, Liang LY, Hui VW, et al. Association of metformin use on metabolic acidosis in diabetic patients with chronic hepatitis B-related cirrhosis and renal impairment. Health Sci Rep. 2021;4:e352.
152. Zhang X, Harmsen WS, Mettler TA, Kim WR, Roberts RO, Therneau TM, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. Hepatology. 2014;60:2008–16.
153. Vilar-Gomez E, Vuppalanchi R, Desai AP, Gawrieh S, Ghabril M, Saxena R, et al. Long-term metformin use may improve clinical outcomes in diabetic patients with non-alcoholic steatohepatitis and bridging fibrosis or compensated cirrhosis. Aliment Pharmacol Ther. 2019;50:317–28.
154. Vilar-Gomez E, Calzadilla-Bertot L, Wong VW, Castellanos M, Aller-de la Fuente R, Eslam M, et al. Type 2 diabetes and metformin use associate with outcomes of patients with nonalcoholic steatohepatitis-related, Child-Pugh A cirrhosis. Clin Gastroenterol Hepatol. 2021;19:136–45.e136.
155. Budd J, Cusi K. Role of agents for the treatment of diabetes in the management of nonalcoholic fatty liver disease. Curr Diab Rep. 2020;20:59.
156. Kawamori R, Kadowaki T, Onji M, Seino Y, Akanuma Y. Hepatic safety profile and glycemic control of pioglitazone in more than 20,000 patients with type 2 diabetes mellitus: postmarketing surveillance study in Japan. Diabetes Res Clin Pract. 2007;76:229–35.
157. Scheen AJ. Pharmacokinetic and toxicological considerations for the treatment of diabetes in patients with liver disease. Exp Opin Drug Metab Toxicol. 2014;10:839–57.
158. Yang JY, Moon AM, Kim H, Pate V, Barritt AST, Crowley MJ, et al. Newer second-line glucose-lowering drugs versus thiazolidinediones on cirrhosis risk among older US adult patients with type 2 diabetes. J Diabetes Complications. 2020;34:107706.
159. Saffo S, Taddei T. SGLT2 inhibitors and cirrhosis: a unique perspective on the comanagement of diabetes mellitus and ascites. Clin Liver Dis (Hoboken). 2018;11:141–4.
160. Saffo S, Garcia-Tsao G, Taddei T. SGLT2 inhibitors in patients with cirrhosis and diabetes mellitus: a tertiary center cohort study and insights about a potential therapeutic target for portal hypertension. J Diabetes. 2021;13:265–9.
161. Saffo S, Kaplan DE, Mahmud N, Serper M, John BV, Ross JS, et al. Impact of SGLT2 inhibitors in comparison with DPP4 inhibitors on ascites and death in veterans with cirrhosis on metformin. Diabetes Obes Metab. 2021;23:2402–8.
162. Patel Chavez C, Cusi K, Kadiyala S. The emerging role of glucagon-like peptide-1 receptor agonists for the management of NAFLD. J Clin Endocrinol Metab. 2022;107:29–38.
163. Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjaer MS, Krarup N, et al. Semaglutide 2.4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol Hepatol. 2023;8:511–22.
164. Yen FS, Lai JN, Wei JC, Chiu LT, Hsu CC, Hou MC, et al. Is insulin the preferred treatment in persons with type 2 diabetes and liver cirrhosis? BMC Gastroenterol. 2021;21:263.
165. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, Ghabril M, Saxena R, Cummings OW, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. Hepatology. 2020;71:495–509.
166. Kim RG, Loomba R, Prokop LJ, Singh S. Statin use and risk of cirrhosis and related complications in patients with chronic liver diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2017;15:1521–30.e1528.
167. Kaplan DE, Serper MA, Mehta R, Fox R, John B, Aytaman A, et al. Effects of hypercholesterolemia and statin exposure on survival in a large national cohort of patients with cirrhosis. Gastroenterology. 2019;156:1693–706.e1612.

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