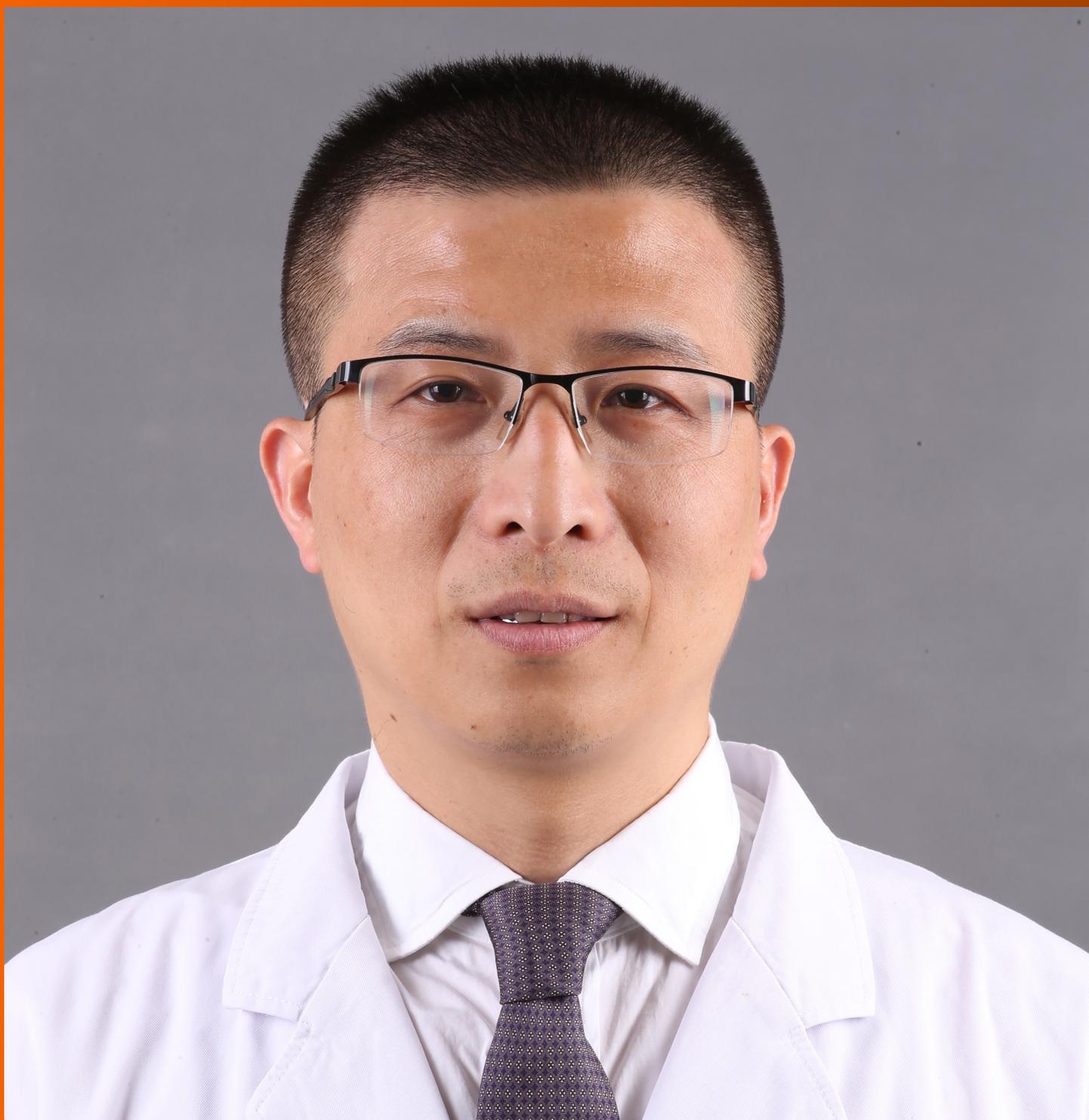


World Journal of *Hepatology*

World J Hepatol 2022 July 27; 14(7): 1269-1529



EDITORIAL

- 1269 Checkpoint inhibitor-induced hepatotoxicity: Role of liver biopsy and management approach
Bessone F, Bjornsson ES

REVIEW

- 1277 Gut microbiota contribution to hepatocellular carcinoma manifestation in non-alcoholic steatohepatitis
Liakina V, Strainiene S, Stundiene I, Maksimaityte V, Kazenaite E
- 1291 Hepatogenous diabetes: Knowledge, evidence, and skepticism
Kumar R, García-Compeán D, Maji T
- 1307 Small extracellular vesicles and liver diseases: From diagnosis to therapy
Tsuchiya A, Natsui K, Ishii Y, Koseki Y, Takeda N, Tomiyoshi K, Yamazaki F, Yoshida Y, Terai S
- 1319 Hepatocellular carcinoma and microbiota: Implications for clinical management and treatment
Spanu D, Pretta A, Lai E, Persano M, Donisi C, Mariani S, Dubois M, Migliari M, Saba G, Zirano P, Pusceddu V, Puzzone M, Astará G, Scartozzi M

MINIREVIEWS

- 1333 Challenge of managing hepatitis B virus and hepatitis C virus infections in resource-limited settings
Said ZNA, El-Sayed MH
- 1344 Alfapump® implantable device in management of refractory ascites: An update
Weil-Verhoeven D, Di Martino V, Stirnimann G, Cervoni JP, Nguyen-Khac E, Thévenot T

ORIGINAL ARTICLE**Basic Study**

- 1357 Tissue pad degradation of ultrasonic device may enhance thermal injury and impair its sealing performance in liver surgery
Kajiwara M, Fujikawa T, Hasegawa S
- 1365 Regulation of PPAR- γ activity in lipid-laden hepatocytes affects macrophage polarization and inflammation in nonalcoholic fatty liver disease
Li XY, Ji PX, Ni XX, Chen YX, Sheng L, Lian M, Guo CJ, Hua J

Clinical and Translational Research

- 1382 Transcriptome changes in stages of non-alcoholic fatty liver disease
Aljabban J, Rohr M, Syed S, Khorfan K, Borkowski V, Aljabban H, Segal M, Mukhtar M, Mohammed M, Panahiazar M, Hadley D, Spengler R, Spengler E

Retrospective Cohort Study

- 1398 Cardiac risk factors limiting survival to liver transplantation in patients with nonalcoholic fatty liver disease
Delicce M, Mauch J, Joseph A, Lyu R, Kren H, Bartow R, Ferchill D, Fares M, Wakim-Fleming J

Retrospective Study

- 1408 Differential distribution of gene polymorphisms associated with hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia among Native American and Mestizo Mexicans
Torres-Valadez R, Roman S, Ojeda-Granados C, Gonzalez-Aldaco K, Panduro A
- 1421 Effect of thrombocytopenia and platelet transfusion on outcomes of acute variceal bleeding in patients with chronic liver disease
Biswas S, Vaishnav M, Pathak P, Gunjan D, Mahapatra SJ, Kedia S, Rout G, Thakur B, Nayak B, Kumar R, Shalimar

Observational Study

- 1438 Polymorphism AGT2 (rs4762) is involved in the development of dermatologic events: Proof-of-concept in hepatocellular carcinoma patients treated with sorafenib
Sapena V, Iavarone M, Boix L, Facchetti F, Guarino M, Sanduzzi Zamparelli M, Granito A, Samper E, Scartozzi M, Corominas J, Marisi G, Diaz A, Casadei-Gardini A, Gramantieri L, Lampertico P, Morisco F, Torres F, Bruix J, Reig M
- 1459 Hepatobiliary phases in magnetic resonance imaging using liver-specific contrast for focal lesions in clinical practice
Fernandes DA, Dal Lago EA, Oliver FA, Loureiro BMC, Martins DL, Penachim TJ, Barros RHO, Araújo Filho JAB, Eloy da Costa LB, da Silva AMO, de Ataíde EC, Boin IFSF, Caserta NMG
- 1470 Efficacy and safety of COVID-19 vaccination in patients with cirrhosis
Ivashkin V, Ismailova A, Dmitrieva K, Maslennikov R, Zharkova M, Aliev S, Bakhitov V, Marcinkevich V
- 1480 Pre-sarcopenia and Mac-2 binding protein glycosylation isomer as predictors of recurrence and prognosis of early-stage hepatocellular carcinoma
Nakai M, Morikawa K, Hosoda S, Yoshida S, Kubo A, Tokuchi Y, Kitagataya T, Yamada R, Ohara M, Sho T, Suda G, Ogawa K, Sakamoto N
- 1495 Hepatitis C virus burden: Treating and educating people without prejudice
Merola E, Menotti E, Branz G, Michielan A, Seligmann S, Ratti A, Agugiaro F, Moser L, Vettori G, Franceschini A, Mantovani W, Pertile R, de Pretis G, Pravadelli C

Prospective Study

- 1504 Volumetric assessment of hepatic grafts using a light detection and ranging system for 3D scanning: Preliminary data
Katsanos G, Karakasi KE, Karolos IA, Kofinas A, Antoniadis N, Tsioukas V, Tsoulfas G

CASE REPORT

- 1512 Hepatitis B virus markers in hepatitis B surface antigen negative patients with pancreatic cancer: Two case reports
Batskikh S, Morozov S, Kostyushev D

- 1520** "Starry liver" - Von Meyenburg complex clinical case presentation and differential diagnosis discussion: A case report

Priadko K, Niosi M, Vitale LM, De Sio C, Romano M, De Sio I

RETRACTION NOTE

- 1528** Retraction Note: Screening and identification of bioactive compounds from citrus against non-structural protein 3 protease of hepatitis C virus genotype 3a by fluorescence resonance energy transfer assay and mass spectrometry

Khan M, Rauf W, Habib FE, Rahman M, Iqbal M

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Fan-Pu Ji, MD, PhD, Professor, Doctor, Department of Infectious Diseases, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China. infection@xjtu.edu.cn

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology (WJH, World J Hepatol)* is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJH* as 0.52. The *WJH*'s CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Hepatology is 42/70.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*, Production Department Director: *Xiang Li*, Editorial Office Director: *Xiang Li*.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos Pylsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

July 27, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

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>

Hepatogenous diabetes: Knowledge, evidence, and skepticism

Ramesh Kumar, Diego García-Compeán, Tanmoy Maji

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Tamori A, Japan;
Wang CR, Taiwan

Received: January 13, 2022

Peer-review started: January 13, 2022

First decision: April 16, 2022

Revised: April 27, 2022

Accepted: July 5, 2022

Article in press: July 5, 2022

Published online: July 27, 2022



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

Diego García-Compeán, Department of Gastroenterology, University Hospital, Universidad Autónoma de Nuevo León, México, Monterrey 64700, México

Corresponding author: Ramesh Kumar, MD, Associate Professor, Department of Gastroenterology, All India Institute of Medical Sciences, Phulwari Sharif, Patna 801507, Bihar, India. docrameshkr@gmail.com

Abstract

The diabetogenic potential of liver cirrhosis (LC) has been known for a long time, and the name "hepatogenous diabetes" (HD) was coined in 1906 to define the condition. Diabetes mellitus (DM) that develops as a consequence of LC is referred to as HD. In patients with LC, the prevalence rates of HD have been reported to vary from 21% to 57%. The pathophysiological basis of HD seems to involve insulin resistance (IR) and pancreatic β -cell dysfunction. The neuro-hormonal changes, endotoxemia, and chronic inflammation of LC initially create IR; however, the toxic effects eventually lead to β -cell dysfunction, which marks the transition from impaired glucose tolerance to HD. In addition, a number of factors, including sarcopenia, sarcopenic obesity, gut dysbiosis, and hyperammonemia, have recently been linked to impaired glucose metabolism in LC. DM is associated with complications and poor outcomes in patients with LC, although the individual impact of each type 2 DM and HD is unknown due to a lack of categorization of diabetes in most published research. In fact, there is much skepticism within scientific organizations over the recognition of HD as a separate disease and a consequence of LC. Currently, T2DM and HD are being treated in a similar manner although no standardized guidelines are available. The different pathophysiological basis of HD may have an impact on treatment options. This review article discusses the existence of HD as a distinct entity with high prevalence rates, a strong pathophysiological basis, clinical and therapeutic implications, as well as widespread skepticism and knowledge gaps.

