ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2022 February 28; 28(8): 775-890

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 28 Number 8 February 28, 2022

World Journal of Gastroenterology

Weekly Volume 28 Number 8 February 28, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Conrado M Fernandez-Rodriguez, MD, PhD, Associate Professor, Chief, Gastroenterology Unit, Hospital Universitario Fundacion Alcorcon, Alcorcon, Madrid 28922, Spain. cfernandez@fhalcorcon.es

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for *WJG* as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Ze-Mao Gong*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
February 28, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2022 February 28; 28(8): 775-793

DOI: 10.3748/wjg.v28.i8.775

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Clinical implications of diabetes in chronic liver disease: Diagnosis, outcomes and management, current and future perspectives

Diego García-Compeán, Emanuela Orsi, Ramesh Kumar, Felix Gundling, Tsutomu Nishida, Jesús Zacarías Villarreal-Pérez, Ángel N Del Cueto-Aguilera, José A González-González, Giuseppe Pugliese

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Darenskaya MA, Jiang W

Received: October 10, 2021
Peer-review started: October 10, 2021
First decision: November 15, 2021
Revised: November 19, 2021
Accepted: January 25, 2022
Article in press: January 25, 2022
Published online: February 28, 2022

Diego García-Compeán, Gastroenterology Service and Department of Internal Medicine, Faculty of Medicine, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo Le ón, Monterrey 64700, Nuevo León, Mexico

Emanuela Orsi, Diabetes Service, Endocrinology and Metabolic Diseases Unit, Fdn IRCCS Ca Granda, Endocrine Unit, Padigl Granelli, Milan 20121, Italy

Ramesh Kumar, Department of Gastroenterology, All India Institute of Medical Sciences, Patna 801507, India

Felix Gundling, Department of Gastroenterology, Gastrointestinal Oncology, Hepatology, Diabetics, Metabolism and Infectious Diseases, Sozialstiftung Bamberg, Bamberg 96049, Germany

Tsutomu Nishida, Department of Gastroenterology, Toyonaka Municipal Hospital, Osaka 560-8565, Japan

Jesús Zacarías Villarreal-Pérez, Department of Endocrinology, University Hospital, Autonomous University of Nuevo León, Monterrey 64700, Mexico

Ángel N Del Cueto-Aguilera, Department of Gastroenterology and Internal Medicine, Faculty of Medicine, University Hospital, Autonomous University of Nuevo León, Monterrey 64700, Nuevo León, Mexico

José A González-González, Gastroenterology Service and Department of Internal Medicine, University Hospital Dr. José E González and Medical School, Monterrey 64460, Nuevo León, Mexico

Giuseppe Pugliese, Department of Clinical and Molecular Medicine, La Sapienza University, Roma 00161, Italy

Corresponding author: Diego García-Compeán, MD, MSc, Professor, Gastroenterology Service and Department of Internal Medicine, Faculty of Medicine, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Madero y Gonzalitos S/N, Monterrey 64700, Nuevo León, Mexico. digarciacompean@prodigy.net.mx

Abstract

Diabetes mellitus (DM) is common in liver cirrhosis (LC). The pathophysiological association is bidirectional. DM is a risk factor of LC and LC is a diabetogenic

condition. In the recent years, research on different aspects of the association DM and LC has been intensified. Nevertheless, it has been insufficient and still exist many gaps. The aims of this review are: (1) To discuss the latest understandings of the association of DM and LC in order to identify the strategies of early diagnosis; (2) To evaluate the impact of DM on outcomes of LC patients; and (3) To select the most adequate management benefiting the two conditions. Literature searches were conducted using PubMed, Ovid and Scopus engines for DM and LC, diagnosis, outcomes and management. The authors also provided insight from their own published experience. Based on the published studies, two types of DM associated with LC have emerged: Type 2 DM (T2DM) and hepatogenous diabetes (HD). High-quality evidences have determined that T2DM or HD significantly increase complications and death pre and post-liver transplantation. HD has been poorly studied and has not been recognized as a complication of LC. The management of DM in LC patients continues to be difficult and should be based on drug pharmacokinetics and the degree of liver failure. In conclusion, the clinical impact of DM in outcomes of LC patients has been the most studied item recently. Nevertheless many gaps still exist particularly in the management. These most important gaps were highlighted in order to propose future lines for research.

Key Words: Diabetes mellitus; Liver cirrhosis; Hepatogenous diabetes; Clinical implications; Therapy

Core Tip: The prevalence of diabetes mellitus (DM) and impaired glucose tolerance in patients with liver cirrhosis (LC) is around 30% and 40% respectively. DM is a risk factor for LC and LC is a diabetogenic condition. Two types of diabetes associated with LC have emerged: Type 2 DM and hepatogenous diabetes (HD). However HD has not been recognized as a complication of LC. It is widely accepted that DM increases complications and mortality in cirrhotic patients. DM treatment is quite difficult due to liver failure. In the present review we will discuss the most recent information published in this field, pointing out the gaps that still exist in the subject.

Citation: García-Compeán D, Orsi E, Kumar R, Gundling F, Nishida T, Villarreal-Pérez JZ, Del Cueto-Aguilera ÁN, González-González JA, Pugliese G. Clinical implications of diabetes in chronic liver disease: Diagnosis, outcomes and management, current and future perspectives. *World J Gastroenterol* 2022; 28(8): 775-793
URL: https://www.wjgnet.com/1007-9327/full/v28/i8/775.htm
DOI: https://dx.doi.org/10.3748/wjg.v28.i8.775

INTRODUCTION

For some time, type 2 diabetes mellitus (T2DM) has been suggested as a risk factor for chronic liver disease (CLD)[1]. Besides, the diabetogenic nature of liver cirrhosis (LC) was described and the term "hepatogenous diabetes" (HD) was coined hepatogenous diabetes (HD) in order to differentiate it from T2DM and attributed it to hepatic dysfunction[2].

In 1994, Bianchi *et al*[3] demonstrated for the first time the negative predictive capability of DM on the outcome of LC patients by observing a significant increase in mortality due to liver complications. Up to date, it is known that DM and impaired glucose tolerance (IGT) are common in LC patients worldwide, particularly in this era of nonalcoholic fatty liver disease (NAFLD) and obesity. From the beginning of this millennium, research on the different aspects of the association between DM and LC has been progressively intensified giving rise to important results. Therefore, we decided to critically review this scientific evidence generated so far highlighting the gaps that still exist in this complex field in order to propose future lines for research.

We also attempt (based on available evidence) to catalyze the recognition of HD as an entity with its own epidemiologic, physiopathological, and clinical implications for patients with LC, creating a template for future refinement of this condition.

EPIDEMIOLOGY

Between 20% and 60% of patients with LC may have overt DM, from 60% to 80% may have IGT and close to 100% insulin resistance (IR)[4,5]. The prevalence of impaired glucose homeostasis seems to be

increased by the severity of CLD. The prevalence of T2DM and HD in compensated LC patients has been determined in 19.2% and 21.5%, respectively[6]. NAFLD, malnutrition, alcohol abuse, hepatitis C virus (HCV) or hepatitis B virus (HBV) infection and primary hemochromatosis are associated to an increased risk of HD[7]. In 2000, the National Health and Nutrition Examination Survey carried out in United States, demonstrated a 3-fold increased prevalence of DM in HCV carriers compared with the average population[8]. In other studies, the extent of fibrosis in patients with hepatitis B and C correlated with an increased prevalence of DM[9,10].

Many clinical studies have shown that DM may increase the severity and accelerate the progression of liver failure leading to a significant increase in liver complications and mortality[4,11]. In the other side, HD has been found to have well defined clinical and pathophysiological characteristics that allow to differentiate it from T2DM[12,13]. HD can be suspected in LC patients without personal or family history of DM and metabolic syndrome (MS)[12].

Notwithstanding, the conceptual term "hepatogenous diabetes" is not included in the currently valid national and international classification systems describing etiologies of DM[14], neither HD is accepted as a complication of LC by the World Health Organization (WHO). Maybe for this reason, the diagnosis and treatment of IGT and DM in LC patients are often overlooked by physicians as was shown by a questionnaire applied to 576 gastroenterologists in Germany. The 90% and 40% of physicians underestimated the prevalence of IGT and DM in cirrhotic patients respectively[15]. In another study, it was found that, in contrast to other complications associated with cirrhosis, HD was underestimated even among medical staff from highly specialized hospital departments[16].

PATHOPHYSIOLOGY

The pathophysiological relationship between DM and LC is bidirectional. In one side, T2DM may lead to liver disease in the context of the MS and NAFLD and, in the other side, LC is a diabetogenic condition[17,18]. The pathophysiology of liver disease due to T2DM (NAFLD) is not discussed in this text as it can be reviewed elsewhere. In contrast, liver failure, portosystemic shunts, hyperinsulinemia, increased glucagon, growth hormone, insulin-like growth factor, free fatty acids and cytokines that induce peripheral IR and β-cells dysfunction play a significant pathogenic role in HD[17,18] (Figure 1).

IR and hyperinsulinemia

The liver plays a key role in glucose metabolism as the major site of glycogen synthesis and gluconeogenesis. Hepatocellular functional impairment results in abnormal glycogen synthesis and decreased hepatic capacity for glycogen deposits[13]. IR in peripheral tissues (adipose and muscular tissues) and liver dysfunction play a central role in the glucose metabolism disturbance[19,20]. Reduced insulin clearance by the damaged liver and portosystemic shunts result in hyperinsulinemia which is potentiated by raised levels of contra-insulin hormones (glucagon, growth hormone, insulin-like growth factor) and free fatty acids and cytokines[20,21].

Hyperinsulinemia can be detected in the early stages of CLD, both in the fasting and postprandial state. A major precipitating factor of hyperinsulinemia is the reactive insulin hypersecretion by the pancreas for compensation of peripheral IR in muscle tissue and impaired hepatic glucose utilization.

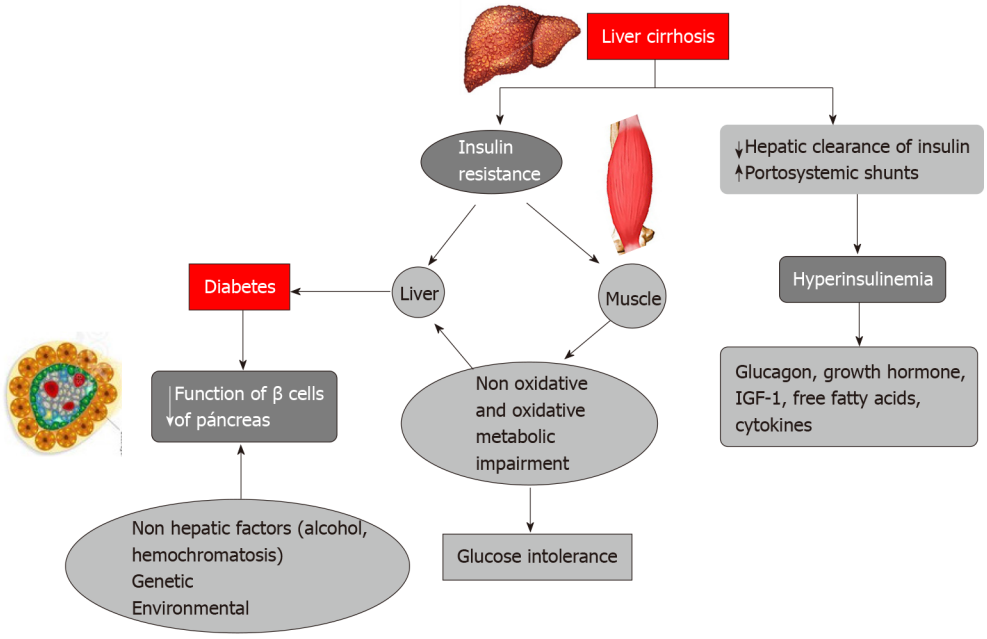
Pancreatic beta cells adaptation

Inadequate early increase in insulin secretion and decreased hepatic glucose production are often observed in LC even in the absence of DM. The progressive loss of insulin secretion culminates in a step-wise fashion in DM[22]. The trigger seems to be glucotoxicity from chronic hyperglycemia, which causes secretory impairment of pancreatic β-cells[23].

