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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (2): Hepatitis C virus

Hepatitis C virus and metabolic disorder interactions towards liver damage and atherosclerosis

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Abstract

Hepatitis C virus (HCV) is one of the main causes of liver disease worldwide, and alterations of glucose metabolism have reached pandemic proportions in western countries. However, the frequent coexistence between these two conditions is more than simply coincidental, since HCV can induce insulin resistance through several mechanisms. Indeed, the virus interferes with insulin signaling both directly and indirectly, inducing the production of pro-inflammatory cytokines. Furthermore, the entire viral life cycle has strict interconnections with lipid metabolism, and HCV is responsible for a "viral" steatosis which is frequently superimposed to a "metabolic" one. Several evidences suggest that HCV-induced metabolic disorders contribute both to the evolution of liver fibrosis and, likely, to the progression of the other disorders which are typically associated with altered metabolism, in particular atherosclerosis. In the present review, we will examine in depth the links between HCV infection and insulin resistance, liver steatosis and diabetes, and analyze the impact of these interactions on the progression of liver fibrosis and atherosclerosis. Special attention will be focused on the highly debated topic of the relationship between HCV infection and cardiovascular disease. The available clinical literature on this item will be broadly reviewed and all the mechanisms possibly implied will be discussed.

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Key words: Hepatitis C virus; Metabolism; Insulin resistance; Diabetes mellitus; Steatosis; Fibrosis; Atherosclerosis; Cardiovascular risk

Core tip: In this review we will analyze the mechanisms possibly contributing to the relationship between hepatitis C virus (HCV) infection and altered metabolism, as well as the clinical data suggesting that HCV-induced metabolic disorders favour both the progression of liver damage in terms of steatosis/fibrosis and the development of atherosclerosis. Particular attention will be devoted to the highly debated topic concerning the link between HCV infection and cardiovascular disease, a time-related interpretation on the factors impacting cardiovascular risk in the course of HCV infection will be provided, and, finally, the complex virus/host interplay will be graphically synthesized to provide an intuitive picture of the item.

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METABOLIC EFFECTS OF HEPATITIS C VIRUS INFECTION

Hepatitis C virus (HCV) is one of the main causes of

liver disease worldwide[1], with more than 150 million of persons chronically infected, at risk of developing liver cirrhosis and cancer. Moreover, HCV infection is associated with glucose and lipid metabolism disturbances. Alterations of glucose metabolism, *i.e.*, impaired fasting glucose, impaired glucose tolerance and diabetes mellitus (DM), have reached pandemic proportions in western countries[2]. Their keystone is insulin resistance (IR), they are closely linked to obesity and increase the risk of cardiovascular events. Given the prevalence of HCV infection and of these glucose metabolism disturbances, their frequent relationship is not unexpected: however, physiopathologically, it is not only coincidental. In fact, the virus causes IR and predisposes to DM. Several studies analyzed the frequency of DM in HCV-infected patients and confirmed this association. IR and DM are more prevalent in the course of HCV infection than in other liver diseases, independently from the stage of fibrosis[3,4], and HCV infection increases the incidence of DM after liver transplantation[5]; on the other side, the prevalence of HCV infection among diabetic patients is higher than in the age-matched general population[6].

The coexistence of these metabolic derangements affects the progression and prognosis of liver disease and, at the same time, contributes to the systemic burden of HCV infection. Indeed the virus, through interactions with glucose and lipid homeostasis, *via* IR and steatosis, adds other mechanisms of liver damage and participates in the pathogenesis of non-liver-related disorders, such as cardiovascular disease[7].

HCV and insulin resistance

Several epidemiological, experimental and clinical studies showed that chronic hepatitis C (CHC), from the early stages of infection, is associated with alterations of glucose metabolism. Indeed, both in retrospective and in longitudinal studies, the risk of developing IR or DM of HCV-infected patients, even when corrected for confounding factors, is approximately two-fold[8]. The most commonly used surrogate measure of insulin-resistance, *i.e.*, the homeostatic model assessment (HOMA) index, is elevated also in early stages of disease[9], and it is higher than in patients with chronic HBV-infection matched for age, body mass index (BMI) and fibrosis[8]. Indeed, although an association between HBV infection and glucose metabolism disorders has been suggested, possibly secondary to HBV-induced pancreatic islet injury, epidemiological data are still highly controversial[10].

In addition, people with HCV infection are predisposed to develop DM approximately one decade earlier that those without the infection[3]. Many studies demonstrated that eradication of HCV infection with antiviral therapy is associated with a decrease of HOMA-index and of the incidence of glucose metabolism alterations[11-13], although these data have not been universally confirmed[14]. Moreover, the relationship between HCV and IR seems to be dependent on viral load[8] and more pronounced in genotypes (G) 1, 2 and 4[15].

