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MINIREVIEWS

Assessing cardiovascular risk in hepatitis C: An unmet need

Javier Ampuero, Manuel Romero-Gómez

Javier Ampuero, Manuel Romero-Gómez, Intercentre Unit of Digestive Diseases, Virgen Macarena - Virgen del Rocio University Hospitals. 41013 Sevilla, Spain

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Correspondence to: Javier Ampuero, MD, PhD, Intercentre Unit of Digestive Diseases, Virgen Macarena - Virgen del Rocio University Hospitals. Avenida Manuel Siurot, s/n, 41013 Sevilla, Spain. javi.ampuero@gmail.com
Telephone: +34-955-015761
Fax: +34-955-015899

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Abstract

Chronic hepatitis C virus (HCV) is associated with significant morbidity and mortality, as a result of the progression towards cirrhosis and hepatocellular carcinoma. Additionally, HCV seems to be an independent risk factor for cardiovascular diseases (CVD) due to its association with insulin resistance, diabetes and steatosis. HCV infection represents an initial step in the chronic inflammatory cascade, showing a direct role in altering glucose metabolism. After achieving sustained virological response, the incidence of insulin resistance and diabetes dramatically decrease. HCV core protein plays an essential role in promoting insulin resistance and oxidative stress. On the other hand, atherosclerosis is a common disease in which the artery wall thickens due to accumulation of fatty deposits. The main step in the formation of atherosclerotic plaques is the oxidation of low density lipoprotein particles, together with the increased production of proinflammatory markers [tumor necrosis factor-α, interleukin (IL)-6, IL-18 or C-reactive protein]. The advent of new direct acting antiviral therapy has dramatically increased the sustained virological response rates of hepatitis C infection. In this scenario, the cardiovascular risk has emerged and represents a major concern after the eradication of the virus. Consequently, the number of studies evaluating this association is growing. Data derived from these studies have demonstrated the strong link between HCV infection and the atherogenic process, showing a higher risk of coronary heart disease, carotid atherosclerosis, peripheral artery disease and, ultimately, CVD-related mortality.

Key words: Hepatitis C; Atherosclerosis; Coronary artery disease; Cardiovascular risk; Oxidative stress; Inflammation

Core tip: Chronic hepatitis C is associated with significant morbidity and mortality, as a result of the progression towards cirrhosis and hepatocellular carcinoma. Furthermore, hepatitis C virus seems to be an independent risk factor for cardiovascular diseases due to its association with insulin resistance, diabetes and steatosis. The advent of new direct acting antiviral therapy has dramatically increased the sustained virological response rates of hepatitis C infection. In this scenario, the cardiovascular risk has emerged and represents a major concern after achieving the eradication of the virus.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem that affects 170 million people worldwide. Hepatitis C is responsible for about 100000 deaths annually[1]. Chronic hepatitis C is associated with significant morbidity and mortality, which result mainly from the progression towards cirrhosis and hepatocellular carcinoma[2]. Extrahepatic manifestations are well-known complications of HCV infection. Similar to non-alcoholic fatty liver disease[3,4], HCV seems to be an independent risk factor for cardiovascular diseases (CVD) due to its association with insulin resistance, diabetes and steatosis[5]. However, our knowledge about this topic requires further studies. In fact, previous studies that assessed the association between HCV infection and CVD risk have been sometimes inconclusive[6]. In this review, our aim is to elucidate the role of HCV infection on the cardiovascular-related affectation.

HCV AND INFLAMMATION

HCV infection represents an initial step in the chronic proinflammatory cascade. It produces proinflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) alpha, leading to increased inflammation and liver fibrosis. In addition, HCV-related steatosis promotes increased expression of inflammatory markers. These molecules are able to inhibit the insulin signaling, causing insulin resistance and steatosis progression[7].

Insulin resistance

Several studies have established a direct role of HCV in altering the glucose metabolism, leading to insulin resistance and diabetes, especially in genotype 3[8]. This relationship could explain, at least in part, the impact of metabolic abnormalities on sustained virological response (SVR), regardless of other variables such as viral or IL28B genotypes. In fact, achieving SVR with antiviral therapy results in a dramatically decrease of the development of insulin resistance and the appearance of diabetes mellitus over time[9].

