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EDITORIAL

Hepatogenous diabetes: Is it a neglected condition in chronic liver disease?

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Abstract

Diabetes mellitus (DM) that occurs because of chronic liver disease (CLD) is known as hepatogenous diabetes (HD). Although the association of diabetes and liver cirrhosis was described forty years ago, it was scarcely studied for long time. Patients suffering from this condition have low frequency of risk factors of type 2 DM. Its incidence is higher in CLD of viral, alcoholic and cryptogenic etiology. Its pathophysiology relates to liver damage, pancreatic dysfunction, interactions between hepatitis C virus (HCV) and glucose metabolism mechanisms and genetic susceptibility. It associates with increased rate of liver complications and hepatocellular carcinoma, and decreased 5-year survival rate. It reduces sustained virological response in HCV infected patients. In spite of these evidences, the American Diabetes Association does not recognize HD. In addition, the impact of glucose control on clinical outcomes of patients has not been evaluated. Treatment of diabetes may be difficult due to liver insufficiency and hepatotoxicity of antidiabetic drugs. Notwithstanding, no therapeutic guidelines have been implemented up to date. In this editorial, authors discuss the reasons why they think that HD may be a neglected pathological condition and call attention to the necessity for more clinical research on different fields of this disease.

Key words: Hepatogenous diabetes; Diabetes mellitus; Outcomes; Therapy; Hepatitis C virus; Chronic liver disease

Core tip: The authors expose arguments, which indicate that hepatogenous diabetes has not received enough attention for many years. They provide published evidences that make them to propose that this entity should be considered as a complication of chronic liver disease, and that an oral glucose tolerance test must be done to patients without previous diabetes mellitus showing normal fasting plasma glucose levels. They also propose that an adequate treatment of hyperglycemia with liver friendly-drugs must be undertaken for reducing complications and mortality. They also highlight the lack of research on long-term treatment of diabetes and the lack of treatment recommendations for these vulnerable patients.

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One of the most important questions regarding chronic liver disease (CLD) and diabetes mellitus (DM) association relates to the clinical implication of this relationship. Currently, it is known that patients with CLD may have two types of DM: hereditary Type 2 DM and hepatogenous diabetes (HD). The former one is frequently associated to metabolic syndrome that gives rise to non-alcoholic fatty liver disease, liver cirrhosis and hepatocellular carcinoma (HCC). The latter one appears after onset of liver disease. HD can be identified in CLD patients without previous history of DM in the absence of standard risk factors of type 2 DM such as high body mass index, family history of diabetes and hyperlipidemia[1]. It has been reported that around 80% to 85% of these patients - even those with normal fasting glucose levels - may have glucose intolerance or DM[2,3]. This abnormality is higher in patients with liver disease due to hepatitis C virus (HCV), alcoholic and cryptogenic etiology. Despite these evidences, the American Diabetes Association[4] does not recognize HD.

Although the diabetogenic potential of liver cirrhosis was initially described in the 60's[5], Petrides *et al*[6] first used the term HD in the 90's. Its use did not extend, probably because the concept was then misunderstood.

HD may result from decreased extraction of insulin by the damaged liver and the presence of portosystemic shunts that lead to hyperinsulinemia, which is potentiated by increases in glucagon, growth hormone, insulin-like growth factor, free fatty acids and cytokines[7]. These abnormalities induce insulin resistance of peripheral tissues (muscles, liver and fat) and pancreatic β cell dysfunction, with the former accounting for transition from impaired glucose tolerance to DM and worsening in parallel with the severity of liver disease[2,8,9]. Liver dysfunction exerts a "toxic" effect on pancreatic islets, playing a major pathophysiological role in the development of diabetes[2]. In fact, HD usually reverses or ameliorates after successful liver transplant, thus suggesting that it directly relates to loss of liver function[10,11].