The target tissues of HCV-related metabolic disturbances are the liver, the primary site of infection, and the skeletal muscle. It is very interesting to note that the glucidic function of adipose tissue is not affected, unlike what is commonly described in the course of "pure" IR conditions[16]. Indeed, during euglycemic hyperinsulinemic clamp, patients with CHC without fibrosis and metabolic syndrome show an endogenous glucose output more than three times the normal and an abnormal muscle uptake of glucose, with a normal suppression of lipolysis from adipose tissue[17]. The presence of hepatic IR results in increased fasting glucose, while peripheral IR determines a reduced uptake of glucose[17,18], with the impairment of glucose oxidation. In a mouse model transgenic for HCV core protein, Shintani *et al*[19] showed that during a clamp with tracers infusion, the main site of resistance was the liver, as demonstrated by the capability to stimulate the muscle uptake of glucose but the failure to inhibit the endogenous glucose output. On the contrary, in humans, Milner *et al*[18] demonstrated that IR is principally peripheral, as evidenced by the decreased glucose disposal in the absence of endogenous glucose production (high dose clamp), without differences compared with healthy patients in glucose output at low dose insulin. In addition, Vanni *et al*[17] confirmed the predominant role of muscle in the development of IR, with an approximate 80% of peripheral contribution, demonstrating the higher glucose disposal during the clamp in controls compared to HCV patients. Finally, after liver transplantation, HCV-diabetic patients show an improvement in glucose tolerance but a persistent insulin resistance in peripheral tissues, particularly in the skeletal muscle[20,21]. All together, regardless of the prevalent site of IR, whose analysis is likely influenced by the technique used (duration of clamp and dose of insulin) and the population selected, it is evident that during CHC it develops an exclusive insulin resistant state which is different, but often superimposed, to the host metabolic derangements and that the two conditions influence and enhance each other.

Molecular pathways of insulin resistance in HCV infection

Many different mechanisms are associated with the development of IR during chronic liver disease and, in particular, in HCV-infection[10]. The virus directly interacts at different points of the insulin signalling cascade. In liver tissue from HCV-infected patients, Aytug *et al*[22] firstly reported an inhibition of the ability of insulin receptor substrate (IRS)-1 to associate with insulin receptor, a critical point in the regulation of hepatic gluconeogenesis, mediated by a reduced tyrosine phosphorylation of IRS-1 and a consequent defective downstream phosphorylation of phosphatidylinositol 3-kinase (PI3K) and protein kinase Akt. In addition, the virus may interfere with this pattern also through the up-regulation of the protein phosphatase 2A (PP2A), which dephosphorylates and inhibits Akt[23], although other studies failed to

demonstrate a correlation between intrahepatic levels of PP2A and HOMA-IR. It is also interesting to note that, *in vitro*, HCV leads to over-expression of PP2A by inducing endoplasmic reticulum stress[24]. In experimental models based on the expression of HCV core protein, Kawaguchi *et al*[25] described the involvement of suppressor of cytokine signalling-3 (SOCS-3), which promotes the ubiquitin-mediated IRS-1 degradation; similarly, HCV may activate the proteasome activator 28 gamma (PA28γ) and, in the transgenic mouse, targeted delection of *PA28*γ gene restores insulin sensitivity[26]. The HCV core protein inhibits also the peroxisome proliferator activated receptors (PPARs). In particular, an inhibition of PPAR-α expressed in hepatocytes has been shown[27], while the effect of the virus on PPAR-γ has been observed only in G3 infection, inducing an alteration of adiponectin levels[28,29].

On the other side, HCV may also indirectly trigger IR inducing the production of pro-inflammatory cytokines, which contribute to the metabolic derangements not only in infected tissues but also in uninfected ones, such as the striated muscle. IL-18 and tumor necrosis factor (TNF) are some of the main molecules involved[17,18]. The capability of these proinflammatory cytokines to disturb insulin signalling is well recognized in the context of DM and metabolic syndrome but it is also described during chronic viral disease, irrespective of aetiology[30]. CHC is in fact associated with the up-regulation of T helper 1 lymphocyte cytokines[19,31] and, in HCV-infected patients, a relationship between the increased serum levels of soluble TNF receptors and HOMA-IR has been described[32]. In a transgenic mice model expressing the HCV core protein, IR was reverted by anti TNF-α antibodies[19]. In contrast, in a controlled study comparing non diabetic patients with HCV infection to matched uninfected controls, although serum levels of TNF-α were significantly higher in the HCV cohort, correlating with the extent of histological injury, they were not associated with IR in the multivariate model[33]. The association between IL-18 and hepatic IR seems more specific[17]. Indeed, IL-18 suppresses adiponectin expression in adipocytes and stimulates SOCS3 expression in the adipose tissue of obese mice, providing an indirect mechanism of IR.

A key role in the development of liver injury and metabolic disturbances is played by both hepatic and systemic oxidative stress. In addition to chronic inflammation itself, the virus specifically induces reactive oxygen species (ROS) *via* multiple mechanisms involving the core and other non-structural proteins. The result is the loss of equilibrium between oxidants and antioxidant defenses, which causes oxidative damage to liver cells and interference with the mechanisms of DNA repair, rendering hepatocytes more susceptible to mutagen-induced alterations[34] and favouring fibrogenesis through increased proliferation of hepatic stellate cells[35]. The production of ROS may also be involved in the peroxidation of membrane lipids and structural proteins, such as those involved in lipid trafficking, therefore blocking very low density lipoprotein (VLDL) secretion and leading to steatosis[36].

HCV and steatosis

Steatosis is a typical feature of CHC, with a reported prevalence of 40%-80%[37]. It is so frequent that, in the past, it has been used as a diagnostic tool for the diagnosis of non-A non-B chronic hepatitis[38,39]. Among viral hepatitides, the association between HCV and steatosis seems somehow specific, since, for example, steatosis in HBV infection is as frequent as in the general population and related to metabolic factors[40]. On the contrary, during CHC, steatosis prevalence remains so high also when adjusted for metabolic risk factors (30%-40%)[41]. In fact, although non-alcoholic fatty liver disease (NAFLD) and CHC are both highly prevalent, epidemiological data confirmed that the rate of steatosis in CHC is greater than twice that expected on the basis of a simple random coexistence[42]. A direct viral effect on steatogenesis is relevant, more frequent and severe in G3[43], where a strong association is further supported by two observations: the correlation between steatosis grade and intrahepatic RNA titers and viral core protein expression[44,45]; the reduced or disappeared content of fat in the liver after a successful antiviral treatment[46,47].

