British Journal of Medicine & Medical Research
4(36): 5715-5728, 2014
ISSN: 2231-0614

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Hepatitis C Virus Infection and Coronary Arteriosclerosis: The Growing Evidences

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Authors' contributions

This work was carried out in collaboration between all authors. Author RHAM selected the review topic, collected the literature, and wrote the first draft of the manuscript. Author HIE managed the literature searches, co-wrote the first draft. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2014/12747
Editor(s):
(1) Fuhong Su, ICU Laboratory, Erasme Hospital, Free University Brussels, Brussels, Belgium.
Reviewers:
(1) Julieta Trinks, Institute of Basic Sciences and Experimental Medicine, Hospital Italiano de Buenos Aires, Argentina.
(2) Shalini Malhotra, Microbiology Department, Delhi University, India.
Peer review History: http://www.sciencedomain.org/review-history.php?iid=628&id=12&aid=5814

Review Article

Received 16th July 2014
Accepted 7th August 2014
Published 21st August 2014

ABSTRACT

Arteriosclerosis is a chronic inflammatory vascular pathology that features a leading cause of coronary artery disease contributing to significant mortality and reduced quality of life. The recent identification of the possible role of infections in the initiation of a serious of inflammatory events represents an interesting development towards the better understanding of immune mediated vascular injury and premature atherosclerosis in patients with chronic HCV infection. A number of factors related to chronic HCV infection have been hypothesized to contribute to arteriosclerosis. The current review displays some of the aspects of interaction between the chronic viral infection, the immune system and cytokine networks and its relation to the increased risk of coronary artery disease.

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Keywords: Coronary arteriosclerosis; chronic hepatitis C virus infection; pro-inflammatory cytokines; metabolic syndromes; dyslipidemia.

1. INTRODUCTION

The advancing recognition of the potential of viral infections to provoke systemic immune mediated inflammatory responses is increasingly attracting researchers' attention. Amongst these infections the hepatitis C virus stands out with its potential to stimulate a variety of autoimmune inflammatory diseases. Being a well-recognized small RNA member of the family Flaviviridae, the HCV induces both acute and chronic necro-inflammatory liver disease. The virus affects 1.6% of the adult population in the United States and 1% in the United Kingdom (UK). The majority of the population infected up to 80% usually progress to chronic infection with persistent viremia (HCV RNA in the blood) and 20% progressing to hepatic cirrhosis with significant hepatic function compromise. In addition to the established viral hepatotropism HCV is additionally quite capable of inducing a striking cluster of extra-hepatic immune mediated syndromes with protean manifestations owing to its recently recognized viral lymphotropism [1-3]. Amidst such extra-hepatic syndromes, HCV induced immune mediated vascular inflammation has been linked to premature arteriosclerosis in a variety of clinical researches in the recent era with its possible potential to induce premature arteriosclerosis of the coronaries establishing its position in the list of such vascular events.

Coronary artery disease (CAD) is currently considered a global vascular epidemic contributing to significant mortality and reduced quality of life in the affected population. In the U.S.A. CAD is responsible for 1 in every 6 deaths and is estimated to cost over US$177.5 billion per annum. The exact trigger for vessel wall injury in CAD remains unclear [1,4-9].

2. PATHOGENIC BASIS OF THE ATHEROMATOUS PLAQUE FORMATION

The pathogenic basis of arteriosclerosis resides in the potential of the provocative agent whether an antigenic stimulant and/or an oxidative stress to induce activation of the local inflammatory response of the vascular endothelium [7-9]. It has been clearly defined that signs of inflammation go hand in hand with the incipient lipid accumulation in the arterial wall. The inflammatory burden within a plaque is usually reflected by the local burden of activated macrophages. Macrophages potentiate localized inflammatory responses by expressing scavenger receptors for modified lipoproteins, permitting them to ingest lipid and become foam cells. Synergistically the macrophage colony-stimulating factor (M-CSF) contributes to the differentiation of the blood monocyte into macrophage foam cells. These macrophages were found to express more than six structurally different scavenger receptors concerned with uptake of modified forms of low-density lipoproteins (LDLs) that promote the cellular accumulation of cholesterol, fatty streak progression and the development of the atherosclerotic plaque. The scavenger receptor-A (SR-A) was first reported in 1990 and was to give rise to 3 differentially spliced mRNAs that code for type I transmembrane receptors predominantly expressed in macrophages. With advancing research it became apparent that these receptors were part of a larger receptor family nominated as class A SRs and renamed SR-AI, SR-AII, and SR-AIII. The A class of SRs has grown to include 5 members that share common collagen-like domains and a homotrimeric structure: SR-AI, SR-AII, SR-AIII, macrophage receptor with collagenous structure (MARCO), and SR with C-type lectin.