Key Words: Cirrhosis; Diabetes; Hepatogenous diabetes; Glucose intolerance; Insulin resistance; Metabolism

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Hepatogenous diabetes appears to be the most prevalent form of diabetes in patients with liver cirrhosis. It is linked to the pathophysiological alterations and severity of cirrhosis. However, it is still an underappreciated problem and is not recognized as a distinct entity by scientific organizations. This article discusses the current state of knowledge about hepatogenous diabetes, including evidence of its existence and clinical implications.

Citation: Kumar R, García-Compeán D, Maji T. Hepatogenous diabetes: Knowledge, evidence, and skepticism. *World J Hepatol* 2022; 14(7): 1291-1306

URL: <https://www.wjgnet.com/1948-5182/full/v14/i7/1291.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v14.i7.1291>

INTRODUCTION

The maintenance of glucose homeostasis necessitates a coordinated response of insulin secretion, hepatic and peripheral glucose uptake, and suppression of hepatic glucose synthesis. The same is achieved *via* a complex control process involving several tissues and inter-organ crosstalk, including the liver, pancreas, muscles, and adipose tissues, as well as a number of circulating factors[1]. The liver plays a key role in glucose homeostasis by regulating multiple glucose metabolism pathways such as glycolysis, glycogenolysis, gluconeogenesis, and glycogenesis[2-4]. Therefore, hepatic dysfunction is likely to have an impact on glucose metabolism. In fact, the association between liver cirrhosis (LC) and diabetes mellitus (DM) has been known for a long time[5,6]. The prevalence of diabetes in patients with LC ranges from 20% to 70%, which is significantly higher than the 6.28% prevalence of type 2 DM (T2DM) in the general population[7,8]. The wide range of reported prevalence rates appears to be due to heterogeneity in the studied population, stage of liver disease, and evaluation method(s).

In 1906, Naunyn first coined the term “hepatogenous diabetes” (HD) to describe DM caused by LC [9]. In the subsequent years, the association between DM and LC was studied more thoroughly, with hyperinsulinemia, insulin resistance (IR), and pancreatic- β -cell dysfunctions being commonly reported [10-14]. Although cirrhosis due alcohol, non-alcoholic fatty liver disease (NAFLD), hepatitis C viruses (HCV), and hemochromatosis has been deemed a diabetogenic condition, multiple studies have shown that diabetogenic potential of cirrhosis cuts across etiologies. Emerging evidences suggest that in patients with LC, a complex interplay between the liver, pancreas, skeletal muscles, gut, and adipose tissues is involved in the pathogenesis of impaired glucose tolerance (IGT) and HD[7,9,15,16]. However, despite plethora of evidence, HD is still not regarded as a distinct disease or a recognized complication of LC[7,17,18]. Such skepticism among scientific bodies appears to be paradoxical. The global acceptance of this term is important in order to spur more research in this area.

DEFINITION AND CHARACTERISTICS OF HD

DM that develops as a result of LC is referred to as HD[19]. For HD to be diagnosed, DM must have occurred after the onset of cirrhosis. In practice, however, distinguishing HD from T2DM can be challenging, especially in early cirrhosis, because both DM and cirrhosis have a long, indolent, and clinically silent course, making it difficult to determine which condition appeared first. Furthermore, the association between diabetes and LC is bidirectional, as patients with T2DM can develop NAFLD which may progress to cirrhosis[20]. Certain etiological agents of LC such as ethanol, NAFLD, HCV, and hemochromatosis, have a direct diabetogenic effect which can lead to DM even before onset of cirrhosis, posing a classification dilemma. Therefore, there is an unmet need to develop a consensus-based criteria for defining HD in LC patients in order to ensure consistency in future clinical research.

There are a number of soft indicators that can help distinguish HD from T2DM[7,17-19]. Unlike T2DM, HD can occur in patients with LC who don't have metabolic risk factors including a high body mass index, hyperlipidemia, or a family history of diabetes. HD patients frequently have normal fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) but abnormal oral glucose tolerance tests (OGTTs), whereas T2DM patients often have high FBG. In addition, the degree of hyperinsulinemia and IR is substantially higher in HD than in T2DM patients (Table 1).

PREVALENCE OF HD IN LC

The prevalence of all types of DM (T2DM + HD) in patients with LC has been reported to range from 20% to 70%[7]. Overall, the prevalence of DM varies depending on the etiology of LC. In a recent

Table 1 Characteristics of diabetes in patients with cirrhosis that favour a diagnosis of hepatogenous diabetes over type-2 diabetes mellitus**Following characteristics favour a diagnosis of HD**

| |
|---|
| Occurrence after the onset of liver cirrhosis |
| Low prevalence of metabolic risk factors ¹ or a family history of DM |
| Normal fasting glycemia but abnormal oral glucose tolerance test |
| Low prevalence of microvascular complications, such as diabetic retinopathy |
| Associated with higher levels of hyperinsulinemia, insulin resistance, and an increased risk of hypoglycemia due to high glycemic variability |
| Higher association with the severity of liver cirrhosis and liver related complications |
| Remission after a liver transplantation |

¹Obesity, hyperlipidemia.

HD: Hepatogenous diabetes; T2DM: Type-2 diabetes mellitus.

systematic review of 58 studies ($n = 9705$), the overall prevalence of DM in adult patients with LC was 31%. Patients with NAFLD-cirrhosis had the highest prevalence of diabetes (56%), followed by cryptogenic cirrhosis (51%), while patients with HCV and HBV cirrhosis had 32.2% and 22.2%, respectively[21]. Due to multiple shared risk factors, the prevalence of DM is higher in metabolic cirrhosis than in viral cirrhosis. However, because HD in its true sense refers to diabetes induced by liver dysfunction *per se*, the etiology of cirrhosis may have little bearing on its occurrence. Many studies, however, have not reported the differential prevalence of T2DM and HD. In studies where prevalence of HD was specifically looked at using OGTT, the rates ranged from 21% to 57% (Table 2). Wang *et al* [22] and Ramachandran *et al*[23] reported HD prevalence rates of 15.9% and 29.2%, respectively, based on clinical history alone, *i.e.*, onset of DM after diagnosis of LC. The relatively lower prevalence rates of HD in their studies signify the relevance of performing an OGTT. To detect DM in LC patients, an OGTT is required because FBG and HbA1c levels may be erroneously low[24,25]. LC patients who have normal FBG and HbA1c values but an abnormal OGTT are likely to have HD. Because of the pathophysiological differences as well as clinical and therapeutic ramifications, HD must be distinguished from T2DM.

The severity of liver disease appears to influence the prevalence of DM in LC[26,27]. In a prospective study on compensated LC patients with a normal glucose tolerance ($n = 100$) at baseline, a diabetic response to OGTT was noted in 4.4% and 21.2% after a 1-year and 4-year follow-up, respectively. The incidence of DM was even higher (35.3% at 2 years) among patients whose Child-Pugh class worsened during follow-up. Notably, the incidence of diabetes was unaffected by gender, etiology, or a family history of diabetes, suggesting that diabetes was likely to be hepatogenous[26]. In another study, DM was present in 20.5%, 56%, and 61% in Child Pugh class A, B, and C, respectively[27]. The presence of HD was significantly related to a higher model for end stage liver disease (MELD) scores (> 15), large varices, and hepatocellular carcinoma (HCC) in a study[28]. HD was significantly associated with a high Child-Pugh's scores [odds ratio (OR) = 1.43] and hepatic venous pressure gradients (HVPG) (OR = 1.15) in a study by Jeon *et al*[29]. Garcia-Compean *et al*[19] found that renal impairment and family history of DM were only two factors significantly differed between T2DM and HD[30]. Holstein *et al*[31] reported a very high prevalence of HD (57%) in a study cohort in which 56% of LC patients belonged to Child-Pugh class B or C. Thus, the available evidence suggests that the severity of LC, rather than the etiology, influences the development of HD[26-29]. In summary, HD seems to constitute a significant proportion of DM in patients with LC. The worsening diabetogenic potential of LC in parallel with the severity of liver disease suggests a detrimental impact of liver failure on glucose metabolism.

PATHOPHYSIOLOGY OF HD

The pathophysiology of HD is complex and poorly understood. This appears to be caused by two major factors: IR and pancreatic β -cell dysfunction (Figure 1). The development of IR is triggered by neurohormonal changes, endotoxemia, and chronic inflammation of LC. The toxic effects eventually reach the pancreatic islets, causing β -cell dysfunction, which leads to the development of HD. Recently, roles of hepatokines, adipokines, gut dysbiosis, hyperammonemia, sarcopenia and myosteatosis have emerged in the pathogenesis of metabolic disturbances in LC, including IR and glucose intolerance (Figure 2). Thus, the identification of mechanisms that connect multi-organ dysfunction might unravel a novel understanding of HD pathophysiology.

Table 2 Reported prevalence rates of hepatogenous diabetes in patients with liver cirrhosis

| Ref. | Patients (n) | Diagnostic method | HD, n (%) | IGT, n (%) |
|----------------------------------|--------------|-------------------------------|----------------------|------------|
| Holstein <i>et al</i> [31] | 35 | OGTT | 20 (57) | 13 (37) |
| Tietge <i>et al</i> [114] | 100 | OGTT | 35 (35) ¹ | 38 (38) |
| Nishida <i>et al</i> [25] | 46 | OGTT | 21 (38) ¹ | 13 (23) |
| García-Compeán <i>et al</i> [30] | 130 | OGTT | 28 (21.5) | 36 (38.5) |
| Jeon <i>et al</i> [29] | 195 | OGTT | 108 (55.4) | 169 (86.7) |
| Ramachandran <i>et al</i> [23] | 202 | Clinical history ² | 59 (29.2) | NS |
| Wang <i>et al</i> [22] | 207 | Clinical history ² | 33 (15.97) | NS |
| Vasepalli <i>et al</i> [28] | 121 | OGTT | 52 (42.9) | 58 (47.9) |

¹Likely hepatogenous diabetes (diabetes diagnosed after oral glucose tolerance test in non-diabetic cirrhosis).

²Onset of diabetes after diagnosis of cirrhosis.

HD: Hepatogenous diabetes; LC: Liver cirrhosis; IGT: Impaired glucose tolerance; OGTT: Oral glucose tolerance test; NS: Not stated.

