World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i48.5240

World J Gastroenterol 2011 December 28; 17(48): 5240-5245
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Impact of liver diseases on the development of type 2 diabetes mellitus

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Author contributions: Hsieh PS conceived and wrote the manuscript; Hsieh YJ performed a literature search and participated in the writing of the manuscript; both authors approved its final version.
Supported by The National Science Council, No. NSC98-2320-B-016-011 MY3T; and Tri-Service General Hospital, No. TSGH-C100-011-015-S03
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Received: September 28, 2010 Revised: September 9, 2011
Accepted: September 16, 2011
Published online: December 28, 2011

Abstract

The prevalence of type 2 diabetes mellitus (T2DM) is higher in patients who have liver diseases such as nonalcoholic fatty liver disease, chronic viral hepatitis, hemochromatosis, alcoholic liver disease and cirrhosis. It is suggested that there is a pathogenic link between the presence of T2DM and the severity of liver injury. However, evidence related to the impact of hepatic inflammation on the development of T2DM has not yet emerged. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases, the impact of liver diseases on insulin resistance and β cell dysfunction, and the potential mechanisms whereby coexistent liver diseases exacerbate the development of T2DM.

Key words: Hepatic inflammation; Insulin resistance; β cell dysfunction; Type 2 diabetes mellitus

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Hsieh PS, Hsieh YJ. Impact of liver diseases on the development of type 2 diabetes mellitus. *World J Gastroenterol* 2011; 17(48): 5240-5245 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i48/5240.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i48.5240

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is higher in patients who have suffered from certain liver diseases. Therefore, it is speculated that there is a pathogenic link between liver disease progression and T2DM. For instance, nonalcoholic fatty liver disease (NAFLD) has been proposed as a term that encompasses a spectrum of fatty liver disease from steatosis to non-alcoholic steatohepatitis (NASH) through cirrhosis to end-stage liver disease[1,2]. Clinical investigations and epidemiologic studies have associated NAFLD and NASH in particular with the metabolic syndrome[3,4], with T2DM[1] as the pivotal pathogenic factor. However, the cause-effect relationship between NAFLD/NASH and diabetes remains elusive. On the other hand, cross-sectional and longitudinal studies have shown that chronic hepatitis C virus (HCV) infection is associated with an increased risk of developing insulin resistance and T2DM[5]. Moreover, high alanine aminotransferase level is associated with decreased hepatic insulin sensitivity and predicts the development of T2DM[6]. Pradhan *et al*[7] have reported that elevated levels of the inflammatory markers interleukin 6 (IL-6) and C-reactive protein (CRP, hepatic acute phase protein) were associated with the development of T2DM in healthy middle-aged women in a prospective, nested-control study. However, only limited evidence is emerging to identify the possible impact of liver diseases on the development of T2DM.

IMPACT OF LIVER DISEASES ON INSULIN RESISTANCE

Fatty liver diseases and insulin resistance

Fatty liver disease (FLD), whether it is alcoholic fatty liver disease (AFLD) or nonalcoholic fatty liver disease (NAFLD), encompasses a morphological spectrum consisting of hepatic steatosis (fatty liver) and steatohepatitis. The indistinguishable spectrum of histological features of both AFLD and NAFLD suggests a possible convergence of pathogenetic mechanisms at some critical juncture that enables the progression of steatohepatitis toward cirrhosis and liver cancer. Moreover, fat accumulation in the liver is, independent of body mass index and intraabdominal and overall obesity, characterized by several features of insulin resistance in normal weight and moderately overweight subjects[8].

Although NAFLD/NASH is generally considered as the result of insulin resistance syndrome including obesity, T2DM and hyperlipidemia, some recent studies implicate that NAFLD could also be a prediabetic condition. For example, Fan *et al*[9] conducted a retrospective study on a cohort of 358 individuals with hepatic ultrasound-defined fatty liver and 788 age-, sex- and occupation-matched controls for 4-7 years, which showed that metabolic syndrome components were present at a greater frequency among those with fatty liver than among controls. Population-based studies showed an association between elevated liver enzymes (as inflammatory markers of NAFLD) and a future potential for development of the metabolic syndrome[10,11].

