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REVIEW

CARDIOVASCULAR RISK IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION

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Abstract. Cardiovascular disease and chronic hepatitis C virus (HCV) infection are major public health problems causing significant morbidity and mortality in millions of people worldwide. There is growing evidence that there is an association between HCV infection, cardiovascular disease and metabolic dysfunction. HCV induces a chronic pro-inflammatory state and promotes atherosclerosis, hepatic steatosis, insulin resistance, and the development of type II diabetes mellitus, thus increasing the cardiovascular risk. It can also have a direct effect on the myocardium causing myocarditis and cardiomyopathy in susceptible individuals.
Keywords: hepatitis C virus, cardiovascular disease, insulin resistance

Background

Cardiovascular diseases cause 30% of all global death with coronary artery disease and stroke being the number one killers. It is estimated that by 2030, cardiovascular diseases will be the leading cause of death worldwide [1]. The increase in life expectancy, and the consequent aging of the population, the sedentary life-style, tobacco use, obesity, and diabetes played a major role in the development of this "epidemic".

Chronic infection with the hepatitis C virus (HCV) is an important cause of chronic liver disease (chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma), and a major public health concern. It is estimated that over 150 million people are infected with HCV worldwide and 350,000 die every year [2].

In Romania, the estimated prevalence of HCV infection is 3.2% [3], higher compared to other European countries [4]. Over 99% of patients are infected with HCV genotype 1 [5].

It appears that people with chronic HCV infection have a higher cardiovascular risk compared to the general population, despite their younger age and the lower prevalence of „traditional" cardiovascular risk factors like hypercholesterolemia or hypertension. A number of hypotheses have been proposed to explain the higher cardiovascular risk in patients with chronic HCV infection observed in some studies. Chronic inflammation caused by persistent viral replication is thought to play a major role in this process, that can eventually lead to accelerated atherosclerosis [6].

Metabolic dysfunction in patients with chronic HCV infection

There are multiple interactions between HCV, glucidic and lipidic metabolism. The virus leads through multiple metabolic pathways to both hepatic and extrahepatic insulin resistance. This dysmetabolic state leads to progressive fibrosis and liver damage, steatosis and reduced response to antiviral therapy. In some susceptible individuals this will progress to diabetes mellitus [7]. Hepatic steatosis is more frequently encountered in patients with HCV infection comparing to general population and may be related to IR [8]. Lately, there are data for a high prevalence of metabolic syndrome in patients infected with HCV irrespective of the presence of diabetes or obesity [9].

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Insulin resistance (IR) is the state in which a given insulin concentration is associated with a suboptimal glycemic response [10]. IR is regarded as a deficient response of insulin secretion, which leads to hyperglycemia, which stimulates in turn the production of more insulin by the pancreatic beta-cells. Estimating IR in current clinical practice can be done using two indices: HOMA (Homeostatic Model Assessment) or QUICKI (Quantitative Insulin Sensitivity Check Index) which can be calculated using the fasting plasma glucose and insulin levels [11].

Molecular pathways leading to IR involved in patients HCV infection are not known, but it is assumed that viral proteins act on the mitochondria and endoplasmic reticulum and promote oxidative stress. This in turn, leads to the expression of cytokines, TNF-α, interleukin 6, interleukin 8, tumour growth factor beta, and Fas ligand. TNF-α inhibits the function of insulin-receptor substrates and decreases the expression of the glucose transporter and of the lipoprotein lipase from the peripheral tissues, which promotes IR [12]. In addition, the decrease in adiponectine, the loss of adiponectine receptors and the lower levels of peroxisome proliferator-activated receptor alpha, with anti-inflammatory activity might contribute to the inflammatory process, the decrease in fatty acid oxidation and possibly to lipotoxicity [12]. The defects in the insulin signalling pathways can also contribute to IR [13]. Insulin resistance is more frequently encountered in people infected with HCV genotypes 1 and 4 as compared to the other genotypes [9,14].

In patients with chronic HCV infection, the prevalence of IR is of 40-70% [15], vs. the general population where the prevalence of IR is much lower (3-16%) [16]. With advancing age, the incidence of newly discovered diabetes in patients with HCV infection increases twofold [17]. It should be said that a study published this year failed to demonstrate a relationship between HCV infection, IR and risk of diabetes, probably because of the high prevalence of other risk factors for diabetes and especially obesity during recent years (2005-2008) in contrast to what happened a decade ago[18].