In addition, recently described evidences of direct interactions of HCV with glucose metabolism mechanisms in non-cirrhotic patients, have placed the HCV also as a diabetogenic agent[12,13]. Autoimmune phenomena, direct cytotoxic effects on pancreatic β cells and a blockage of insulin receptors at the cellular level induced by HCV proteins have been demonstrated[14-16]. HCV core up regulates suppressor of cytokine signaling 3 expression that induces proteosomal degradation of insulin receptor substrates 1 and 2 (which are central molecules of the insulin-signaling cascade)[17] and increases gluconeogenesis[18]. In one study, the clearance of HCV with antiviral therapy in patients with chronic hepatitis C, significantly reduced insulin resistance, improved pancreatic β cell function and increased hepatic expression of insulin receptor substrate 1 and 2[19]. Notwithstanding, these relevant findings need to be reproduced in prospective studies with large number of patients.

Furthermore, in alcoholic CLD, pancreatic damage may be involved in the genesis of diabetes[10,20]. Finally, genetic factors rather than only liver or pancreatic damage may also be involved in the susceptibility to develop HD as it was shown in a recent study with 367 patients with liver cirrhosis of diverse etiology. Polymorphisms of the transcription factor 7-like 2 gene, (a gene that has been associated with DM and cancer risk) were significantly associated with HD[21].

In the other side, diagnosis of HD may be difficult since clinical manifestations of HD in the early stages of liver disease are virtually absent. Fasting plasma glucose may be normal. Only insulin resistance (measured by HOMA-IR Index) and glucose intolerance detected by OGTT may be observed. As liver disease progresses, diabetes becomes clinically manifested, therefore overt HD may be considered as a marker of liver function deterioration[22]. When diabetes is overt, discrimination between HD and type 2 DM may be difficult. HD should be suspected in lean patients without family history of diabetes, hyperlipidemia or arterial hypertension. In a recent study comparing patients with HD *vs* patients with type 2 DM, the ratios of postprandial plasma glucose to fasting plasma glucose, fasting insulin and HOMA-Insulin Resistance index were significantly higher in patients with HD[23].

What is the importance of diagnosing HD? For answering this question, it is mandatory to be aware of the impact of this entity on the clinical outcomes of patients with CLD. Though some reports described the diabetogenic nature of liver cirrhosis four decades

ago, only three prospectively conducted studies have assessed its impact on survival up to date[24-26]. All of them demonstrated that HD was significantly associated with lower 5-year cumulated survival. The majority of deceased patients died of liver-related causes. They also found that besides HD, liver failure and old age were independent predictors of death, which suggest that these conditions may combine synergistically[24-26].

HD is also associated with increased rate of liver complications such as hepatic encephalopathy, esophageal variceal hemorrhage, spontaneous primary peritonitis and renal impairment[27-30]. In HCV infected patients, HD and insulin resistance are significantly associated with liver fibrosis, increased complications and mortality rates[31,32]. HD also associates with decreased sustained virological response rates to interferon-based treatments[16,33]. Unexpectedly, reported cardiovascular complications are low compared to liver-related ones[24-26]. This may be explained because of presumptive acceleration of liver failure induced by HD probably shortens the time in which diabetic cardiovascular complications can take place. In addition, coagulation impairment induced by liver failure, which would act as protective factor, has been evoked.

In the other side, pre-transplant DM is a risk factor for the development of diabetes after transplant[34]. This post-transplant diabetes associates with increased mortality, infections and acute graft rejection[35,36]. Therefore, identification of HD before transplant is of primary importance in order to improve post-transplant outcomes.

Finally, DM and glucose intolerance were found to be associated with the development of HCC and biliary tract cancer in a study with infected HCV patients and in a large European cohort of individuals with self-reported diabetes data[37,38]. In addition, diabetes was associated with significant lower cumulative survival rate in male patients with HCC and HCV[37]. It is unclear how diabetes influences hepatocarcinogenesis. Oxidative stress may be an important factor, also hyperinsulinemia, which acts as growth factor through activation of 5' adenosine monophosphate-activated protein kinase, may be involved[39]. Recent studies suggested that liver inflammation, induced by diabetes, might lead to exposure of hepatocytes to increased activation of signaling pathways, followed by lack of apoptosis and uncontrolled hepatocyte proliferation[40].