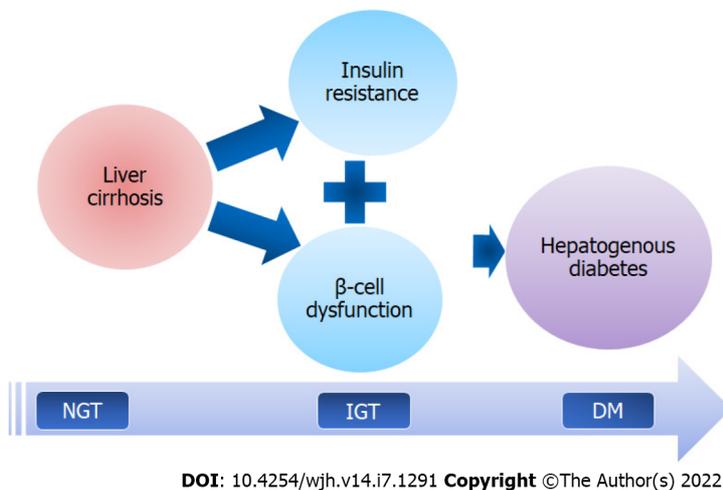
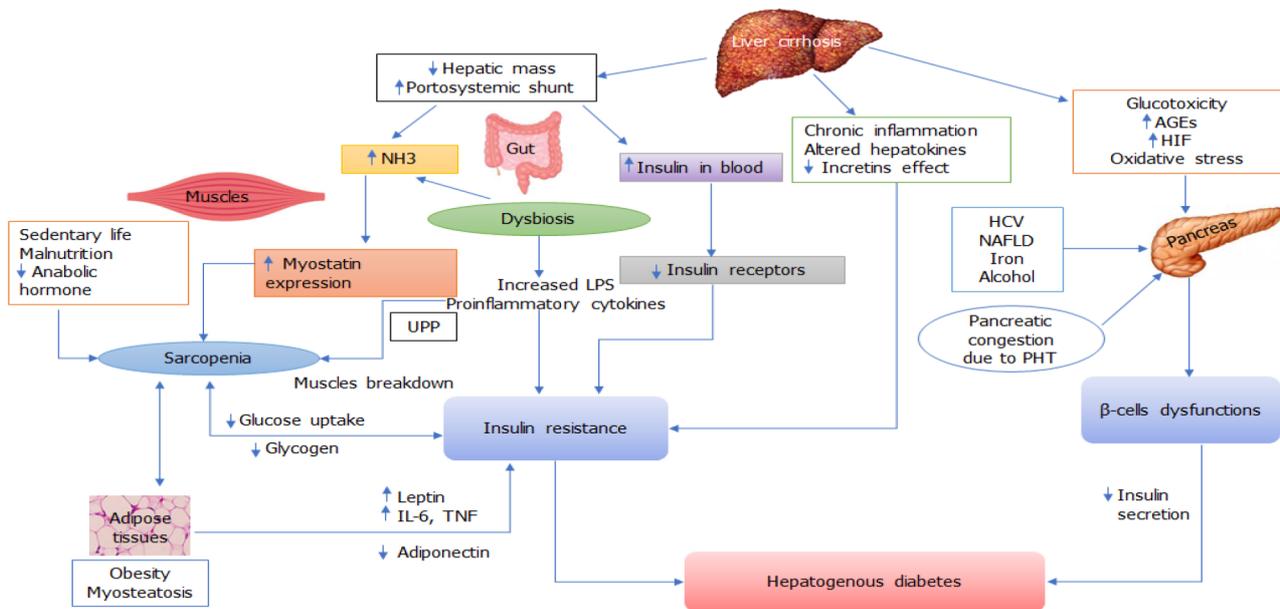


Figure 1 Key events leading to development of hepatogenous diabetes in patients with liver cirrhosis. Insulin resistance, followed by β-cell dysfunction, occurs as a result of liver cirrhosis, culminating in a progressive worsening of glucose tolerance and the onset of hepatogenous diabetes. Both of these occurrences are linked to the pathophysiological changes in the body caused by liver cirrhosis. NGT: Normal glucose tolerance; IGT: Impaired glucose tolerance; DM: Diabetes mellitus.

Hyperinsulinemia and IR

Several studies have confirmed hyperinsulinemia and IR in LC patients[10-12,32]. Hyperinsulinemia appears to be caused primarily by two abnormalities: decreased hepatic extraction and portosystemic shunting of insulin. Hyperglucagonemia, due to insufficient hepatic metabolism, may also contribute to hyperinsulinemia[33]. An augmented insulin secretion due to pancreatic islet hypertrophy may contribute to hyperinsulinemia before the development of significant β-cell dysfunction[34]. Persistent hyperinsulinemia leads to IR as insulin receptors are downregulated over target cell membranes[35]. Insulin sensitivity has been reported to be normalized when hyperinsulinemia is reduced[36]. Many studies have found a link between clinically significant portal hypertension and elevated IR[37,38], which could be due to the existence of a portosystemic shunt. In LC patients, hyperinsulinemia deteriorates after the placement of a trans jugular intrahepatic portosystemic shunt (TIPS)[39]. In contrast, balloon-occluded retrograde transvenous obliteration (BRTO) of portosystemic shunts has been shown to ameliorate hyperinsulinemia in portal hypertensive patients[40].

Clamp studies of whole-body glucose utilization have shown that IR in patients with LC is due to reduction in nonoxidative glucose disposal, which includes glucose conversion to glycogen or fat, as well as anaerobic glycolysis[41,42]. Since extrahepatic glucose metabolism accounts for majority (approximately 85%) of total body glucose metabolism under glucose clamp condition, reduction in nonoxidative glucose disposal leads to significant IR at peripheral tissues[43,44]. Many other studies have consistently demonstrated that diminished insulin-dependent glucose transport into skeletal muscle and a reduction in glycogen synthesis are mainly responsible for the reduction in peripheral



DOI: 10.4254/wjh.v14.i7.1291 Copyright ©The Author(s) 2022.

Figure 2 Complex pathophysiological mechanisms likely to play important roles in the development of hepatogenous diabetes.

Neurohormonal alterations, endotoxemia, and chronic inflammation induced by cirrhosis and portal hypertension all contribute to the development of insulin resistance and β -cell dysfunction. These changes may be further modulated by other concomitant abnormalities, such as gut dysbiosis, hyperammonemia, sarcopenia, adiposity, and myosteatosis. NH₃: Ammonia; AGE: Advanced glycation end products; HIF: Hypoxia inducible factor; HCV: Hepatitis C virus; NAFLD: Non-alcoholic fatty liver disease; LPS: Lipopolysaccharides; IL-6: Interleukin-6; TNF: Tumour necrosis factor; UPP: Ubiquitin proteasome pathways.

glucose turnover in patients with LC[45,46]. On the other hand, there appears to be no significant hepatic IR in LC[47]. Thus, skeletal muscle is the primary site of IR in patients with LC.

Pancreatic dysfunction

Despite reports of pancreatic islet cell proliferation in patients with LC, insulin-positive islet area was found to be considerably reduced[34,48,49]. In comparison to the control and T2DM groups, Sakata *et al* [49] found that patients with LC have lower insulin expression and higher expression of the pancreatic transcription factor PDX-1 in their islets. Studies on animal models of LC and portal hypertension have also found a decreased insulin secretion from the pancreatic islets despite hyperinsulinemia[13,14]. In a recent study, pancreas in LC patients showed congestive changes on dynamic contrast enhanced ultrasound and histopathology. In addition, decreased insulin secretion was found to be associated with pancreatic congestive changes. Despite the islets' expansion, the fraction of insulin-positive region per islet decreased, and this was negatively correlated with thickness of pancreatic vein due to portal hypertension[14]. These data indicate that even when glucose tolerance is impaired, pancreatic hyposecretion can occur in LC patients. The inability of the pancreatic β -cell to compensate for worsening IR appears signal the switch from IGT to HD. An improved β -cell function is also required for the regression of diabetes after liver transplantation (LT)[50].

Chronic hyperglycemia can produce toxic damage to the pancreatic islets, resulting in β -cells' dysfunction[51-53]. The accumulation of advanced glycation end products (AGEs), which are normally eliminated by the liver, accelerates this process by causing oxidative stress in β -cells. The systemic low-grade hypoxia generated by advanced LC contributes to the further deterioration of β -cells function[54]. Increased expression of hypoxia-inducible factors (HIF, mainly HIF-1 α) has been reported in many liver diseases, including NAFLD and alcoholic liver disease[55]. HIF-1 α is known to regulate cellular glucose uptake, glycolytic enzyme activity, and insulin sensitivity[56,57]. Apart from directly affecting glucose metabolism, activation of HIF-1 in patients with LC can elicit an inflammatory response in β -cells, contributing to the development of overt DM[58].

In patients with LC, a number of disease-specific mechanisms of β -cell dysfunction may be operating. Chronic alcohol use and hemochromatosis produce glucokinase downregulation and increased oxidative stress, resulting in increased β -cells apoptosis and decreased glucose-induced insulin production, respectively[59,60]. The combination of chronic hyperglycemia and high free fatty acid levels in NAFLD causes glucolipotoxicity, leading to pancreatic β -cells injury[61]. Chronic HCV infection, on the other hand, causes pancreatic islets injury by a combination of autoimmune-mediated and direct cytopathic processes[62-64].

Reduced incretins effect

Incretins serve an important function in maintaining glucose homeostasis. Enteroendocrine cells produce two naturally occurring incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, which regulate glycemic control by boosting insulin secretion and lowering glucagon secretion during postprandial period. Dipeptidyl peptidase 4 (DPP-4) is a membrane-associated peptidase that has a wide range of organ distribution and exhibits pleiotropic effects through its peptidase activity. DPP4 inactivates GLP-1, which leads to the development of IGT and DM[65]. Cirrhotic patients had higher serum DPP-4 activity and hepatic DPP-4 expression, which reduces incretin effects[66]. Thus, decreased incretin effects could play a role in the development of HD.

Gut dysbiosis

The gut microbiota is involved in the host immunity, metabolism, and intestinal endocrine function[67]. Patients with LC frequently have changes in the composition and function of the gut microbiota with associated damage to the gut barrier, bacterial translocation, and systemic inflammation[68,69]. The translocation of gut-derived endotoxins (notably lipopolysaccharide, LPS), which activates toll-like receptors, is involved in the pathogenesis of IR[70]. Metabolic endotoxemia mediated by LPS/CD14 system dysregulates inflammatory tone, leading to diabetes and adiposity[70]. Dysbiosis of the gut has been associated with obesity, metabolic diseases, and DM[71]. Gut dysbiosis also contributes to hyperammonemia in LC patients which has some role in the development of peripheral IR[72]. The human gut microbiota produces a variety of compounds, including branched-chain amino acids, whose circulation levels are linked to the risk of IR and DM[73]. The gut microbiome of CLD patients with sarcopenia was found to be pro-diabetogenic in a recent study, with a high abundance of gram-negative bacteria containing LPS on the one hand and a low Firmicutes/Bacteroidetes ratio on the other[74]. Therefore, gut dysbiosis could play an important role in the pathogenesis of HD in advanced LC.

Hyperammonemia

Hyperammonemia is a frequent abnormality in LC due to impaired hepatic detoxification to urea and bypass *via* portosystemic shunt. Hyperammonemia has been associated with IR for a long time[75]. Hyperammonemia in LC is linked to enhanced myostatin expression in the skeletal muscle[76]. Because myostatin is a negative regulator of muscle protein synthesis, a greater serum ammonia level can promote a rise in myostatin in skeletal muscle, leading to sarcopenia progression and its adverse consequences[77,78]. Hyperammonemia is also associated with myosteatorosis which affects glucose transport and glycogen synthesis by downregulating muscle insulin receptors[79,80]. Thus, myostatin appears to have a role in cirrhosis-induced peripheral IR, as it causes sarcopenia and myosteatorosis.

Sarcopenia

Skeletal muscle is responsible for the majority of postprandial glucose consumption, making it an essential insulin target organ for glucose uptake and utilization[81]. As a result, skeletal muscle loss might result in substantial IR[81,82]. Sarcopenia, or the loss of skeletal muscle mass, quality, and strength, is common in LC patients and is linked to IR and DM[83,84]. Sarcopenia in LC is caused by an imbalance in muscle protein turnover, which is influenced by a number of metabolic variables such as hyperammonemia, amino acid deficiency, hormone imbalance, gut dysbiosis, IR, and chronic inflammation[81-84]. Sarcopenia and DM appear to have a bidirectional link. On the one hand, sarcopenia is common among DM patients; on the other hand, sarcopenia has been linked to an increased risk of DM [85]. Sarcopenia is frequently accompanied by myosteatorosis, mitochondrial dysfunction, macrophage infiltration, and inflammatory cytokine release, all of which contribute to IR as well as lower glucose uptake and utilization[83,84]. Previous studies have shown that skeletal muscles secrete a variety of cytokines, such as IL-6 and irisin, that regulate insulin sensitivity and promote metabolism[86,87]. Thus, impairment of muscle secretory function due to sarcopenia may contribute to the development of DM in LC patients. Sarcopenic obesity, which affects up to 35% of patients waiting for a liver transplant, has a higher influence on metabolic profile than either condition alone[88].