HCV core protein plays a fundamental role in the induction of insulin resistance. The PI3K/Akt pathway, whose phosphorylation is impaired upon insulin stimulation, is crucial for the inhibition of gluconeogenesis in the liver. HCV core protein is able to degrade the insulin receptor substrates (IRS) 1 and 2, by increasing the expression of TNFα and suppressing cytokine signalling-3, leading to defective downstream PI3K and Akt phosphorylation[10]. In fact, when viral clearance is obtained, the expression of IRS-1 and IRS-2 is restored and HOMA-IR index decreases, which indicates the independent role of HCV in insulin resistance[11]. Furthermore, there are other non-structural proteins, like NS5A and NS5B, which also promote insulin resistance, enhancing TNFα and IL-6. The ability of these molecules to disturb insulin signaling is well recognized. IL-1β is other interesting molecule. It is produced by hepatic macrophages, and is related to liver inflammation and, ultimately, to disease progression[12]. Finally, the role of toll-like receptors is growing in importance. HCV infection activates these molecules, which are closely associated with proinflammatory cytokines, contributing to the vicious circle[13].

Oxidative stress

Oxidative stress is the other main pathway of HCV-mediated inflammation, as insulin resistance promotes fatty acid accumulation in the liver, resulting in increased β-oxidation and reactive oxygen species (ROS)[14]. On the one hand, mitochondrial fat oxidation upregulates nuclear factor κB (NF-κB). This latter activates the transcription of several proinflammatory genes and the production of proinflammatory cytokines[15]. On the other hand, ROS play an important role in fibrogenesis by proliferating hepatic stellate cells and collagen synthesis and by inducing tumor growth factor-β[16]. An imbalance between oxidant agents and antioxidant defenses is the final result of all these processes, causing oxidative damage to hepatocyte and altering the reparation of DNA.

ATHEROSCLEROSIS

Lipid oxidation

Atherosclerosis is a common disease in which the artery wall thickens due to the accumulation of fatty deposits, called atheromatous plaques. Cholesterol-rich low density lipoprotein (LDL) is the main atherogenic lipoprotein. LDL infiltrates into the endothelium and adheres to extracellular matrix components, resulting in accumulation in the vascular intima[17]. Interestingly, LDL particle size seems to facilitate the passing between the endothelial cells because small dense LDL represents a major component of an atherogenic lipoprotein phenotype[18].

The main step in the formation of atherosclerotic plaques is the oxidation of LDL particles, being the risk higher in the wall than in the bloodstream[19]. Monocytes penetrate into endothelium and are able to transform into macrophages. This latter kind of cells is able to phagocyte oxidized LDL (oxLDL) particles triggering a cascade of immune responses and producing an atherosclerotic plaque[20]. During oxidation, LDL converts to oxLDL involving some enzymes (such as lipoprotein-associated phospholipase A2) with several consequences: (1) oxLDL activates T cells and macrophages, stimulating the production of foam cells; (2)

oxLDL induces the expression of endothelial adhesion molecules and the stimulation of several growth factors; and (3) oxLDL affects nitric oxide releasing and vascular smooth muscles, contributing to impair the vascular contraction[21]. As a result, oxLDL is able to thicken the intima and enhance atherosclerosis.

Inflammation

Many markers, such as proinflammatory cytokines (TNFα, IL-6 and IL-18), C-reactive protein, and adhesion molecules, are increased in plasma in situation of chronic inflammation. C-reactive protein may promote inflammation and atherogenesis through effects on monocytes and endothelial cells[22]. Regarding to proinflammatory cytokines, TNFα activates NF-κB after interacting with the vascular endothelium[23]. On the other hand, there are other cells with the capacity of enhancing proinflammatory cytokines such as activated macrophages, Th1 lymphocytes, and foam cells. Furthermore, several receptors (*i.e.*, CD-36 and toll-like receptors) located on the membrane of macrophages leads to uncontrolled phagocytosis of oxLDL[24].