The mechanism by which HD may deteriorate liver function giving rise to adverse outcomes is not precisely known. It may increase fibrosis and inflammation through the activity of pro-inflammatory and fibrogenic adipokynes such as: tumor necrosis factor alpha, tumor growth factor beta-1, resistin, leptin, hepatic growth factor and adiponectine[41-43]. In addition, immunosuppression induced by HD, may also be involved in mortality by increasing incidence of infections[27]. More studies are necessary in order to clear these issues.

Based on the above-discussed evidences, HD should be considered as a complication of CLD in the same way as hepatic encephalopathy, ascites, portal hypertension or hepatorenal syndrome. In addition, the described differences between hereditary type 2 DM and HD regarding pathophysiology, risk factors, clinical features, effects on outcome and therapeutic results are strong reasons for diagnosing them as separated entities.

Whether or not, therapeutic control of hyperglycemia reduces complications and mortality rates of patients with HD is unknown[3]. Pharmacological treatment of diabetes is challenging and may be potentially harmful, particularly in those from Child-Pugh C group, due to altered drug metabolism and increased susceptibility of hypoglycemia and lactic acidosis[44,45]. Probably due to this reason, adequate control of hyperglycaemia can be achieved in only one third of patients, as was recently reported[46,47]. In addition, therapeutic guidelines or recommendations have not been established for these patients, and only few studies have assessed the long-term safety of antidiabetic drugs in CLD patients, particularly in those with severe liver failure[44]. In spite of this lack of information, it is highly recommended to undertake an adequate control of plasma glucose levels through diet and lifestyle changes as soon as HD can be detected. For pharmacological treatment, sulphonylureas should be avoided in case of hepatic impairment[48]. Pioglitazone, metformin and acarbose have been proved safe and efficacious therapeutic agents[45]. Metformin has been administered during a mean period of 8 years with low frequency of noxious side effects, even in patients with moderate and advanced liver insufficiency. This medication reduced mortality and hepatocellular cancer in diabetic patients with liver cirrhosis[49,50]. It was suggested that there is an independent association of the use of exogenous insulin and sulphonylureas with the development of HCC and extrahepatic cancer. A recently published metanalysis, that evaluated whether the use of antidiabetic medications has any influence on the risk of HCC, showed metformin as protective agent and sulphonylureas and insulin as negative factors. Nevertheless, there was a high heterogeneity among studies included in the analysis and post-hoc analysis of randomized controlled trial did not reveal significant association between antidiabetic medications use and the risk of HCC[51]. More prospective studies are required for clearing if insulin therapy or sulphonylureas use increase the risk of HCC in CLD patients.

Currently, incretin-based therapies, composed by drugs that target the incretin system and are not metabolized by the liver (such as injectable glucagon-like peptide-1 receptor agonists and oral inhibitors of dipeptidylpeptidase-4), are being assayed in cirrhotic patients and seem to be promising. In contrast to old glucose-lowering agents, these new

drugs were evaluated in specifically designed acute pharmacokinetic studies in patients with various degrees of hepatic impairment, and their safety was carefully analyzed in large clinical trials[52]. In patients from Child-Pugh C group and decompensated liver disease, insulin administration should be started only in in-hospital patients[53,54].

Finally, pending further research on these issues and based on the evidences currently available, we propose to undertake the following recommendations for CLD patients care: (1) Search DM in all patients. An OGTT must be done to patients without previous DM showing normal fasting plasma glucose levels[2,24-26]; (2) Classify DM as HD or T2 DM based on clinical and biochemical features previously described[1]; (3) Monitor liver and cardiovascular complications in patients with HD; (4) Begin a timely treatment of HD. For pharmacological therapy, liver function must be taken into account. Use only liver-friendly drugs[44,45]; (5) In HCV infected patients, administer preferably insulin sensitizers in order to increase sustained virological response to antiviral therapy; (6) Search DM before transplant in order to administer a treatment for improving post-transplant outcomes[34-36]; and (7) In Child-Pugh C patients with decompensated liver function start therapy with hypoglycemic drugs or insulin preferably in in-hospital patients.