Hepatokines and adipokines

Hepatokines and adipokines, proteins that regulate systemic metabolism and energy homeostasis, are secreted by the liver and adipose tissues, respectively[89-91]. Crosstalk between hepatokines, adipokines, and myokines influences inflammation and fat metabolism in adipose and skeletal muscle, which can contribute to IR[90,92,93]. Additionally, some hepatokines influence insulin secretion by the pancreas, which can independently affect peripheral tissue glucose uptake and metabolism. Hepatokines are known to contribute to the pathogenesis of metabolic syndrome, NAFLD, and 2DM[90, 92]. Furthermore, several hepatokines control pancreatic insulin secretion, which can affect glucose uptake and metabolism in peripheral tissues independently. Many hepatokines, including fetuin A, fetuin B, retinol-binding protein 4, and selenoprotein P, have been linked to the induction of metabolic dysfunction[93]. Therefore, their significance in metabolic abnormalities of LC is worth investigating. Resistin is an adipokine that reduces insulin sensitivity in adipocytes, skeletal muscles, and hepatocytes. Serum resistin level has been found to be significantly elevated in patients with LC, which may

contribute to IR[94].

CLINICAL IMPACT OF DM ON LC

The presence of DM (HD+T2DM) in patients with LC is associated with numerous complications and poor outcomes (Table 3). Because most studies have not stratified DM into HD and T2DM, the individual impact of HD cannot be ascertained[16,18,95,96]. However, because HD is a direct complication of liver cirrhosis, it is likely to have a greater negative impact on prognosis of liver cirrhosis than T2DM.

Impact on complications of LC

Many complications of LC, including hepatic encephalopathy (HE), variceal hemorrhage (VH), sepsis, and hepatocellular carcinoma (HCC) have been associated with DM. DM has been associated with an increased incidence and severity of HE in patients with LC. In a study, the proportion of patients with severe HE was found to be higher in diabetic than in nondiabetic patients (60% vs 20%, $P = 0.007$)[97]. Jepsen *et al*[98] reported that diabetic LC patients had a higher incidence of first-time overt HE in a year (26% vs 15.8%) as well as greater risk of HE progression > grade 2 (64% vs 42%), compared to non-diabetic LC. DM is an independent predictor of HE after TIPS in LC patients[99,100]. Possible mechanisms by which DM can promote HE include induction of intestinal glutaminase, intestinal bacterial overgrowth, hyperammonemia, sepsis, and development of a chronic inflammatory state[101-103].

Chronic hyperglycemia may induce splanchnic hyperemia in LC patients leading to an increased portal pressure and risk of VH[22,29,104]. In a prospective study ($n = 194$), HD (55.4%) was significantly associated with increased portal pressure and risk of VH[29]. Yang *et al*[104] also reported DM as an independent predictor of VH in LC patients (OR = 2.99). Wang *et al*[22] have reported an increased risk of rebleeding following endoscopic variceal ligation in HD patients (44% vs 13.9% in 6 mo). DM also increases the mortality risk following upper gastrointestinal bleeding in LC patients (OR = 5.7)[105].

DM increases the risk of bacterial infections in patients with LC[106]. In a study on hospitalized LC patients ($n = 178$), the prevalence of bacterial infections was higher among diabetics than non-diabetic (85% vs 48%, $P < 0.0001$)[107]. DM increases the risk of spontaneous bacterial peritonitis in LC (HR = 1.51)[108]. Furthermore, uncontrolled DM in LC has greater risk of bacterial infection, suggesting that glycemic control could be a modifiable target[108,109]. DM is also a risk factor for HCC in LC patients. In a cohort study, DM increased the risk of HCC in patients with non-HCV cirrhosis (HR = 2.1) but not in HCV-cirrhosis, who already have a very high risk of developing HCC[110]. Takahashi *et al*[111] have reported that 2-hours post-glucose-challenge hyperglycemia was significant factor for HCC development in HCV-RNA-positive patients (HR = 6.9).

Impact on outcome and LT

The survival rate in patients with LC is significantly reduced in presence of DM[25,106,112,113]. Bianchi *et al*[112] reported that 5-year survival of LC patients with or without DM was 41% and 56%, respectively, $P = 0.005$. In a prospective study on 100 compensated LC patients, 5-year cumulated survival rates were lower (31.7% vs 71.6%) in those with abnormal OGTT normal OGTT ($P = 0.02$)[113]. In another prospective study, the cumulative 5-year survival was 94.7% in LC with normal glucose tolerance compared to 56.6% in those with DM on OGTT[25]. In a recent French study, DM had a greater impact on survival in early stages of LC patients (MELD score < 10), suggesting that the severity of liver disease can mask the deleterious effect of DM[106]. In a longitudinal study, Holstein *et al*[31] also found that all deaths in HD patients were due to complications related to LC rather than diabetes-related complications. This could be because of advanced liver failure in HD patients which shortens the time for diabetes complications to emerge.

The pre-transplant DM also has adverse impact on outcomes of liver transplantation. Tietge *et al*[114] demonstrated that pre-liver transplant IGT or DM are the major risk factors for post-transplant diabetes. In a meta-analysis of 20 studies ($n = 4580$), impaired glucose metabolism was among the risk factors for new onset DM after LT[115]. Post-LT DM is associated with increased risk of mortality and multiple morbid outcomes such as cardiovascular disease, infection, biliary complications, renal impairment, and graft rejection[116-118].

SKEPTICISM ABOUT HD

Ever since Naunyn first coined the term "hepatogenous diabetes" in 1906, there has been a lot of research on this subject, especially in the 1970s and 1980s, but the momentum faded little bit and the term HD began to lose its recognition and appeal. To date, the most scientific bodies, such as the American Diabetes Association (ADA) and the American Association for the Study of Liver Disease

Table 3 Studies depicting clinical impact of diabetes mellitus/hepatogenous diabetes in patients with liver cirrhosis

| Ref. | Design | n | Main outcomes/remarks |
|-----------------------------------|-----------------------------------|--------|--|
| Bianchi <i>et al</i> [112] | Retro-prospective | 354 | 5 yr survival: 41% with DM and 56% without DM ($P = 0.005$) |
| Holstein <i>et al</i> [31] | Prospective cohort | 52 | 51% of HD patients died within median of 5.7 yr after diagnosis of DM. Remark: No data on non-diabetic control |
| Moreau <i>et al</i> [136] | Prospective cohort | 75 | Survival in patients with and without DM: 18% and 58%, respectively |
| Sigal <i>et al</i> [97] | Cross-sectional | 65 | Incidence and severity of HE was higher in diabetics and DM was an independent risk factor for HE ($P = 0.0008$). Remark: study involved only HCV cirrhosis |
| Nishida <i>et al</i> [25] | Prospective cohort | 56 | 5 yr survival was 94%, 68% and 56%, with NGT, IGT and DM, respectively |
| Tietge <i>et al</i> [114] | Case-control study | 100 | Pre-transplant IGT or DM was risk factor for post-LT DM. Remark: Only 31 patients were prospectively evaluated |
| Jeon <i>et al</i> [29] | Prospective cohort | 195 | HD correlated significantly with HVPG and VH. Post-prandial hyperglycemia correlation with risk of VH in 6 mo |
| García-Compeán <i>et al</i> [113] | Prospective cohort | 100 | 5 yr cumulated survival was lower in IGT patients than NGT (31.7% vs 71.6%, $P = 0.02$) |
| Elkrief <i>et al</i> [106] | Retrospective cohort | 348 | DM was independently associated with ascites, infections, HE, HCC and mortality. Remarks: Only HCV cirrhosis studied |
| Yang <i>et al</i> [104] | Prospective cohort | 146 | DM was among independent predictors of VH (OR = 4.90) |
| Jepsen <i>et al</i> [98] | Database analysis | 863 | Diabetic patients had a higher episode of first-time overt HE and HE progression beyond grade 2 than non-diabetics. Remarks: Original trials used vaptan which could be a confounder |
| Khafaga <i>et al</i> [137] | Prospective case-control | 60 | Proportion of VH (46.4% vs 10%), HE (36% vs 10%) and mortality (16.6% vs 6.7%) was higher among diabetics compared to non-diabetic LC |
| Qi <i>et al</i> [105] | Retrospective | 145 | In-hospital mortality was 20.6% in diabetics and 4.3% in nondiabetics ($P = 0.003$) |
| Hoehn <i>et al</i> [116] | Retrospective | 12442 | Diabetic recipients had longer hospitalization (10 vs 9 d) and higher peri-transplant mortality (5% vs 4%) |
| Yang <i>et al</i> [110] | Retrospective cohort | 739 | DM increased the risk of HCC in non-HCV cirrhosis (HR = 2.1) |
| Routhu <i>et al</i> [100] | Retrospective cohort | 895 | DM was an independent predictor of HE |
| Ramachandran <i>et al</i> [23] | Prospective cohort | 222 | HD patients had higher incidence of gall stones (27% vs 13%) and urinary infection (28% vs 7%), compared to those without DM |
| Tergast <i>et al</i> [108] | Prospective | 475 | DM patients had an increased risk for SBP (HR = 1.51), especially when HbA1c values $\geq 6.4\%$ |
| Wang <i>et al</i> [22] | Retrospective | 207 | Rebleeding rate following variceal endotherapy was higher (approximately 5 times) in diabetics, including HD, than non-diabetics at 1, 3, and 6 mo |
| Rosenblatt <i>et al</i> [109] | Retrospective (National database) | 906559 | Uncontrolled DM was associated with an increased risk of bacterial infection (OR = 1.33) and death (OR = 1.62) |
| Labenz <i>et al</i> [138] | Prospective cohort s | 240 | DM was independently associated with covert HE. The risk of HE and overt HE was more pronounced when HbA1c $\geq 6.5\%$ |

DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HD: Hepatogenous diabetes; HE: Hepatic encephalopathy; HR: Hazard ratio; IGT: Impaired glucose tolerance; NGT: Normal glucose tolerance; OR: Odds ratio; VH: Variceal hemorrhage.

(AASLD), do not recognize HD as a distinct entity. As a result, HD is underestimated by most medical fraternity belonging to gastroenterology and endocrinology departments. There are no consensus-based diagnostic criteria or therapeutic guidelines for HD. Such skepticism does not appear to be justified. A strong link between LC and diabetes, several evidences of impaired glucose metabolism in LC patients, and a number of characteristics that distinguish HD from T2DM, all point to HD being a separate disease (Table 1). In addition, a number of factors have recently been identified as playing a role in the pathogenesis of impaired glucose metabolism in LC, including sarcopenia, sarcopenic obesity, gut dysbiosis, hyperammonemia, and hepato-adipokines. We believe that the time has arrived for scientific bodies to acknowledge HD as a distinct entity. This will pave the road and create doors for a large number of researchers to work on this topic in greater depth.

THERAPEUTIC CONSIDERATION

There are no standardized guidelines for managing diabetes in LC patients. Currently, T2DM and HD

are being treated in a similar manner[7,20,50,96]. In general, insulin is recommended for LC at all stages, while many oral hypoglycemic agents (OHA) are being used in LC up to Child-Pugh class B. A number of pathophysiological changes caused by LC, such as changes in the hepatic blood flow, fluid balance, hypoalbuminemia, and gut dysbiosis, might impact the bioavailability, distribution, and metabolism of antidiabetic medicines, posing a risk to patients. As a result, the majority of current OHA are considered unsafe for LC in Child-Pugh class-C, the stage which has the highest frequency of HD. Because the pathophysiology of T2DM and HD differs, the therapeutic approach should differ accordingly. However, because the pathophysiology of T2DM and HD differs, the therapeutic approach may need to be adjusted. Several pathophysiological changes produced by cirrhosis, such as degree of hepatic dysfunction, large portosystemic shunt, sarcopenia, gut dysbiosis, and hyperammonemia, all of which have an indirect impact on HD, could influence treatment choices, including drug selection (Table 4).