NAFLD AND DM

NAFLD is the most common CLD in the world and its prevalence in the general population is between 17% and 46%. NAFLD is closely related to MS and DM. For this reason an international consensus panel of experts have recommended the redefinition of this disease with the term of metabolism associated fatty liver disease[24,25]. Notwithstanding, NAFLD may also affect lean or non-obese subjects in the absence of other metabolic risk factors[26]. Lean NAFLD is most commonly seen in the Asian population where the parameters for defining obesity are different than those of western population. Non-alcoholic steatohepatitis (NASH) is the severe manifestation since it causes steatosis, inflammation, ballooning and fibrosis which can progress to cirrhosis and hepatocellular carcinoma (HCC). The prevalence of NASH is estimated at 2%-3%[24].

The pathophysiological relationship between DM and NAFLD is bidirectional and complex. On the one hand, T2DM has been suggested as a strong risk factor for NAFLD, LC and HCC[17,18]. In a recently published study with 561 patients with T2DM attending primary care outpatient clinics and



DOI: 10.3748/WJG.v28.i8.775

Figure 1 Pathophysiology of hepatogenous diabetes in cirrhotic liver. Hepatogenous diabetes develops directly from insulin resistance in the liver, and indirectly from impaired glucose metabolism due to insulin resistance in muscle. Hyperinsulinemia can result from reduced insulin clearance by the damaged liver and the presence of portosystemic shunts. With progression of diabetes, there is a reduction in the sensitivity of pancreatic b cells due to glucotoxicity, and reduced production of insulin. IGF: Insulin-like growth factor.

unaware of having NAFLD, 15% showed moderate-to advanced fibrosis by transient elastography and confirmed with liver biopsy. Only a minority of patients showed elevated aspartate aminotransaminase or alanine aminotransaminase[27].

On the other hand, NAFLD in the absence of metabolic disorders may be a risk factor for incidental DM and MS, as it has been demonstrated in lean subjects with NAFLD[28,29]. However, the two conditions have additional common risk factors (Figure 2).

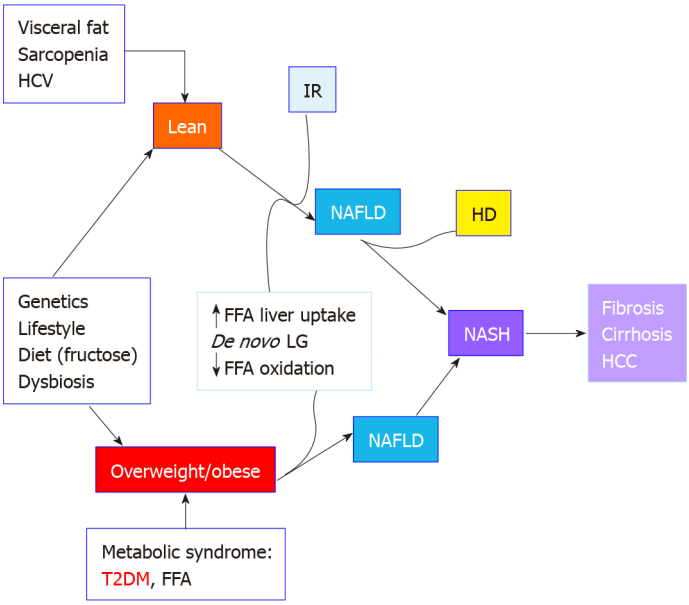
DM in lean patients with NAFLD has clinical characteristics similar to HD. Compared with obese NAFLD patients, leans or non-obese tend to be younger, have lower levels of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), blood pressure, and homeostasis model assessment IR index (HOMA-IR), and lower prevalence of MS[30]. However, compared with healthy individuals, they tend to have more dyslipidemia and higher FPG, body mass index (BMI), visceral fat, blood pressure and HOMA-IR[31].

HCV AND DM

Numerous prospective studies have shown higher prevalence of DM in patients with chronic hepatitis C virus (CHC) compared to those with HBV liver infection or without liver disease[8,32]. A meta-analysis of 32 studies found that DM was associated with CHC regardless of the presence of fibrosis or LC[33]. The prevalence of DM in patients without LC was 12.6% to 17% and that of IGT was 40%[20,34].

The HCV has diabetogenic properties through several mechanisms. First, autoimmune phenomena, as massive stimulation of the immune system induced by HCV may result in the nonspecific activation of potentially self-reactive lymphocytes that might develop autoimmunity, inducing an immune cascade that could culminate in islet cell dysfunction in susceptible individuals[35]. As a consequence, organ nonspecific antibodies are more frequent in HCV-positive patients with mixed cryoglobulinemia and diabetes than in non-diabetic HCV-negative patients with mixed cryoglobulinemia[36]. Second, direct cytotoxicity to islet β-cells, as rough endoplasmic reticulum morphological changes have been observed in the β-cells of HCV-infected patients, accompanied by reduced glucose-stimulated insulin release[35]. Third, blockade of insulin receptors at the cellular level, as HCV core up-regulates suppressor of cytokine signaling 3 expression that induces proteasomal degradation of insulin receptor substrates 1 and 2 (which are central molecules of the insulin-signaling cascade) and increases gluconeogenesis[37].

The CHC patients with DM have been shown to have an attenuated DM phenotype: They are thinner and have lower levels of low-density lipoprotein (LDL) cholesterol, which could be due to hypobetalipoproteinemia as a result of binding competition between HCV and hepatic LDL receptor, giving rise to



DOI: 10.3748/WJG.v28.i8.775 **Copyright** ©The Author(s) 2022.

Figure 2 The pathophysiological relationship between diabetes mellitus and nonalcoholic fatty liver disease. This is bidirectional: On the one hand, type 2 diabetes mellitus (T2DM) is a strong risk factor (alone or as part of metabolic syndrome) for nonalcoholic fatty liver disease (NAFLD), liver cirrhosis and hepatocellular carcinoma. On the other hand, NAFLD in the absence of metabolic disorders is a risk factor for incidental DM as it has been demonstrated in lean subjects with NAFLD. In both cases genetics, [PNPLA3 rs738409 polymorphism (G allele), SREBF-2 rs133291 C/T polymorphism, TM6SF2 rs58542926 C>T and CETP rs12447924 and rs1259700 polymorfisms], as well as sedentary life style, diet and dysbiosis may also play an important role. HCV: Hepatitis C virus; IR: Insulin resistance; NAFLD: Nonalcoholic fatty liver disease; HD: Hepatogenous diabetes; FFA: Free fatty acids; LG: Lactoglobulin; T2DM: Type 2 diabetes mellitus; NASH: Non-alcoholic steatohepatitis; HCC: Hepatocellular carcinoma.

steatosis[38] which is frequently observed in this disease.

Numerous studies have shown that DM has negative clinical implications for the outcomes of HCV liver infection with or without LC[39]. It has been demonstrated that regardless of BMI and age, DM can accelerate the progression of CHC to LC and HCC. In patients with compensated cirrhosis, DM induces an increased risk of decom-pensation with the onset of liver failure and significant increase in mortality [11,40,41]. DM was also associated with an increased risk for HCC development in treatment-naïve CHC patients in Asia. Furthermore, LC and an early DM diagnosis further increased the risk of HCC development in patients diagnosed with both CHC and DM.

With the introduction of direct-acting antiviral (DAA) drugs for the treatment of HCV liver infection, the eradication rate is close to 100% regardless of viral genotype and degree of fibrosis. In multiple studies, the elimination of the virus had a short- and medium-term beneficial effect on DM in CHC patients. In these studies, patients showed improved blood glucose and insulin levels, insulin sensitivity and HbA1c values. These changes were independent of BMI, age and degree of fibrosis[42,43].

In one of these studies with 893 CHC patients, 15.7% with LC, the persistence of normalization of glucose metabolism parameters was demonstrated 44.5 mo after virus eradication[43]. In a recent systematic review and metanalysis HCV eradication with DAAs produced a significant mean reduction in HbA1c levels of 0.45% [95% confidence interval (CI): 0.60-0.30%; $P < 0.001$] and in FPG levels of 22.03 mg/dL (95%CI: 41.61-2.44 mg/dL; $P = 0.03$)[44]. Nevertheless, not all studies have obtained similar results, this may be due to differences in study design, sample size and time of follow up[45]. For this reason, large prospective cohort studies using appropriate stratifications are urgently needed to evaluate the extent of such an amelioration.

CLINICAL MANIFESTATIONS OF DM IN LC, HD

Diagnosis of HD may be difficult since clinical manifestations in the early stages of liver disease are absent. FPG and HbA1c may be normal and in most patients, an oral glucose tolerance test (OGTT) is required for diagnosis[46]. As liver failure progresses, DM becomes clinically manifested[6]. Some clinical parameters may be useful for distinguishing between T2DM and HD. The time of onset is important, as T2DM usually precedes while HD follows the occurrence of LC. Nevertheless, this distinction may be difficult when the two conditions are simultaneously detected. In this case, presence of MS, family history of DM and vascular complications are less frequent, whereas liver-related complications are more frequent in HD compared to T2DM[4,47,48].

Finally, unlike T2DM, orthotopic liver transplantation (LT) may reverse or improve HD confirming its origin from liver dysfunction[49] (Table 1).

Diagnosis

In a study comparing patients with HD to those with T2DM, the ratios of postprandial plasma glucose to FPG, fasting insulin and HOMA-IR index were significantly higher in patients with HD[50]. Consequently, the diagnosis of HD often requires an OGTT. It has been determined that around 50% to 70% of patients with compensated LC will require this test in order to diagnose IGT or DM[4,6,48]. In addition, research is being made to identify genetic and biochemical markers aimed to establish the differentiation among the two types of DM more precisely[50,51].

OGTT

In 1997, the American Diabetes Association determined the cut-off value of FPG in 126 mg/dL for the diagnosis of DM because it corresponded to a 2 h value of 200 mg/dL in the OGTT[52]. A study in 60 LC patients based on the results of OGTT, however, showed that mean values of FPG levels corresponding to a 2 h value of 200 mg/dL were lower (107 mg/dL)[53]. Besides, nine of 42 patients (21%) with FPG levels < 110 mg/dL from this study, were diagnosed with DM using OGTT.

Therefore, lower FPG levels may be required in LC patients for predicting IGT or DM, so the use of lower cut-off values to diagnose HD should be considered in these patients.

HbA1c

HbA1c levels > 6.5%, are used to diagnose DM[54]. However, a previous study showed that LC patients with DM had lower HbA1c levels (mean 5.7%), and 40% of patients with compensated LC had levels below in the non-DM range[55]. The poor diagnostic performance of HbA1c in LC patients is due to the curvilinear relationship between HbA1c and erythrocyte turnover, which can occur in patients with advanced LC as a result of hemorrhage related to portal hypertension and coagulopathy, hemolysis caused by splenomegaly and impaired erythropoiesis due to bone marrow suppression[56]. HbA1c values can also be affected by blood transfusion, which are frequently prescribed to LC patients[57]. A study showed that in non-anemic CLD patients with DM with HbA1c < 7%, the decrease in liver functional reserve is associated with worsening of parameters of glycemic variability determined with continuous glucose monitoring. Mean blood glucose levels and the difference between highest and lowest blood glucose increased significantly with worsening of liver functional reserve[58].

IMPLICATIONS OF DM IN LC

T2DM or HD are associated with numerous complications and high mortality in patients with LC (Tables 2 and 3).

Complications

Hepatic encephalopathy: Several studies have linked DM to an increased incidence of hepatic encephalopathy (HE) in patients with LC. Among patients with HCV-related LC, the severity of HE was higher in DM than in non-DM patients[59]. In a further study in LC patients, the association between DM and HE was independent of the model for end-stage liver disease (MELD) score[39]. In a large prospective study, LC patients with DM had more episodes of first-time overt HE compared to those without DM in one year. In addition, a greater proportion of first-time HE progressed beyond grade 2 in DM patients. Notably, the proportion of Child-Pugh class C LC was lower in the DM group, which suggested that DM conferred an additional risk of HE irrespective of liver disease severity[60].