Certainly, the precise value of some of the above-proposed recommendations on the clinical outcomes of patients with CLD has not rigorously been assessed in well-conducted and high-quality clinical studies. Such studies will be welcomed since their information will allow the improvement of therapeutic results and clinical outcomes of these vulnerable patients. In addition, therapeutic guidelines diligently elaborated and supervised by endocrinologists and hepatologists together are extremely necessary.

REFERENCES

1 **García-Compeán D**, Jáquez-Quintana JO, Lavalle-González FJ, Reyes-Cabello E, González-González JA, Muñoz-Espinosa LE, Vázquez-Elizondo G, Villarreal-Pérez JZ, Maldonado-Garza HJ. The prevalence and clinical characteristics of glucose metabolism disorders in patients with liver cirrhosis. A prospective study. *Ann Hepatol* 2012; **11**: 240-248 [PMID: 22345342 DOI: 10.1016/s0016-5085(12)62087-3]

2 **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]

3 **García-Compeán D**, González-González JA, Lavalle-González FJ, González-Moreno EI, Villarreal-Pérez JZ, Maldonado-Garza HJ. Current Concepts in Diabetes Mellitus and Chronic Liver Disease: Clinical Outcomes, Hepatitis C Virus Association, and Therapy. *Dig Dis Sci* 2016; **61**: 371-380 [PMID: 26462490 DOI: 10.1007/s10620-015-3907-2]

4 **American Diabetes Association**. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012; **35** Suppl 1: S64-S71 [PMID: 22187472 DOI: 10.2337/dc12-s064]

5 **Conn HO**, Schreiber W, Elkington SG, Johnson TR. Cirrhosis and diabetes. I. Increased incidence of diabetes in patients with Laennec's cirrhosis. *Am J Dig Dis* 1969; **14**: 837-852 [PMID: 5361079 DOI: 10.1007/BF02233205]

6 **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]

7 **Kawaguchi T**, Taniguchi E, Itou M, Sakata M, Sumie S, Sata M. Insulin resistance and chronic liver disease. *World J Hepatol* 2011; **3**: 99-107 [PMID: 21731901 DOI: 10.4254/wjh.v3.i5.99]

8 **Tappy L**, Minehira K. New data and new concepts on the role of the liver in glucose homeostasis. *Curr Opin Clin Nutr Metab Care* 2001; **4**: 273-277 [PMID: 11458020 DOI: 10.1097/00075197-200107000-00005]

9 **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]

10 **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 DOI: 10.1002/hep.510310320]

11 **Ramos-Prol A**, Hervás-Marín D, Rodríguez-Medina B, Campos-Alborg V, Berenguer M, Moya-Herraiz Á, Merino-Torres JF. Alterations in carbohydrate metabolism in cirrhotic patients before and after liver transplant. *Diabetes Res Clin Pract* 2015; **110**: 123-128 [PMID: 26506435 DOI: 10.1016/j.diabres.2015.10.002]

12 **Anty R**, Gelsi E, Giudicelli J, Mariné-Barjoan E, Gual P, Benzaken S, Saint-Paul MC, Sadoul JL, Huet PM, Tran A. Glucose intolerance and hypoadiponectinemia are already present in lean patients with chronic hepatitis C infected with genotype non-3 viruses. *Eur J Gastroenterol Hepatol* 2007; **19**: 671-677 [PMID: 17625437 DOI: 10.1097/MEG.0b013e3281532b9a]

