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Review Article

The impact of infection with hepatitis C virus on cardiovascular risk

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Abstract: Chronic hepatitis C virus (HCV) infection represents a systemic disease, with a natural progression to hepatic steatosis, fibrosis, and finally, cirrhosis, with an increased risk of hepatocellular carcinoma. Besides the hepatic alterations, the systemic manifestations of chronic HCV infection, such as endothelial dysfunction and atherosclerosis, oxidative stress, insulin resistance, immunological alterations, are nowadays recognized as cardiovascular risk factors. Hepatitis C is associated with insulin resistance and increased risk for type 2 diabetes mellitus, carotid atherosclerosis and stroke, coronary artery disease and chronic heart failure, with a significant impact on the mortality and morbidity. This article represents an overview of the most prevalent and important systemic alterations of chronic HCV infection, with emphasis on their cardiovascular and metabolic effects due to a treatable disease.

Keywords: Hepatitis C virus, insulin resistance, cardiovascular risk, metabolic syndrome, diabetes mellitus

Introduction

Worldwide, approximately 1% of the global population was infected with the hepatitis C virus (HCV) in 2015, emphasizing the importance of national strategies to decrease the prevalence and disease burden [1]. Over 50% of infected patients develop chronic hepatitis, frequently in a slowly progressive manner, that can associate extrahepatic manifestations on the skin, kidneys, hematopoietic system, but also the cardiovascular system, leading to an increased risk of atherosclerosis, cardiomyopathies, peripheral artery disease, and stroke and thus increasing mortality [2].

Chronic HCV infection is characterized by hepatic and systemic inflammation due to direct and indirect viral activities, with increased levels of pro-inflammatory cytokines and chemokines. Chronic systemic inflammation represents a well-known pro-atherogenic factor. Chronic HCV infection is recognized as an independent risk factor for cardiovascular diseases, incriminated in the appearance of endothelial dysfunction, oxidative stress, chronic inflammation, insulin resistance, etc. HCV-infected patients can also present other cardiovascular risk factors, such as age, sex, smoking, obesity, dyslipidemia, diabetes mellitus, arterial hypertension, chronic kidney disease and metabolic syndrome. In this case, the HCV infection represents a promoter of these factors, exponentially increasing the cardiovascular deleterious effects.

The studies and systematic reviews published in the last two decades recognized the impact of chronic HCV infection on the cardiovascular system. Although initially many studies were small, the increased interest in the extra-hepatic effects of chronic HCV infection determined the researchers to continue finding evidence through observational studies, prospective clinical studies, and outcome studies regarding the cardiovascular impact of this disease. In the light of recent findings, chronic HCV infection represents an independent cardiovascular risk factor for coronary artery disease, heart failure [3, 4] and stroke [5], an early diagnosis and

appropriate treatment of HCV infection becoming increasingly important. Given the fact that HCV infection is treatable with a high rate of success and the benefits of viral eradication are significant in many studies, the chronic HCV infection may be considered an important modifiable cardiovascular risk factor [6, 7].

HCV and its role in inflammation

HCV is a single-stranded RNA virus, a member of the Flaviviridae family. Its genome encodes a large polyprotein which will form the four structural proteins of the virus, but also non-structural proteins and enzymes, such as RNA polymerase, responsible for the heterogeneity of the virus [8]. One of the non-structural proteins, NS5A, determines the over-expression of cyclooxygenase-2, thus promoting the production of prostaglandins and thromboxane A2 and release of matrix-metalloproteinases, finally leading to inflammation, fibrosis, and carcinogenesis, irrespectively of viral load [9]. These effects are perpetuated by the activation of hepatic and extrahepatic inflammatory cells. Liver macrophages and stellate cells have increased production of interleukin 1-beta and tumor necrosis factor-alpha (TNF-alpha) [8].

Increased oxidative stress promotes chronic inflammation, with alterations of hepatocytes, endothelial cells, and liver macrophages and induces fibrosis by stimulating hepatic stellate cells. The imbalance between reactive oxygen species and antioxidants favors DNA damage and even mutations and alterations of the intracellular metabolism. One major effect is represented by lipid peroxidation that leads to liver steatosis, which appears to affect half of the infected patients [8].

Elevated pro-inflammatory cytokines, such as TNF-alpha, inhibit insulin signaling, with dysregulation of glucose and lipid metabolism, that contributes to steatosis, increasing the risk to develop type 2 diabetes (T2D), which, in turn, favors the oxidative stress and perpetuates the chronic inflammation, accelerated liver fibrosis and impaired antiviral treatment efficacy [10].