The exact mechanisms at the base of HCV-induced steatosis are not definitely explained. HCV core protein is able to increase free fatty acids synthesis[48], favours the intracytoplasmic accumulation of lipids and reduces their mechanisms of export and degradation[48,49]. The entire HCV life cycle is in strict contact with lipid metabolism. HCV entry may be mediated by the low density lipoprotein (LDL) receptor[50]; HCV core protein modifies VLDL secretion[51]; the virus diverts the host lipoprotein assembly and secretion pathways for virion export[52]; virions circulate complexed with lipoproteins in low density lipo-viro particles that facilitate reuptake by hepatocytes by fastening to the LDL receptor[53]. In addition, it has been recently demonstrated that HCV-induced overexpression of seipin, a protein implicated in maturation of lipid droplets whose surface is the seat of the virus start of assembly[54], decreases virion export and induces steatosis, possibly representing a defensive mechanism against viral export. If confirmed, this evidence will lead to consider "viral steatosis" a defensive mechanism. The accumulation of fatty acids in the form of triglycerides may in fact represent a mechanism through which render them not available for replication complexes involving HCV. This hypothesis is supported by the evidence that, when the degree of steatosis correlates with virus replication level, viral replication precedes fat accumulation and not viceversa[46,55,56]. On the contrary, in metabolic patients, whose steatosis precedes viral infection, the level of viral replication is not associated with the severity of fatty liver.

Going back to mechanisms specifically involved in triglyceride accumulation, impaired secretion of lipids

from the infected hepatocytes has been the first historically considered. In fact, patients with CHC have low levels of total cholesterol and triglycerides[57] and phenotypic similarities with familiar hypobetalipoprotinemia[58]. HCV induced hypobetalipoproteinemia is more commonly seen with G3 infection than with G1[59]. Moreover, in patients with G3 infection, but not in those with G1, sustained virological response (SVR) significantly reduced steatosis[46], and the disappearance of steatosis in patients who responded to therapy was parallel to the normalization of cholesterol and apolipoprotein B levels[59,60]. Experimental models in transgenic mouse showed that HCV core protein interfere with VLDL assembly by reducing the activity of microsomal triglyceride transfer protein (MTTP)[61,62], which is a rate-limiting enzyme in lipoprotein metabolism. These data are confirmed by the reduced intrahepatic levels of MTTP mRNA observed in human liver of patients with CHC, especially in those with G3[61]. Another contribute to the blockage of lipoprotein secretion may be offered by oxidative stress. In fact, the HCV core protein may accumulate in mitochondria and induce liver damage through reactive oxygen species production[63], lipid peroxidation of microsomal membranes and impaired VLDL secretion.

HCV induces steatosis also *via ex-novo* synthesis of fatty acids. The virus activates the steroid responsive element binding proteins (SREBP 1c e 2) that control expression of enzymes involved in the fatty acid and cholesterol metabolism[64], inducing de novo lipogenesis. The virus can cause steatosis also by impairing metabolism and degradation of fatty acids. Indeed, HCV has been shown to inhibit transcription of the nuclear factor PPAR-α and this inhibition would reduce transcription of enzymes involved in fatty acid oxidation, such as the carnitine palmitoyltransferase-1 (CPT-1), which is the rate-limiting enzyme of mitochondrial beta oxidation[65,66]. Finally, a great attention has been pointed on the cytokines secreted by adipose tissue. For example, serum adiponectin levels are low in patients with CHC, with the lowest value observed in G3 infection[67], and HCV can induce the overexpression of retinol binding protein (RBP)-4 which is a steatogenic adipokine associated with the development of steatosis not related to insulin resistance[68-70].

All these evidences are very important because they highlight different possible meanings of the word "steatosis" in a patient with CHC. The virus can induce two types of steatosis, *i.e.*, metabolic and viral, with different pathogenetic mechanisms, often overlapped. In addition, virus-induced steatosis may exist together with a fatty liver due to other causes. The degree of steatosis does not always have a direct correlation with the degree of IR. It has been shown that patients with G1 and G4 infection have a level of IR, measured by the HOMA-index, greater than that of patients with G3 infection but with a lower degree of steatosis (greater in G3)[8,9,19,57]. In most patients with non-G3 infection the steatosis score is not correlated with HCV-RNA but with BMI[37], and the steatosis is not or it is only partially modified by antiviral treatment. Therefore, in patients with non-G3 infection, steatosis is regarded as more "metabolic" and less "viral", while in G3 ones, as more "viral" and less "metabolic". At the same time, it is not possible to assign exclusively a type of steatosis to a specific or to a group of genotypes. Indeed, it is clear that also genotypes non-3 may induce some degree of viral steatosis and, at the same time, also G3 may induce metabolic abnormalities. Many mechanisms, such as oxidative stress induced by core protein, may simultaneously induce steatosis ("viral") and impair insulin signalling ("metabolic"). In conclusion, the two types of steatosis can be observed in all genotypes but steatosis phenotype, modulated by metabolic abnormalities (primary metabolic dysfunctions and host factors) and by all microheterogeneities in viral genomic regions, will be more "viral" in G3 and more "metabolic" in others.