General measures

A moderate caloric restriction may be recommended for HD patients, particularly those who are overweight or obese. However, because of sarcopenia and sarcopenic obesity, it is important to maintain a sufficient protein intake to avoid muscle loss. Physical exercise may aid in the preservation and restoration of muscle function and mass while also improving IR. Physical exercise has also been shown to improve the HVPG and nutritional status in LC patients[119,120]. Because HD is a direct complication of LC and is associated with severity of cirrhosis, improving hepatic dysfunction and portal hypertension should be one of the important goals of HD treatment. Etiology-specific therapy (for HCV, hepatitis B, autoimmune hepatitis, *etc.*) and non-selective β -blocker to control portal hypertension may play a role in preventing, delaying, or attuning HD in LC patients. In a recent prospective study of 96 acute-on-chronic liver failure patients, 51 (53.1%) of whom had new-onset diabetes, most likely HD, the glycemic indices improved in one-third of patients following improvement of their liver function without taking anti-hyperglycemic medication[121].

OHA

Among the OHAs that can be considered for HD patients are metformin, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI) and sodium glucose co-transporter-2 (SGLT2) inhibitors[[7,20,50,96]. Glycemic targets for HD patients should be set based on postprandial glucose levels rather than HbA1c or FBG. Metformin can be an important therapeutic agent for HD, because it is free of hepatic metabolism, plasma protein binding, and hypoglycemia risk, as well as having other benefits like cardio protection and a lower risk of HCC and HE[122-124]. However, metformin should be avoided if there is concurrent renal impairment with an eGFR of less than 45 mL/min per 1.73 m² due to the significant risk of lactic acidosis[50]. Upregulation of DPP-4 expression in LC patients contributes to the development IR[66]. Therefore, incretin-based antidiabetic agents, like GLP-1 receptor agonists (Liraglutide) and DPP-4 inhibitors can be an important agent for HD. They are generally safe in LC patients, increase muscle mass, and pose little risk of hypoglycemia or weight gain[125,126]. Recently, a group of investigators from Taiwan have raised safety concerns about use of metformin and DPP4 inhibitors in LC[127,128]. From analysis of Taiwan's National Health Insurance Research Database, investigators found that metformin use (> 1000 mg/d) in patients with compensated LC patients was associated with higher risks of mortality and decompensation[127]. Similarly, DPP-4 inhibitor was found to be associated with higher risks of hepatic decompensation and failure in another study[128]. These results should be viewed with caution, as the findings need to be validated in prospective studies. In a recent study, sulfonyleureas (SU) was found to be associated with lower risks of all-cause mortality and major cardiovascular events in LC patients with diabetes[129]. However, SU should be better avoided in HD patients because of a high risk of hypoglycemia. HD patients are already at high risk of hypoglycemia due to poor glycogen storage and reduced gluconeogenesis capacity. Due to hypoglycemia, stringent glycemic control should not be attempted in HD patients.

In obese HD patients, metformin, SGLT2i, and GLP-1 agonists can be preferred because they tend to promote weight loss. When sarcopenia is severe, metformin, GLP-1 agonist (Liraglutide), and DPP-4 inhibitors are preferable[123]. SUs and SGLT2 inhibitors may increase the risk of sarcopenia[130,131]. Metformin or AGI, both of which have a positive effect on blood ammonia levels and the risk of HE, should be considered in hyperammonemic HD patients. Metformin effect is mediated partially by inhibition of glutaminase activity in enterocytes, while AGI (acarbose) stimulates the gut peristalsis and proliferation of the saccharolytic bacteria[132,133]. If there is a large portosystemic shunt in such patients, shunt occlusion using BRTO may be considered. Alteration of gut dysbiosis using probiotics is another option that requires investigation.

Insulin

Insulin therapy is considered to be the safest and most effective for patients with LC, and it is currently the sole option available for LC patients of Child-Pugh class C. However, there are many concerns about the use of insulin in HD patients who have a higher degree of hyperinsulinemia and IR than LC patients with T2DM. The insulin requirements in such patients might vary greatly, making it difficult to

Table 4 Factors that might influence selection of antidiabetic medication for hepatogenous diabetes

| Condition | Antidiabetic drug with pros and cons | Preferences |
|--|---|--|
| Obesity | Metformin, SGLT2i, and GLP-1 agonists promote weight loss; DPP-4 inhibitors are weight neutral; Sulfonylureas, Pioglitazone, and Insulin promote weight gain | Should be preferred; May be considered; Consider alternative |
| Sarcopenia | Metformin and TZD appears to have favorable effect on muscles mass; SGLT2 inhibitors, SUs (especially glibenclamide and glinides) may increase the risk of sarcopenia | Should be preferred; Consider alternative |
| Hyperammonemia/Recurrent HE | Metformin and AGIs cause reduction of blood ammonia levels and risk of HE | May be preferred |
| Renal impairment | Insulin and linagliptin appear to be safe; SGLT-2 inhibitors may be considered with dose modification. It has added diuretic advantage; Metformin increases the risk of lactic acidosis | Should be preferred; May be considered; Should be avoided |
| Hypoglycemia | Insulin in SU have high risk of hypoglycaemia; Metformin, PZD, DPP4i and SGLT2 inhibitors have low risk of hypoglycaemia | Should be avoided; May be considered |
| LC with dysplastic liver lesion/high serum AFP | Metformin decreases the risk of HCC; DPP4 inhibitors and pioglitazone inhibit HCC development in experimental model; Insulin increases risk of HCC | Should be preferred; May be consider; Should be avoided |

TZD: Thiazolidinedione; SU: Sulfonylurea; GLP-1: Glucagon-like peptide-1; DPP-4: Dipeptidyl peptidase 4; AGI: Alpha-glucosidase inhibitors; SGLT2: Sodium glucose co-transporter-2; HE: Hepatic encephalopathy; HCC: Hepatocellular carcinoma; AFP: Alfa-fetoprotein.

maintain glycemic control without increasing the risk of hypoglycemia. Insulin use has also been associated with HCC in LC patients[133]. Hence, it should be avoided in patients who are at high risk of developing HCC, such as those with dysplastic liver nodules and elevated serum alpha fetoprotein levels. In a recent study, insulin use in LC patients with diabetes was found to be associated with increased risks of hypoglycemia, cardiovascular events, liver-related complications, and mortality compared to insulin nonusers[134]. Given these considerations, insulin cannot be regarded an optimal anti-diabetic treatment for LC patients, and the search for a better alternative should be prioritized.

LT

Finally, HD should be reversible after LT because it is caused by LC. There have been reports of HD reversibility with LT, however this does not occur in all patients[135]. In one study, DM regressed in 63.9% of patients after LT, while DM never regressed in 36% of patients after two years of follow-up. The reversibility of HD appears to be determined by the level of pre-LT pancreatic β -cell injury and its improvement after LT. Grancini *et al*[50] found that improved β -cell function plays a major role in favoring diabetes regression following LT, in the presence of a sustained improvement of IR. With progression of LC, progressive accumulation of toxic materials (AGEs, HIF, *etc.*) may lead to severe non-repairable β -cells injury, making the chances of HD reversibility less likely. The diabetogenic potential of immunosuppressive therapies could also be one of the reasons behind non-reversibility of diabetes following LT.

CONCLUSION

In conclusion, the evidence suggests that patients with LC can have two forms of diabetes: T2DM and HD, with HD appearing to be the predominant type. HD is a direct complication of LC since it is strongly linked to the pathophysiological alterations and severity of LC. However, HD is still an underappreciated problem that isn't even recognized as a separate entity by scientific organizations. To maintain consistency in clinical research, future directions will first require recognition of HD as a distinct entity, followed by the creation of a consensus definition for HD. Understanding the complex pathophysiology of LC leading to HD, including changes in the liver-multiorgan cross-talk, will also be critical for providing evidence-based management recommendations.

FOOTNOTES

Author contributions: Kumar R contributed in concept and design of manuscript, data collection and manuscript writing; Garcia-Compeán D and Maji T contributed in concept, data collection and manuscript writing.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-

NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: India

ORCID number: Ramesh Kumar [0000-0001-5136-4865](https://orcid.org/0000-0001-5136-4865); Diego García-Compeán [0000-0002-9642-8567](https://orcid.org/0000-0002-9642-8567); Tanmoy Maji [0000-0002-5115-3563](https://orcid.org/0000-0002-5115-3563).

S-Editor: Ma YJ

L-Editor: A

P-Editor: Ma YJ

REFERENCES

- 1 **Chadt A**, Al-Hasani H. Glucose transporters in adipose tissue, liver, and skeletal muscle in metabolic health and disease. *Pflugers Arch* 2020; **472**: 1273-1298 [PMID: [32591906](https://pubmed.ncbi.nlm.nih.gov/32591906/) DOI: [10.1007/s00424-020-02417-x](https://doi.org/10.1007/s00424-020-02417-x)]
- 2 **Han HS**, Kang G, Kim JS, Choi BH, Koo SH. Regulation of glucose metabolism from a liver-centric perspective. *Exp Mol Med* 2016; **48**: e218 [PMID: [26964834](https://pubmed.ncbi.nlm.nih.gov/26964834/) DOI: [10.1038/emmm.2015.122](https://doi.org/10.1038/emmm.2015.122)]
- 3 **Roden M**, Bernroider E. Hepatic glucose metabolism in humans--its role in health and disease. *Best Pract Res Clin Endocrinol Metab* 2003; **17**: 365-383 [PMID: [12962691](https://pubmed.ncbi.nlm.nih.gov/12962691/) DOI: [10.1016/s1521-690x\(03\)00031-9](https://doi.org/10.1016/s1521-690x(03)00031-9)]
- 4 **Adeva-Andany MM**, Pérez-Felpete N, Fernández-Fernández C, Donapetry-García C, Pazos-García C. Liver glucose metabolism in humans. *Biosci Rep* 2016; **36** [PMID: [27707936](https://pubmed.ncbi.nlm.nih.gov/27707936/) DOI: [10.1042/BSR20160385](https://doi.org/10.1042/BSR20160385)]
- 5 **del Olmo JA**, Serra MA, Rodrigo JM. Liver cirrhosis and diabetes mellitus. *J Hepatol* 1996; **24**: 645 [PMID: [8773923](https://pubmed.ncbi.nlm.nih.gov/8773923/) DOI: [10.1016/s0168-8278\(96\)80154-1](https://doi.org/10.1016/s0168-8278(96)80154-1)]
- 6 **Muting D**, Wohlgenuth D, Dorsett R. Liver cirrhosis and diabetes mellitus. *Geriatrics* 1969; **24**: 91-99 [PMID: [5782543](https://pubmed.ncbi.nlm.nih.gov/5782543/)]
- 7 **Orsi E**, Grancini V, Menini S, Aghemo A, Pugliese G. Hepatogenous diabetes: Is it time to separate it from type 2 diabetes? *Liver Int* 2017; **37**: 950-962 [PMID: [27943508](https://pubmed.ncbi.nlm.nih.gov/27943508/) DOI: [10.1111/liv.13337](https://doi.org/10.1111/liv.13337)]
- 8 **Khan MAB**, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. *J Epidemiol Glob Health* 2020; **10**: 107-111 [PMID: [32175717](https://pubmed.ncbi.nlm.nih.gov/32175717/) DOI: [10.2991/jegh.k.191028.001](https://doi.org/10.2991/jegh.k.191028.001)]
- 9 **Perseghin G**, Mazzaferro V, Sereni LP, Regalia E, Benedini S, Bazzigaluppi E, Pulvirenti A, Leão AA, Calori G, Romito R, Baratti D, Luzi L. Contribution of reduced insulin sensitivity and secretion to the pathogenesis of hepatogenous diabetes: effect of liver transplantation. *Hepatology* 2000; **31**: 694-703 [PMID: [10706560](https://pubmed.ncbi.nlm.nih.gov/10706560/) DOI: [10.1002/hep.510310320](https://doi.org/10.1002/hep.510310320)]
- 10 **Johnson DG**, Alberti KG, Faber OK, Binder C. Hyperinsulinism of hepatic cirrhosis: Diminished degradation or hypersecretion? *Lancet* 1977; **1**: 10-13 [PMID: [63654](https://pubmed.ncbi.nlm.nih.gov/63654/) DOI: [10.1016/s0140-6736\(77\)91652-x](https://doi.org/10.1016/s0140-6736(77)91652-x)]
- 11 **Letixhe MR**, Scheen AJ, Gérard PL, Bastens BH, Pirotte J, Belaiche J, Lefèbvre PJ. Insulin secretion, clearance, and action on glucose metabolism in cirrhotic patients. *J Clin Endocrinol Metab* 1993; **77**: 1263-1268 [PMID: [8077319](https://pubmed.ncbi.nlm.nih.gov/8077319/) DOI: [10.1210/jcem.77.5.8077319](https://doi.org/10.1210/jcem.77.5.8077319)]
- 12 **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](https://pubmed.ncbi.nlm.nih.gov/12427792/) DOI: [10.1136/gut.51.6.870](https://doi.org/10.1136/gut.51.6.870)]
- 13 **Gomis R**, Fernández-Alvarez J, Pizcueta P, Fernández M, Casamitjana R, Bosch J, Rodés J. Impaired function of pancreatic islets from rats with portal hypertension resulting from cirrhosis and partial portal vein ligation. *Hepatology* 1994; **19**: 1257-1261 [PMID: [8175150](https://pubmed.ncbi.nlm.nih.gov/8175150/)]
- 14 **Kuroda T**, Hirooka M, Koizumi M, Ochi H, Hisano Y, Bando K, Matsuura B, Kumagi T, Hiasa Y. Pancreatic congestion in liver cirrhosis correlates with impaired insulin secretion. *J Gastroenterol* 2015; **50**: 683-693 [PMID: [25283134](https://pubmed.ncbi.nlm.nih.gov/25283134/) DOI: [10.1007/s00535-014-1001-8](https://doi.org/10.1007/s00535-014-1001-8)]
- 15 **Armandi A**, Rosso C, Caviglia GP, Bugianesi E. Insulin Resistance across the Spectrum of Nonalcoholic Fatty Liver Disease. *Metabolites* 2021; **11** [PMID: [33800465](https://pubmed.ncbi.nlm.nih.gov/33800465/) DOI: [10.3390/metabo11030155](https://doi.org/10.3390/metabo11030155)]
- 16 **Nath P**, Anand AC. Hepatogenous Diabetes: A Primer. *J Clin Exp Hepatol* 2021; **11**: 603-615 [PMID: [34511822](https://pubmed.ncbi.nlm.nih.gov/34511822/) DOI: [10.1016/j.jceh.2021.04.012](https://doi.org/10.1016/j.jceh.2021.04.012)]
- 17 **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](https://pubmed.ncbi.nlm.nih.gov/26973383/) DOI: [10.3748/wjg.v22.i10.2869](https://doi.org/10.3748/wjg.v22.i10.2869)]
- 18 **Kumar R**. Hepatogenous Diabetes: An Underestimated Problem of Liver Cirrhosis. *Indian J Endocrinol Metab* 2018; **22**: 552-559 [PMID: [30148106](https://pubmed.ncbi.nlm.nih.gov/30148106/) DOI: [10.4103/ijem.IJEM_79_18](https://doi.org/10.4103/ijem.IJEM_79_18)]
- 19 **García-Compeán D**, Jaquez-Quintana JO, Maldonado-Garza H. Hepatogenous diabetes. Current views of an ancient problem. *Ann Hepatol* 2009; **8**: 13-20 [PMID: [19221528](https://pubmed.ncbi.nlm.nih.gov/19221528/)]
- 20 **Kumar R**, Priyadarshi RN, Anand U. Non-alcoholic Fatty Liver Disease: Growing Burden, Adverse Outcomes and Associations. *J Clin Transl Hepatol* 2020; **8**: 76-86 [PMID: [32274348](https://pubmed.ncbi.nlm.nih.gov/32274348/) DOI: [10.14218/JCTH.2019.00051](https://doi.org/10.14218/JCTH.2019.00051)]
- 21 **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 [PMID: [30901133](https://pubmed.ncbi.nlm.nih.gov/30901133/) DOI: [10.1002/dmrr.3157](https://doi.org/10.1002/dmrr.3157)]
- 22 **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](https://pubmed.ncbi.nlm.nih.gov/32742363/) DOI: [10.3892/etm.2020.8876](https://doi.org/10.3892/etm.2020.8876)]
- 23 **Ramachandran TM**, Rajneesh AHR, Zacharia GS, Adarsh RP. Cirrhosis of Liver and Diabetes Mellitus: The Diabolic