In a recent study, the risk of both covert and overt HE was more pronounced among patients with poor glycaemic control[61]. Finally, DM increased significantly the risk of HE after a trans-jugular intrahepatic portosystemic shunt (TIPSS)[62].

Variceal haemorrhage: Hyperglycaemia may lead to splanchnic hyperaemia and increased portal pressure which may increase the risks of haemorrhage[59,63]. In a prospective study, DM was associated with increased hepatic venous pressure gradient, variceal haemorrhage (VH), and Child-Pugh's score. Postprandial hyper-glycaemia had a significant association with VH within 6 mo[64]. In another study, DM was a risk factor for rebleeding following endoscopic variceal ligation[65]. In a retrospective study, DM was also an independent predictor of in-hospital death in LC patients with acute gastro-intestinal bleeding[66]. Finally, in another study, LC patients with DM had a higher incidence of re-bleeding and hospitalizations, and a higher mortality rate than those without DM[67].

Infectious complications

An impaired immunological response has been observed in patients with DM and LC[68]. DM was an independent predictor of bacterial infections in hospitalized patients with LC[40]. In hospitalized LC patients, the prevalence of bacterial infections was significantly higher in DM compared to non-DM

Table 1 Clinical differences between hepatogenous diabetes and type 2 diabetes mellitus

Variables	Hepatogenous diabetes	Type 2 diabetes mellitus
Onset	After cirrhosis onset	Before cirrhosis onset
Clinical presentation	Normal FPG and HbA1c; Abnormal OGTT	Increased FPG and HbA1c
Metabolic risk Factors	Less frequent	More frequent
Vascular complications	Less frequent	More frequent
Liver complication	More frequent	Less frequent
Effect of OLT	Reversal or improvement	Non modification
Mortality	More than non-diabetics	More than non-diabetics

FPG: Fasting plasma glucose; OGTT: Oral glucose tolerance test; OLT: Orthotopic liver transplantation; HbA1c: Glycated hemoglobin.

Table 2 Studies depicting implications of diabetes on complications of patients with liver cirrhosis

Ref.	Design	Population, *n*	Outcomes	Limitations
Sigal *et al*[59], United States, 2006	Cross-sectional	65 HCV-LC; 31% diabetics	HE and severe HE was higher in diabetics. DM was independent risk factor for HE	Small sample size. HE was not standardized
Tietge *et al*[81], Germany, 2004	Case-control, prospective	100 LC, 35% diabetics, 62 post-LT	Pre-LT IGT or DM was the major risk factor for post-LT DM	Only 31 patients were prospectively evaluated
Takahashi *et al*[77], Japan, 2011	Prospective	203 CHC	Two hours post-challenge hyperglycaemia associated with HCC	Patients received IFN
Jeon *et al*[64], Republic of Korea, 2013	Prospective	195 LC, 55.4% with HD	HD correlated with HVPG, VH and large varices. Most patients with VH within 6 mo, had post-prandial hyperglycaemia	Risk stratification of varices and prophylaxis for VH were not taken into account
Zheng *et al*[75], China, 2013	Retrospective case-control	1568 CLD, 852 with HCC	DM associated with increased risk of HCC regardless of cirrhosis. Synergistic interaction between DM and HBV for HCC	Hospital based study. Temporal relationship between DM and HCC could not be established
Yang *et al*[63], Taiwan, 2014	Prospective	146 LC, 25% diabetics	DM was predictor of VH. Patients with VH had worse glycaemic control (HBA1c ≥ 7%)	DM associated with decompensated cirrhosis, renal disease and VH
Jepsen *et al*[60], Denmark, 2015	Database from randomized trials	863 LC, 22% diabetics	Diabetics had more episodes of first-time overt HE in one year. First-time HE progression beyond grade 2 higher in diabetics	Diagnosis of DM was not standardized. Vaptan could be a confounder
Yang *et al*[73], United States, 2016	Retrospective	739 LC, 34% diabetics	DM increased the risk of HCC in patients with non-HCV cirrhosis	Single-centre probably with referral bias
Tergast *et al*[69], Germany, 2018	Prospective case-control	475 decompensated LC, 118 diabetics	DM increased risk for SBP and was higher with HbA1c values ≥ 6.4%	Criteria for diagnosis of DM not clearly defined
Wang *et al*[65], China, 2020	Retrospective	207 LC, 137 diabetics; 68 had HD	Rebleeding rate following EST or EVL higher in diabetics, including HD at 1, 3, and 6 mo	Relatively small number of patients with shorter follow-up
Labenz *et al*[61], Germany, 2020	Prospective	240 LC, 27% diabetics	DM associated with covert HE at inclusion and follow-up. The risk of covert HE and overt HE was more pronounced when HbA1c ≥ 6.5%	Spontaneous porto-systemic shunts, GIB, drugs were not taken into account

DM: Diabetes mellitus; EST: Endoscopic sclerotherapy; EVL: Endoscopic variceal ligation; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HD: Hepatogenous diabetes; HE: Hepatic encephalopathy; IGT: Impaired glucose tolerance; OGTT: Oral glucose tolerance test; VH: Variceal hemorrhage; LT: Liver transplantation; HVPG: Hepatic venous pressure gradient; HBV: Hepatitis B virus; IFN: Interferon; GIB: Gastrointestinal bleeding; SBP: Spontaneous bacterial peritonitis; LC: Liver cirrhosis; HbA1c: Glycated hemoglobin.

subjects[68]. In a prospective study in LC patients with ascites, those with DM had an increased risk of developing spontaneous bacterial peritonitis (SBP) and the incidence of SBP was significantly higher when HbA1c values were ≥ 6.4%[69]. In a retrospective analysis of LC patients with DM, uncontrolled DM was associated with an increased overall risk of bacterial infection and a higher hospital mortality rate in the elderly[70].

Table 3 Prospective and retrospective studies depicting implications of diabetes on mortality of patients with liver cirrhosis

Ref.	Design	Population	Outcomes	Limitations
Bianchi *et al*[3], Italy, 1994	Retro-prospective	354 LC, 98 with DM	5-yr survival rate: DM: 41%, non-DM 56%	Diagnosis of DM not standardized
Holstein *et al*[4], Germany, 2002	Prospective	52 LC, 71% with DM	5.6-yr survival rate after diagnosis of LC: 51% of HD patients. 80% of deaths were cirrhosis-related causes	Small sample size. Comparative outcome data of non-DM patients not available
Moreau *et al*[79], France, 2004	Prospective	75 LC and refractory ascites	DM, older age, and HCC were predictors of poor survival. The survival rate of patients without DM was higher	OGTT was not used to diagnose DM
Nishida *et al*[48], Japan, 2006	Prospective	56 LC, 38% diabetics	The 5-yr survival rate was 94%, 68% and 56%, with NGT, IGT and DM, respectively	Small sample size
Quintana *et al*[80], México, 2011	Prospective	110 compensated LC, 45% diabetics	2.5 yr cumulated survival years: DM: 48 *vs* non-DM: 69% ($P < 0.05$). DM was not predictor of death	Maybe DM death- prediction capability was masked by Child-Pugh C score
García-Compeán *et al*[78], México, 2014	Prospective	100 compensated LC and normal FPG	Patients with IGT + DM had lower 5-yr cumulated survival rate. Death causes in 90 % were cirrhosis related	Small sample size
Elkrief *et al*[40], Canada, 2014	Retrospective	348 HCV-LC, 40% diabetics	DM significantly associated with ascites, renal dysfunction, infections, HCC and mortality during the follow-up period	Retrospective. Potential errors in the diagnosis of DM
Khafaga *et al*[67], Egypt, 2015	Case-control	60 LC, 50% diabetics	Diabetics had higher incidence of VH, hospitalizations, HE and mortality rate	Small sample size
Qi *et al*[66], China, 2015	Retrospective	145 LC, 29 diabetics	In-hospital mortality was higher in diabetics	Small number of patients
Hoehn RS *et al*[82], United States, 2015	Retrospective	12442 pos- LT, 24% with DM	Diabetic recipients had longer hospitalization, higher peri-transplant mortality and 30-d readmission rates	More diabetic patients were on haemodialysis and received allografts from older donors
Rosenblatt *et al*[70], United States, 2021	Retrospective	906559 LC with DM, and 109694 uncontrolled DM	Uncontrolled DM associated with increased risk of bacterial infection and increased risk of death in elderly patients	Subject to administrative error. Criteria for DM was not standardized

DM: Diabetes mellitus; FPG: Fasting plasma glucose; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HD: Hepatogenous diabetes; HE: Hepatic encephalopathy; IGT: Impaired glucose tolerance; NGT: Normal glucose tolerance; OGTT: Oral glucose tolerance test; VH: Variceal hemorrhage; LT: Liver transplantation; LC: Liver cirrhosis.

HCC

The increased risk of HCC in diabetic patients was reported in two large meta-analyses[71,72]. DM was also found to increase the risk of mortality in HCC patients[71]. However, the published studies are somewhat inconsistent on this issue. In a retrospective study with LC patients, DM did not increas the risk of HCC in those with HCV infection compared to other causes of liver disease[73]. Another study in patients with chronic hepatitis B, reported a higher prevalence of DM among HCC patients without LC than in those with LC[74]. A large case control study found that DM was associated with an increased risk of HCC regardless of the prevalence of LC[75]. In another study, DM could not be confirmed as a major risk factor for HCC in general; however, DM did become an independent predictor when "traditional" risk factors such as LC, alcohol abuse, hepatitis B or C and smoking were excluded[76]. The inconsistent criteria for diagnosing DM may be an important cause of this discrepancy. Recently, it was observed that while high FPG levels were not associated with HCC, 2 h post-challenge hyperglycaemia remained as significant predictor for HCC development in HCV-RNA-positive patients [77].

Mortality

Many studies have indicated that DM significantly reduced the survival rate in patients with CLD and LC[3,4,40,48,66,67,78,79]. Nevertheless, only some of them have been prospective. Bianchi *et al*[3] reported the adverse impact of DM on the 5-year cumulated survival in a study in patients with LC. Refractory ascites, DM, older age, and HCC, but not Child-Pugh score were independent predictors of poor survival[3]. Even subclinical abnormalities in glucose homeostasis have been found to adversely affect prognosis. In a recent prospective study of 100 compensated LC patients with normal FPG, those with abnormal OGTT had lower 5-year cumulated survival than those with a normal test[78]. In a similar prospective study, the cumulative 5-year survival rates of patients were 94.7%, 68.8% and 56.6%, in those with normal glucose tolerance, IGT and DM, respectively[48]. In another study, DM had an

impact on survival only in patients with a baseline MELD score < 10. This implies that the severity of CLD may mask the deleterious effect of DM[40,80]. The results of these studies suggest that DM can be detected more clearly as reliable predictor of morbidity and mortality in the early stages of LC. In the advanced stages, its effect can be masked by other complications of LC. Therefore, further studies, based on the dynamic assessment of glycaemic parameters using OGTT, are needed to obtain a robust conclusion on this important issue (Table 3).

LT

Pre-transplant DM is the major risk factor for DM after LT (7%-45%)[81-83]. Increased FPG levels were a risk factor for new-onset DM after LT[84]. Pre-operative β-cell function determined by an OGTT may be a useful predictive tool for the recurrence of DM after LT[85]. Post-LT DM is associated with increased risk of graft rejection, severe complications and mortality[81,86,87]. A study on adult LT recipients showed that post-LT DM incidence was 34.7%, 46.9%, and 56.2% at 1, 3, and 5 years, respectively, with overall survival rates of 90%, 80.9%, and 71.7%, respectively. The post-LT DM group had more rejection episodes and worse 5-year survival rates[86]. Persistent or new-onset DM after LT is also associated with cardiovascular disease, biliary complications, renal dysfunction, infections and graft rejection[81, 87]. In patients with HCV-related LC, a pre-existing or new onset DM is associated with increased risk of HCV recurrence and hepatic fibrosis after LT[88]. Some studies have demonstrated improvement in glucose homeostasis after LT[49,89]. In a study where LT failed to cure overt DM in 33% of patients, a persistently reduced β-cell function was found[88]. However, normalized glucose production and insulin sensitivity after LT have the potential to reverse β-cell dysfunction and thus lead to remission in most cases of HD[90].