Another scavenger molecule include CD36 a known type III receptor (multiple transmembrane domains) that was originally identified in the late 1980s as glycoprotein IV, a platelet receptor that binds thrombospondin, in 1993 it was shown to act as a macrophage receptor for moderately oxidized LDL. This class of scavenger receptors contains 2 additional members with similar structure: SR-BI and lysosomal integral membrane protein–II. CD36 binds several ligands in common with SR-A (β-amyloid, anionic phospholipids, apoptotic cells, advanced glycation end-products. However, CD 36 is distinct in its ability to bind native lipoproteins (LDL, high-density lipoprotein [HDL], and very low–density lipoprotein [VLDL]), as well as thrombospondin-1, collagen, fatty acids, and pathogen-derived ligands (*P. falciparum* peptides, bacterial lipopeptides). As a result of its broad specificity, CD36 has been reported to contribute to a varied list of normal and pathologic processes such as apoptotic cell clearance, fatty acid transport, adhesion, angiogenesis and atherosclerosis. In addition to its contribution to macrophage activation and lipid deposition CD36 was found to further promote pro-inflammatory signaling that may drive chronic inflammation in the arterial wall.

It is becoming clear that it is actually the disruption and inflammation of vascular endothelium that represents the trigger insult after which lipid-rich fatty streaks start to develop. The triggered active endothelial cells react by a downstream of chemokines (TNF alpha, IL-1, IL-6) and adhesion molecules, such cascade of immune mediators attracts the monocyte/lymphocyte system and by their recruitment macrophages start to accumulate and locally infiltrate into the sub-endothelium. Inflammatory activity within these lesions flourishes as more lipids and more macrophages progressively accumulate, resulting in complex remodeling of the fibro-fatty atheromatous plaques. Such cascade of inflammatory events gets established by the aid of the immune cell responses, particularly the monocyte macrophage as well as the natural killer cell and T cell responses. The presence of a significant T lymphocyte burden around the atheromatous plaque and in the fibrous cap has been another important feature supporting their immune-pathogenic role in atherosclerosis. These T cells likewise were found to encounter signals that cause them to elaborate inflammatory cytokines such as γ-interferon and lymphotoxin (tumor necrosis factor-β [TNF–β] that in turn can stimulate macrophages, vascular endothelial cells as well as SMCs. As this inflammatory process continues, the activated leukocytes and intrinsic arterial cells can release fibrogenic mediators (peptide growth factors) with deposition of dense extracellular matrix promoting more advanced atherosclerotic lesions. The tissue factor produced by the macrophage system is another recognized major pro-coagulant that triggers thrombosis in the atheromatous plaques [7-15].

3. PATHOGENESIS OF ATHEROSCLEROSIS WITH HCV INFECTION IN LIGHT OF THE CURRENT UNDERSTANDINGS

With the initial HCV infection the inflammatory response gets triggered by the viral RNA particles and infection of hepatocytes. The initial assult comes from the innate immune system with its complement cascade, natural killer cells and macrophage phagocytes set into immediate action, producing a series of pro-inflammatory cytokines, orchestrating presentation of antigens to T-and B cells. This is accompanied by activation of the humoral innate immune proteins, which act as Pattern Recognition Receptors (PRRs) namely pentraxins and defense collagens such as lectins and ficolins. Such PRRs function to recognize Pathogen-Associated Molecular Patterns (PAMPs) defined in this case as HCV glycoproteins located either on the virus particles, or on the surface of infected cells. The process of binding of PAMPs to the antigen presenting cells results in activation and

initiation of the inflammatory responses and presentation of viral antigens to T cells. HCV stimulates a sustained T cell response that persists and presents a fluctuating potency throughout the course of the infection.

Activation of T cells by viral proteins results in production of the soluble cytokines IFN-γ, IL-1α, IL-1β and TNF-α, and the IL-6 family of cytokines. Oligoclonal expansion of T cells has been reported within atherosclerotic lesions. Another recently recognized T cell subset, Th17 cells with its specific cytokine signature (Il-17, IL-23) has been linked to the pro-inflammatory responses in HCV patients in association with vascular inflammation.