Insulin resistance and steatosis: synergism with the virus in the progression of liver disease

The clinical relevance of IR and steatosis in CHC resides in the role played by insulin and fat accumulation in the progression of fibrosis, response to antiviral therapy and occurrence of hepatocarcinoma (HCC). While the annual risk of developing HCC in HCV-related cirrhosis has been estimated to be 3% (2%-6%) per year[71], a recent metanalysis calculated that it is increased 17% by overweight and 90%, almost doubled, by obesity[72]. Moreover, this risk is increased 3-fold by the presence of DM, 37-fold by the co-existence of HCV and DM and up to 100-fold by the association between HCV, DM and obesity[42,72]. Despite most studies described an association between steatosis and the degree of fibrosis, at present, data are not univocal. Most of these studies have a low statistical power and often lack multivariate analysis. Moreover, this association may not be causal as both conditions may simply represent the marker and the consequence of the inflammatory activity[73-75]. In this sense, in particular metabolic steatosis would also be a marker of IR, responsible for both steatosis and increasing fibrosis. In fact, by multivariate analysis, it was IR and not steatosis that correlated with fibrosis, also in G3[76,77]. IR represents a link between steatosis and fibrosis through the capability of insulin, glucose, and leptin, whose receptors are expressed on stellate cells, to induce the production of connective tissue growth factor[78]. Although the exact pathogenetic mechanisms are not clearly understood, available data suggest a role also for oxidative stress, lipid peroxidation and the higher levels of proinflammatory cytokines, which are able to activate stellate cells[79,80].

Concerning antiviral treatment, many studies reported that hepatic steatosis is negatively correlated with SVR rates after peg-interferon and ribavirin treatment[69,81]. This association may be explained through mechanisms that involve IR-induced SOCS, which in

turn are responsible for a reduced activation of signal transducer and activator of transcription (STAT) proteins involved in interferon signalling[82]. On the other side, hepatic IR increases viral replication[83] and produces lipo-viro particles[84]. Since steatosis observed in G3 patients has not been related to decreased likelihoods of SVR[47], it seems that the central and more specific role is played by metabolic steatosis. At the same time, the rationale of reducing IR to increase response to antiviral treatment is not completely supported. A recent randomized clinical trial (TRIC-1) examined the effect of adding metformin to standard therapy in the treatment of CHC. The study demonstrated that patients infected with G1 and with HOMA index > 2, treated with metformin, showed an early greater drop in viral load and doubled SVR in women[85]. On the other hand, the correction of IR with pioglitazone didn't improve response to therapy in two different trials[86,87]. The different genotypes and design of the studies could explain, at least in part, the discrepancies between these results. Further evidence is needed in order to define the optimal therapeutic strategy for improving response to therapy in insulin resistant patients undergoing antiviral treatment.

HCV INFECTION AND ATHEROSCLEROSIS

As previously described, HCV is able to directly induce metabolic and inflammatory alterations and is responsible for the occurrence of IR and DM. In view of this complex interplay between HCV infection, metabolic disorders and "classical" cardiovascular risk factors, several studies aimed to evaluate the possible role of HCV in the development and progression of atherosclerosis and in the incidence of vascular events and vascular mortality (Table 1). To note, several retrospective and cross-sectional studies have clearly demonstrated that different infectious agents, such as chlamydia pneumoniae[88,89], cytomegalovirus[90], herpes simplex virus[91], and hepatitis A virus[92], can participate the process of atherosclerosis[93], suggesting that also HCV may play a role through the potentiation of the inflammatory boost, which is a key event in atherosclerosis.

Clinical evidences of the association between HCV and atherosclerosis

In 2002 and 2003, Ishizaka *et al*[94,95] firstly described the association between the presence of anti-HCV antibodies and/or serum HCV core protein and an increased risk of carotid artery plaques. These findings were corroborated by other studies, which found intima-media thickness (IMT) and the prevalence of carotid plaques to be increased in HCV patients[96-100], and in which HCV genomic and antigenomic RNA strands were identified within carotid plaques tissue of HCV-positive patients (even in three patients positive for anti-HCV antibodies but with undetectable HCV-RNA in serum)[98,101], suggesting a possible direct local pathogenetic role of HCV in atherosclerotic plaque formation. More recently, HCV seropositivity was identified as an independent predictor of increased coronary atherosclerosis[102-104], even though an increased incidence of acute myocardial infarction (AMI) was demonstrated only in HIV/HCV coinfected patients[105,106], but not in HCV mono infected ones[107-110]. Furthermore, the incidences of vascular events and of cardiovascular mortality of HCV-positive patients were reported to be either higher[104,105,111-116] or, at least, comparable to those observed in the general population[117,118].

In contrast with these data, other studies failed to demonstrate any significant difference in IMT and in the prevalence of carotid plaques between HCV-positive and HCV-negative patients[107,119,120], and some others reported an even lower risk of atherosclerosis in HCV patients with respects to controls[121-123]. Three large population studies gave conflicting results concerning the association between HCV-infection and the incidence of stroke[107,113,124] and, recently, Younossi *et al*[125] found HCV infection to be independently associated with IR, hypertension and congestive heart failure, but not with ischemic heart disease and stroke.