MANAGEMENT OF DM IN LC

In the absence of specific guidelines, the treatment of DM in patients with LC (T2DM or HD) starts from the general principles of management of T2DM, according to current established guidelines[91].

Lifestyle

Diet and physical activity are a cornerstone of T2DM management. On the one hand, prevalence of obesity and NAFLD is increasing worldwide and > 10% of weight reduction has been shown to significantly reduce inflammation and fibrosis in patients with this disease[92]. On the other hand, malnutrition remains a common feature among LC individuals (20%-50%), mostly in those with decompensated liver disease[93]. Both obesity and malnutrition may be associated with sarcopenia, causing a major risk factor for frailty, conditions associated with a higher rate of severe complications [94].

Diet

A moderate caloric restriction is recommended for overweight/obese LC patients in order to achieve a weight reduction of > 5% to 10%, but paying a special attention to maintain an adequate protein intake to avoid loss of muscle mass (85%). A widely accepted approach is to supply at least 35 kcal/kg body weight/d, using the actual body weight, then subtracting a 5%, 10%, or 15% in case of mild, moderate, or severe ascites, respectively, plus an additional 5% in case of peripheral oedema[93].

Protein intake should be increased up to 1.2-1.5 g/kg body weight/d to avoid sarcopenia, unless moderate-to-severe renal insufficiency is present, but oral protein supplements, especially branched-chain amino acids[95], or short-term enteral or parenteral nutrition[93] may be necessary in some patients. The common deficits of vitamins should be corrected with supplementation[93].

Physical activity

Physical exercise is associated with increments of insulin sensitivity and is highly recommended in patients with NAFLD. However it may be limited in LC patients by the presence of asthenia, sarcopenia, and ascites[96,97]. A combination of aerobic and resistance training of moderate intensity is also recommended[93], as it may result in the concurrent improvement of muscle function and mass.

Pharmacological therapy

Despite the growing problem of management of DM in patients with CLD the existing literature data, especially on newer antidiabetic agents is very limited and furthermore, no guidelines exist. The recommended use of antidiabetic drugs and insulins is based mostly on available data on pharmacokinetics and safety drug studies taking into account the degree of liver dysfunction and the presence of comorbidities[98] (Tables 4 and 5).

Non-insulin agents

The inhibitors of alpha-glucosidase such as the acarbose, inhibit α-glucosidases, which contribute to

Table 4 Kinetics, metabolism and excretion of the currently available anti-hyperglycaemic drugs[102]

Drug	Half life	Metabolism	Excretion
Short-acting insulins			
Human	140 min	Proteolytic degradation	
Lyspro	80 min	Proteolytic degradation	
Aspart	80 min	Proteolytic degradation	
Glulisine	80 min	Proteolytic degradation	
Long-acting insulins			
Human-NPH	6.6 h	Proteolytic degradation	
Glargine	12.1 h	Proteolytic degradation	
Levemir	5-7 h	Proteolytic degradation	
Degludec	25 h	Proteolytic degradation	
Glargine-300	19 h	Proteolytic degradation	
Sulfonylureas			
Glibenclamide	10 h	Liver 100%	Urines 50%; feces 50%[1]
Glimepiride	9 h	Liver 100%	Urines 60%; feces 40%[1]
Gliclazide	10-11 h	Liver 100%	Urines 80%; feces 20%
Glipizide	2-5 h	Liver 90%	Urines mainly
Meglitinides			
Repaglinide	1 h	Liver 100%	Bile 92%; urines 8%
Biguanides			
Metformin	1.5-3 h	Not metabolised	Urines 100%
Thiazolidinediones			
Pioglitazone	3.7 h	Liver 100%	Feces 55%; urines 45%
DPP-4 inhibitors			
Sitagliptin	8–24 h	Limited	Urines
Vildagliptin	1.5–4.5 h	Limited	Urines
Saxagliptin	2–4 h	Moderate	Urines
Linagliptin	10–40 h	Extensive	Feces
Alogliptin	12–21 h	Limited	Urines
GLP-1RAs			
Exenatide	2.4 h	Proteolytic degradation	Renal
Liraglutide	13 h	Proteolytic degradation	No specific organ
Lixisenatide	3 h	Proteolytic degradation	Renal
Exenatide LAR	5-6 d	Proteolytic degradation	Renal
Dulaglutide	5 d	Proteolytic degradation	No specific organ
Semaglutide	7 d	Proteolytic degradation	No specific organ
α-glicosidase inhibitors			
Acarbose	4 h	Intestine	Urines 35%; feces 65%
SGLT2 inhibitors			
Dapaglifozin	10-13 h	Glucuronidation	Urines 33%; feces 42%
Canaglifozin	12.9 h	Glucuronidation	Urines 75%; feces 21%
Empaglifozin	12.4 h	Glucuronidation	Urines 54%; feces 41%

Ertugliflozin	17 h	Glucuronidation	Urines 50%; feces 41%

[1]Excreted as weakly active metabolite.

DPP-4: Dipeptidyl peptidase 4; GLP-1RAs: Glucagon-like peptide 1 receptor agonists; SGLT2: Sodium-glucose cotransporter 2; LAR: Long-acting release; NPH: Neutral protamine Hagedorn.

degradation of disaccharides in the intestine. It results in reduction in the absorption of carbohydrates and in the risk of postprandial hyperglycemia. Its safety has been evaluated in patients with DM and CLD[99,100]. Its use was associated with a significant reduction of fasting and postprandial hyperglycemia, HbA1c and C-peptide as well as improvement of mild HE in compensated cirrhosis [100].

The secretagogues sulfonylureas and glinides are extensively metabolized by the liver in a cytochrome P450-dependent manner and may accumulate in LC patients[99], thus increasing the risk of hypoglycemia[101]. Thus, it is recommended to avoid these agents in patients with moderate-to-severe liver failure.

The insulin-sensitizing agent metformin is not metabolized by the liver[102]. It has been associated with risk of lactic acidosis. However, this complication was reported only in anecdotal cases, particularly with concomitant alcohol intake[103]. Chronic use of metformin has been associated with a reduced risk of HCC[104-107], reduced liver-related complications[105,107], and increase survival in LC patients[105-107].

Probably, glycemic control of the patients contributed for obtaining these effects. Nevertheless, an independent anti oncogenetic mechanism has been recently described experimentally[108]. The other insulin-sensitizing agents, thiazolidinediones, are metabolized entirely by the liver, so they accumulate in patients with hepatic failure[101]. Therefore, their use is restricted to patients with Child-Pugh class A LC, also because of the fluid retention and decrease in bone mineral density caused by these drugs[109]. The significant reduction of liver fibrosis reported in NASH patients with and without T2DM supports the use of these drugs in early-stage LC due to this aetiology.

Despite the fact that all the inhibitors of dipeptidyl peptidase 4 (DPP-4) are metabolized by the liver, their use is generally allowed in patients with Child-Pugh class A or B LC with no dose adjustment[101,110]. A dose reduction of these drugs is however required in case of estimated glomerular filtration rate (eGFR) < 50 mL · min^{-1} · 1.73m^{-2}, except for linagliptin, which is not excreted by the kidney[111]. Notwithstanding, in a recently published population based cohort study with 2828 DPP-4 inhibitor user and nonuser patients with T2DM and LC, the incidence rate of decompensated cirrhosis during follow-up was significantly higher for DPP-4 inhibitor users. The adjusted hazard ratios (aHRs) (95%CI) of variceal bleeding and hepatic failure were 1.67 (1.11-2.52) and 1.35 (1.02-1.79), respectively, for DPP-4 inhibitor users over nonusers. The risk of all-cause mortality, HCC, and major cardiovascular events were not statistically different[112]. In another population-based, retrospective cohort study including patients with DM and LC treated with GLP-1 receptor agonists (GLP-1RAs), DPP-4 inhibitors, sulfonylureas or sodium-glucose co-transporter-2 (SGLT-2) inhibitors, GLP-1RAs use was associated to significantly reduced number of liver related complications compared to DPP-4 inhibitors and sulfonylureas. In contrast, complication rates were similar when GLP-1RAs and SGLT-2 inhibitors were directly compared[113]. The results of these studies suggest that patients using DPP-4 inhibitors should heave a tight monitoring.

The GLP-1RAs, are not metabolized by the liver and, hence, no dose adjustment is required[101,110]. As pharmacokinetic information in patients with end-stage liver disease are available only for liraglutide, dulaglutide, and semaglutide, so the use of these GLP-1RAs is allowed in Child-Pugh class A or B patients, whereas that of exenatide and lixisenatide should be restricted to Child-Pugh class A individuals[101,110]. The use of exenatide and lixisenatide should be avoided also if eGFR is < 30 mL · min^{-1} · 1.73 m^{-2}, as these agents are excreted by the kidney[111]. The reported beneficial impact of this class of drugs on NASH may support their use in patients with NASH-related LC. Conversely, these agents may not be suitable for malnourished sarcopenic individuals, due to their energy wasting effect [101].

The inhibitors of the SGLT-2 are all metabolized in the liver, but have significant accumulation only in severe liver failure[114]. Therefore, the use of SGLT2 inhibitors is allowed in Child-Pugh class A and B LC with no dose adjustment[101], unless impaired renal function is present[111]. Their diuretic properties might be useful for potentiating the effect of therapy with loop diuretics and mineralocorticoid receptor agonists[115], though they may cause dehydration that may further reduce effective plasma volume and precipitate renal dysfunction[101].

In general terms, the use of non-insulin agents (except secretagogues) is generally allowed in mild-to-moderate LC, whereas all of them should be avoided in severe LC, in which insulin represents the sole treatment option[101]. In HD, metformin alone may be sufficient. However, drugs potentially capable of preserving β-cell function (*e.g.*, thiazolidinediones, incretin-based drugs, and SGLT2 inhibitors) may be also suggested[101].

Table 5 Use of anti-hyperglycaemic agents in cirrhotic individuals according to Child-Pugh class[102]

Drug	Child-Pugh class A	Child-Pugh class B	Child-Pugh class C
Short-acting insulins			
Human	Allowed	Allowed	Allowed (dose reduction)
Lyspro	Allowed	Allowed	Allowed
Aspart	Allowed	Allowed	Allowed
Glulisine	Allowed	Allowed	Allowed
Long-acting insulins			
Human-NPH	Allowed	Allowed	Allowed (dose reduction)
Glargine	Allowed	Allowed	Allowed
Levemir	Allowed	Allowed	Allowed
Degludec	Allowed	Allowed	Allowed
Glargine-300	Allowed	Allowed	Allowed
Sulfonylureas			
Glibenclamide	Not recommended	Contraindicated	Contraindicated
Glimepiride	Allowed (caution)	Not recommended	Contraindicated
Gliclazide	Allowed (caution)	Not recommended	Contraindicated
Glipizide	Allowed (caution)	Not recommended	Contraindicated
Meglitinides			
Repaglinide	Allowed (caution)	Not recommended	Contraindicated
Biguanides			
Metformin	Allowed	Allowed (dose reduction)	Contraindicated
Thiazolidinediones			
Pioglitazone	Allowed	Contraindicated	Contraindicated
DPP-4 inhibitors			
Sitagliptin	Allowed	Allowed	Contraindicated
Vildagliptin	Contraindicated	Contraindicated	Contraindicated
Saxagliptin	Allowed	Allowed	Contraindicated
Linagliptin	Allowed	Allowed	Contraindicated
Alogliptin	Allowed	Allowed	Contraindicated
GLP-1RAs			
Exenatide	Allowed	Contraindicated	Contraindicated
Liraglutide	Allowed	Contraindicated	Contraindicated
Lixisenatide	Allowed	Allowed	Contraindicated
Exenatide LAR	Allowed	Allowed	Contraindicated
Dulaglutide	Allowed	Allowed	Contraindicated
Semaglutide	Allowed	Allowed	Contraindicated
α-glicosidase inhibitors			
Acarbose	Allowed	Allowed (caution)	Contraindicated
SGLT2 inhibitors			
Dapaglifozin	Allowed	Allowed	Contraindicated
Canaglifozin	Allowed	Allowed	Contraindicated
Empaglifozin	Allowed	Allowed	Contraindicated

Ertugliflozin	Allowed	Allowed	Contraindicated

DPP-4: Dipeptidyl peptidase 4; GLP-1 RAs: Glucagon-like peptide 1 receptor agonists; SGLT2: Sodium-glucose cotransporter 2; NPH: Neutral protamine Hagedorn; LAR: Long-acting release.