The patients with chronic HCV infection, IR and diabetes have a more severe liver disease and they are less likely to respond to antiviral therapy [11]. Therefore therapeutic intervention with the scope of decreasing IR before the initiation of antiviral therapy is now being considered.

In patients with genotype 1 infection – the majority of patients in Romania – the estimated IR using the HOMA index was inversely correlated with the rate of sustained virologic response (SVR) [11]. In a study on SVR, the levels of response were 60.5% in patients without IR and 32.8% [19] in the individuals with increased resistance to insulin. Predictors for response to therapy in another study were higher LDL-C levels, lower baseline viral load, and statin use, while patients on insulin therapy, who probably had higher levels of IR, had decreased SVR. Statin use was also associated with a better SVR in all patients irrespective of the presence of diabetes [20].

A study by Mostafa and colleagues that compared three groups of patients with: chronic HCV infection, cleared infection, and individuals without previous HCV infection, suggested that only the favourable lipid profile associated with chronic infection was reversed after viral clearance, while IR and visceral adiposity were similar in HCV-infected patients and those with cleared infection, and higher than in the never-infected group. After adjusting for cardiovascular risk factors, intima-media thickness was found to be increased in chronically infected patients vs. the never-infected group [21].

Over 50% of patients with chronic HCV infection also have hepatic steatosis [22]. The probability that an individual with chronic HCV infection also has steatosis is 2-4 times greater than that of a non-HCV infected individual. Steatosis can accompany the infection with any of the genotypes, but in the case of genotype 3 infection, it is caused by the direct virus-induced cytopathic effect on the hepatocytes which blocks the secretion of lipoproteins during viral replication [12], and is independent from IR (cytopathic steatosis) [11]. For the other genotypes, steatosis is associated with IR and the conventional risk factors for steatosis. This type can be regarded as "metabolic steatosis" [23]. In a recent study, viral load and steatosis were independently associated with carotid atherosclerosis [24].

HCV infection also has an effect on plasma lipids. Total cholesterol (TC) levels, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) are lower in patients with chronic HCV infection than in the general population [25]. The same study suggested that LDL-C is lower in patients with steatosis vs. individuals without steatosis, and patients infected with the 3a genotype had significantly lower levels of TC, LDL-C, and HDL-C, vs. patients infected with other genotypes [25]. These lipid profile features of patients with chronic HCV infection might be caused by a reduction in LDL-C production brought about by chronic inflammation or by the relationship between HCV infection and beta-lipoprotein metabolism [16].

In conclusion, the presence of diabetes, dyslipidemia and metabolic syndrome might be regarded as extrahepatic manifestations of chronic HCV infection contributing to an increased cardiovascular risk in this patients.

Chronic HCV infection and atherosclerosis

The relationship between HCV infection and coronary or carotid atherosclerosis is still subject to debate. Hepatitis C virus infection promotes atherosclerosis via viral load and steatosis leading to an inflammatory and immune-mediated response and a dysmetabolic state [24].

The presence of anti-HCV antibodies is an independent predictor both for the presence of coronary artery disease [26], severe coronary involvement assessed using the modified Reardon severity score [27] carotid artery atheromas, and an increase in the intima-media thickness [28].

In a study conducted by Butt and colleagues which compared 82,083 patients with chronic HCV infection to 89,582 non-infected controls, the risk for coronary artery disease (defined as myocardial infarction, coronary artery by-pass grafting, percutaneous coronary angioplasty or congestive heart failure) was 25% greater in the infected individuals vs. the control group. Nevertheless patients of non-Caucasian race and female sex, had a lower risk for coronary artery disease. The study also showed that hypertension, dyslipidemia, and surprisingly, diabetes were less frequent in the HCV infected population [29]. A more recent study [30] failed to demonstrate increased rates of incident myocardial infarction among 4809 patients with virus C infection comparing to 71688 uninfected patients. The finding is consistent with other studies [31] that found no association between VHC infection and acute myocardial infarction in 582 males compared to matched controls. These results can be partially explained by differences in study population, outcomes and other confounding variables [30].

