Digestive and Liver Disease 48 (2016) 105–111

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Treatment of type 2 diabetes mellitus by viral eradication in chronic hepatitis C: Myth or reality?

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ARTICLE INFO

Article history:
Received 13 May 2015
Accepted 16 October 2015
Available online 27 October 2015

Keywords:
Chronic hepatitis C
Diabetes mellitus
Hepatitis C virus
Impaired fasting glucose
Insulin resistance
Interferon
Microangiopathy
Ribavirin

ABSTRACT

Chronic hepatitis C is a systemic disease inducing metabolic alterations leading to extrahepatic consequences. In particular, hepatitis C virus (HCV) infection seems to increase the risk of incident type 2 diabetes mellitus in predisposed individuals, independently of liver disease stage. The mechanisms through which hepatitis C induces T2DM involve direct viral effects, insulin resistance, pro-inflammatory cytokines and other immune-mediated processes. Many studies have reported the clinical consequences of type 2 diabetes mellitus on hepatitis C outcome, but very few studies have addressed the issue of microangiopathic complications among patients with hepatitis C only, who develop type 2 diabetes mellitus. Moreover, clinical trials in HCV-positive patients have reported improvement in glucose metabolism after antiviral treatment; recent studies have suggested that this metabolic amelioration might have a clinical impact on type 2 diabetes mellitus-related complications. These observations raise the question as to whether the HCV eradication may also have an impact on the future morbidity and mortality due to type 2 diabetes mellitus. The scope of this review is to summarise the current evidence linking successful antiviral treatment and the prevention of type 2 diabetes mellitus and its complications in hepatitis C-infected patients.

1. Introduction

Infection with hepatitis C virus (HCV) is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma worldwide [1,2]. Chronic HCV infection has been associated with several extrahepatic complications, such as essential mixed cryoglobulinaemia, porphyria cutanea tarda, glomerulonephritis, autoimmune thyroiditis, sialadenitis, and cardiomyopathy [3–7]. The available data suggest that patients with chronic hepatitis C (CHC) might be characterised by a high prevalence of metabolic derangements [8–10], some of which appear to be profoundly modified following viral eradication [8,11,12]. Growing evidence shows that HCV increases the risk of incident type 2 diabetes mellitus (T2DM) in predisposed individuals [12–16]. The mechanism whereby HCV induces T2DM is insulin resistance (IR) [17]. HCV was shown to impair the hepatocyte insulin signalling pathway by several mechanisms [18], including the stimulus to the production of tumour necrosis factor-α (TNF-α), the serine phosphorylation of the insulin receptors (IRS), the overexpression of the suppressor of cytokines (SOC-3) [19,20] and the induction of SOC-7 [21]. However, although HCV infects mainly the liver, whole body insulin sensitivity is also impaired in CHC patients without metabolic syndrome, as shown by recent studies [22,23]. This suggests that the infected hepatocytes might produce mediators that induce endocrine effects at extrahepatic sites, such as the skeletal muscle (Fig. 1). The virus-induced metabolic derangements may interact with host-related genetic and environmental factors, aggravating insulin resistance and possibly leading to the development of T2DM. An imbalance in the adipocytokine profile and the presence of liver steatosis/steatohepatitis could contribute to this scenario [24–32]. Once it has occurred, T2DM contributes to the acceleration of the progression of liver damage, to an increase in the risk of hepatocellular carcinoma (HCC) development and to impairment of the response to antiviral therapy. Finally, a possible direct viral effect, together with a systemic chronic inflammatory state and the interaction with metabolic derangements, could play a role in the development of cardiovascular disease.

T2DM seems not only to accelerate the course of CHC [33–39], but also to influence the response to antiviral therapy [40–45].

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http://dx.doi.org/10.1016/j.dld.2015.10.016
1590-8658/