Many possible confounding elements should be considered while comparing these different studies and trying to interpret their sometimes divergent results. First of all, the study populations were recruited from different contexts, namely hepatitis or cardiology outpatient clinics, population registries or general health screening programs. Some studies included and some others excluded HIV and HBV coinfected patients. Moreover, not in all of these studies multivariate models were created in order to analyze if the association between HCV-infection and markers of subclinical atherosclerosis or incidences of vascular events/cardiovascular mortality was independent from the other metabolic risk factors. In this regard, it should also be stressed that data on the duration of HCV infection and of DM are not available in any of these works, and that liver histology of HCV patients, which gives the opportunity to correlate vascular outcomes with the histological grading and staging of the hepatic disease, was available from only one study[99]. Finally, another important point to be considered is that cirrhotic patients were frequently excluded or poorly represented in the study populations. Notwithstanding epidemiological data are very limited, cirrhosis is currently considered a condition associated with a decreased risk of cardiovascular events[126]. Indeed, although clearly predisposing to DM, cirrhosis is characterized by an overall favourable risk profile (low blood pressure, low cholesterol, impaired procoagulative cascade and low platelet count).

In conclusion, even if literature on this topic is scant and sometimes ambiguous, current evidence seems to support an association between HCV and atherosclerosis, which can account for the increased prevalence and incidence of vascular disease in patients with HCV infection. As supported by some studies, it seems reason-

Table 1 Overview of the main studies assessing the association between hepatitis C virus infection and the prevalence or incidence of cardio-cerebrovascular disease

Ref.	Study design	Country-setting	Total patients (%HCV$^+$)	Main results
Prevalence of cardio- or cerebrovascular disease				
Ishizaka *et al*[94], 2002	Cross-sectional	Japan-general health screening	4784 (2.1)	HCV$^+$ independently associated with increased IMT [OR = 2.9 (2.3-3.6)] and CP [OR = 1.9 (1.6-2.4)]
Bilora *et al*[121], 2002	Case-control	Italy-hepatitis outpatient clinic	98 (49)	HCV$^+$ have lower prevalence of CP, no significant difference of FP
Ishizaka *et al*[95], 2003	Cross-sectional	Japan-general health screening	1992 (1.3)	HCV$^+$ associated with CP [OR = 5.5 (2.4-12.8)] and IMT [OR = NA] HCV$^+$ independently associated with CP [OR = 5.6 (2.1-15.3)], but not with IMT
Fukui *et al*[96], 2003	Cross-sectional	Japan-ultrasound carotid screening	210 (14.8)	HCV$^+$ have higher prevalence of increased IMT and CP. HCV$^+$ is independently associated with CP [OR = NA]
Volzke *et al*[107], 2004	Cross-sectional	Germany-population registry data	4266 (5.5)	HCV$^+$ or HBV$^+$ not associated with IMT, CP, MI or S
Vassalle *et al*[102], 2004	Case-control	Not specified	686 (5.1)	HCV$^+$ independently associated with CAD [OR = 4.2 (1.4-13)]
Arcari *et al*[108], 2006	Case-control	United States-United States army	582 (8.9)	HCV$^+$ not associated with MI
Targher *et al*[97], 2007	Cross-sectional	United Kingdom-outpatient clinic	120 (50)	HCV$^+$ independently associated with IMT [OR = 1.6 (1.1-2.5)]
Boddi *et al*[98], 2007	Cross-sectional	Italy-cardiovascular risk factor centre	151 (20.5)	HCV$^+$ independently associated with IMT [OR = 4.4 (1.4-13.9)] , but not with CP
Alyan *et al*[103], 2008	Case-control	Turkey-cardiology unit	364 (38.2)	HCV$^+$ independently associated with CAD [OR = 2.0 (1.6-2.6)]
Tien *et al*[119], 2009[5]	Cross-sectional	United States-women's interagency HIV study	503 (10.5)	HCV$^+$ not associated with IMT or CP
Mostafa *et al*[120], 2010	Cross-sectional	Egypt-village metabolic study	494 (37.9)	IMT and CP not different in HCV$^+$; HCV$^+$ independently associated with IMT and CP [OR = 3.5 (1.2-9.9)]
Adinolfi *et al*[100], 2012	Case-control	Italy-liver outpatient clinic and general population screening	803 (40.6)	Increased IMT and CP more prevalent in HCV$^+$; HCV-RNA independently associated with CP [OR = 5.2 (2.6-10.5)]
Petta *et al*[99], 2012	Case-control	Italy-liver and cardiology outpatient unit	348 (50)	Increased IMT and CP more prevalent in HCV$^+$; HCV$^+$ independently associated with IMT [OR = NA]. In HCV patient, older age [OR = 1.04 (1.01-1.08)] and severe fibrosis [OR = 2.18 (1.04-4.54)] are independently associated with CP
Younossi *et al*[125], 2013	Cross-sectional	United States-NHANES database	19741 (0.9)	HCV$^+$ independently associated with CHF [OR = 2.5 (1.1-6)], but not with CHD
Miyajima *et al*[123], 2013	Cross-sectional	Japan-seven country study	1908 (2.1)	IMT significantly reduced in HCV$^+$
Incidence of cardio- or cerebrovascular disease				
Younossi *et al*[116], 1999[6]	Retrospective 24.6 yr FU	United States-transplant centre	54 (22.2)	HCV$^+$ associated with CHD mortality [HR NA], but not with CHD
Haji *et al*[104], 2004[7]	Retrospective 4.2 yr FU	United States-transplant centre	417 (8.2)	HCV$^+$ independently associated with increased mortality [HR 2.8 (1.3-5.7)] and CAD [HR 3.1 (1.5-6.2)]
Amin *et al*[111], 2006[1]	Retrospective	Australia-Australian national death index	117547 (66.7)	HCV$^+$ independently associated with cardiovascular mortality [HR 1.3 (1.2-1.5)]
Neal *et al*[117], 2007	Prospective 6.7 yr FU	United Kingdom-trent hepatitis C cohort	2285[8]	HCV$^+$ not associated with cardiovascular mortality
Bilora *et al*[122], 2008	Case-control prospective 5 yr FU	Italy-not specified	67 (50.7)	HCV$^+$ have lower prevalence of CP, no difference in FP
Caliskan *et al*[133], 2009[2]	Prospective 59 mo FU	Turkey-hemodialysis unit	72 (50)	HCV$^+$ have lower increase of IMT, not significant difference in increase of CP and FP No differences in IMT, FMD and CP in HCV$^+$
Butt *et al*[109], 2009	Prospective 5 yr FU	United States-ERCHIVES database	171665 (47.8)	HCV$^+$ not associated with CHD in univariate analysis, but independently associated with CHD [HR 1.25 (1.2-1.3)], in adjusted models
Lee *et al*[113], 2010	Prospective 16.9 yr FU	Taiwan-general population	23665 (5.5)	HCV$^+$ independently associated with CVD mortality [HR 2.2 (1.5-3.2)]. CVD risk increases with HCV-RNA
Bedimo *et al*[105], 2010[3]	Retrospective 3.9 yr FU	United States-HIV infected United States veterans	19424 (31.6)	HCV$^+$ independently associated with CVD [HR 1.2 (1.1-1.4)], but not MI
Ohsawa *et al*[114], 2011[2]	Prospective 5 yr FU	Japan-KAREN Study	1077 (10.1)	HCV$^+$ independently associated with cardiovascular mortality [HR 1.8 (1.1-3)]