Insulin

As human insulin is metabolized by insulinase in the liver, it may be necessary to reduce dosage[116]. Conversely, as no significant changes in the kinetics of insulin analogues, either both short-acting[117], or long-acting insulins[101,116] have been reported, no dose adjustment is required for these agents.

For these reasons, use of insulin (with preference for insulin analogues) is allowed at all stages of cirrhosis (Table 5) and represents the first-choice treatment in LC patients with DM. Insulin requirements can be high in patients with compensated cirrhosis and low in decompensated patients. Few clinical studies have evaluated its long-term effects and safety. In a recently published retrospective cohort study, insulin use in people with T2DM and compensated LC was associated with higher risks of hypoglycemia, cardiovascular events, liver-related complications, and mortality than insulin nonusers. However, no information regarding important risk factors such as body weight, physical activity, alcohol consumption, and cigarette smoking was given and effective glycemic control or treatment adherence was not evaluated[118]. More studies are needed to confirm these findings. Anyway, insulin treatment should be started with close monitoring to avoid hypoglycemia. The insulin regimen may consist of basal insulin only or a combination of basal and prandial insulin (basal-plus or basal-bolus).

In the Figure 3 an algorithm for the diagnosis and management of DM in CLD and LC is depicted.

Treatment of post-transplantation DM

HD may be improved with LT, nevertheless it may persist in 30% of cases or DM may occur *de novo* after LT due to several factors with diabetogenic potential, such as immunosuppressant treatment, viral infections, and donor- and procedure-related factors[101].

The intra-operative and immediate post-LT periods are often characterized by severe hyperglycemia that may be transient and reverse with appropriate management[101]. Intravenous or subcutaneous intensive insulin therapy using validated algorithms is the standard of care, as a strict intra-operative glycemic control is recommended to reduce the associated increased risk of morbidity and mortality [119]. With reduction of steroid dose, insulin requirement rapidly decreases and insulin treatment may be interrupted in many instances[101].

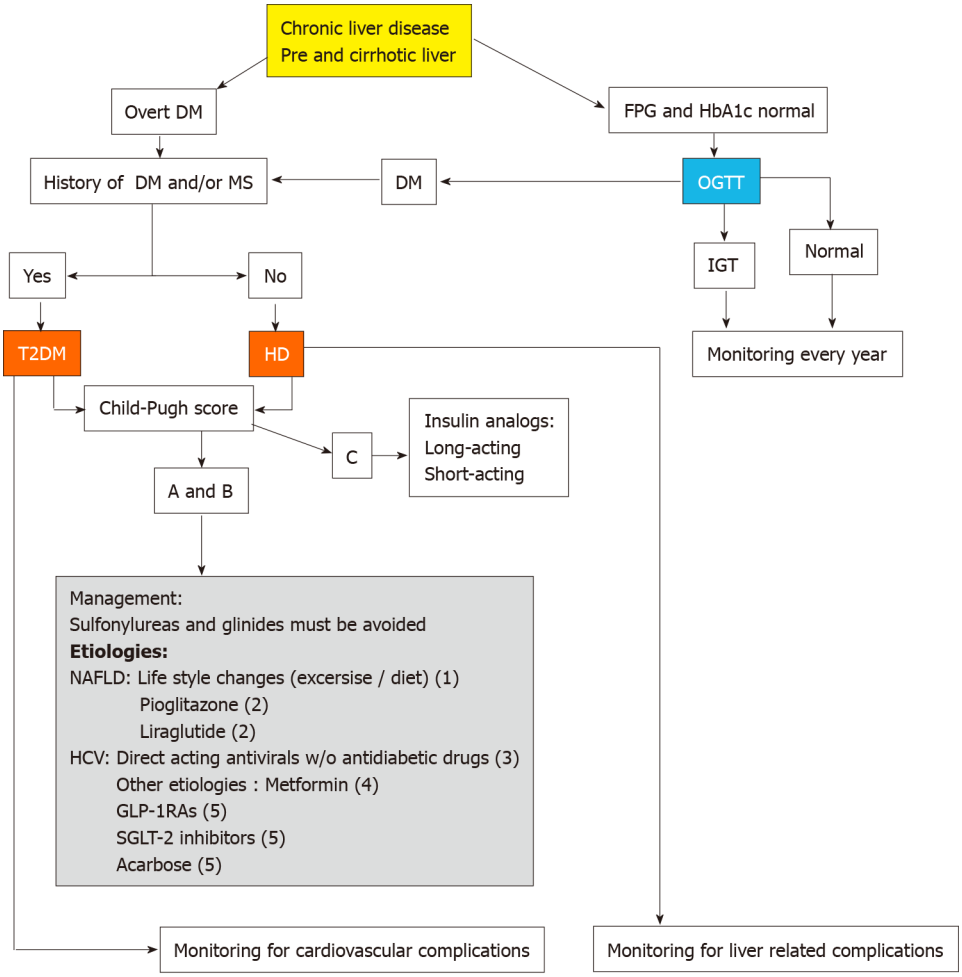
Specific guidelines for the treatment of post-LT DM were released in 2014[83]. While lifestyle measures are identical to those for T2DM patients[91], there are insufficient data to recommend specific anti-hyperglycemic agents[101]. Indeed, all the available agents can be used to treat post-transplant DM [120], with limitations in case of renal dysfunction[121].

CONCLUSION

DM and IGT are common in LC patients worldwide, particularly in this current era of NAFLD and obesity. The pathophysiological relationship of DM and LC is bidirectional. Over the years, the evidences that LC is a diabetogenic condition have been consolidated and the mechanisms are better understood. High-quality evidences have also determined that DM is associated to increased complications and death in CLD patients. Although the existence of two types of DM in LC patients has been confirmed, the practical usefulness of taxonomic separation of the two types of DM is unknown. In part because they have not been separately studied.

However, the research carried out to date has permitted to clearly understand the pathophysiologic mechanisms of HD and to define its clinical characteristics. Despite this, HD is not currently recognized as secondary diabetes nor as a complication of LC.

Based on the arguments presented in this review, we think that, it is time to classify LC-associated DM into T2DM and HD in order to standardize clinical research studies, which will make it possible to evaluate separately their impact on outcomes of LC patients. It is also urgent to determine standardized therapeutic guidelines for this vulnerable patients based on prospective randomized clinical trials with great number of patients and long term follow up taking into account clinical surrogates such as complication and mortality rates. Because these patients are referred from primary care levels to specialized services, we believe that the hepatologists should have the basic knowledge in the management of uncomplicated DM and equally the diabetologists should have the basic competences in the early detection and management of CLD. Complicated and severe patients should be treated by a multidisciplinary team.



DOI: 10.3748/WJG.v28.i8.775 **Copyright** ©The Author(s) 2022.

Figure 3 Algorithm for diagnosis and management of diabetes mellitus and nonalcoholic fatty liver disease based on the published evidences. As follows: (1) This treatment has been evaluated only in nonalcoholic fatty liver disease (NAFLD); (2) These drugs have been evaluated in NAFLD showing improvement of non-alcoholic steatohepatitis and fibrosis; (3) Direct-acting antiviral have demonstrated improvement of short and long term glycemic control after hepatitis C virus eradication; (4) Long term administration of metformin has demonstrated association to significant reduction of liver related complications, hepatocellular carcinoma and mortality; and (5) GLP-1 receptor agonists and sodium-glucose co-transporter-2 inhibitor drugs have demonstrated effectiveness for glycemic control and good tolerance in liver cirrhosis patients. NAFLD: Nonalcoholic fatty liver disease; DM: Diabetes mellitus; GLP-1Ras: GLP-1 receptor agonists; SGLT-2: Sodium-glucose co-transporter-2; HCV: Hepatitis C virus; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; HD: Hepatogenous diabetes; MS: Metabolic syndrome; OGTT: Oral glucose tolerance test; IGT: Impaired glucose tolerance.

FOOTNOTES

Author contributions: García-Compeán D, Orsi E, Kumar R, Gundling F and Nishida T made a bibliographic research and wrote sections of the manuscript, reviewed and corrected the final text; Cueto-Aguilera ÁN made a bibliographic research; Villarreal-Pérez JZ, González-González JA and Pugliese G critically reviewed the manuscript; García-Compeán D conceived and coordinated the whole project.

Conflict-of-interest statement: Pugliese G reported lecture fees from Novo Nordisk, Astra-Zeneca, Eli-Lilly. The other authors have no conflict to declare.