A more sensitive method than HCV serology in appreciating the risk for carotid artery atherosclerosis is measuring the level of HCV core protein. When compared to routine HCV serologic testing, the core protein is a better marker for active viral replication and identifies the majority of patients with persistent viral infection. In addition to the pro-atherogenic role of the inflammatory response to chronic HCV infection, the virus may also have local effects, at plaque level; the viral genome was identified in atheromatous material from patients with carotid artery revascularization [32].

Ishizaka et al. have shown that the prevalence of carotid artery atheromas is much greater in patients with increased levels of the HCV core protein (64%) vs. seronegative individuals (24%). Thus, seropositivity for the HCV core protein is an independent predictor for carotid artery atherosclerosis (OR 5.61) [33].

The presence of chronic inflammation in patients with persistent HCV infection can be assessed by measuring plasma inflammatory markers, for example C reactive protein (CRP), plasma fibrinogen, tumour necrosis factor alpha (TNF-α), which are increased in these patients [24,27]. In vitro studies have shown that the exposure of macrophages originating from healthy individuals to HCV, increases their production of TNF-α [34]. The monocytes, macrophage precursors, isolated from patients with chronic HCV infection remain activated indefinitely and continuously produce TNF-α [35]. The treatment with pegylated interferon-a plus ribavirin has a persistent favourable effect on three atherosclerosis biomarkers (VCAM-1, ICAM-1 and TNF-α) in patients with coinfection HIV and HCV who attained sustained virological response [36].

A number of studies have shown an association between HCV and cerebrovascular disease. In a community-based prospective cohort study that enrolled 23,665 residents between 1991 and 1992 the authors found that HCV infection is linked to an increased risk of cerebrovascular death. The risk was higher with increasing levels of HCV RNA [37]. The same relationship emerged from another study where the risk of stroke was significantly higher among HCV infected population comparing to noninfected 2.5% and 1.9%, respectively ($p < 0.0001$) [38].

Hepatitis C virus induced myocarditis and cardiomyopathy

The hepatitis C virus can also directly damage cardiac structures causing myocarditis and cardiomyopathy; nevertheless the exact way through which the virus affects the myocardium is yet to be explained [39]. It appears that HCV induced cardiomyopathy occurs only in patients who possess a certain genetic susceptibility. Myocardial damage is thought to be caused by viral replication, local immune response and apoptosis [39]. Viral replication in the myocardium can lead to myocarditis which can in turn progress to cardiomyopathy in genetically susceptible individuals [39].

Matsumori and colleagues showed that the prevalence of anti-HCV antibodies was greater in subjects with myocarditis and heart failure than in the general population, therefore HCV infection may be a cause of myocarditis and heart failure in regions with high HCV prevalence [40]. This may be of importance in patients with HCV infection and non-ischemic cardiomyopathy where prompt antiviral treatment may lead to viral clearance and the recovery of normal cardiac function. At present some of these patients are not regarded as candidates for antiviral therapy because of the adverse effects potentially associated with the treatment [39].

The prevalence of anti-HCV antibodies in patients with hypertrophic cardiomyopathy (HCM)

was 13.8% vs. 2.41% in a control population of Japanese blood donors. Most patients with HCM and HC infection had apical left ventricle hypertrophy. On examining cardiac tissue, an increase in heart muscle mass as well as myocyte disorganisation were observed. In the majority of these patients HCV-RNA was detected in the myocardial tissue obtained from biopsy. The presence of inflammation and myocardial fibrosis in these patients is probably linked to chronic myocarditis. These data suggest that HCV can be a cause of HCM in general, and apical HCM in particular [41]. A recent study showed diastolic dysfunction in HCV infected patients suggesting a subclinical cardiac involvement [42].

Conclusions

HCV infection and cardiovascular diseases are significant public health problems. At present there is a considerable body of evidence suggesting there is a cause and effect relationship between HCV infection and an increased cardiovascular risk. HCV infection is associated with carotid artery atherosclerosis, coronary heart disease, the presence of cardiomyopathy, and more importantly with insulin resistance, type II diabetes mellitus and hepatic steatosis, thus leading to an increased cardiovascular risk and metabolic dysfunction. Even though the increase in cardiovascular risk caused by chronic HCV infection remains to be confirmed with certainty, the possibility of decreasing the mortality and morbidity associated with cardiovascular diseases and diabetes, by treating chronic HCV infection is an appealing approach in the management of patients with increased cardiovascular risk and chronic HCV infection.

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