At the hepatocyte level HCV stimulates local parenchymal production of chemokines by the liver cells, including IFN-gamma-inducible protein (IP-10/CXCL10), IFN-gamma-induced monokine (MIG/CXCL9), IFN-inducible T-cell alpha chemo-attractant (I-TAC/CXCL11), macrophage inflammatory protein (MIP)-1alpha (MIP/CCL3), and MIP-1beta/CCL4, with up regulation of vascular adhesion molecules which has been specifically observed in patients with extra-hepatic disease. These cytokines have been directly involved in vessel injury, endothelial activation, plaque formation and thrombosis where up-regulation of a variety of pro-inflammatory cytokines have been observed in patients with atherosclerosis amongst these cytokines the most recognized are the TGF-beta, TNF superfamily members, IL-1, IL-2, IL-6, IL-12, IL-18, and IFN- γ [2,3,9,16-19].

Activation of NF-k B has been another well recognized signaling pathway associating the HCV induced pro inflammatory drive, where the HC viral proteins tend to associate with the mitochondria and the endoplasmic reticulum provoking oxidative stress that initiate and propagate signals involving the p38 mitogen-activated protein kinase that leads to activation of nuclear factor kappa B. Activated NF-k B induces up-regulation of genes encoding pro-inflammatory cytokines, adhesion molecules, chemokines, growth factors, matrix metalloproteinases MMP-1,-3 and -9and inducible enzymes such as cyclooxygenase-2 (COX2) and inducible nitric oxide synthase (iNOS) which contributes to further activation of the local inflammatory endothelial response and establishment of atheromatous plaque. Additionally, it promotes pro-coagulant state via up-regulation of the expression and local production of tissue factor by the activated macrophages. Evidences from late researches demonstrated activated NF-kB in smooth muscle cells, macrophages and endothelial cells of human atherosclerotic lesions supporting the role of this signaling pathway in vascular injury [17-26].

Still working at the hepatocytes level, the viral induced pro-inflammatory profile particularly IL-6 stimulates the production of acute-phase proteins. These proteins are being sub-classified to Class I and II. Class I proteins include complement components, C-reactive protein (CRP), serum Amyloid A, and α1-acid glycoprotein. These are induced by the action of IL-1α, IL-1β and TNF-α and Class II proteins are induced by IL-6 produced from macrophages and include fibrinogen, haptoglobin, α1-antichmotrypsin and α1-antitrypsin. Elevated values of circulating inflammatory markers such as CRP, serum amyloid A, IL-6, and IL-1 receptor antagonist were found to be a common finding in patients with acute coronary syndrome and such elevations correlated with in-hospital and short-term adverse prognosis, not only a high prevalence of myocardial necrosis, ischemia-reperfusion damage, or severe coronary atherosclerosis but also a primary inflammatory instigator of coronary instability. CRP is a component of the “acute phase response” associated with infection, inflammation, and tissue damage. Over the last decades, evidences has accumulated that systemic inflammatory activity plays a key pathogenic role in atherosclerosis and CVD. Elevated serum CRP level, as detected by the hs-CRP assay, has been shown to be a

stronger predictor of incident cardiovascular events in healthy men than LDL cholesterol and to be additive to the Framingham risk score and was consistently found to be an independent predictor of coronary vascular diseases (CVD). In the most recent comprehensive meta-analysis, high-sensitivity C-reactive protein (hs-CRP) was consistently found to be an independent predictor of cardiovascular disease CVD. Increased hs-CRP has been associated with increased risk for development of hypertension, transient ischemic attack, stroke, peripheral arterial disease, and sudden coronary deaths. B-type natriuretic peptide is a novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. NT-pro-BNP has been demonstrated to be independent risk markers in heart failure patients, and in patients with acute coronary syndrome, and also in non-hospitalized subjects without known cardiovascular disease. One study has showed that, in patients with heart failure from HCV myocarditis, NT-pro-BNP is a more sensitive marker of myocardial injury than cardiac troponins. Another study by Antonelli et al. [19] demonstrated that patients with hepatitis C showed significantly higher plasma NT-proBNP levels than healthy controls. Increased NT-pro-BNP has been proposed as a marker for detecting subclinical LV diastolic dysfunction in HCV-infected patients in some studies. Late studies have also illustrated a statistically significant linear correlation between NT-pro-BNP and hs-CRP in HCV-infected patients [27-34].