Freiberg *et al*[106], 2011[4]	Retrospective 7.5 yr FU	United States-veterans aging cohort study	8579 (16.8)	HCV^+/HIV^+ independently associated with incident CHD as compared with $HCV^-/HIV+$ or controls. HCV^+ not associated with incident CHD
Kristiansen *et al*[118], 2011	Prospective 7 yr FU	Norway-population registry data	1010[8]	HCV^+ not associated with increased risk of cardiovascular mortality
Forde *et al*[110], 2012	Retrospective 3.9 yr FU	United Kingdom-health improvement network	4809 (6.3)	HCV^+ not associated with incident MI
Lee *et al*[115], 2012	Prospective 16.9 yr FU	Taiwan-general population	1095 (5.6)	HCV^+ associated with vascular mortality [HR 1.5 (1.1-2)]
Hsu *et al*[124], 2013	Retrospective case-control 5 yr FU	Taiwan-Taiwan national health insurance program	3113 (20)	HCV^+ independently associated with S [HR 1.2 (1.1-1.4)]

[1]Carried out in hepatitis C virus (HCV) and/or hepatitis B virus patient; [2]Carried out in patients in hemodialysis; [3]Carried out in human immunodeficiency virus (HIV) mono-infected and HIV/HCV coinfected veterans; [4]Carried out in HIV and/or HCV United States veterans (only males); [5]Carried out in women HIV and/or HCV positive: 220 HCV^+/HIV^+; 53 HCV^+; 950 HIV^+; 452 controls; [6]Carried out in kidney transplant recipients with allografts functioning over 20 years; [7]Carried out in cardiac transplant recipients who received hearths from HCV+ or - donors; [8]Carried out on HCV patients compared to their reference general population. IMT: Intima-media thickness; CP: Carotid plaques; FP: Femoral plaques; FMD: Flow-mediated-dilation; FU: Follow-up; CAD: Coronary artery disease, angiographically documented; MI: Myocardial infarction; S: Stroke; CHD: Coronary hearth disease (myocardial infarction, unstable angina, need for revascularization procedures); CHF: Congestive hearth failure; CVD: Cerebrovascular disease (transient ischemic attack or stroke); NA: Not available.

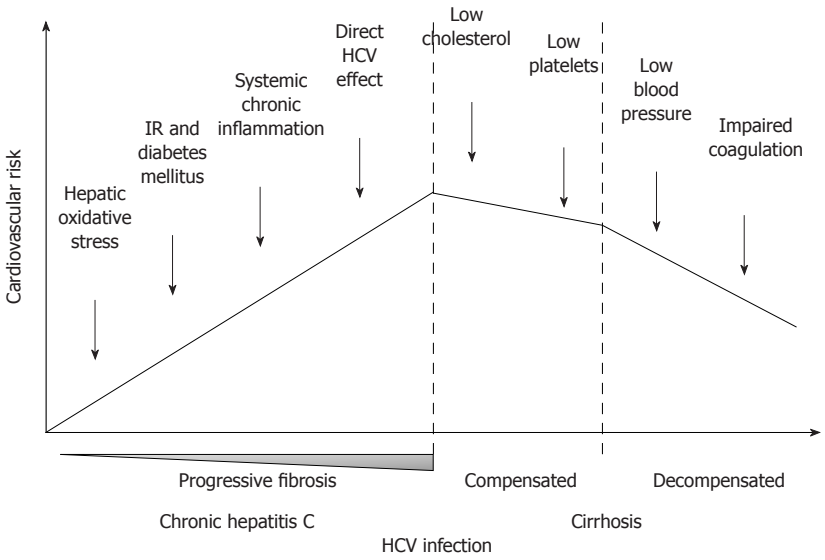

Figure 1 Hypothetical trend of cardiovascular risk during the natural history of hepatitis C virus infection, from chronic hepatitis to decompensated cirrhosis. IR: Insulin resistance; HCV: Hepatitis C virus.