Country/Territory of origin: Mexico

ORCID number: Diego García-Compeán 0000-0002-9642-8567; Emanuela Orsi 0000-0002-1255-8437; Ramesh Kumar 0000-0001-5136-4865; Felix Gundling 0000-0002-1481-7674; Tsutomu Nishida 0000-0003-4037-9003; Jesús Zacarías Villarreal-Pérez 0000-0002-6814-062X; Ángel N Del Cueto-Aguilera 0000-0002-6506-1977; José A González-González 0000-0003-4858-5717; Giuseppe Pugliese 0000-0003-1574-0397.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Conn HO**, Schreiber W, Elkington SG, Johnson TR. Cirrhosis and diabetes. I. Increased incidence of diabetes in patients with Laennec's cirrhosis. *Am J Dig Dis* 1969; **14**: 837-852 [PMID: 5361079 DOI: 10.1007/BF02233205]
2 **Vido I**, Valovicová E, Belajová E. [Hepatogenic diabetes]. *Munch Med Wochenschr* 1969; **111**: 1898-1902 [PMID: 5395276]
3 **Bianchi G**, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E. Prognostic significance of diabetes in patients with cirrhosis. *Hepatology* 1994; **20**: 119-125 [PMID: 8020880 DOI: 10.1002/hep.1840200119]
4 **Holstein A**, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol* 2002; **17**: 677-681 [PMID: 12100613 DOI: 10.1046/j.1440-1746.2002.02755.x]
5 **Wlazlo N**, Beijers HJ, Schoon EJ, Sauerwein HP, Stehouwer CD, Bravenboer B. High prevalence of diabetes mellitus in patients with liver cirrhosis. *Diabet Med* 2010; **27**: 1308-1311 [PMID: 20968111 DOI: 10.1111/j.1464-5491.2010.03093.x]
6 **García-Compeán D**, Jáquez-Quintana JO, Lavalle-González FJ, Reyes-Cabello E, González-González JA, Muñoz-Espinosa LE, Vázquez-Elizondo G, Villarreal-Pérez JZ, Maldonado-Garza HJ. The prevalence and clinical characteristics of glucose metabolism disorders in patients with liver cirrhosis. A prospective study. *Ann Hepatol* 2012; **11**: 240-248 [PMID: 22345342 DOI: 10.1016/s1665-2681(19)31030-0]
7 **Nath P**, Anand AC. Hepatogenous Diabetes: A Primer. *J Clin Exp Hepatol* 2021; **11**: 603-615 [PMID: 34511822 DOI: 10.1016/j.jceh.2021.04.012]
8 **Mehta SH**, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000; **133**: 592-599 [PMID: 11033586 DOI: 10.7326/0003-4819-133-8-200010170-00009]
9 **Papatheodoridis GV**, Chrysanthos N, Savvas S, Sevastianos V, Kafiri G, Petraki K, Manesis EK. Diabetes mellitus in chronic hepatitis B and C: prevalence and potential association with the extent of liver fibrosis. *J Viral Hepat* 2006; **13**: 303-310 [PMID: 16637860 DOI: 10.1111/j.1365-2893.2005.00677.x]
10 **Li X**, Jiao Y, Xing Y, Gao P. Diabetes Mellitus and Risk of Hepatic Fibrosis/Cirrhosis. *Biomed Res Int* 2019; **2019**: 5308308 [PMID: 31080822 DOI: 10.1155/2019/5308308]
11 **Calzadilla-Bertot L**, Vilar-Gomez E, Torres-Gonzalez A, Socias-Lopez M, Diago M, Adams LA, Romero-Gomez M. Impaired glucose metabolism increases risk of hepatic decompensation and death in patients with compensated hepatitis C virus-related cirrhosis. *Dig Liver Dis* 2016; **48**: 283-290 [PMID: 26797261 DOI: 10.1016/j.dld.2015.12.002]
12 **Gundling F**, Schumm-Draeger PM, Schepp W. [Hepatogenous diabetes - diagnostics and treatment]. *Z Gastroenterol* 2009; **47**: 436-445 [PMID: 19418413 DOI: 10.1055/s-0028-1109200]
13 **Vasepalli P**, Noor MT, Thakur BS. Hepatogenous Diabetes- A Report from Central India. *J Clin Exp Hepatol* 2021 [DOI: 10.1016/j.jceh.2021.08.018]
14 **Forouhi NG**, Wareham NJ. Epidemiology of diabetes. *Medicine (Abingdon)* 2014; **42**: 698-702 [PMID: 25568613 DOI: 10.1016/j.mpmed.2014.09.007]
15 **Gundling F**, Schepp W, Schumm-Draeger PM. Hepatogenous diabetes in cirrhosis: academic sport or a neglected disease? *Exp Clin Endocrinol Diabetes* 2012; **120**: 469-471 [PMID: 22976313 DOI: 10.1055/s-0032-1311641]
16 **Gundling F**, Schmidt T, Schepp W. Common complications of cirrhosis: do we follow too often the 'Casablanca strategy'? *Liver Int* 2011; **31**: 1598-1600 [PMID: 21745306 DOI: 10.1111/j.1478-3231.2011.02565.x]
17 **Kumar R**. Hepatogenous Diabetes: An Underestimated Problem of Liver Cirrhosis. *Indian J Endocrinol Metab* 2018; **22**: 552-559 [PMID: 30148106 DOI: 10.4103/ijem.IJEM_79_18]
18 **Petrides AS**. [Hepatogenic diabetes: pathophysiology, therapeutic options and prognosis]. *Z Gastroenterol* 1999; Supp 1: 15-21 [PMID: 10444811]
19 **García-Compeán D**, González-González JA, Lavalle-González FJ, González-Moreno EI, Villarreal-Pérez JZ, Maldonado-Garza HJ. Current Concepts in Diabetes Mellitus and Chronic Liver Disease: Clinical Outcomes, Hepatitis C Virus Association, and Therapy. *Dig Dis Sci* 2016; **61**: 371-380 [PMID: 26462490 DOI: 10.1007/s10620-015-3907-2]
20 **García-Compean D**, Jaquez-Quintana JO, Maldonado-Garza H. Hepatogenous diabetes. Current views of an ancient problem. *Ann Hepatol* 2009; **8**: 13-20 [PMID: 19221528]
21 **Greco AV**, Mingrone G, Mari A, Capristo E, Manco M, Gasbarrini G. Mechanisms of hyperinsulinaemia in Child's disease grade B liver cirrhosis investigated in free living conditions. *Gut* 2002; **51**: 870-875 [PMID: 12427792 DOI: 10.1136/gut.51.6.870]
22 **Siegel EG**, Jakobs R, Riemann JF. [Pancreatic insufficiency-induced and hepatogenic diabetes. Special aspects in pathophysiology and treatment]. *Internist (Berl)* 2001; **42** Suppl 1: S8-19 [PMID: 11370613 DOI: 10.1007/s001080170002]
23 **Grancini V**, Trombetta M, Lunati ME, Zimbalatti D, Boselli ML, Gatti S, Donato MF, Resi V, D'Ambrosio R, Aghemo A, Pugliese G, Bonadonna RC, Orsi E. Contribution of β-cell dysfunction and insulin resistance to cirrhosis-associated diabetes: Role of severity of liver disease. *J Hepatol* 2015; **63**: 1484-1490 [PMID: 26297917 DOI: 10.1016/j.jhep.2015.08.011]
24 **Sberna AL**, Bouillet B, Rouland A, Brindisi MC, Nguyen A, Mouillot T, Duvillard L, Denimal D, Loffroy R, Vergès B, Hillon P, Petit JM. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the

management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes. *Diabet Med* 2018; **35**: 368-375 [PMID: 29247558 DOI: 10.1111/dme.13565]

25 **Eslam M**, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1999-2014.e1 [PMID: 32044314 DOI: 10.1053/j.gastro.2019.11.312]

26 **Albhaisi S**, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. *JHEP Rep* 2019; **1**: 329-341 [PMID: 32039383 DOI: 10.1016/j.jhepr.2019.08.002]

27 **Lomonaco R**, Godinez Leiva E, Bril F, Shrestha S, Mansour L, Budd J, Portillo Romero J, Schmidt S, Chang KL, Samraj G, Malaty J, Huber K, Bedossa P, Kalavalapalli S, Marte J, Barb D, Poulton D, Fanous N, Cusi K. 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 [PMID: 33355256 DOI: 10.2337/dc20-1997]

28 **Wei L**, Cheng X, Luo Y, Yang R, Lei Z, Jiang H, Chen L. Lean non-alcoholic fatty liver disease and risk of incident diabetes in a euglycaemic population undergoing health check-ups: A cohort study. *Diabetes Metab* 2021; **47**: 101200 [PMID: 33075504 DOI: 10.1016/j.diabet.2020.08.008]

29 **Mantovani A**, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut* 2021; **70**: 962-969 [PMID: 32938692 DOI: 10.1136/gutjnl-2020-322572]

30 **Zou B**, Yeo YH, Nguyen VH, Cheung R, Ingelsson E, Nguyen MH. Prevalence, characteristics and mortality outcomes of obese, nonobese and lean NAFLD in the United States, 1999-2016. *J Intern Med* 2020; **288**: 139-151 [PMID: 32319718 DOI: 10.1111/joim.13069]

31 **Zou ZY**, Wong VW, Fan JG. Epidemiology of nonalcoholic fatty liver disease in non-obese populations: Meta-analytic assessment of its prevalence, genetic, metabolic, and histological profiles. *J Dig Dis* 2020; **21**: 372-384 [PMID: 32369237 DOI: 10.1111/1751-2980.12871]

32 **Hong YS**, Chang Y, Ryu S, Cainzos-Achirica M, Kwon MJ, Zhang Y, Choi Y, Ahn J, Rampal S, Zhao D, Pastor-Barriuso R, Lazo M, Shin H, Cho J, Guallar E. Hepatitis B and C virus infection and diabetes mellitus: A cohort study. *Sci Rep* 2017; **7**: 4606 [PMID: 28676706 DOI: 10.1038/s41598-017-04206-6]

33 **Fabiani S**, Fallahi P, Ferrari SM, Miccoli M, Antonelli A. Hepatitis C virus infection and development of type 2 diabetes mellitus: Systematic review and meta-analysis of the literature. *Rev Endocr Metab Disord* 2018; **19**: 405-420 [PMID: 29322398 DOI: 10.1007/s11154-017-9440-1]

34 **Arao M**, Murase K, Kusakabe A, Yoshioka K, Fukuzawa Y, Ishikawa T, Tagaya T, Yamanouchi K, Ichimiya H, Sameshima Y, Kakumu S. Prevalence of diabetes mellitus in Japanese patients infected chronically with hepatitis C virus. *J Gastroenterol* 2003; **38**: 355-360 [PMID: 12743775 DOI: 10.1007/s005350300063]

35 **Parvaiz F**, Manzoor S, Tariq H, Javed F, Fatima K, Qadri I. Hepatitis C virus infection: molecular pathways to insulin resistance. *Virol J* 2011; **8**: 474 [PMID: 22008087 DOI: 10.1186/1743-422X-8-474]

36 **Antonelli A**, Ferri C, Fallahi P, Sebastiani M, Nesti C, Barani L, Barale R, Ferrannini E. Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients. *Rheumatology (Oxford)* 2004; **43**: 238-240 [PMID: 13130149 DOI: 10.1093/rheumatology/keh011]

37 **Bose SK**, Ray R. Hepatitis C virus infection and insulin resistance. *World J Diabetes* 2014; **5**: 52-58 [PMID: 24567801 DOI: 10.4239/wjd.v5.i1.52]

38 **Kralj D**, Virović Jukić L, Stojsavljević S, Duvnjak M, Smolić M, Čurčić IB. Hepatitis C Virus, Insulin Resistance, and Steatosis. *J Clin Transl Hepatol* 2016; **4**: 66-75 [PMID: 27047774 DOI: 10.14218/JCTH.2015.00051]

39 **Patel S**, Jinjuvadia R, Patel R, Liangpunsakul S. Insulin Resistance is Associated With Significant Liver Fibrosis in Chronic Hepatitis C Patients: A Systemic Review and Meta-Analysis. *J Clin Gastroenterol* 2016; **50**: 80-84 [PMID: 26302498 DOI: 10.1097/MCG.0000000000000400]

40 **Elkrief L**, Chouinard P, Bendersky N, Hajage D, Larroque B, Babany G, Kutala B, Francoz C, Boyer N, Moreau R, Durand F, Marcellin P, Rautou PE, Valla D. Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. *Hepatology* 2014; **60**: 823-831 [PMID: 24841704 DOI: 10.1002/hep.27228]

41 **Saeed MJ**, Olsen MA, Powderly WG, Presti RM. Diabetes Mellitus is Associated With Higher Risk of Developing Decompensated Cirrhosis in Chronic Hepatitis C Patients. *J Clin Gastroenterol* 2017; **51**: 70-76 [PMID: 27306942 DOI: 10.1097/MCG.0000000000000566]

42 **Ciancio A**, Bosio R, Bo S, Pellegrini M, Sacco M, Vogliotti E, Fassio G, Bianco Mauthe Degerfeld AGF, Gallo M, Giordanino C, Terzi di Bergamo L, Ribaldone D, Bugianesi E, Smedile A, Rizzetto M, Saracco GM. Significant improvement of glycemic control in diabetic patients with HCV infection responding to direct-acting antiviral agents. *J Med Virol* 2018; **90**: 320-327 [PMID: 28960353 DOI: 10.1002/jmv.24954]

43 **Gilad A**, Fricker ZP, Hsieh A, Thomas DD, Zahorian T, Nunes DP. Sustained Improvement in Type 2 Diabetes Mellitus is Common After Treatment of Hepatitis C Virus With Direct-acting Antiviral Therapy. *J Clin Gastroenterol* 2019; **53**: 616-620 [PMID: 30614943 DOI: 10.1097/MCG.0000000000001168]

44 **Carnovale C**, Pozzi M, Dassano A, D'Addio F, Gentili M, Magni C, Clementi E, Radice S, Fiorina P. The impact of a successful treatment of hepatitis C virus on glyco-metabolic control in diabetic patients: a systematic review and meta-analysis. *Acta Diabetol* 2019; **56**: 341-354 [PMID: 30478781 DOI: 10.1007/s00592-018-1257-1]

45 **Vanni E**, Bugianesi E, Saracco G. Treatment of type 2 diabetes mellitus by viral eradication in chronic hepatitis C: Myth or reality? *Dig Liver Dis* 2016; **48**: 105-111 [PMID: 26614641 DOI: 10.1016/j.dld.2015.10.016]

46 **Taguchi K**, Yamanaka-Okumura H, Mizuno A, Nakamura T, Shimada M, Doi T, Takeda E. Insulin resistance as early sign of hepatic dysfunction in liver cirrhosis. *J Med Invest* 2014; **61**: 180-189 [PMID: 24705764 DOI: 10.2152/jmi.61.180]

47 **García-Compeán D**, González-González JA, Lavalle-González FJ, González-Moreno EI, Villarreal-Pérez JZ, Maldonado-Garza HJ. Hepatogenous diabetes: Is it a neglected condition in chronic liver disease? *World J Gastroenterol* 2016; **22**: 2869-2874 [PMID: 26973383 DOI: 10.3748/wjg.v22.i10.2869]

48 **Nishida T**, Tsuji S, Tsujii M, Arimitsu S, Haruna Y, Imano E, Suzuki M, Kanda T, Kawano S, Hiramatsu N, Hayashi N, Hori M. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. *Am J Gastroenterol* 2006; **101**: 70-75 [PMID: 16405536 DOI: 10.1111/j.1572-0241.2005.00307.x]

