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Review

Challenges in diagnosing and monitoring diabetes in patients with chronic liver diseases

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ABSTRACT

The prevalence and mortality of diabetes mellitus and liver disease have risen in recent years. The liver plays an important role in glucose homeostasis, and various chronic liver diseases have a negative effect on glucose metabolism with the consequent emergence of diabetes. Some aspects related to chronic liver disease can affect diagnostic tools and the monitoring of diabetes and other glucose metabolism disorders, and clinicians must be aware of these limitations in their daily practice. In cirrhotic patients, fasting glucose may be normal in up until 23% of diabetes cases, and glycated hemoglobin provides falsely low results, especially in advanced cirrhosis. Similarly, the performance of alternative glucose monitoring tests, such as fructosamine, glycated albumin and 1,5-anhydroglucitol, also appears to be suboptimal in chronic liver disease. This review will examine the association between changes in glucose metabolism and various liver diseases as well as the particularities associated with the diagnosis and monitoring of diabetes in liver disease patients. Alternatives to routinely recommended tests will be discussed.

Contents

1. Introduction

Diabetes and liver diseases are major causes of morbidity and mortality worldwide. The prevalence and mortality related to

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diabetes mellitus (DM) has increased significantly in recent decades, resulting in significant economic and social burden [1,2]. Similarly, mortality related to liver disease is growing, with more than one million deaths from liver cirrhosis in 2010 [3]. When the deaths from liver cancer and acute hepatitis are combined, the annual number of fatalities due to liver disease can exceed two million [4]. The coexistence of changes in glucose metabolism and chronic liver disease is common, partially due to the high prevalence of both conditions. However, the liver plays a key role in glucose homeostasis, and its malfunction is related to the onset of hepatogenous diabetes [5,6]. Furthermore, even outside of the context of liver failure, various chronic liver diseases are associated with the appearance of DM through different mechanisms. Thus, tools for the diagnosis and monitoring of DM and other glucose metabolism disorders are especially important in patients with liver disease. However, some aspects related to chronic liver diseases can affect the results of these tests, and clinicians should be aware of the limitations in their daily practice. In this review, we discuss the association between changes in glucose metabolism and various liver diseases as well as the particularities related to the diagnosis and monitoring of DM in patients with liver disease. Alternatives to routinely recommended tests are also discussed.

2. Effects of chronic liver disease on glucose metabolism

Several chronic liver diseases exert a negative effect on glucose metabolism through various mechanisms (Table 1).

2.1. Nonalcoholic fatty liver disease (NAFLD)

NAFLD refers to the presence of hepatic steatosis with no other secondary cause, such as alcohol, hypothyroidism or certain medications. The global prevalence of NAFLD is approximately 20% and the progression rates to cirrhosis and hepatocellular carcinoma are around 2.5% [51]. NAFLD is strongly related to the pathogenesis of metabolic syndrome and insulin resistance, and there is strong evidence that NAFLD increases the risk of type 2 diabetes mellitus (T2DM) irrespective of other factors [52–56]. However, common genetic variants may also be related to NAFLD. A variant of patatin-like phospholipase domain-containing 3 (PNPLA3) has been associated with steatosis, steatohepatitis and fibrosis [57]. A genetic variant in transmembrane 6 superfamily member 2 (TM6SF2) has also been related to increased liver fat concentrations and steatohepatitis [58]. Although genetic and metabolic risk factors for NAFLD can coexist in the same individual, the cited mutations do not appear to increase the risk of insulin resistance and type 2 diabetes [56].

2.2. Hepatic cirrhosis

Liver cirrhosis is the final stage of many chronic liver diseases that are associated with progressive hepatic fibrosis. Cirrhosis is a major public health problem, with increasingly morbidity and mortality worldwide [3]. Changes in glucose metabolism are observed in most cirrhotic patients, with glucose intolerance observed in approximately one-quarter of patients and DM in up to 70% [19,59–61]. Additionally, some studies indicate that DM is associated with increased mortality in patients with cirrhosis [60–65]. DM also seems to be related to an increased risk of complications of cirrhosis, such as ascites, bacterial infections and hepatic encephalopathy [63]. Glucose intolerance and DM secondary to cirrhosis occur as a result of peripheral resistance to the action of insulin and hyperinsulinemia. Several mechanisms seem to be involved in the pathogenesis of insulin resistance in cirrhotic patients. Decreased insulin clearance due to a reduced hepatocytic mass or secondary to a reduction in hepatic extraction as a result of portosystemic collaterals may result in hyperinsulinemia. Hyperinsulinemia is associated with a reduction in insulin receptor affinity, a reduction in the number of receptors exposed on the cell surface and functional changes to these receptors. Thus, hyperinsulinemia may induce insulin resistance [21–23]. Other phenomena secondary to chronic liver disease that appear to contribute to insulin resistance in cirrhotic individuals include the accumulation of advanced glycation end products and hypoxia-inducible factor [25]. The difference between hepatogenic

Table 1
Estimated prevalence and proposed mechanisms for DM in various liver diseases.

Liver disease	Estimated prevalence of DM	Proposed mechanisms
NAFLD	14%–23.2% [7,8]	• Increased hepatic insulin resistance secondary to adipose tissue dysfunction [9,10]. • Changes in liver mitochondrial function (secondary to lipotoxicity, oxidative stress and inflammatory response) with an effect on hepatic energy metabolism (adenosine triphosphate) [11]. • Changes in the entero-insular axis, such as increased dipeptidyl peptidase 4 (DPP-4) enzyme activity, and changes in the beta cell response to glucose and incretins [12,13]. • Genetic polymorphisms, such as TCF7L2, WFS1 and KCNQ1 [14–16].
Cirrhosis	37%–71% [17–19]	• Reduction in insulin clearance by the liver (as a result of a reduction in the hepatocytic mass and portosystemic shunting) [20,21]. • Reduction in insulin receptor affinity, reduction in the number of receptors exposed on the cellular surface and functional changes to these receptors as a result of hyperinsulinemia [22–24]. • Accumulation of advanced glycation end products and hypoxia-induced factor [25].
Hepatitis C	17.5%–37.8% [26,27]	• Morphological and functional changes to pancreatic beta cells infected with HCV [28]. • Change in insulin signaling through direct and indirect actions of HCV [29–33].
Hemochromatosis	10.5%–21.9% [34,35]	• Excess iron causes oxidative stress in pancreatic beta cells with islet apoptosis, reducing insulin secretion capacity [36,37]. • Insulin resistance secondary to liver injury by iron overload [38,39]. • Genetic predisposition[40].
Post-liver transplantation	13.7%–44% [41,42]	• Changes in gluconeogenesis, glycogenolysis and/or insulin signaling [41,43–45]. • Reduction in the activity of pancreatic beta cells resulting from pre-existing dysfunction, use of immunosuppressive drugs or genetic changes [44,46–49]. • Change in intestinal microbiota due to functional metabolic interaction or after transplantation secondary to multiple factors, such as surgical stress and immunosuppression [44,50].

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