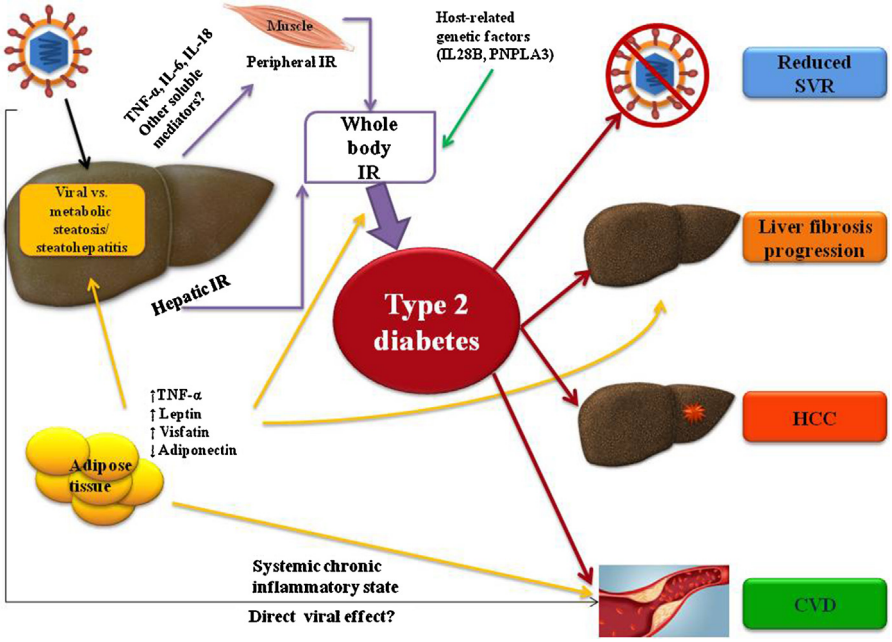

Fig. 1. Tentative explanation of the pathogenesis of hepatitis C virus-induced type 2 diabetes mellitus and related clinical outcomes. SVR, sustained virological response; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; IL-18, interleukin-18; IL-28B, interleukin-28B; IR, insulin resistance; PNPLA3, patatin-like phospholipase domain-containing protein 3; HCC, hepatocellular carcinoma; CVD, cardiovascular disease.

Importantly, T2DM occurring in the course of CHC greatly increases the risk of HCC [46–50], even in patients without cirrhosis and after the eradication of HCV infection [51].

If HCV is directly involved in the development of IR and T2DM, it is reasonable to hypothesise that its clearance might result in a parallel decrease in the risk of T2DM incidence. Conversely, a successful eradication of HCV would improve clinical outcomes in patients with established T2DM.

The aim of this review is to carry out an extensive examination of data on the response of HCV-induced IR to successful antiviral treatment to evaluate its efficacy in preventing the development of T2DM in CHC patients and in improving the clinical outcomes of diabetic patients.

To analyse the pertinent data, we searched for published studies in English in selected databases, including PubMed, ISI Web of Science, Google Scholar, and Scopus, covering the period from 1998 to December 2014. The literature search was performed using combinations of selected key- and text-words including "insulin resistance", "diabetes", "type 2 diabetes mellitus", "T2DM", "microangiopathy", "diabetic microangiopathy", "hepatitis", "chronic hepatitis C", "hepatitis C virus", "HCV", "risk factor", "meta-analysis", "systematic review", "review".

2. Impact of SVR on T2DM incidence

Studies addressing the clinical impact of sustained virological response (SVR) on IR or T2DM incidence are reported in Table 1. Several studies [41,52–57] reported a reduction in the number of patients with IR treated with interferon (IFN)-based plus ribavirin (RBV) therapies after achievement of SVR. Aghemo et al. [58] confirmed the persistence of this beneficial effect in cured patients during a prolonged follow-up, preventing the potential bias represented by weight loss during IFN/RBV treatment. The mechanism through which antiviral therapy ameliorates IR has not been fully established, but it is most likely mediated via viral clearance, rather than a direct pharmacological effect of IFN/RBV. Anyway, the above-mentioned studies provided the proof-of-concept on the possibility of obtaining a significant decrease in IR incidence in patients with SVR; however, this epidemiological finding did not by default translate into any definite clinical benefit for patients; in fact, the really strong endpoint is the reduction in the incidence of T2DM and its complications. This issue was addressed by a few studies [52,55,59] that reported a significantly reduced incidence of T2DM among sustained responders. Only one study [60] failed to show a statistically significant lower incidence of T2DM in eradicated patients compared with non-responders. The discrepancy may be explained by the different baseline features (low number of cirrhotics, predisposition to hepatogenous T2DM) of the patients and by the weight increase observed among sustained responders included in the Italian study. T2DM occurrence is associated with a genetic predisposition, but it is also influenced by lifestyle-related aspects, such as dietary habits and physical activity. For this reason, epidemiological variations concerning T2DM in CHC patients should always take into account important demographic and clinical features such as family history, age, sex, obesity, smoking habit and physical activity. In other words, how much is the virus and how much is lifestyle (and genetics) responsible for inducing T2DM? Does viral eradication per se afford protection from T2DM development, or do the above-mentioned factors play a pivotal role in disease occurrence?

According to Arase et al. [59], viral eradication induced a two-thirds reduction in the risk of incident T2DM, independent of age, presence of cirrhosis and of pre-diabetes before therapy. Unfortunately, the authors did not report data regarding important baseline variables such as family history for T2DM, smoking habit, physical activity and IR. Moreover, the retrospective design of the study did not provide us with results on BMI at the end of follow-up and, last but not least, patients included in this study showed pre-therapy characteristics (low BMI, high rate of genotype 2, high antiviral efficacy) that are infrequent in most Western countries. Caution is thus recommended before extrapolating the results to non-Asian populations. On the other hand, analysis of Western series [52,55] led to similar conclusions; in particular, Romero-Gómez et al. [55] showed that eradication of HCV reduced the incidence of T2DM by half in a large cohort of CHC patients during the post-treatment follow-up. Interestingly, the authors reported older age, abnormal glucose values and steatosis, all