- Duo? *J Clin Diagn Res* 2017; **11**: OC01-OC05 [PMID: 29207749 DOI: 10.7860/JCDR/2017/30705.10529]
- 24 **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 [PMID: 10563758 DOI: 10.2169/internalmedicine.38.918]
- 25 **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]
- 26 **Gentile S**, Loguercio C, Marmo R, Carbone L, Del Vecchio Blanco C. Incidence of altered glucose tolerance in liver cirrhosis. *Diabetes Res Clin Pract* 1993; **22**: 37-44 [PMID: 8137715 DOI: 10.1016/0168-8227(93)90130-w]
- 27 **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]
- 28 **Vasepalli P**, Noor MT, Thakur BS. Hepatogenous Diabetes - A Report from Central India. *J Clin Exp Hepatol* 2022; **12**: 312-318 [PMID: 35535090 DOI: 10.1016/j.jceh.2021.08.018]
- 29 **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]
- 30 **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]
- 31 **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]
- 32 **Bosch J**, Gomis R, Kravetz D, Casamitjana R, Terés J, Rivera F, Rodés J. Role of spontaneous portal-systemic shunting in hyperinsulinism of cirrhosis. *Am J Physiol* 1984; **247**: G206-G212 [PMID: 6383074 DOI: 10.1152/ajpgi.1984.247.3.G206]
- 33 **Sherwin R**, Joshi P, Hendler R, Felig P, Conn HO. Hyperglucagonemia in Laennec's cirrhosis. The role of portal-systemic shunting. *N Engl J Med* 1974; **290**: 239-242 [PMID: 4808927 DOI: 10.1056/NEJM197401312900502]
- 34 **Saitoh M**. [Studies on histopathology of pancreas in portal hypertension]. *Nihon Shokakibyō Gakkai Zasshi* 1984; **81**: 1444-1452 [PMID: 6381823]
- 35 **Shanik MH**, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? *Diabetes Care* 2008; **31** Suppl 2: S262-S268 [PMID: 18227495 DOI: 10.2337/dc08-s264]
- 36 **Petrides AS**, Stanley T, Matthews DE, Vogt C, Bush AJ, Lambeth H. Insulin resistance in cirrhosis: prolonged reduction of hyperinsulinemia normalizes insulin sensitivity. *Hepatology* 1998; **28**: 141-149 [PMID: 9657106 DOI: 10.1002/hep.510280119]
- 37 **Erice E**, Llop E, Berzigotti A, Abraldes JG, Conget I, Seijo S, Reverter E, Albillos A, Bosch J, García-Pagán JC. Insulin resistance in patients with cirrhosis and portal hypertension. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G1458-G1465 [PMID: 22492691 DOI: 10.1152/ajpgi.00389.2011]
- 38 **Zardi EM**, Di Matteo FM, Pacella CM, Sanyal AJ. Invasive and non-invasive techniques for detecting portal hypertension and predicting variceal bleeding in cirrhosis: a review. *Ann Med* 2014; **46**: 8-17 [PMID: 24328372 DOI: 10.3109/07853890.2013.857831]
- 39 **Deschênes M**, Somberg KA. Effect of transjugular intrahepatic portosystemic shunt (TIPS) on glycemic control in cirrhotic patients with diabetes mellitus. *Am J Gastroenterol* 1998; **93**: 483 [PMID: 9517672 DOI: 10.1111/j.1572-0241.1998.481_4.x]
- 40 **Ishikawa T**, Shiratsuki S, Matsuda T, Iwamoto T, Takami T, Uchida K, Terai S, Yamasaki T, Sakaida I. Occlusion of portosystemic shunts improves hyperinsulinemia due to insulin resistance in cirrhotic patients with portal hypertension. *J Gastroenterol* 2014; **49**: 1333-1341 [PMID: 24096983 DOI: 10.1007/s00535-013-0893-z]
- 41 **Petrides AS**, Groop LC, Riely CA, DeFronzo RA. Effect of physiologic hyperinsulinemia on glucose and lipid metabolism in cirrhosis. *J Clin Invest* 1991; **88**: 561-570 [PMID: 1864966 DOI: 10.1172/JCI115340]
- 42 **Müller MJ**, Fenk A, Lautz HU, Selberg O, Canzler H, Balks HJ, von zur Mühlen A, Schmidt E, Schmidt FW. Energy expenditure and substrate metabolism in ethanol-induced liver cirrhosis. *Am J Physiol* 1991; **260**: E338-E344 [PMID: 2003588 DOI: 10.1152/ajpendo.1991.260.3.E338]
- 43 **Petrides AS**, DeFronzo RA. Glucose metabolism in cirrhosis: a review with some perspectives for the future. *Diabetes Metab Rev* 1989; **5**: 691-709 [PMID: 2693018 DOI: 10.1002/dmr.5610050805]
- 44 **Meyer-Alber A**, Hartmann H, Stümpel F, Creutzfeldt W. Mechanism of insulin resistance in CCl₄-induced cirrhosis of rats. *Gastroenterology* 1992; **102**: 223-229 [PMID: 1727757 DOI: 10.1016/0016-5085(92)91804-d]
- 45 **Selberg O**, Burchert W, vd Hoff J, Meyer GJ, Hundeshagen H, Radoch E, Balks HJ, Müller MJ. Insulin resistance in liver cirrhosis. Positron-emission tomography scan analysis of skeletal muscle glucose metabolism. *J Clin Invest* 1993; **91**: 1897-1902 [PMID: 8486761 DOI: 10.1172/JCI116407]
- 46 **Kruszynska Y**, Williams N, Perry M, Home P. The relationship between insulin sensitivity and skeletal muscle enzyme activities in hepatic cirrhosis. *Hepatology* 1988; **8**: 1615-1619 [PMID: 3142811 DOI: 10.1002/hep.1840080624]
- 47 **Proietto J**, Alford FP, Dudley FJ. The mechanism of the carbohydrate intolerance of cirrhosis. *J Clin Endocrinol Metab* 1980; **51**: 1030-1036 [PMID: 6999005 DOI: 10.1210/jcem-51-5-1030]
- 48 **Takei K**, Suda K. [Study of mechanisms of pancreatic fibrosis and structural changes in liver cirrhotic patients]. *Nihon Shokakibyō Gakkai Zasshi* 1997; **94**: 92-100 [PMID: 9071172]
- 49 **Sakata M**, Kawahara A, Kawaguchi T, Akiba J, Taira T, Taniguchi E, Abe M, Koga H, Kage M, Sata M. Decreased expression of insulin and increased expression of pancreatic transcription factor PDX-1 in islets in patients with liver cirrhosis: a comparative investigation using human autopsy specimens. *J Gastroenterol* 2013; **48**: 277-285 [PMID:

- 22790351 DOI: [10.1007/s00535-012-0633-9](https://doi.org/10.1007/s00535-012-0633-9)]
- 50 **Grancini V**, Trombetta M, Lunati ME, Boselli ML, Gatti S, Donato MF, Palmieri E, Resi V, Pugliese G, Bonadonna RC, Orsi E. Central role of the β -cell in driving regression of diabetes after liver transplantation in cirrhotic patients. *J Hepatol* 2019; **70**: 954-962 [PMID: [30677460](https://pubmed.ncbi.nlm.nih.gov/30677460/) DOI: [10.1016/j.jhep.2019.01.015](https://doi.org/10.1016/j.jhep.2019.01.015)]
 - 51 **Kruszynska YT**, Goulas S, Wollen N, McIntyre N. Insulin secretory capacity and the regulation of glucagon secretion in diabetic and non-diabetic alcoholic cirrhotic patients. *J Hepatol* 1998; **28**: 280-291 [PMID: [9514541](https://pubmed.ncbi.nlm.nih.gov/9514541/) DOI: [10.1016/0168-8278\(88\)80015-1](https://doi.org/10.1016/0168-8278(88)80015-1)]
 - 52 **Picardi A**, D'Avola D, Gentilucci UV, Galati G, Fiori E, Spataro S, Afeltra A. Diabetes in chronic liver disease: from old concepts to new evidence. *Diabetes Metab Res Rev* 2006; **22**: 274-283 [PMID: [16506276](https://pubmed.ncbi.nlm.nih.gov/16506276/) DOI: [10.1002/dmrr.636](https://doi.org/10.1002/dmrr.636)]
 - 53 **Petrides AS**, Vogt C, Schulze-Berge D, Matthews D, Strohmeyer G. Pathogenesis of glucose intolerance and diabetes mellitus in cirrhosis. *Hepatology* 1994; **19**: 616-627 [PMID: [1819686](https://pubmed.ncbi.nlm.nih.gov/1819686/) DOI: [10.1002/hep.1840190312](https://doi.org/10.1002/hep.1840190312)]
 - 54 **Moreau R**, Lee SS, Soupison T, Roche-Sicot J, Sicot C. Abnormal tissue oxygenation in patients with cirrhosis and liver failure. *J Hepatol* 1988; **7**: 98-105 [PMID: [3183357](https://pubmed.ncbi.nlm.nih.gov/3183357/) DOI: [10.1016/s0168-8278\(88\)80512-9](https://doi.org/10.1016/s0168-8278(88)80512-9)]
 - 55 **Corpechot C**, Barbu V, Wendum D, Kinnman N, Rey C, Poupon R, Housset C, Rosmorduc O. Hypoxia-induced VEGF and collagen I expressions are associated with angiogenesis and fibrogenesis in experimental cirrhosis. *Hepatology* 2002; **35**: 1010-1021 [PMID: [11981751](https://pubmed.ncbi.nlm.nih.gov/11981751/) DOI: [10.1053/jhep.2002.32524](https://doi.org/10.1053/jhep.2002.32524)]
 - 56 **Nagao A**, Kobayashi M, Koyasu S, Chow CCT, Harada H. HIF-1-Dependent Reprogramming of Glucose Metabolic Pathway of Cancer Cells and Its Therapeutic Significance. *Int J Mol Sci* 2019; **20** [PMID: [30634433](https://pubmed.ncbi.nlm.nih.gov/30634433/) DOI: [10.3390/ijms20020238](https://doi.org/10.3390/ijms20020238)]
 - 57 **Regazzetti C**, Peraldi P, Grémeaux T, Najem-Lendom R, Ben-Sahra I, Cormont M, Bost F, Le Marchand-Brustel Y, Tanti JF, Giorgetti-Peraldi S. Hypoxia decreases insulin signaling pathways in adipocytes. *Diabetes* 2009; **58**: 95-103 [PMID: [18984735](https://pubmed.ncbi.nlm.nih.gov/18984735/) DOI: [10.2337/db08-0457](https://doi.org/10.2337/db08-0457)]
 - 58 **Cheng K**, Ho K, Stokes R, Scott C, Lau SM, Hawthorne WJ, O'Connell PJ, Loudovaris T, Kay TW, Kulkarni RN, Okada T, Wang XL, Yim SH, Shah Y, Grey ST, Biankin AV, Kench JG, Laybutt DR, Gonzalez FJ, Kahn CR, Gunton JE. Hypoxia-inducible factor-1 α regulates beta cell function in mouse and human islets. *J Clin Invest* 2010; **120**: 2171-2183 [PMID: [20440072](https://pubmed.ncbi.nlm.nih.gov/20440072/) DOI: [10.1172/JCI35846](https://doi.org/10.1172/JCI35846)]
 - 59 **Kim JY**, Song EH, Lee HJ, Oh YK, Park YS, Park JW, Kim BJ, Kim DJ, Lee I, Song J, Kim WH. Chronic ethanol consumption-induced pancreatic β -cell dysfunction and apoptosis through glucokinase nitration and its down-regulation. *J Biol Chem* 2010; **285**: 37251-37262 [PMID: [20855893](https://pubmed.ncbi.nlm.nih.gov/20855893/) DOI: [10.1074/jbc.M110.142315](https://doi.org/10.1074/jbc.M110.142315)]
 - 60 **Cooksey RC**, Jouihan HA, Ajioka RS, Hazel MW, Jones DL, Kushner JP, McClain DA. Oxidative stress, beta-cell apoptosis, and decreased insulin secretory capacity in mouse models of hemochromatosis. *Endocrinology* 2004; **145**: 5305-5312 [PMID: [15308612](https://pubmed.ncbi.nlm.nih.gov/15308612/) DOI: [10.1210/en.2004-0392](https://doi.org/10.1210/en.2004-0392)]
 - 61 **Weir GC**. Glucolipotoxicity, β -Cells, and Diabetes: The Emperor Has No Clothes. *Diabetes* 2020; **69**: 273-278 [PMID: [31519699](https://pubmed.ncbi.nlm.nih.gov/31519699/) DOI: [10.2337/db19-0138](https://doi.org/10.2337/db19-0138)]
 - 62 **Antonelli A**, Ferrari SM, Ruffilli I, Fallahi P. Cytokines and HCV-related autoimmune disorders. *Immunol Res* 2014; **60**: 311-319 [PMID: [25381483](https://pubmed.ncbi.nlm.nih.gov/25381483/) DOI: [10.1007/s12026-014-8569-1](https://doi.org/10.1007/s12026-014-8569-1)]
 - 63 **Bose SK**, Ray R. Hepatitis C virus infection and insulin resistance. *World J Diabetes* 2014; **5**: 52-58 [PMID: [24567801](https://pubmed.ncbi.nlm.nih.gov/24567801/) DOI: [10.4239/wjd.v5.i1.52](https://doi.org/10.4239/wjd.v5.i1.52)]
 - 64 **Chen J**, Wang F, Zhou Y, Jiang J, Ksimu S, Zhang X, Li JZ, Niu J, Wang Q. Chronic hepatitis C virus infection impairs insulin secretion by regulation of p38 δ MAPK-dependent exocytosis in pancreatic β -cells. *Clin Sci (Lond)* 2020; **134**: 529-542 [PMID: [32100852](https://pubmed.ncbi.nlm.nih.gov/32100852/) DOI: [10.1042/CS20190900](https://doi.org/10.1042/CS20190900)]
 - 65 **Drucker DJ**, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; **368**: 1696-1705 [PMID: [17098089](https://pubmed.ncbi.nlm.nih.gov/17098089/) DOI: [10.1016/S0140-6736\(06\)69705-5](https://doi.org/10.1016/S0140-6736(06)69705-5)]
 - 66 **Itou M**, Kawaguchi T, Taniguchi E, Sata M. Dipeptidyl peptidase-4: a key player in chronic liver disease. *World J Gastroenterol* 2013; **19**: 2298-2306 [PMID: [23613622](https://pubmed.ncbi.nlm.nih.gov/23613622/) DOI: [10.3748/wjg.v19.i15.2298](https://doi.org/10.3748/wjg.v19.i15.2298)]
 - 67 **Lynch SV**, Pedersen O. The Human Intestinal Microbiome in Health and Disease. *N Engl J Med* 2016; **375**: 2369-2379 [PMID: [27974040](https://pubmed.ncbi.nlm.nih.gov/27974040/) DOI: [10.1056/NEJMr1600266](https://doi.org/10.1056/NEJMr1600266)]
 - 68 **Bajaj JS**. Altered Microbiota in Cirrhosis and Its Relationship to the Development of Infection. *Clin Liver Dis (Hoboken)* 2019; **14**: 107-111 [PMID: [31632660](https://pubmed.ncbi.nlm.nih.gov/31632660/) DOI: [10.1002/cld.827](https://doi.org/10.1002/cld.827)]
 - 69 **Muñoz L**, Borrero MJ, Úbeda M, Conde E, Del Campo R, Rodríguez-Serrano M, Lario M, Sánchez-Díaz AM, Pastor O, Díaz D, García-Bermejo L, Monserrat J, Álvarez-Mon M, Albillos A. Intestinal Immune Dysregulation Driven by Dysbiosis Promotes Barrier Disruption and Bacterial Translocation in Rats With Cirrhosis. *Hepatology* 2019; **70**: 925-938 [PMID: [30414342](https://pubmed.ncbi.nlm.nih.gov/30414342/) DOI: [10.1002/hep.30349](https://doi.org/10.1002/hep.30349)]
 - 70 **Cani PD**, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007; **56**: 1761-1772 [PMID: [17456850](https://pubmed.ncbi.nlm.nih.gov/17456850/) DOI: [10.2337/db06-1491](https://doi.org/10.2337/db06-1491)]
 - 71 **Vrieze A**, Van Nood E, Holleman F, Salojarvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylekama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Stroes ES, de Vos WM, Hoekstra JB, Nieuwdorp M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; **143**: 913-6.e7 [PMID: [22728514](https://pubmed.ncbi.nlm.nih.gov/22728514/) DOI: [10.1053/j.gastro.2012.06.031](https://doi.org/10.1053/j.gastro.2012.06.031)]
 - 72 **Ahluwalia V**, Betrapally NS, Hylemon PB, White MB, Gillevet PM, Unser AB, Fagan A, Daita K, Heuman DM, Zhou H, Sikaroodi M, Bajaj JS. Impaired Gut-Liver-Brain Axis in Patients with Cirrhosis. *Sci Rep* 2016; **6**: 26800 [PMID: [27225869](https://pubmed.ncbi.nlm.nih.gov/27225869/) DOI: [10.1038/srep26800](https://doi.org/10.1038/srep26800)]
 - 73 **Gojda J**, Cahova M. Gut Microbiota as the Link between Elevated BCAA Serum Levels and Insulin Resistance. *Biomolecules* 2021; **11** [PMID: [34680047](https://pubmed.ncbi.nlm.nih.gov/34680047/) DOI: [10.3390/biom11101414](https://doi.org/10.3390/biom11101414)]
 - 74 **Yamamoto K**, Ishizu Y, Honda T, Ito T, Imai N, Nakamura M, Kawashima H, Kitaura Y, Ishigami M, Fujishiro M.