Diagnostic tests

Noninvasive and inexpensive tests to anticipate and facilitate the prediction of cardiovascular risk are growing in importance. Atherosclerosis can be detected by several methods, depending on the organ or tissue affected. Carotid intima-media thickness and the presence of carotid plaques serve as marker of subclinical atherosclerosis and can be measured by ultrasound. They are especially considered to be independent stroke predictors[25] and related to cardiovascular events[26]. Other tests have been developed with the same proposal. Coronary artery calcification, judged by computed tomography, is a good predictor of coronary heart disease[27]. Brachial artery flow-mediated vasodilation is a test of endothelial dysfunction that is associated with early stages of atherosclerosis[28]. Pulse-wave velocity seems to be the gold standard of arterial stiffness and an early indicator for atherosclerosis[29]. Other methods, such as left ventricular hypertrophy (by electrocardiogram and echocardiogram)[30] or peripheral arterial disease (PAD) (by ankle-brachial pressure index)[31], are not extended in clinical practice due to costs or specialized personal requirement.

BIOLOGICAL MECHANISMS LINKING HCV AND ATHEROSCLEROSIS

A large body of evidence shows that infective agents contribute to promote chronic inflammation which could be associated, ultimately, with atherosclerosis[32]. Therefore, HCV infection has been widely assesed and biological mechanisms have been reported.

On the one hand, HCV infection seems to be associated with a higher risk of cardiovascular disease by indirect mechanisms. Firstly, HCV infection is strongly associated with metabolic abnormalities, including diabetes mellitus and liver steatosis, as well as metabolic syndrome. All of these risk factors are well-known predictors of cardiovascular disease[33]. Secondly, HCV infection interrelates with the host immune response. As it is commented above, it is able to stimulate the production of proinflammatory cytokines[34]. Thirdly, HCV infection comprises other extra-hepatic manifestations. In particular, cryoglobulinemia has been associated with higher prevalence of arterial hypertension and CVD compared to those patients without this entity[35].

On the other hand, the HCV seems to be directly related to atherosclerosis. HCV RNA sequences have been investigated by highly sensitive reverse transcriptase-polymerase chain reaction in plaque tissues of patients who underwent to carotid revascularization, demonstrating the presence of genomic and antigenomic HCV RNA strands. Consequently, additionally to the role of HCV on the development of chronic inflammation due to insulin resistance and steatosis, HCV RNA sequences seems to play a local effect on the endothelium[36].

IMPACT OF HCV-RELATED ATHEROSCLEROSIS

Coronary heart disease

Several studies have investigated the association between atherosclerosis and HCV infection, with conflicting results. In a systematic review, the majority of studies were of poor quality although revealed a tendency towards a higher risk of coronary heart disease (CHD) among patients with HCV infection. However, the studies showed heterogeneity in terms of methods and conclusions[37]. Other studies have showed similar conclusions. Forde *et al*[38] did not observe any difference in the incidence rates of CHD between HCV-infected and uninfected patients, as well as in terms of coronary revascularization procedures. Main limitation of studies showing no HCV-related effect on CHD is the inclusion of some patients who could have had spontaneously cleared HCV infection.

There are no many studies differentiating HCV antibody and RNA positivity, regarding to CHD events. In a very large study, authors found an increased risk of CHD in patients with HCV seropositivity, being an independent risk factor for CHD events. HCV seropositive patients had a higher incidence of CHD events compared with controls (4.9% *vs* 3.2%). Additionally, patients with detectable HCV-RNA had a significantly higher incidence of CHD events compared with patients who were only HCV antibody positive (5.9% *vs* 4.7%). Therefore, there was an increased incidence of CHD events in patients with HCV seropositivity and the incidence was much higher in patients with detectable HCV-RNA compared with patients with remote infection who were only antibody positive[39]. Electrocardiogram abnormalities are strongly associated with cardiovascular disease. HCV infection has been associated with