HCV and atherosclerosis

Another effect of the persistence of inflammatory cytokines is the up-regulation of adhesion molecules on endothelial cells, inducing an immune-mediated atherogenic state [11]. This relationship was evaluated in several studies that demonstrated the increased risk of heart failure and cardiovascular events in HCV infected patients compared to the normal population. In a cohort of patients with stable coronary heart disease, it was observed that HCV patients have higher levels of serum TNF-alpha (7.1 vs. 4.8; $P < 0.01$), but lower levels of C reactive protein (2.6 vs. 4.4; $P < 0.01$) [12]. Also, cardiovascular events and heart failure were significantly more prevalent in patients with HCV infection (HR = 2.13; 95% CI: 1.19-3.80) [12].

One cross-sectional study investigated atherosclerosis, by measuring the carotid intima-media thickness, and demonstrated that patients with chronic HCV infection have a higher frequency of atherosclerotic changes compared to non-infected individuals [13]. Moreover, there were isolated RNA strands of HCV within the atherosclerotic plaques in carotid arteries, independent of serum viral presence, highlighting the direct effect of the virus on atherosclerosis plaques formation through local inflammation [14].

The mechanisms by which the HCV is involved in atherosclerosis are not entirely understood. The direct and indirect effects of the virus, such as inflammation, lipid, and glucose metabolism alterations, were incriminated, all these factors being well known as responsible for atherosclerosis [2]. An interesting fact is that successful treatment of HCV infected patients determined a significant decrease of intima-media thickness (from 0.94 mm to 0.81 mm, $P < 0.001$) as compared to infected and untreated patients. On the other hand, the HCV clearance had no benefit on already-formed plaques, highlighting the important role of early treatment [6].

Pathogenesis

Chronic HCV infection induces a pro-inflammatory state due to enzymatic over-expression of cyclooxygenase-2, pro-inflammatory cytokines, increased oxidative stress, and immune stimulation, leading to endothelial dysfunction, atherosclerosis and finally, to cardiovascular disease [15]. Nonetheless, HCV infection affects glucose metabolism, increasing insulin resistance, and the prevalence of type 2 diabetes. The mechanism of insulin resistance begins

with the down-regulation of glucose-transporter 2, which is responsible for the transportation of glucose into the hepatocytes and increases the gluconeogenesis enzymes, alongside with degradation of insulin receptor induced by viral core proteins [16, 17]. Endothelial dysfunction represents the first and foremost pathogenic change that leads to cardiovascular diseases, characterized by nitric oxide deficit, platelet and leukocyte adhesion, pro-inflammatory cytokines production, increased permeability for oxidized lipoproteins and plaque formation [18]. Treatment with direct-acting antivirals significantly improved the endothelial function, measured by flow-mediated dilation, in patients with chronic HCV infection, regardless the presence of other cardiovascular risk factors [7].

HCV and cardiovascular events

Chronic HCV infection was demonstrated to be an independent risk factor for coronary artery disease and heart failure, and, interestingly, with lower plasmatic levels of cholesterol and triglycerides than the control group [3]. However, there are discrepancies between trials' results regarding the existence of an association between HCV infection and cardiovascular outcomes. Some of the conflicting results derive from the poor methodology, inappropriate stratification, and the insufficient number of patients. One example is a case-control study that found no association between the presence of serum antibodies, atheromatous plaques, and cardiovascular events, but the study pooled treated and not treated patients, thus influencing the results [19].

A large meta-analysis demonstrated that chronic HCV infection was associated with a higher risk for cardiovascular and cerebrovascular disease, such as coronary artery disease, acute coronary syndromes, and stroke [20]. In another large cohort study, the HCV-infected patients had a higher risk of acute myocardial infarction compared with non-infected patients, with similar high cholesterol levels, and, interestingly, younger patients were more affected than older patients with the same risk profile [4]. Lipid-lowering treatment significantly decreased the risk of acute myocardial infarction in HCV-infected patients as compared to non-infected patients, independently of lipid levels [21]. Prevalence of ischemic stroke was higher in HCV-infected patients than in the control group in an observational study (26.8% vs. 6.6%, P = 0.0001). The mechanism is probably due to chronic inflammation that leads to carotid plaques formation and thus carrying a higher risk of stroke, independently of serum lipids level [5].

Apart from plaque rupture and thrombosis that can cause acute cardiovascular events, vasculitis represents a rare but important etiology, mainly through the presence of cryoglobulinemia, frequently found in HCV-infected patients, determined by cold-precipitating antibodies. The precipitation of circulating immune complexes can involve any organ and tissue [2]. Other cardiovascular pathologies that imply a poor prognostic in this setting are dilated cardiomyopathy and hypertrophic cardiomyopathy. Even if these patients initially could respond to aggressive immunotherapy and glucocorticoid therapy, the mortality is high [22].