Activation of TLRs through PAMPs represents another co-stimulatory pathway that leads to the production of cytokines by macrophages and vascular cells. In vitro studies showed that the peripheral blood mononuclear cells from HCV-infected individuals showed a higher expression level of TLR4 compared with those of healthy individuals. Among all of the viral proteins, only NS5A caused TLR4 induction in hepatocytes and B cells which was found to significantly increase beta interferon (IFN- β) and interleukin-6 (IL-6) secretion from B cells particularly after lipopolysaccharide stimulation. TLR4 appears to be involved in several aspects of the inflammatory response even in the absence of infection, by recognizing endogenous ligands produced during inflammation. Enhanced expression of TLR4 was detected in murine and human carotid and coronary atherosclerotic plaques. Functional TLR4 expression has also been found to correlate with the development of aortic intimal hyperplasia in a mouse model of artery injury. Furthermore, TLR4 may exert LPS-independent atherogenic activities, a hypothesis supported by the facts that oxLDL enhances TLR4 expression in macrophages. Interestingly, the TLR4 and/or its intracellular adaptor protein, MyD88, were found to reduce the risk of atherosclerosis with a concomitant marked reduction in macrophage infiltration and MCP-1 expression in the atherosclerotic lesions as well as the circulating levels of IL-12 and MCP-1 in uninfected apoE-deficient mice [35-40]. The newly announced population of T lymphocytes referred to as regulatory T cells Treg cells CD4+, CD25+ were found to selectively express TLR 4–5-7–8 a response that might be triggered by TGF beta and IL-2 suggesting a possible pathogenic role of these cells in vascular development of inflammatory atheroma [41,42].

The Smad dependent genes pathway represents another interesting pro-atherogenic pathway with HCV infection. HCV has been capable of up-regulating the expression of Smad dependent genes via its induced TGF beta response. Despite that the TGF beta signaling has been found to confer protection against excessive plaqueinflammation, effector leukocyte function, loss of collagen content, and induction of regulatory immunity an action suggested to be related to the TGF beta induction of IL-11. On the other hand, TGF beta single nucleotide polymorphism has been associated by increased atherogenic potential and CAD. In the settings of HCV infection such TGF beta response has been found to trigger the Smad dependent proteins pathway. A family of proteins that appeared to have a good share in regulating the inflammatory response in atherosclerosis as evidenced by results from

immune-histochemical and RT-PCR analysis of human plaques in different studies. Such studies disclosed an over-expression Smad2, Smad3, and Smad4 in macrophages of fibro-fatty lesions and in SMC of fibrous caps raising alerts to their possible pro-fibro-atherogenic potential [43-45].

3.1 Metabolic Associates of HCV Infection and Coronary Artery Disease

The metabolic syndrome (MS) represents a complicated disorder that confers a significant risk for micro- and macro-vascular pathologies. Multiple studies clearly highlighted that anti-HCV positivity was significantly associated with MS, however, the data concerning the cause effect relationship between specific viral genotypes and MS remain controversial. Approximately 6% of HCV patients have steato-hepatitis a metabolic event that interestingly develops accompanied by other metabolic abnormalities including hyper-uricemia, reversible hypo-cholesterolemia, insulin resistance, arterial hypertension and expansion of visceral adipose tissue collectively referred to as “hepatitis C-associated dysmetabolic syndrome” (HCADS) [46-49]. It is probably the viral lipotropism that causes the virus to bind to circulating low density lipoproteins (LDL) using their LDL receptors to stick on the hepatocyte surface. This LDL-R on the hepatocyte surface sequesters cholesterol-containing lipoproteins from the circulation for uptake of cholesterol into the infected cells. Despite its primary affinity to the circulating LDL the receptor has also a high affinity for VLDL particles that contains multiple copies of apoE. Lipoprotein particles complexed to LDL-R are internalized by endocytosis via clathrin-coated pits and then transported to endosomes. HCV entry to hepatocytes is primarily mediated by this clathrin coated pits and patients with HCV infection were found to have an increased risk of developing hepatic steatosis, which shares many clinical features with the metabolic syndrome. Experimental evidences from microarray studies in chimpanzees have indicated that both acute and chronic HCV infection correlates with changes in the expression patterns of genes, which have either a direct role in lipid metabolism or regulate the fatty acid and cholesterol biosynthesis pathways suggesting a link between viremia and lipid metabolism. The possibly involved mechanisms by which the virus can develop such effects on lipid metabolism include: 1- Viral induced hepatic steatosis which has been associated with elevated levels of markers of inflammation and endothelial dysfunction. 2- Chronic infection with hepatitis C virus (HCV) can induce insulin resistance (IR) in a genotype-dependent fashion, thus contributing to steatosis. 3- TNF-alpha produced as a part of the virus induced pro-inflammatory response was found to inhibit the function of insulin receptor substrates and decreases the expression of the glucose transporter and lipoprotein lipase in peripheral tissues, which is responsible for the promotion of insulin resistance with HCV, 4- A fourth hypothesis suggesting that reduced adiponectin levels, loss of adiponectin receptors, and decreased anti-inflammatory peroxisome proliferator-activated receptor alpha in the liver of HCV patients may contribute to reduced fatty acid oxidation, inflammation, and eventually lipotoxicity. However, patients with HCV infection were found to have lower levels of LDL, triglycerides and total cholesterol compared to healthy controls which is not in favor of proposing dyslipidemia as one mechanism involved in viral induced coronary artery disease a rather remote hypothesis [6,16,47-49].