increased risk to ischemic electrocardiogram when compared with non-HCV subjects, revealing a possible relationship between HCV seropositivity and ischemic electrocardiogram[40]. Other study, performed by Butt *et al*[41], demonstrated that HCV-infected subjects had lower lipid levels and a lower prevalence of hypertension than those non-infected. Despite a favorable risk profile, HCV infection was associated with a higher risk of CHD after adjustment for traditional risk factors. In diabetic population, similar results have been obtained. Authors included three cohorts: patients who received pegylated interferon plus ribavirin (treated cohort), HCV-matched patients (untreated cohort) and diabetic patients without HCV infection (uninfected cohort). Main conclusion was that the incidences of ischemic stroke and CHD were all lower in HCV-infected patients treated with peginterferon and ribavirin, compared with infected individuals without antiviral treatment and diabetic patients without HCV infection. It is interesting to note that the risk of ischemic stroke and CHD were not attenuated in treated patients with PAD. This finding suggests that the pathogenic role of HCV can be limited at the early phase of atherosclerosis and that antiviral treatment could not reduce cardiovascular morbidity at an advanced stage[42].

Carotid atherosclerosis

A large body of evidence has assessed the association between HCV infection and carotid atherosclerosis. First study was carried out by Ishizaka *et al*[43], in which they evaluated the relationship between positivity for HCV and carotid-artery plaque and carotid intima-media thickening. After adjustment for cofounding risk factors, HCV seropositivity was found to be associated with an increased risk of carotid-artery plaque (OR = 1.92) and carotid intima-media thickening (OR = 2.85). A definite study was performed by Petta *et al*[44] One-hundred-and-seventy-four consecutive biopsy-proven HCV genotype 1 patients were evaluated by anthropometric and metabolic measurements and other 174 patients used as controls. Authors found that patients with HCV genotype 1 had a higher prevalence of carotid atherosclerosis compared with a control population (carotid plaques: 42% *vs* 23%; IMT: 1.04 ± 0.21 *vs* 0.90 ± 0.16). However, no direct association was found between viral load and atherosclerosis. The novel finding was the independent association of the presence of carotid plaques with severe hepatic fibrosis, after adjustment for age. Authors concluded that severe fibrosis and the associated cascade of proinflammatory and profibrogenic pathways generated in the liver might promote carotid atherosclerosis at a much younger age[44].

Peripheral artery disease

PAD is an under-diagnosed and under-treated disease. Some data suggest that HCV influences on the presence of PAD. In a retrospective cohort study, 7641 HCV-infected patients and 30564 matched controls were included. An excess risk of PAD development in HCV-infected patients was observed compared with non-HCV patients. The increased incidence of PAD in HCV-infected patients appeared since within first year. This study showed that gender had no effect on the risk of PAD development, but did aging. However, this study showed lack of evaluation of smoking, obesity or exercise[45].

Cardiovascular mortality

Given that the HCV infection seems to be related to several atherogenic processes, many authors have evaluated its role on CVD-associated mortality similar to other viral infections[46]. Guiltinan *et al*[47] performed a retrospective study including HCV antibody-positive and HCV antibody-negative patients matched for age and gender. HCV infection was associated with a significant increase in overall mortality including significantly increased mortality from liver and cardiovascular causes. In the REVEAL cohort, including 1095 anti-HCV-positive and 760 detectable HCV RNA, was observed that those anti-HCV-positive patients showed a higher risk of CVD-related mortality compared with seronegative subjects[48].

CONCLUSION

New direct acting antiviral therapy has dramatically increased the sustained virological response rates of hepatitis C infection[49]. Infected patients are going to live longer due to the eradication of the virus, so other HCV-related comorbidities have emerged. Specifically, cardiovascular disease is a major concern in this scenario. All the data provided in this review suggest a strong relationship between HCV infection and the atherogenic process, showing a high risk of coronary heart disease, carotid atherosclerosis, peripheral artery disease and, ultimately, CVD-related mortality. However, little is known about the precise mechanisms by which HCV enhances atherogenic processes. Therefore, we should be cautious when patients achieve SVR because maybe the cardiovascular risk remains after the virus eradication.

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