HCV and type 2 diabetes mellitus (T2D)

The insulin resistance represents the background of T2D development and also, its prevalence is significantly higher in HCV infected patients compared to non-infected individuals (nearly four times), correlating with the grade of fibrosis and inflammation [20, 23]. In the setting of chronic HCV infection, insulin resistance is associated with endothelial dysfunction, persistent inflammation, and lipid imbalance that lead to atherosclerosis, measured by carotid intima-media thickness [24]. However, T2D represents a significant risk factor for cardiovascular disease, as half of the diabetic patients die from cardiovascular causes [25]. If several meta-analyses already showed that chronic HCV infection significantly increased the risk to develop T2D, the prediction to develop T2D is still under investigation. Hepatic fibrosis, duration of HCV infection, a positive family history of T2D, and the presence of insulin resistance have been identified as predisposing factors [20]. The relationship between chronic HCV infection and T2D is reciprocal. It was observed that the new onset of T2D in patients with chronic HCV infection predicts cirrhosis decompensation [4]. Treatment of T2D is associated with an improvement of the metabolic profile and cardiovascular risk, already expected, but

also with a decrease of liver steatosis and fibrosis [20].

HCV infection and metabolic syndrome

Frequently, HCV-infected patients have decreased lipid levels compared to non-infected patients, probably because of viral alteration of lipoprotein metabolism, which may shunt the production to viral lipoprotein. This effect is reversible as soon as viral clearance takes place [16, 17, 20, 26]. The metabolic syndrome is less frequently identified in HCV-infected patients than expected, even comparable with controls [27]. However, over 50% of HCV-infected patients have liver steatosis but, in contrast to non-infected patients, it is associated with hypolipidemia. The presence of the non-alcoholic fatty liver disease is an additional risk factor for liver fibrosis [28]. Statin therapy was observed to improve the viral clearance in active treatment and to slow the hepatic fibrosis. It could be possible also to reduce the risk of hepatic cirrhosis and hepatic carcinoma, but the modality of action, in this case, is still unknown [20].

Discussions

In this review, we summarized the pleiotropic effects of chronic HCV infection, mainly on the cardiovascular system and the pathogenic mechanisms known, enhancing the importance of treatment and prevention of the devastating effects [2].

Chronic HCV infection is responsible for the metabolic and immunological imbalance due to increased levels of pro-inflammatory cytokines produced as a response to viral activity. The non-structural proteins, such as NS5A, are implicated in this process, creating the perfect milieu for the deleterious effects on the various tissues. Inflammatory cells perpetuate this process, which eventually leads to fibrosis [8, 9]. Another significant effect of the inflammation is the DNA damage, with subsequent mutations and metabolic alterations [9].

The systemic inflammation is an essential contributor to atherosclerotic plaques formation, thus, increasing the risk of cardiovascular diseases [11, 13]. However, the isolation of DNA strands from plaques does not yet demonstrate the direct pathogenic mechanism, but it is essential to note that the HCV could have a significant impact on accelerated atherosclerosis through direct viral activity [14]. The intima-media thickness index is a valuable marker of vascular disease that can be easily measured in clinical practice due to the low cost and the non-invasive nature of the investigation [13].

Several studies demonstrated that the impact on glucose and lipid metabolism is significant, leading eventually to liver steatosis and type 2 diabetes mellitus [4, 16, 20]. Although the chronic HCV infection is associated with lower plasmatic levels of cholesterol and triglycerides, the cardiovascular risk was higher in the infected patients, compared to non-infected patients [16, 17, 20, 26] and the lipid-lowering therapy had proved a significant benefit in preventing myocardial infarction and could even reduce the risk of hepatic cirrhosis and hepatic carcinoma [20].

An ongoing interventional trial on counseling HCV-positive patients for cardiovascular disease risk factors aims to reduce the disease burden by raising awareness, increasing the treatment of cardiovascular comorbidities and improving patients willingness to treat the chronic HCV infection [29]. Treatment of chronic HCV infection can prevent and even reverse the negative effects on the cardiovascular system, with important benefits on disease outcome and economic impact of healthcare systems. This hypothesis is the subject of an ongoing interventional study that focuses on sustained virological response with direct-acting anti-hepatitis C viral drugs. The objective of this study is to evaluate the endothelial dysfunction and to assess the cardiovascular risk, before and after treatment [30].

Conclusions

Chronic HCV infection, in addition to hepatic alterations, has multiple systemic effects, in close relationship with the traditional cardiovascular risk factors. These effects led to the hypothesis that chronic HCV infection may be considered a cardiovascular risk factor. The importance of recognition of its metabolic and immunological effects as a systemic disease (endothelial dysfunction, atherosclerosis, chronic inflammation, oxidative stress, cryoglobulinemia, insulin resistance, hepatic steatosis)

emphasizes the need for early diagnosis and treatment of HCV infection.

Disclosure of conflict of interest

None.

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