13 **Custro N**, Carroccio A, Ganci A, Scafidi V, Campagna P, Di Prima L, Montalto G. Glycemic homeostasis in chronic viral hepatitis and liver cirrhosis. *Diabetes Metab* 2001; **27**: 476-481 [PMID: 11547221]

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

15 **Masini M**, Campani D, Boggi U, Menicagli M, Funel N, Pollera M, Lupi R, Del Guerra S, Bugliani M, Torri S, Del Prato S, Mosca F, Filipponi F, Marchetti P. Hepatitis C virus infection and human pancreatic beta-cell dysfunction. *Diabetes Care* 2005; **28**: 940-941 [PMID: 15793203 DOI: 10.2337/diacare.28.4.940]

16 **Romero-Gómez M**. Insulin resistance and hepatitis C. *World J Gastroenterol* 2006; **12**: 7075-7080 [PMID: 17131467 DOI: 10.3748/wjg.v12.i44.7075]

17 **Kawaguchi T**, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T, Taniguchi E, Kumemura H, Hanada S, Maeyama M, Baba S, Koga H, Kumashiro R, Ueno T, Ogata H, Yoshimura A, Sata M. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol* 2004; **165**: 1499-1508 [PMID: 15509521 DOI: 10.1016/S0002-9440(10)63408-6]

18 **Parvaiz F**, Manzoor S, Iqbal J, Sarkar-Dutta M, Imran M, Waris G. Hepatitis C virus NS5A promotes insulin resistance through IRS-1 serine phosphorylation and increased gluconeogenesis. *World J Gastroenterol* 2015; **21**: 12361-12369 [PMID: 26604643 DOI: 10.3748/wjg.v21.i43.12361]

19 **Kawaguchi T**, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, Nagao Y, Yanagimoto C, Hanada S, Koga H, Sata M. Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *Am J Gastroenterol* 2007; **102**: 570-576 [PMID: 17222321 DOI:

10.1111/j.1572-0241.2006.01038.x]
20 **Ichihara S**, Sato M, Kozuka S. Prevalence of pancreatitis in liver diseases of various etiologies: an analysis of 107,754 adult autopsies in Japan. *Digestion* 1992; **51**: 86-94 [PMID: 1499877 DOI: 10.1159/000200881]
21 **Ling Q**, Dong F, Geng L, Liu Z, Xie H, Xu X, Zheng S. Impacts of TCF7L2 gene polymorphisms on the susceptibility of hepatogenous diabetes and hepatocellular carcinoma in cirrhotic patients. *Gene* 2013; **522**: 214-218 [PMID: 23558246]
22 **Garcia-Compean D**, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. *World J Gastroenterol* 2009; **15**: 280-288 [PMID: 19140227 DOI: 10.3748/wjg.15.280]
23 **Kim MG**, Choi WC. [Differential diagnosis of diabetes mellitus caused by liver cirrhosis and other type 2 diabetes mellitus]. *Korean J Hepatol* 2006; **12**: 524-529 [PMID: 17237630]
24 **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]
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 **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]
27 **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]
28 **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]
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 **Huo TI**, Hsu CY, Huang YH, Hsia CY, Lin HC, Lee PC, Loong CC, Chiang JH, Chiou YY, Lee SD. Diabetes mellitus as an independent prognostic predictor and its association with renal dysfunction in patients with hepatocellular carcinoma. *Liver Int* 2010; **30**: 198-207 [PMID: 19849777 DOI: 10.1111/j.1478-3231.x]
31 **Moucari R**, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, Sobesky R, Martinot-Peignoux M, Maylin S, Nicolas-Chanoine MH, Paradis V, Vidaud M, Valla D, Bedossa P, Marcellin P. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008; **134**: 416-423 [PMID: 18164296 DOI: 10.1053/j.gastro.2007.11.010]
32 **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]
33 **Romero-Gómez M**, Del Mar Viloria M, Andrade RJ, Salmerón J, Diago M, Fernández-Rodríguez CM, Corpas R, Cruz M, Grande L, Vázquez L, Muñoz-De-Rueda P, López-Serrano P, Gila A, Gutiérrez ML, Pérez C, Ruiz-Extremera A, Suárez E, Castillo J. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005; **128**: 636-641 [PMID: 15765399 DOI: 10.1053/j.gastro.2004.12.049]
34 **Lunati ME**, Grancini V, Agnelli F, Gatti S, Masserini B, Zimbalatti D, Pugliese G, Rossi G, Donato MF, Colombo M, Beck-Peccoz P, Orsi E. Metabolic syndrome after liver transplantation: short-term prevalence and pre- and post-operative risk factors. *Dig Liver Dis* 2013; **45**: 833-839 [PMID: 23816695 DOI: 10.1016/j.dld.2013.03.009]
35 **John PR**, Thuluvath PJ. Outcome of liver transplantation in patients with diabetes mellitus: a case-control study. *Hepatology* 2001; **34**: 889-895 [PMID: 11679959 DOI: 10.1053/jhep.2001.29134]
36 **Younossi ZM**, Stepanova M, Saab S, Kalwaney S, Clement S, Henry L, Frost S, Hunt S. The impact of type 2 diabetes and obesity on the long-term outcomes of more than 85 000 liver transplant recipients in the US. *Aliment Pharmacol Ther* 2014; **40**: 686-694 [PMID: 25040315 DOI: 10.1111/apt.12881]
37 **Sumie S**, Kawaguchi T, Komuta M, Kuromatsu R, Itano S, Okuda K, Taniguchi E, Ando E, Takata A, Fukushima N, Koga H, Torimura T, Kojiro M, Sata M. Significance of glucose intolerance and SHIP2 expression in hepatocellular carcinoma patients with HCV infection. *Oncol Rep* 2007; **18**: 545-552 [PMID: 17671700 DOI: 10.3892/or.18.3.545]
38 **Schlesinger S**, Aleksandrova K, Pischon T, Jenab M, Fedirko V, Trepo E, Overvad K, Roswall N, Tjønneland A, Boutron-Ruault MC, Fagherazzi G, Racine A, Kaaks R, Grote VA, Boeing H, Trichopoulou A, Pantzalis M, Kritikou M, Mattiello A, Sieri S, Sacerdote C, Palli D, Tumino R, Peeters PH, Bueno-de-Mesquita HB, Weiderpass E, Quirós JR, Zamora-Ros R, Sánchez MJ, Arriola L, Ardanaz E, Tormo MJ, Nilsson P, Lindkvist B, Sund M, Rolandsson O, Khaw KT, Wareham N, Travis RC, Riboli E, Nöthlings U. Diabetes mellitus, insulin treatment, diabetes duration, and risk of biliary tract cancer and hepatocellular carcinoma in a European cohort. *Ann Oncol* 2013; **24**: 2449-2455 [PMID: 23720454 DOI: 10.1093/annonc/mdt204]
39 **Konishi I**, Hiasa Y, Shigematsu S, Hirooka M, Furukawa S, Abe M, Matsuura B, Michitaka K, Horiike N, Onji M. Diabetes pattern on the 75 g oral glucose tolerance test is a risk factor for hepatocellular carcinoma in patients with hepatitis C virus. *Liver Int* 2009; **29**: 1194-1201 [PMID: 19422477 DOI: 10.1111/j.1478-3231.2009.02043.x]
40 **He G**, Yu GY, Temkin V, Ogata H, Kuntzen C, Sakurai T, Sieghart W, Peck-Radosavljevic M, Leffert HL, Karin M. Hepatocyte IKKbeta/NF-kappaB inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation. *Cancer Cell* 2010; **17**: 286-297 [PMID: 20227042 DOI: 10.1016/j.ccr.2009.12.048]
41 **Spahr L**, Giostra E, Frossard JL, Bresson-Hadni S, Rubbia-Brandt L, Hadengue A. Soluble TNF-R1, but not tumor necrosis factor alpha, predicts the 3-month mortality in patients with alcoholic hepatitis. *J Hepatol* 2004; **41**: 229-234 [PMID: 15288471 DOI: 10.1016/j.jhep.2004.04.028]
42 **Ikejima K**, Honda H, Yoshikawa M, Hirose M, Kitamura T, Takei Y, Sato N. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. *Hepatology* 2001; **34**: 288-297 [PMID: 11481614 DOI: 10.1053/jhep.2001.26518]
43 **Tarantino G**, Conca P, Riccio A, Tarantino M, Di Minno MN, Chianese D, Pasanisi F, Contaldo F, Scopacasa F, Capone D. Enhanced serum concentrations of transforming growth factor-beta1 in simple fatty liver: is it really benign? *J Transl Med* 2008; **6**: 72 [PMID: 19038040 DOI: 10.1186/1479-5876-6-72]
44 **Scheen AJ**. Pharmacokinetic and toxicological considerations for the treatment of diabetes in patients with liver disease. *Expert Opin Drug Metab Toxicol* 2014; **10**: 839-857 [PMID: 24669954 DOI: 10.1517/17425255.2014.902444]
45 **García-Compeán D**, González-González JA, Lavalle-González FJ, González-Moreno EI, Maldonado-Garza HJ, Villarreal-Pérez JZ. The treatment of diabetes mellitus of patients with chronic liver disease. *Ann Hepatol* 2015; **14**: 780-788 [PMID: 26436350 DOI: 10.5604/16652681.1171746]
46 **Gundling F**, Seidl H, Strassen I, Haller B, Siegmund T, Umgelter A, Pehl C, Schepp W, Schumm-Draeger PM. Clinical manifestations