On the other hand, it has also been reported that subjects with alcoholic liver disease have been shown to be at increased risk for T2DM[12]. Wei *et al*[13] showed that subjects with high alcohol intake (> 270 g/wk) have a 2-fold increased risk of developing T2DM compared with those with moderate alcohol intake (60-120 g/wk) in a prospective follow-up study of 8663 men. This association was independent of other risk factors, such as age, obesity, blood pressure, smoking and family history of diabetes. However, a similar relationship was not shown in a study with female subjects[14].

The pathogenesis of alcoholic fatty liver disease and NASH is multifactorial and includes several overlapping events. The accumulation of fat in hepatocytes (steatosis) and the onset of steatohepatitis may reflect successive stages in FLD. The "two-hit" hypothesis proposed by Day and James in 1998[15] postulates that the steatotic liver is susceptible to secondary insults including a vulnerability to reactive oxygen species, gut-derived endotoxins, and adipocytokines such as tumor necrosis factor-α (TNF-α) and other cytokines. The first "hit" is thought to be an accumulation of fatty acids and triglycerides within the liver, possibly due to insulin resistance. Chronic stress such as portal endotoxemia (the second "hit") leads to mitochondrial dysfunction and Kupffer cell adaptive changes[16,17], which in turn result in hepatocyte survival adaptation[18] and subsequent necrosis and/or apoptosis. Concomitant release of liver-derived inflammatory cytokines, i.e., TNF-α[19] and acute-phase proteins such as CRP, LPS binding protein and serum amyloid-P component[20] may induce some extrahepatic effects and then affect the development of T2DM. However, this hypothesis has not been directly examined in human and animal studies.

Viral hepatitis and insulin resistance

Recent studies have suggested that HCV infection is associated with an increased risk of development of T2DM, and that T2DM is more common among patients with chronic HCV infection than in patients with other liver diseases or in the general population, irrespective of whether or not hepatic cirrhosis is present[21]. Moreover, the conclusion of a prospective, case-cohort study conducted within a community-based cohort of 1084 persons aged 44-65 years suggests that pre-existing HCV infection may increase the incidence of T2DM in persons with known risk factors[22]. A community-based cohort survey performed in southern Taiwan enrolled 4958 persons aged ⩾ 40 years without T2DM. After a follow-up of 7 years, 474 cases of incident T2DM were recorded: overall, 14.3% of anti-HCV positive, 7.5% of HBsAg positive, and 8.6% of seronegative individuals developed T2DM during the study. Compared to anti-HCV negative individuals, anti-HCV positive persons had a higher cumulative incidence of T2DM ($P < 0.0001$)[23].

Hepatogenous diabetes

Up to 96% of cirrhotic subjects have impaired glucose tolerance or diabetes[24]. The term "hepatogenous diabetes" is used to describe the close association between cirrhosis and impaired glycemic control. There is less association with other T2DM-related risk factors such as age, obesity, smoking history, family history of diabetes and hypertension[24]. Cirrhosis may contribute to the development of T2DM through numerous factors such as reduced insulin clearance with peripheral hyperinsulinemia[25], which could contribute to the development of insulin resistance through the down-regulation of insulin receptors. Nevertheless, interaction of the cause of liver cirrhosis with environmental factors may also play a significant role in the link between cirrhosis and diabetes rather than development of cirrhosis alone.

IMPACT OF LIVER DISEASES ON β CELL DYSFUNCTION

The pancreas and the liver are in close proximity and many of the blood vessels and ducts in these organs are anatomically associated with each other. It was suggested that liver disease, regardless of the etiology, may predispose the patient to develop acute or chronic pancreatitis in an analysis of 107 754 adult autopsies in Japan[26]. In addition, exocrine pancreatic function has been reported to be damaged in chronic liver disease[27] and chronic viral hepatitis[28]. An animal study showed exacerbation of

acute pancreatitis in the presence of chronic liver injury in rats[29].

