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Facts and fictions of HCV and comorbidities: Steatosis, diabetes mellitus, and cardiovascular diseases

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Summary

The hepatitis C virus (HCV) is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma worldwide. A significant portion of the morbidity and mortality associated with HCV is a consequence of numerous HCV-associated comorbidities. Type 2 diabetes and atherosclerosis, two known complications of the metabolic syndrome, are noteworthy, because HCV has been suggested to play a role in their pathogenesis. In addition, HCV also causes steatosis, which may increase the risk of cardiovascular events. This review summarizes the evidence supporting the association between HCV and steatosis, insulin resistance/type 2 diabetes and cardiovascular morbidity and mortality. Their diagnostic, prognostic and management aspects are discussed.

Introduction

The hepatitis C virus (HCV) is a major cause of cirrhosis and hepatocellular carcinoma worldwide. In a recent systematic literature review, the global HCV prevalence was estimated to be ~2.8% of the world's population, corresponding to ~185,000,000 persons infected [1]. The same study reported recently that in 2010 there were approximately 10 times more deaths attributable to viral hepatitis in the European Union than to human immunodeficiency virus (HIV), with two thirds of the viral hepatitis deaths associated with HCV [2]. Similar data have been reported in the USA, where HCV-associated mortalities surpassed those due to HIV in 2007 [3]. This already worrisome mortality rate is bound to increase at least until 2030 [4], as complications of end stage liver disease occur decades after infection, the vast majority of which occurred in the 1960's and 1970's. This will impose a significant burden on the health care systems worldwide [5].

Although cost-effectiveness studies on measures aimed at battling the HCV epidemic have essentially focused on liver disorder-related costs, a significant portion of the health burden associated with HCV is the consequence of a number of HCV-associated comorbidities [6] (Fig. 1). Among these, type 2 diabetes and atherosclerosis, two otherwise well-known, major complications of the metabolic syndrome, are noteworthy, because HCV infection has been linked to their pathogenesis [7]. In addition, HCV also causes steatosis [8], which has been suggested to increase the risk of cardiovascular morbidity [9]. This raises the legitimate question as to whether the successful management of HCV may also impact the future morbidity and mortality due to diabetes and atherosclerosis. The scope of this review is to discuss some aspects related to the epidemiology and pathogenesis of such manifestations, and to discuss their management.

Key Points

- Chronic hepatitis C patients often present with steatosis, which shows a strong genotype dependence, correlates with viral load, and disappears in case of successful therapy
- Viral steatosis is not associated with rapid fibrosis progression or poor response to IFN-α, but may be a risk factor for HCC
- HCV is associated with insulin resistance that may progress to type 2 diabetes in patients at risk, and leads to poor response to IFN-α, accelerated fibrosis progression and HCC
- HCV-infected persons are at higher risk of cardiovascular events, independently of other risk factors
- Successful antiviral therapy may reduce the risk of developing type 2 diabetes and ischaemic stroke

Keywords: Hepatitis C virus; Steatosis; Insulin resistance; Diabetes; Coronary artery disease; Atherosclerosis; Stroke.
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Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDL, low density lipoprotein; HCC, hepatocellular carcinoma; PTEN, phosphatase and tensin homologue deleted on chromosome 10; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HBV, hepatitis B virus; IR, insulin resistance; HOMA-IR, homeostasis model for assessment of insulin resistance; BMI, body mass index; SVR, sustained virological response; CCL2, chemokine [C-C motif] ligand 2; IFN, interferon; IMT, intima-media thickness.

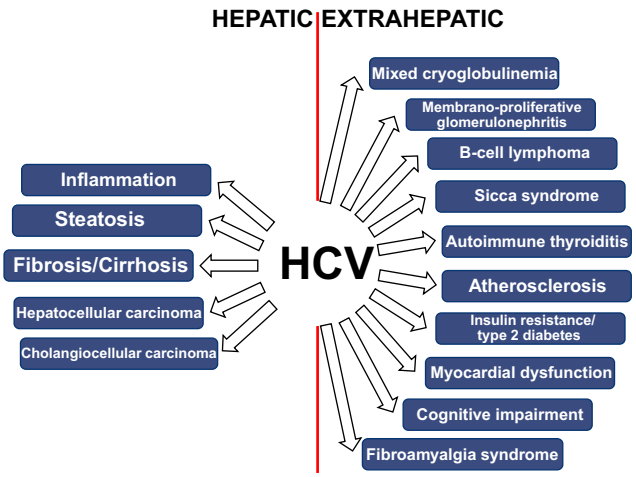

Fig. 1. Hepatic and extrahepatic disorders associated with HCV infection.