and treatment options in patients with cirrhosis and diabetes mellitus. *Digestion* 2013; **87**: 75-84 [PMID: 23306648 DOI: 10.1159/000343458]

47 **Kwon SY**, Kim SS, Kwon OS, Kwon KA, Chung MG, Park DK, Kim YS, Koo YS, Kim YK, Choi DJ, Kim JH. Prognostic significance of glycaemic control in patients with HBV and HCV-related cirrhosis and diabetes mellitus. *Diabet Med* 2005; **22**: 1530-1535 [PMID: 16241918 DOI: 10.1111/j.1464-5491.2005.01687.x]

48 **Inkster B**, Zammitt NN, Frier BM. Drug-induced hypoglycaemia in type 2 diabetes. *Expert Opin Drug Saf* 2012; **11**: 597-614 [PMID: 22690846 DOI: 10.1517/14740338.2012.694424]

49 **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]

50 **Zhang X**, Harmsen WS, Mettler TA, Kim WR, Roberts RO, Therneau TM, Roberts LR, Chaiteerakij R. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology* 2014; **60**: 2008-2016 [PMID: 24798175 DOI: 10.1002/hep.27199]

51 **Singh S**, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol* 2013; **108**: 881-91; quiz 892 [PMID: 23381014 DOI: 10.1038/ajg.2013.7]

52 **Graefe-Mody U**, Rose P, Retlich S, Ring A, Waldhauser L, Cinca R, Woerle HJ. Pharmacokinetics of linagliptin in subjects with hepatic impairment. *Br J Clin Pharmacol* 2012; **74**: 75-85 [PMID: 22242621 DOI: 10.1111/j.1365-2125.2012.04173.x]

53 **Jespersen MJ**, Knop FK, Christensen M. GLP-1 agonists for type 2 diabetes: pharmacokinetic and toxicological considerations. *Expert Opin Drug Metab Toxicol* 2013; **9**: 17-29 [PMID: 23094590 DOI: 10.1517/17425255.2013.731394]

54 **Scheen AJ**. A review of gliptins in 2011. *Expert Opin Pharmacother* 2012; **13**: 81-99 [PMID: 22149369 DOI: 10.1517/14656566.2012.642866]

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