Diabetes mellitus and liver disease

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Nonalcoholic fatty liver disease (NAFLD) is characterized by accumulation of fat in hepatocytes with or without evidence of significant necro-inflammation or fibrosis.

NAFLD has a histologic spectrum that ranges from the relatively benign NAFLD to the aggressive form of nonalcoholic steatohepatitis with or without liver fibrosis to nonalcoholic steatohepatitis-cirrhosis leading to end-stage liver disease (1).

Today, NAFLD is a major cause of hepatocellular carcinoma (HCC) (2). HCC is one of the most common cancer in the world. Incidence varies across the world and generally follows geographical distribution of viral hepatitis B and C (3).

NAFLD is considered the hepatic manifestation of insulin resistance that characterizes type 2 diabetes mellitus (T2DM) (1).

The prevalence of diabetes mellitus in the world is steadily increasing due to the increase in the average age of the general population and changes in lifestyle (4). The global prevalence of diabetes mellitus has doubled in the last thirty years (5). In 2010, an estimated 285 million people had diabetes mellitus, 90% of whom T2DM (4). Globally, prevalence of diabetes mellitus is estimated to rise to 439 million by 2030, that represents 7.7% of the total adult population of the world aged 20–79 years (6).

In fact, diabetes mellitus can be considered a silent killer and a possible trigger of multiple diseases, both cardiovascular and liver related.

A recent prospective study of 0.5 million people showed that individuals with known diabetes and those not aware to have diabetes with higher blood glucose levels have significantly increased risk of major chronic liver diseases and HCC. Compared with those without diabetes, those with diabetes had adjusted hazard ratios (HRs) of 1.49 (95% CI, 1.30–1.70) for HCC, 1.81 (1.57–2.09) for cirrhosis, 1.76 (1.47–2.16) for NAFLD, and 2.24 (1.42–3.54) for alcoholic liver disease (ALD). Among those without previously diagnosed diabetes, random plasma glucose (RPG) was significantly associated with liver diseases, with adjusted HRs per 1 mmol/L higher RPG of 1.04 (1.03–1.06) for HCC, 1.07 (1.05–1.09) for cirrhosis, 1.07 (1.05–1.10) for NAFLD, and 1.10 (1.05–1.15) for ALD. According to the authors, one of the most important mechanisms that could explain the association between diabetes and liver disease is insulin resistance. In fact, insulin promotes tumor cell growth both directly and indirectly through the insulin-like growth factor (IGF). Authors concluded that early detection of diabetes could help identify patients at increased risk for chronic liver disease, reducing progression to cirrhosis and HCC (7).

A possible correlation between diabetes and liver disease has also been suggested by other studies.

In particular, a retrospective court study reported HCC incidence to be significantly more frequent in diabetic than in non-diabetic people. Moreover, risk of HCC increased in patients with diabetes and comorbidities, such as cirrhosis, hepatitis C and B. Increased risk of HCC in patients with diabetes and cirrhosis, hepatitis C, and/or B may be due to a synergistic effect between diabetes and these concomitant liver comorbidities (8).

Seven cohort studies and two case-control studies evaluated the associations between diabetes mellitus, body

mass index and steatosis and the risk of HCC in patients with chronic hepatitis C. The risk of HCC associated with diabetes mellitus was significantly increased in 5 of the 7 studies (9).

Recently, some diabetes medications have been evaluated for the treatment of NAFLD with encouraging results.

Metformin, despite being first-line therapy for T2DM, does not correlate with a histological improvement of NAFLD as demonstrated by several randomized controlled trials (RCTs) (10,11).

It has been reported that both treatment with sulfonylureas and insulin could be responsible for an increased risk of NAFLD and HCC (12).

In a randomized study, Sitagliptin, dipeptidyl peptidase-4 inhibitor, was not shown to be useful in improving hepatic steatosis and fibrosis (13).

Pioglitazone has been related to a histological improvement of NASH in both diabetic and non-diabetic patients (14,15).

A recent multicenter, double-blind, randomized study has shown that liraglutide improves NASH. The liraglutide has been linked to a slowing of the progression of liver fibrosis and to an improvement of its biomarkers (16). Moreover, Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, was reported to improve NASH. Exenatide has been associated with weight loss, reduced levels of glucose, insulin, lipid and transaminase, representing a possible resource in the treatment of NAFLD (17).

In conclusion, there is a clear association of diabetes with both advanced liver disease and HCC. Further studies are needed to provide more information about the role of anti-diabetes therapies as prevention of liver disease progression.

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