On the other hand, pancreatogenic diabetes, regarded as a form of "secondary diabetes"[30], accounts for 1% to 2% of all diabetic patients in North America but as many as 15% to 20% of diabetic patients in the Southeast Asian continents[31]. Many issues remain unknown regarding the etiology of pancreatic inflammation in pancreatogenic diabetes. In addition, clinical studies showed that the impairment of exocrine pancreatic function was more frequently seen in subjects with alcoholic and non-alcoholic liver diseases[32]. A recent investigation has been undertaken to clarify the effect of the inflammatory change of fatty liver on the development of β cell dysfunction in T2DM. It showed that the inflamed liver induced by mild portal endotoxemia was concomitantly combined with an impairment of pancreatic insulin secretion[33], suggesting that this may be a detrimental factor in the pathogenesis of β cell failure during development of T2DM and also pancreatogenic diabetes.

MECHANISMS UNDERLYING THE EFFECTS OF LIVER DISEASES ON T2DM

Gut microbiota

Wigg *et al*[34] reported a higher prevalence of small intestinal bacterial overgrowth (SIBO) and increased circulating TNF-α levels in patients with NASH. In addition, inflammatory liver damage in various rat models of SIBO is improved by antibiotic treatments[34,35]. A recent study from Brun *et al*[36] has demonstrated that genetically obese mice (*ob*/*ob* and *db*/*db* mice) display enhanced intestinal permeability leading to increased intraportal endotoxemia that can contribute to the liver inflammatory damage. These studies provide evidence to suggest that portal endotoxemia is a major risk factor in the pathogenesis of NASH. Furthermore, a recent investigation demonstrated that mild portal endotoxemia induced by low-dose intraportal LPS infusion intensified the inflammatory changes of fructose-induced fatty liver and also caused low-grade systemic inflammation in the absence of an increase in blood endotoxin levels, providing strong evidence to support the causal role of portal endotoxemia in development of NASH[37] .

On the other hand, Backhed *et al*[38] showed that germ-free mice gained significantly less weight and fat mass than conventionalized mice, and were protected against high-fat diet-induced glucose intolerance and insulin resistance, suggesting that a bacterially related factor/mechanism other than energy harvesting may be responsible for the development of diet-induced obesity and diabetes. In addition, gut microbiota, especially bacterial LPS, has recently been speculated to contribute to the low-grade inflammation in obesity, diabetes, NAFLD and cardiovascular disease[39]. Cani *et al*[40,41] showed that there was a significant increase in circulating LPS levels in mice on high-fat feeding for 2-4 wk. They reproduced metabolic endotoxemia in these high-fat fed mice by chronically infusing low-dose LPS for 4 wk to develop the same phenotype as those on a high-fat diet such as obesity, insulin resistance, diabetes, hepatic steatosis and adipose tissue macrophage infiltration. However, this high-fat associated phenotype was not exhibited in LPS receptor knockout mice (CD-14KO) with a high-fat diet. Moreover, CD14KO mice were hypersensitive to insulin, even when they were fed a normal diet, suggesting that CD14 could be a modulator of insulin sensitivity under physiological conditions.

Furthermore, recent study using chronic low-dose portal LPS infusion in rats to simulate low-grade portal endotoxemia and hepatic injury showed that increasing oxidative (malondialdehyde) and inflammatory TNF-α and IL-6 markers with pathogenic changes were not only exhibited in liver but also in the pancreas of experimental rats[33]. This data also showed that the sequential effects of inflamed fatty liver could further impair pancreatic β cell function in the absence of change in homeostasis model assessment-insulin resistance index, suggesting that the low-grade hepatic inflammation induced by intraportal low-dose LPS infusion is the significant detrimental factor for the early development of T2DM.

