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Diabetes and hepatocellular carcinoma: A pathophysiological link and pharmacological management

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ABSTRACT

Both diabetes mellitus (DM) and cancer are multifarious, dissimilar, and long-lasting, fatal diseases with a remarkable influence on health worldwide. DM is not only related to cardiovascular diseases, neuropathy, nephropathy, and retinopathy, but also related to a number of liver diseases such as nonalcoholic fatty liver disease, steatohepatitis, and liver cirrhosis. Recently, it is hypothesized that DM has a greater risk for many forms of cancer, such as breast, colorectal, endometrial, pancreatic, gallbladder, renal, and liver cancer including hepatocellular carcinoma (HCC). Both DM and cancer have many common risk factors, but the association between these two is poorly stated. Several epidemiologic studies have revealed the association between pathogenic and prognostic characteristics of DM and a higher incidence of HCC, thus representing DM as an independent risk factor for HCC development.

The etiological and pathophysiological relationship between DM and HCC has been presented in this review by linking hyperglycemia, hyperinsulinemia, insulin resistance, and activation of insulin-like growth factor signaling pathways and pharmacological management of HCC associated with DM.

1. Introduction

Diabetes mellitus (DM), especially type-2, is a group of metabolic disorders distinguished by hyperglycemia, hyperinsulinemia, and insulin resistance because of the abnormal secretion and function of insulin. In present scenario, DM is considered as a major cause of morbidity and mortality worldwide, affecting overall health of population, and the prevalence is likely to increase significantly in both developed and developing countries. The International Diabetes Federation gives a comprehensive estimate of people suffering from DM in 2015 at 415 million, and it will be 642 million by 2040 [1].

DM has been associated with an augmented risk of different type of cancers, such as breast, colorectal, endometrial, pancreatic, gallbladder, renal, and liver cancers [2–7].

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer growing rapidly at a higher rate with increased mortality worldwide. HCC instigates on a background of chronic liver diseases and cirrhosis in 70–90%, and hepatitis B virus (HBV), hepatitis C virus (HCV) and alcohol together accounts for 50–85% of new cases [8]. A susceptible condition that may arise HCC includes advanced fibrosis, predominantly cirrhosis, and hepatitis B [9]. Additional risk factors are aflatoxin, obesity, primary biliary cirrhosis, nonalcoholic fatty liver disease (NAFLD), etc. [10–13]. Exceptional risk factors are hemochromatosis, glycogen storage disease, α-1 anti-trypsin deficiency, hereditary tyrosinemia type 1, and Wilson's disease [14–18].

The pathogenic and prognostic characteristics of DM in addition to other metabolic syndrome had been studied. According to the several epidemiologic studies, the association between presence of DM and higher incidence of HCC has been established, representing DM as an independent risk factor for HCC development.

In this review, the etiological and pathophysiological relationship between DM and HCC has been studied by linking hyperglycemia, hyperinsulinemia, insulin resistance and activation of insulin-like growth factor (IGF) signaling pathways, and pharmacological management of HCC associated with DM.

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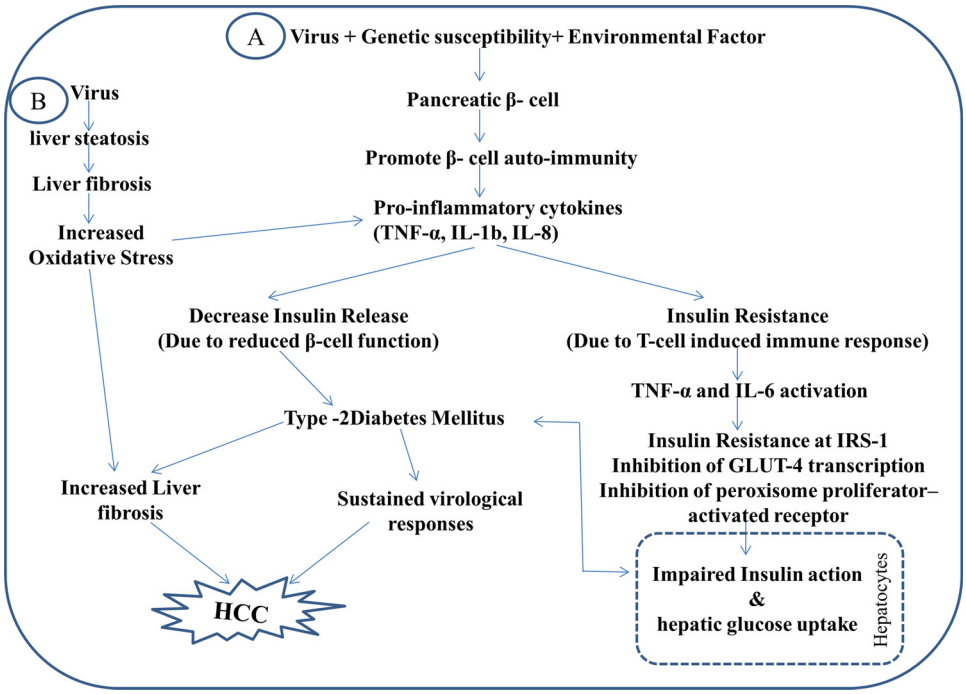