Steatosis

Evidence for a viral role in inducing fatty liver

Chronic HCV infection is associated with steatosis [8,10]. This is suggested by the strong association of steatosis with HCV genotype 3: patients with this genotype have a ~5-fold probability of having moderate to severe steatosis, more than those with non-3 genotypes [11], hinting at viral sequences responsible for the fat accumulation. Occurrence and severity of steatosis in patients with HCV genotype 3 correlates with the viral load and the response to antivirals: fat accumulation disappears in patients who reach a sustained virological response (SVR), and reappears when infection relapses [12]. The dependence of HCV replication and spread on the host lipid metabolism partly explains this close association: (i) specific lipid species are essential for the HCV life cycle, as their depletion inhibits viral replication; (ii) virion assembly and egress depend on lipid droplets and exploit the hepatocyte lipoprotein secretion pathway; (iii) HCV circulates in blood associated with lipoproteins forming so-called lipoviroparticles; (iv) the latter ones bind to hepatocytes via interaction, among others, with the low-density lipoprotein (LDL) receptor [13].

Although HCV alters the host lipid metabolism to favour its own replication and virion production, these pathophysiological changes are shared by all viral genotypes while steatosis is more frequent and severe in genotype 3 infection, suggesting the involvement of additional mechanisms in case of an infection with this genotype. Unfortunately, the differential efficiency, shown by the various viral genotypes, in leading to the appearance of large fat droplets has been poorly studied [10]. In addition, although several mechanisms have been proposed to account for the viral steatosis (for a review, see [10]), no experimental model recapitulates the phenotype observed in humans. There are multiple reasons for the difference between *in vivo* and *in vitro* observations: (i) most models use hepatoma cells, (ii) the sequences used to induce metabolic alterations, supposed to lead to steatosis, are often derived from non-3 genotype isolates, and (iii) a direct comparison between different genotypes has been rarely performed, using the same model and experimental conditions.

Finally, some claims based on evidence gathered *in vitro* are in conflict with the observations made in humans. A typical case is represented by the activation of transcription factors responsible for neolipogenesis, such as *SREBF1* and *SREBF2*. Although these factors have been repeatedly found activated in hepatoma cells expressing HCV proteins [14–18], oddly enough, their levels in livers have been inversely correlated with steatosis severity [19]. This suggests that their activation – albeit necessary for the HCV life cycle – may not be sufficient to bring about steatosis.

Clinical impact of steatosis in HCV infection

Whatever the mechanism, viral steatosis does not seem to impact liver fibrosis progression rate [20], although HCV genotype 3 is independently associated with increased fibrosis progression [20,21]. Viral steatosis does not impair response to interferon-α (IFN-α) [22,23]. Alternatively, steatosis due to the metabolic syndrome is associated with both accelerated fibrosis progression [24,25] and poor response to IFN-α-based therapy [22,23]. A distinct issue is the association between steatosis and hepatocellular carcinoma (HCC). Several studies have associated steatosis and the risk for HCC in chronic hepatitis C [26–28]. Due to the paucity of patients with HCV genotype 3 included in these studies, making any inference about a causal link between viral steatosis and HCC is problematic. More likely, this association may have been accounted for by the known relationship between overweight (leading to steatosis) and HCC [29]. On the other hand, HCV genotype 3 infection is indeed associated with an increased risk for HCC [21,30,31], but whether this is due to viral steatosis is unknown. Association does not imply causation and, besides, steatosis is often reduced or absent in late stages of liver disease, i.e., at the time HCC occurs [32–34]. Thus, evidence supporting the argument that viral steatosis directly leads to HCC is lacking. Some patients with genotype 3 may present a deregulation of intracellular pathways leading to both steatosis and HCC: potential culprits include the production of reactive oxygen species [35] or the downregulation of the tumour suppressor PTEN [36].

Viral vs. metabolic steatosis

Based on the discussion above, it seems important, from the prognostic point of view, to distinguish viral steatosis from steatosis of a different origin, especially metabolic (Table 1). Unfortunately, viral steatosis does not present clear-cut histopathological features allowing to differentiate it from steatosis due to other causes. Thus, the differential diagnosis must rely on the history, the presence of risk factors, serum biochemistry assays and responsiveness to antivirals. HCV infected patients tend to have lower levels of circulating components of lipoproteins, such as cholesterol [25,37], especially in patients with genotype 3 [37]. This peculiar lipid profile is reverted after successful therapy [37,38], but a precise correlation between hypocholesterolemia and steatosis has rarely been reported [23].

Both HCV and the metabolic syndrome are frequent disorders, hence there is the probability of overlap. Non-alcoholic fatty liver disease (NAFLD) is the liver manifestation of the metabolic syndrome. The occurrence and significance of NAFLD and – more importantly – non-alcoholic steatohepatitis (NASH) in HCV infection have rarely been studied. In an important work, the features of patients with hepatitis C and NASH were analysed in detail [39]. Patients with chronic hepatitis C and NASH had higher