HCV infection

It is suggested that HCV may alter glucose homeostasis by its direct action[42], or *via* indirect mechanisms such as through cytokine stimulation. For instance, in the transgenic mouse model[43], the core-encoding region of HCV is sufficient to induce insulin resistance. The effect was reversed by treatment with anti-TNF-antibodies, which suggested an increased level of serine phosphorylation of IRS-1 as induced by TNF-α. Nevertheless, direct but genotype-specific mechanisms have been reported[44], in which down-regulation of peroxisome proliferator-activated receptor-γ (PPARγ) and up-regulation of SOCS-7 were observed in cells transfected with the core protein of genotype 3, whereas the core protein of genotype 1b activated the mammalian target of rapamycin. These findings were confirmed by using agonists for PPARγ or short interfering RNAs for SOCS-7[45]. Accordingly, the *in vitro* study of Kawaguchi *et al*[46] demonstrated that HCV proteins inhibit insulin signaling.

In addition, studies on chronically infected patients have suggested that increased oxidative stress and intrahepatic inflammation may also play a role[47]. In fact, an increased intrahepatic TNF-α response, which results in insulin resistance and a higher risk of developing T2DM in chronic HCV, has been described[48]. It is necessary to further investigate at a more in-depth level the causal relationship between HCV-induced hepatic inflammation and the development of T2DM.

Hepatic inflammation and obesity-associated insulin resistance

Subclinical inflammation is predictive of both cardiovascular diseases and T2DM. Inflammatory changes in visceral adiposity in obesity and chronic hepatic inflammation are etiologically and functionally intertwined, and

both may be associated with chronic systemic inflammation in the pre-diabetic state. To isolate the potential systemic effects of chronic subacute hepatic inflammation, Cai *et al*[49] conducted a study with non-obese transgenic mice expressing constitutively active I-Kappa-B kinase-β (IKK-β) in hepatocytes. Their data suggest that chronic low-grade hepatic inflammation could cause systemic insulin resistance mediated by elevated circulating IL-6 levels. Arkan *et al*[50] recently presented similar findings in mice lacking IKK-β in hepatocytes. Liver-specific deletion of IKK-β resulted in relative insulin sensitivity in the liver when animals were placed on a high-fat diet or were intercrossed with the *ob/ob* model of genetic obesity, but development of insulin resistance in muscle and fat occurred.

Hepatic fat accumulation

However, a recent study in rats with hepatic overexpression of glycerol-sn-3-phosphate acyltransferase 1 demonstrated that increased flux through the pathway of hepatic *de novo* triacylglycerol synthesis can cause hepatic and systemic insulin resistance in the absence of increased hepatic inflammation, suggesting that an excess flux of lipid intermediates in the pathway of triacyglycerol synthesis are sufficient to cause insulin resistance[51]. Accordingly, studies showing that liver fat content, much more strongly than visceral fat mass, determines insulin sensitivity in humans, support a direct and major role of fatty liver in the pathogenesis of insulin resistance[52,53].

Reactive oxygen species

Oxidative stress due to generation of reactive oxygen species and/or decreased antioxidant defenses[54] has been proposed as the root cause underlying the development of insulin resistance, β cell dysfunction, impaired glucose tolerance and T2DM. In both nonalcoholic steatohepatitis and experimental steatohepatitis, hepatic expression of CYP2E1 is increased, leading to oxidative stress, which has been demonstrated to impair insulin signaling[55].

Hepatokines

Recent studies have suggested that the mechanisms of fatty liver-induced metabolic diseases may differ from those of expanded adipose tissue mass. The new concept proposed is that the fatty liver releases factors in the circulation, similarly to expanded and inflamed adipose tissue (adipokines), which can be called hepatokines, and they have direct effects on target tissues. There is strong evidence to support the concept that hepatokines such as protein fetuin-A, sex hormone-binding globulin and selenoprotein P play an important role in the pathogenesis of insulin resistance and also subclinical inflammation[56,57].

CONCLUSION

The prevalence of T2DM is higher in patients who have liver diseases such as NAFLD, chronic viral hepatitis, alcoholic liver disease and cirrhosis. However, the cause-effect relationship between liver diseases and T2DM remains ambiguous. This article provides an overview of the evidence for the impact of chronic liver diseases on T2DM and examines up-to-date studies about the possible underlying mechanism. A better understanding of the deleterious factors which affect progression of chronic liver diseases are of clinical importance in order to monitor and treat T2DM patients with liver diseases.

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S- Editor Tian L **L- Editor** Logan S **E- Editor** Xiong L