49 **Shetty A**, Wilson S, Kuo P, Laurin JL, Howell CD, Johnson L, Allen EM. Liver transplantation improves cirrhosis-associated impaired oral glucose tolerance. *Transplantation* 2000; **69**: 2451-2454 [PMID: 10868659 DOI: 10.1097/00007890-200006150-00043]

50 **Kim MG**, Choi WC. [Differential diagnosis of diabetes mellitus caused by liver cirrhosis and other type 2 diabetes mellitus]. *Korean J Hepatol* 2006; **12**: 524-529 [PMID: 17237630]

51 **Zhang L**, Shi YL, Hong WX, Jia WD, Li LH. [Diagnostic value of serum islet autoantibody in hepatogenic diabetes mellitus]. *Nan Fang Yi Ke Da Xue Xue Bao* 2006; **26**: 1034-1036 [PMID: 16864107]

52 **American Diabetes Association**. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care* 2021; **44**: S15-S33 [PMID: 33298413 DOI: 10.2337/dc21-S002]

53 **Nishida T**. Diagnosis and Clinical Implications of Diabetes in Liver Cirrhosis: A Focus on the Oral Glucose Tolerance Test. *J Endocr Soc* 2017; **1**: 886-896 [PMID: 29264539 DOI: 10.1210/js.2017-00183]

54 **Schnell O**, Crocker JB, Weng J. Impact of HbA1c Testing at Point of Care on Diabetes Management. *J Diabetes Sci Technol* 2017; **11**: 611-617 [PMID: 27898388 DOI: 10.1177/1932296816678263]

55 **Bhattacharjee D**, Vracar S, Round RA, Nightingale PG, Williams JA, Gkoutos GV, Stratton IM, Parker R, Luzio SD, Webber J, Manley SE, Roberts GA, Ghosh S. Utility of HbA_{1c} assessment in people with diabetes awaiting liver transplantation. *Diabet Med* 2019; **36**: 1444-1452 [PMID: 30474191 DOI: 10.1111/dme.13870]

56 **Nadelson J**, Satapathy SK, Nair S. Glycated Hemoglobin Levels in Patients with Decompensated Cirrhosis. *Int J Endocrinol* 2016; **2016**: 8390210 [PMID: 27882051 DOI: 10.1155/2016/8390210]

57 **Sehrawat T**, Jindal A, Kohli P, Thour A, Kaur J, Sachdev A, Gupta Y. Utility and Limitations of Glycated Hemoglobin (HbA1c) in Patients with Liver Cirrhosis as Compared with Oral Glucose Tolerance Test for Diagnosis of Diabetes. *Diabetes Ther* 2018; **9**: 243-251 [PMID: 29305791 DOI: 10.1007/s13300-017-0362-4]

58 **Honda F**, Hiramatsu A, Hyogo H, Aikata H, Daijo K, Teraoka Y, Inagaki Y, Morio K, Kobayashi T, Nakahara T, Nagaoki Y, Kawaoka T, Yoneda M, Tsuge M, Imamura M, Kawakami Y, Ochi H, Chayama K. Evaluation of glycemic variability in chronic liver disease patients with type 2 diabetes mellitus using continuous glucose monitoring. *PLoS One* 2018; **13**: e0195028 [PMID: 29614124 DOI: 10.1371/journal.pone.0195028]

59 **Sigal SH**, Stanca CM, Kontorinis N, Bodian C, Ryan E. Diabetes mellitus is associated with hepatic encephalopathy in patients with HCV cirrhosis. *Am J Gastroenterol* 2006; **101**: 1490-1496 [PMID: 16863551 DOI: 10.1111/j.1572-0241.2006.00649.x]

60 **Jepsen P**, Watson H, Andersen PK, Vilstrup H. Diabetes as a risk factor for hepatic encephalopathy in cirrhosis patients. *J Hepatol* 2015; **63**: 1133-1138 [PMID: 26206073 DOI: 10.1016/j.jhep.2015.07.007]

61 **Labenz C**, Nagel M, Kremer WM, Hilscher M, Schilling CA, Toenges G, Kuchen R, Schattenberg JM, Galle PR, Wörns MA. Association between diabetes mellitus and hepatic encephalopathy in patients with cirrhosis. *Aliment Pharmacol Ther* 2020; **52**: 527-536 [PMID: 32598080 DOI: 10.1111/apt.15915]

62 **Yin X**, Zhang F, Xiao J, Wang Y, He Q, Zhu H, Leng X, Zou X, Zhang M, Zhuge Y. Diabetes mellitus increases the risk of hepatic encephalopathy after a transjugular intrahepatic portosystemic shunt in cirrhotic patients. *Eur J Gastroenterol Hepatol* 2019; **31**: 1264-1269 [PMID: 31136318 DOI: 10.1097/MEG.0000000000001452]

63 **Yang CH**, Chiu YC, Chen CH, Tsai MC, Chuah SK, Lee CH, Hu TH, Hung CH. Diabetes mellitus is associated with gastroesophageal variceal bleeding in cirrhotic patients. *Kaohsiung J Med Sci* 2014; **30**: 515-520 [PMID: 25438683 DOI: 10.1016/j.kjms.2014.06.002]

64 **Jeon HK**, Kim MY, Baik SK, Park HJ, Choi H, Park SY, Kim BR, Hong JH, Jo KW, Shin SY, Kim JM, Kim JW, Kim HS, Kwon SO, Kim YJ, Cha SH, Kim DJ, Suk KT, Cheon GJ, Kim YD, Choi DH, Lee SJ. Hepatogenous diabetes in cirrhosis is related to portal pressure and variceal hemorrhage. *Dig Dis Sci* 2013; **58**: 3335-3341 [PMID: 23912248 DOI: 10.1007/s10620-013-2802-y]

65 **Wang X**, Mei X, Kong D. Effects of diabetes on the rebleeding rate following endoscopic treatment in patients with liver cirrhosis. *Exp Ther Med* 2020; **20**: 1299-1306 [PMID: 32742363 DOI: 10.3892/etm.2020.8876]

66 **Qi X**, Peng Y, Li H, Dai J, Guo X. Diabetes is associated with an increased risk of in-hospital mortality in liver cirrhosis with acute upper gastrointestinal bleeding. *Eur J Gastroenterol Hepatol* 2015; **27**: 476-477 [PMID: 25874528 DOI: 10.1097/MEG.0000000000000324]

67 **Khafaga S**, Khalil K, Mohamed A, Mahmoud S, Mohammad M. Acute Variceal Bleeding in Patients with Liver Cirrhosis with and without Diabetes. *Liver Res Open J* 2015; 14-20 [DOI: 10.17140/LROJ-1-103]

68 **Wlazlo N**, van Greevenbroek MM, Curvers J, Schoon EJ, Friederich P, Twisk JW, Bravenboer B, Stehouwer CD. Diabetes mellitus at the time of diagnosis of cirrhosis is associated with higher incidence of spontaneous bacterial peritonitis, but not with increased mortality. *Clin Sci (Lond)* 2013; **125**: 341-348 [PMID: 23566037 DOI: 10.1042/CS20120596]

69 **Tergast TL**, Laser H, Gerbel S, Manns MP, Cornberg M, Maasoumy B. Association Between Type 2 Diabetes Mellitus, HbA1c and the Risk for Spontaneous Bacterial Peritonitis in Patients with Decompensated Liver Cirrhosis and Ascites. *Clin Transl Gastroenterol* 2018; **9**: 189 [PMID: 30250034 DOI: 10.1038/s41424-018-0053-0]

70 **Rosenblatt R**, Atteberry P, Tafesh Z, Ravikumar A, Crawford CV, Lucero C, Jesudian AB, Brown RS Jr, Kumar S, Fortune BE. Uncontrolled diabetes mellitus increases risk of infection in patients with advanced cirrhosis. *Dig Liver Dis* 2021; **53**: 445-451 [PMID: 33153928 DOI: 10.1016/j.dld.2020.10.022]

71 **El-Serag HB**, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; **4**: 369-380 [PMID: 16527702 DOI: 10.1016/j.cgh.2005.12.007]

72 **Yang WS**, Va P, Bray F, Gao S, Gao J, Li HL, Xiang YB. The role of pre-existing diabetes mellitus on hepatocellular carcinoma occurrence and prognosis: a meta-analysis of prospective cohort studies. *PLoS One* 2011; **6**: e27326 [PMID: 22205924 DOI: 10.1371/journal.pone.0027326]

73 **Yang JD**, Mohamed HA, Cvinar JL, Gores GJ, Roberts LR, Kim WR. Diabetes Mellitus Heightens the Risk of Hepatocellular Carcinoma Except in Patients With Hepatitis C Cirrhosis. *Am J Gastroenterol* 2016; **111**: 1573-1580 [PMID: 27527741 DOI: 10.1038/ajg.2016.330]

74 **Li Q**, Li WW, Yang X, Fan WB, Yu JH, Xie SS, Liu L, Ma LX, Chen SJ, Kato N. Type 2 diabetes and hepatocellular carcinoma: a case-control study in patients with chronic hepatitis B. *Int J Cancer* 2012; **131**: 1197-1202 [PMID: 22052244 DOI: 10.1002/ijc.27337]

75 **Zheng Z**, Zhang C, Yan J, Ruan Y, Zhao X, San X, Mao Y, Sun Q, Zhang K, Fan Z. Diabetes mellitus is associated with hepatocellular carcinoma: a retrospective case-control study in hepatitis endemic area. *PLoS One* 2013; **8**: e84776 [PMID: 24386416 DOI: 10.1371/journal.pone.0084776]

76 **Karagozian R**, Baker E, Houranieh A, Leavitt D, Baffy G. Risk profile of hepatocellular carcinoma reveals dichotomy among US veterans. *J Gastrointest Cancer* 2013; **44**: 318-324 [PMID: 23609167 DOI: 10.1007/s12029-013-9499-1]

77 **Takahashi H**, Mizuta T, Eguchi Y, Kawaguchi Y, Kuwashiro T, Oeda S, Isoda H, Oza N, Iwane S, Izumi K, Anzai K, Ozaki I, Fujimoto K. Post-challenge hyperglycemia is a significant risk factor for the development of hepatocellular carcinoma in patients with chronic hepatitis C. *J Gastroenterol* 2011; **46**: 790-798 [PMID: 21331763 DOI: 10.1007/s00535-011-0381-2]

78 **García-Compeán D**, Jáquez-Quintana JO, Lavalle-González FJ, González-González JA, Muñoz-Espinosa LE, Villarreal-Pérez JZ, Maldonado-Garza HJ. Subclinical abnormal glucose tolerance is a predictor of death in liver cirrhosis. *World J Gastroenterol* 2014; **20**: 7011-7018 [PMID: 24944496 DOI: 10.3748/wjg.v20.i22.7011]

79 **Moreau R**, Delègue P, Pessione F, Hillaire S, Durand F, Lebrec D, Valla DC. Clinical characteristics and outcome of patients with cirrhosis and refractory ascites. *Liver Int* 2004; **24**: 457-464 [PMID: 15482343 DOI: 10.1111/j.1478-3231.2004.0991.x]

80 **Quintana JO**, García-Compean D, González JA, Pérez JZ, González FJ, Espinosa LE, Hernández PL, Cabello ER, Villarreal ER, Rendón RF, Garza HM. The impact of diabetes mellitus in mortality of patients with compensated liver cirrhosis-a prospective study. *Ann Hepatol* 2011; **10**: 56-62 [PMID: 21301011 DOI: 10.1016/s1665-2681(19)31588-1]

81 **Tietge UJ**, Selberg O, Kreter A, Bahr MJ, Pirlich M, Burchert W, Müller MJ, Manns MP, Böker KH. Alterations in glucose metabolism associated with liver cirrhosis persist in the clinically stable long-term course after liver transplantation. *Liver Transpl* 2004; **10**: 1030-1040 [PMID: 15390330 DOI: 10.1002/Lt.20147]

82 **Hoehn RS**, Singhal A, Wima K, Sutton JM, Paterno F, Steve Woodle E, Hohmann S, Abbott DE, Shah SA. Effect of pretransplant diabetes on short-term outcomes after liver transplantation: a national cohort study. *Liver Int* 2015; **35**: 1902-1909 [PMID: 25533420 DOI: 10.1111/liv.12770]

