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

Diego García-Compeán, José Alberto González-González, Fernando Javier Lavalle-González, Emmanuel Irineo González-Moreno, Jesús Zacarías Villarreal-Pérez, Héctor Jesús Maldonado-Garza

Diego García-Compeán, José Alberto González-González, Emmanuel Irineo González-Moreno, Héctor Jesús Maldonado-Garza, Gastroenterology Service and Department of Internal Medicine, University Hospital “Dr. José E. González” and Medical School, Universidad Autónoma de Nuevo León, Monterrey 64320, México

Fernando Javier Lavalle-González, Jesús Zacarías Villarreal-Pérez, Endocrinology Service and Department of Internal Medicine, University Hospital “Dr. José E. González” and Medical School, Universidad Autónoma de Nuevo León, Monterrey 64320, México

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Correspondence to: Diego García-Compeán, MD, MMSc, Gastroenterology Service and Department of Internal Medicine, University Hospital “Dr. José E. González” and Medical School, Universidad Autónoma de Nuevo León, Madero y Gonzalitos S/N, Monterrey 64320, México. digarciaacompean@prodigy.net.mx Telephone: +52-81-83487315 Fax: +52-81-89891381

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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

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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.


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[14-18]. 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)[19] and increases gluconeogenesis[20]. 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[20]. 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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[27-30]}. In HCV infected patients, HD and insulin resistance are significantly associated with liver fibrosis, increased complications and mortality rates\textsuperscript{[31,32]}. HD also associates with decreased sustained virological response rates to interferon-based treatments\textsuperscript{[16,43]}. Unexpectedly, reported cardiovascular complications are low compared to liver-related ones\textsuperscript{[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\textsuperscript{[34]}. This post-transplant diabetes associates with increased mortality, infections and acute graft rejection\textsuperscript{[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\textsuperscript{[37,38]}. In addition, diabetes was associated with significant lower cumulative survival rate in male patients with HCC and HCV\textsuperscript{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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[41-43]}. In addition, immunosuppression induced by HD, may also be involved in mortality by increasing incidence of infections\textsuperscript{[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\textsuperscript{[35]}. 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\textsuperscript{[44,45]}. Probably due to this reason, adequate control of hyperglycaemia can be achieved in only one third of patients, as was recently reported\textsuperscript{[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\textsuperscript{[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\textsuperscript{[48]}. Pioglitazone, metformin and acarbose have been proved safe and efficacious therapeutic agents\textsuperscript{[49]}. 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\textsuperscript{[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 metaanalysis, 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\textsuperscript{[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
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[24-26], (2) Classify DM as HD or T2 DM based on clinical and biochemical features previously described[11]; (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.

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