able to speculate that the contribution of HCV to the atherogenic process, either direct or indirect, or both, could increase with the duration of the infection, the development of IR and eventually DM, and the increase of circulating products of oxidative stress and inflammation. On the contrary, once cirrhosis has developed, several mechanisms determining a reduction of the cardiovascular risk progressively come into play (Figure 1).

Hypothetical pathogenic processes "directly" or "indirectly" linking HCV to atherosclerosis

Nowadays, it is widely accepted that infective agents contribute to the progression of chronic immuno-mediated cell inflammation underlying atherosclerosis through the inflammatory response elicited in the host[127]. They can accelerate the occurrence of several key steps in the plaque formation since they can promote endothelial dysfunction, potentiate the recruitment and activation of T-lympho-monocytes and enhance the proliferation and migration of smooth-muscle cells. However, the detection of HCV-RNA in carotid atherosclerotic plaques, predominantly in patients with G2 HCV-infection, strongly suggested also a direct local role of HCV in atherogenesis[98,101]. Consistent with this finding, viral load has been recently associated with carotid atherosclerosis[100], and with the risk of cerebrovascular mortality[113]. This hypothesis is also supported by several experimental studies. For instance, some HCV proteins can enhance local oxidative stress[128], and increase the concentration of soluble intracellular adhesion molecules[129]. HCV particles have affinity with circulating lipoproteins in the blood and HCV G2 seems to be the most closely associated with these lipoproteins[130]. In addition to hepatocytes, HCV can also infect lymphocytes and through these can induce vasculitis and the production of anti-endothelial antibodies[131].

HCV may also "indirectly" favour atherosclerosis, *via* liver damage or virus-induced, metabolic disorders. Ac-