83 **Sharif A**, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, Berlakovich G, Krebs M, Kautzky-Willer A, Schernthaner G, Marchetti P, Pacini G, Ojo A, Takahara S, Larsen JL, Budde K, Eller K, Pascual J, Jardine A, Bakker SJ, Valderhaug TG, Jenssen TG, Cohney S, Säemann MD. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant* 2014; **14**: 1992-2000 [PMID: 25307034 DOI: 10.1111/ajt.12850]

84 **Carey EJ**, Aqel BA, Byrne TJ, Douglas DD, Rakela J, Vargas HE, Moss AA, Mulligan DC, Reddy KS, Chakkera HA. Pretransplant fasting glucose predicts new-onset diabetes after liver transplantation. *J Transplant* 2012; **2012**: 614781 [PMID: 22461975 DOI: 10.1155/2012/614781]

85 **Li DW**, Lu TF, Hua XW, Dai HJ, Cui XL, Zhang JJ, Xia Q. Risk factors for new onset diabetes mellitus after liver transplantation: A meta-analysis. *World J Gastroenterol* 2015; **21**: 6329-6340 [PMID: 26034369 DOI: 10.3748/wjg.v21.i20.6329]

86 **Ichikawa T**, Taura N, Miyaaki H, Miuma S, Shibata H, Honda T, Hidaka M, Soyama A, Takatsuki M, Eguchi S, Nakao K. β-cell function prior to liver transplantation contributes to post-operative diabetes. *Biomed Rep* 2016; **5**: 749-757 [PMID: 28101345 DOI: 10.3892/br.2016.788]

87 **Lieber SR**, Lee RA, Jiang Y, Reuter C, Watkins R, Szempruch K, Gerber DA, Desai CS, DeCherney GS, Barritt AS 4th. The impact of post-transplant diabetes mellitus on liver transplant outcomes. *Clin Transplant* 2019; **33**: e13554 [PMID: 30927288 DOI: 10.1111/ctr.13554]

88 **Lv C**, Zhang Y, Chen X, Huang X, Xue M, Sun Q, Wang T, Liang J, He S, Gao J, Zhou J, Yu M, Fan J, Gao X. New-onset diabetes after liver transplantation and its impact on complications and patient survival. *J Diabetes* 2015; **7**: 881-890 [PMID: 25676209 DOI: 10.1111/1753-0407.12275]

89 **Morbitzer KA**, Taber DJ, Pilch NA, Meadows HB, Fleming JN, Bratton CF, McGillicuddy JW, Baliga PK, Chavin KD. The impact of diabetes mellitus and glycemic control on clinical outcomes following liver transplant for hepatitis C. *Clin Transplant* 2014; **28**: 862-868 [PMID: 24893750 DOI: 10.1111/ctr.12391]

90 **Alvarez-Sotomayor D**, Satorres C, Rodríguez-Medina B, Herrero I, de la Mata M, Serrano T, Rodríguez-Perálvarez M, D'Avola D, Lorente S, Rubín A, Berenguer M. Controlling Diabetes After Liver Transplantation: Room for Improvement. *Transplantation* 2016; **100**: e66-e73 [PMID: 27653229 DOI: 10.1097/TP.0000000000001399]

91 **Reuben A**. Long-term management of the liver transplant patient: diabetes, hyperlipidemia, and obesity. *Liver Transpl* 2001; **7**: S13-S21 [PMID: 11689772 DOI: 10.1053/jlts.2001.29167]

92 Introduction: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care* 2021; **44**: S1-S2 [PMID: 33298409 DOI: 10.2337/dc21-Sint]

93 **Koutoukidis DA**, Astbury NM, Tudor KE, Morris E, Henry JA, Noreik M, Jebb SA, Aveyard P. Association of Weight Loss Interventions With Changes in Biomarkers of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. *JAMA Intern Med* 2019; **179**: 1262-1271 [PMID: 31260026 DOI: 10.1001/jamainternmed.2019.2248]

94 **European Association for the Study of the Liver**. ; European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol* 2019; **70**: 172-193 [PMID: 30144956 DOI: 10.1016/j.jhep.2018.06.024]

95 **Dhaliwal A**, Armstrong MJ. Sarcopenia in cirrhosis: A practical overview. *Clin Med (Lond)* 2020; **20**: 489-492 [PMID: 32934043 DOI: 10.7861/clinmed.2020-0089]

96 **Kawaguchi T**, Izumi N, Charlton MR, Sata M. Branched-chain amino acids as pharmacological nutrients in chronic liver

disease. *Hepatology* 2011; **54**: 1063-1070 [PMID: 21563202 DOI: 10.1002/hep.24412]
97 **Gautier JF**, Mauvais-Jarvis F. [Physical exercise and insulin sensitivity]. *Diabetes Metab* 2001; **27**: 255-260 [PMID: 11452219]
98 **Aamann L**, Dam G, Rinnov AR, Vilstrup H, Gluud LL. Physical exercise for people with cirrhosis. *Cochrane Database Syst Rev* 2018; **12**: CD012678 [PMID: 30575956 DOI: 10.1002/14651858.CD012678.pub2]
99 **Boursier J**, Anty R, Carette C, Cariou B, Castera L, Caussy C, Fontaine H, Garioud A, Gourdy P, Guerci B, Guillaume M, Michot N, Minello A, Ouizeman DJ, Serfaty L, Bonnet F, Vergès B, Petit JM; AFEF and SFD. Management of diabetes mellitus in patients with cirrhosis: An overview and joint statement. *Diabetes Metab* 2021; **47**: 101272 [PMID: 34363981 DOI: 10.1016/j.diabet.2021.101272]
100 **Kihara Y**, Ogami Y, Tabaru A, Unoki H, Otsuki M. Safe and effective treatment of diabetes mellitus associated with chronic liver diseases with an alpha-glucosidase inhibitor, acarbose. *J Gastroenterol* 1997; **32**: 777-782 [PMID: 9430016 DOI: 10.1007/BF02936954]
101 **Gentile S**, Guarino G, Romano M, Alagia IA, Fierro M, Annunziata S, Magliano PL, Gravina AG, Torella R. A randomized controlled trial of acarbose in hepatic encephalopathy. *Clin Gastroenterol Hepatol* 2005; **3**: 184-191 [PMID: 15704053 DOI: 10.1016/s1542-3565(04)00667-6]
102 **Grancini V**, Resi V, Palmieri E, Pugliese G, Orsi E. Management of diabetes mellitus in patients undergoing liver transplantation. *Pharmacol Res* 2019; **141**: 556-573 [PMID: 30690071 DOI: 10.1016/j.phrs.2019.01.042]
103 **Harrower AD**. Comparative tolerability of sulphonylureas in diabetes mellitus. *Drug Saf* 2000; **22**: 313-320 [PMID: 10789825 DOI: 10.2165/00002018-200022040-00004]
104 **DeFronzo R**, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. *Metabolism* 2016; **65**: 20-29 [PMID: 26773926 DOI: 10.1016/j.metabol.2015.10.014]
105 **Vilar-Gomez E**, Vuppalanchi R, Desai AP, Gawrieh S, Ghabril M, Saxena R, Cummings OW, Chalasani N. 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**: 317-328 [PMID: 31157422 DOI: 10.1111/apt.15331]
106 **Nkontchou G**, Cosson E, Aout M, Mahmoudi A, Bourcier V, Charif I, Ganne-Carrie N, Grando-Lemaire V, Vicaut E, Trinchet JC, Beaugrand M. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. *J Clin Endocrinol Metab* 2011; **96**: 2601-2608 [PMID: 21752887 DOI: 10.1210/jc.2010-2415]
107 **Bhat A**, Sebastiani G, Bhat M. Systematic review: Preventive and therapeutic applications of metformin in liver disease. *World J Hepatol* 2015; **7**: 1652-1659 [PMID: 26140084 DOI: 10.4254/wjh.v7.i12.1652]
108 **DePeralta DK**, Wei L, Ghoshal S, Schmidt B, Lauwers GY, Lanuti M, Chung RT, Tanabe KK, Fuchs BC. Metformin prevents hepatocellular carcinoma development by suppressing hepatic progenitor cell activation in a rat model of cirrhosis. *Cancer* 2016; **122**: 1216-1227 [PMID: 26914713 DOI: 10.1002/cncr.29912]
109 **Loke YK**, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009; **180**: 32-39 [PMID: 19073651 DOI: 10.1503/cmaj.080486]
110 **Scheen AJ**. Pharmacokinetics in patients with chronic liver disease and hepatic safety of incretin-based therapies for the management of type 2 diabetes mellitus. *Clin Pharmacokinet* 2014; **53**: 773-785 [PMID: 25091053 DOI: 10.1007/s40262-014-0157-y]
111 **Pugliese G**, Penno G, Natali A, Barutta F, Di Paolo S, Reboldi G, Gesualdo L, De Nicola L; Italian Diabetes Society and the Italian Society of Nephrology. Diabetic kidney disease: New clinical and therapeutic issues. Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology on "The natural history of diabetic kidney disease and treatment of hyperglycemia in patients with type 2 diabetes and impaired renal function". *Nutr Metab Cardiovasc Dis* 2019; **29**: 1127-1150 [PMID: 31586514 DOI: 10.1016/j.numecd.2019.07.017]
112 **Yen FS**, Wei JC, Yip HT, Hwu CM, Hou MC, Hsu CC. Dipeptidyl peptidase-4 inhibitors may accelerate cirrhosis decompensation in patients with diabetes and liver cirrhosis: a nationwide population-based cohort study in Taiwan. *Hepatol Int* 2021; **15**: 179-190 [PMID: 33423239 DOI: 10.1007/s12072-020-10122-1]
113 **Simon TG**, Patorno E, Schneeweiss S. Glucose-Like Peptide-1 Receptor Agonists and Hepatic Decompensation Events in Patients With Cirrhosis and Diabetes. *Clin Gastroenterol Hepatol* 2021 [PMID: 34256144 DOI: 10.1016/j.cgh.2021.07.010]
114 **Macha S**, Rose P, Mattheus M, Cinca R, Pinnetti S, Broedl UC, Woerle HJ. Pharmacokinetics, safety and tolerability of empagliflozin, a sodium glucose cotransporter 2 inhibitor, in patients with hepatic impairment. *Diabetes Obes Metab* 2014; **16**: 118-123 [PMID: 23859534 DOI: 10.1111/dom.12183]
115 **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**: 141-144 [PMID: 30992805 DOI: 10.1002/cld.714]
116 **Khan R**, Foster GR, Chowdhury TA. Managing diabetes in patients with chronic liver disease. *Postgrad Med* 2012; **124**: 130-137 [PMID: 22913901 DOI: 10.3810/pgm.2012.07.2574]
117 **Home PD**. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabetes Obes Metab* 2012; **14**: 780-788 [PMID: 22321739 DOI: 10.1111/j.1463-1326.2012.01580.x]
118 **Yen FS**, Lai JN, Wei JC, Chiu LT, Hsu CC, Hou MC, Hwu CM. Is insulin the preferred treatment in persons with type 2 diabetes and liver cirrhosis? *BMC Gastroenterol* 2021; **21**: 263 [PMID: 34118892 DOI: 10.1186/s12876-021-01773-x]
119 **Wallia A**, Parikh ND, Molitch ME, Mahler E, Tian L, Huang JJ, Levitsky J. Posttransplant hyperglycemia is associated with increased risk of liver allograft rejection. *Transplantation* 2010; **89**: 222-226 [PMID: 20098286 DOI: 10.1097/TP.0b013e3181c3c2ff]
120 **Oliveira CP**, Stefano JT, Alvares-da-Silva MR. Cardiovascular risk, atherosclerosis and metabolic syndrome after liver transplantation: a mini review. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 361-364 [PMID: 23639094 DOI: 10.1586/egh.13.19]
121 **Malvezzi P**, Rostaing L. The safety of calcineurin inhibitors for kidney-transplant patients. *Expert Opin Drug Saf* 2015; **14**: 1531-1546 [PMID: 26329325 DOI: 10.1517/14740338.2015.1083974]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com