- Patients with low muscle mass have characteristic microbiome with low potential for amino acid synthesis in chronic liver disease. *Sci Rep* 2022; **12**: 3674 [PMID: 35256716 DOI: 10.1038/s41598-022-07810-3]
- 75 Schlienger JL, Imler M. Effect of hyperammonemia on insulin-mediated glucose uptake in rats. *Metabolism* 1978; **27**: 175-183 [PMID: 622048 DOI: 10.1016/0026-0495(78)90163-4]
 - 76 Qiu J, Thapaliya S, Runkana A, Yang Y, Tsien C, Mohan ML, Narayanan A, Eghtesad B, Mozdziaik PE, McDonald C, Stark GR, Welle S, Naga Prasad SV, Dasarathy S. Hyperammonemia in cirrhosis induces transcriptional regulation of myostatin by an NF- κ B-mediated mechanism. *Proc Natl Acad Sci U S A* 2013; **110**: 18162-18167 [PMID: 24145431 DOI: 10.1073/pnas.1317049110]
 - 77 Nishikawa H, Enomoto H, Ishii A, Iwata Y, Miyamoto Y, Ishii N, Yuri Y, Hasegawa K, Nakano C, Nishimura T, Yoh K, Aizawa N, Sakai Y, Ikeda N, Takashima T, Takata R, Iijima H, Nishiguchi S. Elevated serum myostatin level is associated with worse survival in patients with liver cirrhosis. *J Cachexia Sarcopenia Muscle* 2017; **8**: 915-925 [PMID: 28627027 DOI: 10.1002/jcsm.12212]
 - 78 Garcia PS, Cabbabe A, Kambadur R, Nicholas G, Csete M. Brief-reports: elevated myostatin levels in patients with liver disease: a potential contributor to skeletal muscle wasting. *Anesth Analg* 2010; **111**: 707-709 [PMID: 20686014 DOI: 10.1213/ANE.0b013e3181eac1c9]
 - 79 Thandassery RB, Montano-Loza AJ. Role of Nutrition and Muscle in Cirrhosis. *Curr Treat Options Gastroenterol* 2016; **14**: 257-273 [PMID: 27023701 DOI: 10.1007/s11938-016-0093-z]
 - 80 Correa-de-Araujo R, Addison O, Miljkovic I, Goodpaster BH, Bergman BC, Clark RV, Elena JW, Esser KA, Ferrucci L, Harris-Love MO, Kritchevsky SB, Lobergs A, Shepherd JA, Shulman GI, Rosen CJ. Myosteatosis in the Context of Skeletal Muscle Function Deficit: An Interdisciplinary Workshop at the National Institute on Aging. *Front Physiol* 2020; **11**: 963 [PMID: 32903666 DOI: 10.3389/fphys.2020.00963]
 - 81 Merz KE, Thurmond DC. Role of Skeletal Muscle in Insulin Resistance and Glucose Uptake. *Compr Physiol* 2020; **10**: 785-809 [PMID: 32940941 DOI: 10.1002/cphy.c190029]
 - 82 Zhang H, Lin S, Gao T, Zhong F, Cai J, Sun Y, Ma A. Association between Sarcopenia and Metabolic Syndrome in Middle-Aged and Older Non-Obese Adults: A Systematic Review and Meta-Analysis. *Nutrients* 2018; **10** [PMID: 29547573 DOI: 10.3390/nu10030364]
 - 83 Marasco G, Dajti E, Ravaioli F, Brocchi S, Rossini B, Alemanni LV, Peta G, Bartalena L, Golfieri R, Festi D, Colecchia A, Renzulli M. Clinical impact of sarcopenia assessment in patients with liver cirrhosis. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 377-388 [PMID: 33196344 DOI: 10.1080/17474124.2021.1848542]
 - 84 Ebadli M, Bhanji RA, Mazurak VC, Montano-Loza AJ. Sarcopenia in cirrhosis: from pathogenesis to interventions. *J Gastroenterol* 2019; **54**: 845-859 [PMID: 31392488 DOI: 10.1007/s00535-019-01605-6]
 - 85 Son JW, Lee SS, Kim SR, Yoo SJ, Cha BY, Son HY, Cho NH. Low muscle mass and risk of type 2 diabetes in middle-aged and older adults: findings from the KoGES. *Diabetologia* 2017; **60**: 865-872 [PMID: 28102434 DOI: 10.1007/s00125-016-4196-9]
 - 86 Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol* 2012; **8**: 457-465 [PMID: 22473333 DOI: 10.1038/nrendo.2012.49]
 - 87 Perakakis N, Triantafyllou GA, Fernández-Real JM, Huh JY, Park KH, Seufert J, Mantzoros CS. Physiology and role of irisin in glucose homeostasis. *Nat Rev Endocrinol* 2017; **13**: 324-337 [PMID: 28211512 DOI: 10.1038/nrendo.2016.221]
 - 88 Eslamparast T, Montano-Loza AJ, Raman M, Tandon P. Sarcopenic obesity in cirrhosis-The confluence of 2 prognostic titans. *Liver Int* 2018; **38**: 1706-1717 [PMID: 29738109 DOI: 10.1111/liv.13876]
 - 89 Watt MJ, Miotto PM, De Nardo W, Montgomery MK. The Liver as an Endocrine Organ-Linking NAFLD and Insulin Resistance. *Endocr Rev* 2019; **40**: 1367-1393 [PMID: 31098621 DOI: 10.1210/er.2019-00034]
 - 90 de Oliveira Dos Santos AR, de Oliveira Zanuso B, Miola VFB, Barbalho SM, Santos Bueno PC, Flato UAP, Detregiachi CRP, Buchaim DV, Buchaim RL, Tofano RJ, Mendes CG, Tofano VAC, Dos Santos Haber JF. Adipokines, Myokines, and Hepatokines: Crosstalk and Metabolic Repercussions. *Int J Mol Sci* 2021; **22** [PMID: 33807959 DOI: 10.3390/ijms22052639]
 - 91 Kucukoglu O, Sowa JP, Mazzolini GD, Syn WK, Canbay A. Hepatokines and adipokines in NASH-related hepatocellular carcinoma. *J Hepatol* 2021; **74**: 442-457 [PMID: 33161047 DOI: 10.1016/j.jhep.2020.10.030]
 - 92 Shi J, Fan J, Su Q, Yang Z. Cytokines and Abnormal Glucose and Lipid Metabolism. *Front Endocrinol (Lausanne)* 2019; **10**: 703 [PMID: 31736870 DOI: 10.3389/fendo.2019.00703]
 - 93 Meex RCR, Watt MJ. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. *Nat Rev Endocrinol* 2017; **13**: 509-520 [PMID: 28621339 DOI: 10.1038/nrendo.2017.56]
 - 94 Yagmur E, Trautwein C, Gressner AM, Tacke F. Resistin serum levels are associated with insulin resistance, disease severity, clinical complications, and prognosis in patients with chronic liver diseases. *Am J Gastroenterol* 2006; **101**: 1244-1252 [PMID: 16771945 DOI: 10.1111/j.1572-0241.2006.00543.x]
 - 95 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** [PMID: 33445629 DOI: 10.3390/jcm10020262]
 - 96 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**: 936-948 [PMID: 26972930 DOI: 10.1111/liv.13115]
 - 97 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]
 - 98 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]
 - 99 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]
 - 100 Routhu M, Safka V, Routhu SK, Fejfar T, Jirkovsky V, Krajina A, Cermakova E, Hosak L, Hulek P. Observational cohort study of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt (TIPS). *Ann Hepatol* 2017; **16**:

- 140-148 [PMID: 28051803 DOI: 10.5604/16652681.1226932]
- 101 **Ampuero J**, Ranchal I, Nuñez D, Díaz-Herrero Mdel M, Maraver M, del Campo JA, Rojas Á, Camacho I, Figueruela B, Bautista JD, Romero-Gómez M. Metformin inhibits glutaminase activity and protects against hepatic encephalopathy. *PLoS One* 2012; 7: e49279 [PMID: 23166628 DOI: 10.1371/journal.pone.0049279]
- 102 **Romero-Gómez M**, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. *J Hepatol* 2015; 62: 437-447 [PMID: 25218789 DOI: 10.1016/j.jhep.2014.09.005]
- 103 **Basu S**, Zethelius B, Helmersson J, Berne C, Larsson A, Arnlöv J. Cytokine-mediated inflammation is independently associated with insulin sensitivity measured by the euglycemic insulin clamp in a community-based cohort of elderly men. *Int J Clin Exp Med* 2011; 4: 164-168 [PMID: 21686140]
- 104 **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]
- 105 **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]
- 106 **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]
- 107 **Diaz J**, Monge E, Roman R, Ulloa V. Diabetes as a risk factor for infections in cirrhosis. *Am J Gastroenterol* 2008; 103: 248 [PMID: 18184135 DOI: 10.1111/j.1572-0241.2007.01562_9.x]
- 108 **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]
- 109 **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]
- 110 **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]
- 111 **Takahashi H**, Mizuta T, Eguchi Y, Kawaguchi Y, Kuwashiro T, Oeda S, Isoda H, Oza N, Iwano 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]
- 112 **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: 10.1016/0270-9139(94)90143-0]
- 113 **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]
- 114 **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]
- 115 **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]
- 116 **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]
- 117 **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]
- 118 **Morbiter 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]
- 119 **Macías-Rodríguez RU**, Ilarraza-Lomelí H, Ruiz-Margáin A, Ponce-de-León-Rosales S, Vargas-Vorácková F, García-Flores O, Torre A, Duarte-Rojo A. Changes in Hepatic Venous Pressure Gradient Induced by Physical Exercise in Cirrhosis: Results of a Pilot Randomized Open Clinical Trial. *Clin Transl Gastroenterol* 2016; 7: e180 [PMID: 27415618 DOI: 10.1038/ctg.2016.38]
- 120 **Brustia R**, Savier E, Scatton O. Physical exercise in cirrhotic patients: Towards prehabilitation on waiting list for liver transplantation. A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2018; 42: 205-215 [PMID: 29162460 DOI: 10.1016/j.clinre.2017.09.005]
- 121 **Hu H**, Hu X, Tian C, Zhu Y, Liu Y, Cheng Q, Yang F, Liu J, Li Y, Lin S. Diabetes is associated with poor short-term prognosis in patients with hepatitis B virus-related acute-on-chronic liver failure. *Hepatol Int* 2021; 15: 1093-1102 [PMID: 34373965 DOI: 10.1007/s12072-021-10243-1]
- 122 **Wu CN**, Tien KJ. The Impact of Antidiabetic Agents on Sarcopenia in Type 2 Diabetes: A Literature Review. *J Diabetes Res* 2020; 2020: 9368583 [PMID: 32695832 DOI: 10.1155/2020/9368583]
- 123 **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]

- 124 **Kaplan DE**, Serper M, John BV, Tessitore KM, Lerer R, Mehta R, Fox R, Aytaman A, Baytarian M, Hunt K, Albrecht J, Taddei TH; Veterans Outcomes and Cost Associated with Liver disease Study Group. Effects of Metformin Exposure on Survival in a Large National Cohort of Patients With Diabetes and Cirrhosis. *Clin Gastroenterol Hepatol* 2021; **19**: 2148-2160.e14 [PMID: [32798709](#) DOI: [10.1016/j.cgh.2020.08.026](#)]
- 125 **Hong Y**, Lee JH, Jeong KW, Choi CS, Jun HS. Amelioration of muscle wasting by glucagon-like peptide-1 receptor agonist in muscle atrophy. *J Cachexia Sarcopenia Muscle* 2019; **10**: 903-918 [PMID: [31020810](#) DOI: [10.1002/jcsm.12434](#)]
- 126 **Bouchi R**, Fukuda T, Takeuchi T, Nakano Y, Murakami M, Minami I, Izumiyama H, Hashimoto K, Yoshimoto T, Ogawa Y. Dipeptidyl peptidase 4 inhibitors attenuates the decline of skeletal muscle mass in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2018; **34** [PMID: [29054111](#) DOI: [10.1002/dmrr.2957](#)]
- 127 **Yen FS**, Huang YH, Hou MC, Hwu CM, Lo YR, Shin SJ, Hsu CC. Metformin use and cirrhotic decompensation in patients with type 2 diabetes and liver cirrhosis. *Br J Clin Pharmacol* 2022; **88**: 311-322 [PMID: [34198358](#) DOI: [10.1111/bcp.14970](#)]
- 128 **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](#)]
- 129 **Yen FS**, Lai JN, Wei JC, Chiu LT, Hwu CM, Hou MC, Hsu CC. Sulfonylureas may be useful for glycemic management in patients with diabetes and liver cirrhosis. *PLoS One* 2020; **15**: e0243783 [PMID: [33315940](#) DOI: [10.1371/journal.pone.0243783](#)]
- 130 **Cetrone M**, Mele A, Tricarico D. Effects of the antidiabetic drugs on the age-related atrophy and sarcopenia associated with diabetes type II. *Curr Diabetes Rev* 2014; **10**: 231-237 [PMID: [25245021](#) DOI: [10.2174/1573399810666140918121022](#)]
- 131 **Sasaki T**. Sarcopenia, frailty circle and treatment with sodium-glucose cotransporter 2 inhibitors. *J Diabetes Investig* 2019; **10**: 193-195 [PMID: [30369086](#) DOI: [10.1111/jdi.12966](#)]
- 132 **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](#)]
- 133 **Donadon V**, Balbi M, Zanette G. Hyperinsulinemia and risk for hepatocellular carcinoma in patients with chronic liver diseases and Type 2 diabetes mellitus. *Expert Rev Gastroenterol Hepatol* 2009; **3**: 465-467 [PMID: [19817667](#) DOI: [10.1586/egh.09.41](#)]
- 134 **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](#)]
- 135 **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](#)]
- 136 **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](#)]
- 137 **Khafaga S**, Khalil K, Mohamed A, Miada M, Mahmoud S, Mohammad M. Acute Variceal Bleeding in Patients with Liver Cirrhosis with and without Diabetes. *Liver Res Open* **1**: 14-20 [DOI: [10.17140/LROJ-1-103](#)]
- 138 **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](#)]



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>