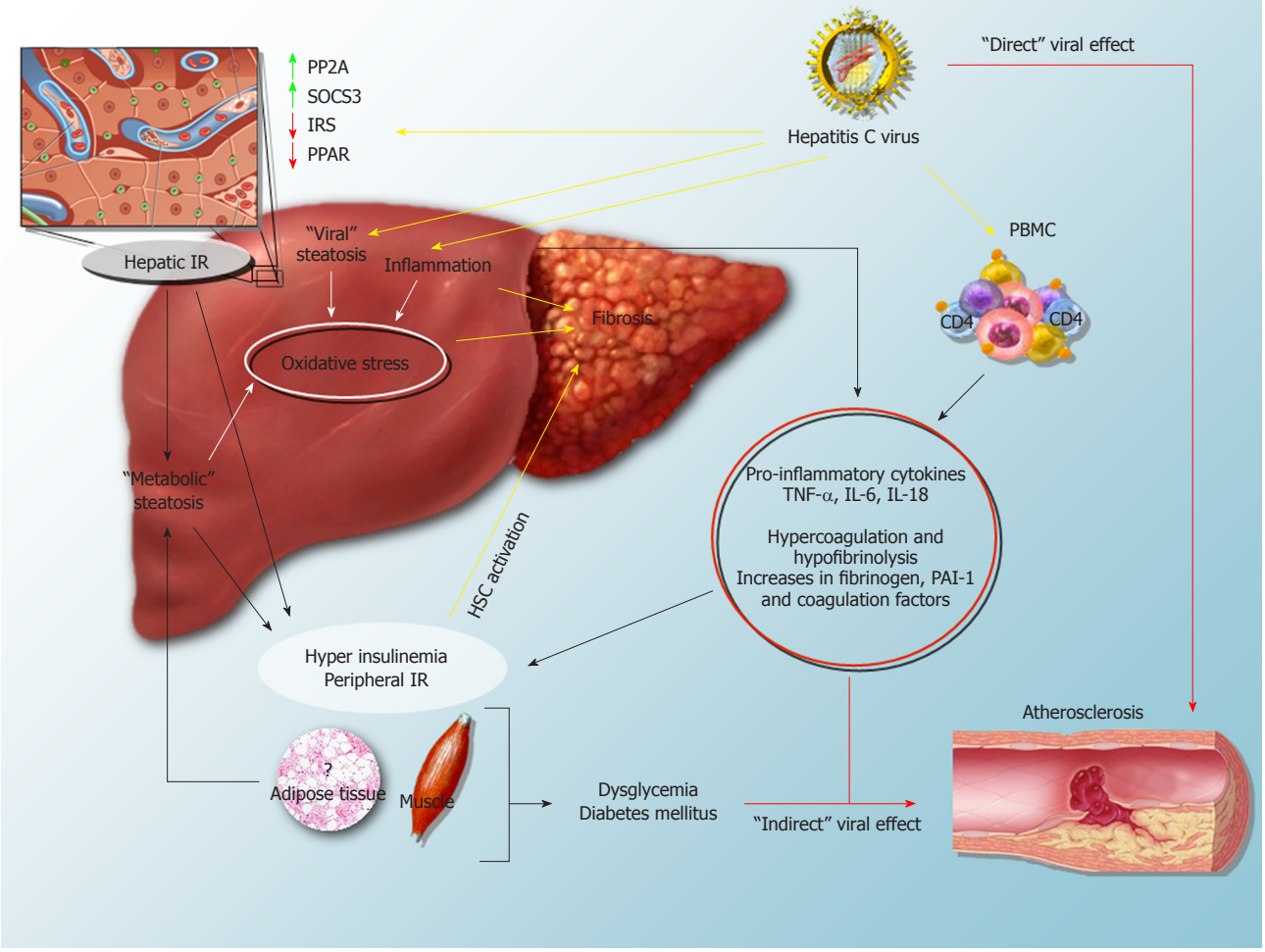

Figure 2 Mechanisms of hepatitis C virus-induced insulin resistance and steatosis and their impact on the progression of fibrosis and cardiovascular disease. In the hepatocyte, the virus interferes with insulin signalling, leads to overexpression of protein phosphatase 2A (PP2A) and suppressor of cytokine signalling-3 (SOCS-3), and down-regulates the expression of peroxisome proliferator activated receptors (PPAR) and of insulin receptor substrate (IRS): all these mechanisms lead to hepatic insulin resistance (IR). By inducing hepatic injury and activating peripheral blood mononuclear cells (PBMC), HCV increases circulating levels of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 and -18 (IL-6 and IL-18), and leads to peripheral IR and hyperinsulinemia. "Viral" and "metabolic" steatosis, together with the direct stimulus of increased insulin levels on hepatic stellate cells (HSCs), likely stimulate the progression of fibrosis. Furthermore, systemic inflammation, the procoagulative state and direct viral effects may contribute to the atherogenic process.

cordingly, in biopsy-proven chronic hepatitis C patients, IMT and prevalence of carotid plaques were recently found to be associated with the severity of fibrosis[99]. It can be speculated that oxidative stress and inflammation, which are associated with the evolution of liver fibrosis, can be associated or directly contribute also to the atherogenic process. After all, the well-known relationship between NAFLD and cardiovascular disease has already demonstrated how liver damage could be directly involved in the pathogenesis of cardiovascular disease, through the systemic release of proatherogenic mediators from the steatotic and inflamed liver or through the worsening of IR and of atherogenic dyslipidemia[132]. However, in contrast with NAFLD, HCV is associated with a favourable lipoprotein profile, namely hypobetalipoproteinemia. The net effect of increased IR and favourable lipoprotein profile on the cardiovascular risk was recently investigated by Mostafa *et al*[120], who found IMT and carotid plaques to be significantly associated with HCV-infection only after adjustment for "classical" cardiovascular risk factors, particularly LDL cholesterol and systolic blood pressure. Accordingly, in a larger prospective study, including HCV infected patient owning better cardiovascular risk profile (lower prevalence of DM and lower cholesterol), HCV-infection was found to be associated with coronary heart disease only after correction for potential metabolic confounders[109]. These results may suggest that HCV affects the cardiovascular risk mainly *via* non-conventional pathways, and not by virus-induced metabolic modifications, *i.e.*, IR and good lipoprotein profile, which possibly balance each other. In agreement with this hypothesis, in studies where HCV was found to be independently associated with vascular disease, the relationship between HCV infection and vascular outcomes was generally adjusted for metabolic risk factors, in contrast to what has been done in the majority of studies failing to demonstrate this association[108,117,118,123,133]. One exception is a big

retrospective population study in which HCV was not associated with AMI even after adjusting for all the metabolic confounders[110].

HCV INFECTION AND METABOLIC DISORDERS: SUMMARY OF A COMPLEX INTERPLAY

All the data provided above suggest a strong interrelationship between HCV infection and metabolic disorders, which is likely implicated in the progression both of liver damage and of the atherogenic process (Figure 2). HCV can directly interact with intracellular mediators of insulin activity, such as PP2A, SOCS3, IRS and PPARs[22-29], or indirectly hamper the insulin message by inducing hepatic and low-grade systemic inflammation[17,18]. Moreover, the virus increases the synthesis of free fatty acids and reduces their mechanisms of export and degradation[48,49], therefore inducing a "viral" steatosis which is often superimposed to a "metabolic" one. Progression of liver damage is favoured by the steatosis-induced hepatic reduction of antioxidant defenses and by a direct stimulatory effect of hyperinsulinemia, oxidative stress and lipid peroxidation on hepatic fibrogenic cells. At the same time, HCV-induced alterations of glucose metabolism and the systemic release of inflammatory and procoagulative mediators by the diseased liver may well contribute to the atherogenic process. Moreover, experimental evidences support a direct role of HCV proteins, which, for example, can enhance oxidative stress and increase the concentration of soluble intracellular adhesion molecules at the atherosclerotic plaque level[128,129].

CONCLUSION

In the present manuscript, an overview of the mechanisms which link HCV infection with insulin resistance and metabolic disorders has been provided, as well as the clinical data confirming that this association may contribute both to the progression of liver damage and to atherosclerosis. All together, a complex scenario emerges where the multiple interactions between the host and the virus determine much more complications than those possibly induced only by the virus itself. Together with cryoglobulinemia, HCV-related arthritis and keratoconjunctivitis sicca, these evidences prompt to consider CHC a systemic disease rather than a simple infection of the liver.

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