Fig. 1. Probable pathogenesis of hepatitis C virus-induced T2DM and related clinical outcomes: (A) Virus, genetic susceptibility, and environmental factor exerts direct cytotoxic effect on pancreatic beta cells, leading to release of excessive pro-inflammatory cytokines such as TNF-α, IL-1b, IL-8. These pro-inflammatory cytokines decrease insulin release and increase insulin resistance, cause further inflammatory cytokines release leading to impaired insulin action and also hepatic glucose uptake by liver, thus exhibits T2DM. (B) HCV causes liver fibrosis with increased oxidative stress leading to further increase in liver fibrosis. Increase in the liver fibrosis along with sustained virological responses and T2DM progresses towards hepatocarcinogenesis.

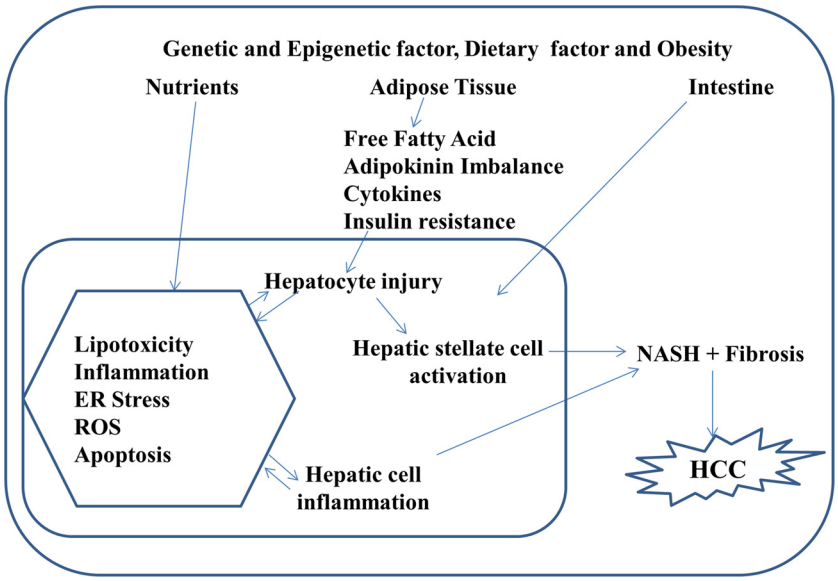

Fig. 2. Probable pathogenesis of NASH and related clinical outcomes: Genetic, epigenetic, obesity, and dietary factors (such as nutrition, activation of adipose tissue and alteration in gut microbiota) causes lipotoxicity, inflammation, ER stress, ROS genereation, and apoptosis in hepatocytes. This causes injury to hepatocytes which triggers activation of hepatic stellate cells leading to NASH with fibrosis and increased risk of developing hepatocarcinogenesis.

2. Etiological factors influencing HCC in diabetes mellitus

2.1. HCV infection

HCV directly infects the pancreatic cell and decreases insulin release via β-cell dysfunction. HCV induces T lymphocyte-mediated immune response, which activates tumor necrosis factor-α (TNF-α) and increases interleukin-6 (IL-6) levels, causing insulin resistance, thus leading to impaired insulin action [19]. Moreover, HCV initially progresses towards liver steatosis followed by fibrosis and also increases oxidative stress, which induces inflammation in the cell, thus aggravating insulin resistance [20]. These metabolic alterations may interact with host-related genetic factors, leading to insulin resistance and finally type 2 diabetes mellitus (T2DM). An imbalance in the adipokine level and the existence of liver fibrosis due to HCV, thus increases the risk of HCC [21]. Pathogenesis of HCV-induced T2DM and related clinical outcomes is depicted in Fig. 1.

2.2. NAFLD, steatohepatitis, and liver cirrhosis

NAFLD, T2DM, insulin resistance, obesity and metabolic syndrome are predominantly closely related [22]. Lipid accumulation, mitochondrial dysfunction, impaired immunity, deficient gut microbiota, genetic factors, nutritional factors, and mordern lifestyle are involved in NAFLD, with insulin resistance strongly allied with NAFLD [23]. A strong association between NAFLD and T2DM has been shown, with a very high rate of nonalcoholic steatohepatitis (NASH) [24]. NASH, a pathologic syndrome, encircled all around the fatty liver disease, characterized by hepatocellular damage, inflammation and fibrosis, is a significant risk factor for cirrhosis and HCC. Insulin resistance in adipose tissue and skeletal muscle is concerned with NAFLD. In hyperinsulinemia, lipid accumulation within the liver is a result of *de novo* lipogenesis [25]. Both NAFLD and T2DM are linked with obesity, insulin resistance, inflammation, and increased oxidative stress, thus may contribute to the advancement of HCC via increased growth and