Recently, there is increasing evidence supporting that patients with chronic HCV infection are at increased risk for the development of type 2 diabetes mellitus (DM). HCV proteins can activate TNF-alpha expression and inhibit the function of insulin receptor substrate (IRS) proteins, which contribute to insulin resistance by decreasing glucose transporter (GLUT-4) expression and lipoprotein lipase in peripheral tissues. The induced hyperglycemia can lead to modification of macromolecules with the formation of advance glycation end products (AGE). AGE subsequently binds to their surface receptor RAGE (receptor for AGE) on

vascular endothelial cells, promoting the production of pro-inflammatory cytokines and vascular endothelial growth factor, as well as adhesion molecules contributing to inflammatory vascular injury and microangiopathies with HCV. Additionally important insulin resistance is frequently associated with steatosis, fibrosis progression and lower response to HCV antiviral therapy with PEGylated interferon and ribavirin. Beyond the hyperglycemia, the diabetic state promotes oxidative stress mediated by reactive oxygen species and carbonyl groups. Asignificant elevation in serum levels of Tissue Plasminogen Activator TPA has been observed in patients with Chronic HCV, such circulating TPA was associated with inflammatory marker CRP and the presence of diabetes in patients with chronic HCV which contributed to the establishment of the associated metabolic syndromes with infection but not with markers of liver injury aminotransferases [47-57].

4. DISCUSSION

Arteriosclerosis is being currently recognized as one of the chronic inflammatory disorders that engages both the innate and adaptive arms of the immune response. Both poles of the immune response synergize to initiate and propagate the downstream of the inflammatory events promoting progression of the vascular injury and atherosclerosis with ultimate thrombosis [8,17]. Coronary artery disease has been recognized as one of the most common complications of atherosclerosis. The different mechanisms contributing to coronary atherosclerosis are one of the important standpoints in the future development of cardiovascular medicine. A number of hypotheses have been proposed in this regard in an effort to improve the understanding of the pathogenesis and approach to successful prevention and treatment. The first hypotheses in 1970s, was the monoclonal hypothesis which proposed that a mutation or a viral antigen might represent the trigger to transformation of a single smooth muscle cell into the progenitor of a proliferative clone, introducing the concept that the plaque may be considered a monoclonal benign neoplasm. A more recent hypothesis involves the role of pro-inflammatory cytokines in vessel wall injury and plaque formation with a number of studies supporting a significant correlation between TNF-alpha, IL-6 and the severity of CAD. TNF-alpha and IL-6 were proven in different studies to be significant predictors of the severity of coronary artery disease. This association was likely an indicator of the chronic inflammatory burden and an important marker of increased atherosclerosis risk [2,6,8]. A third non inflammatory hypothesis suggests that a hypoxic insult might be the stimulus for neovascularization of the normally avascular coronary intima. Such neovascularization contributes to increased vascular permeability from the adventitial vasa vasorum which subsequently leads to diffuse coronary intimal thickening. According to this alternative proposal, coronary atherosclerosis is not solely related to inflammation or dyslipidemia and may occur in individuals with normal circulating levels of LDL, a hypothesis that has been found consistent with findings reported in few late researches.

Currently, the most identified consensus defines atherosclerosis to be a systemic disease, initiated by endothelial dysfunction due to inflammation and high levels of LDL, leading to lipid and macrophage deposition in the tunica intima from blood of the coronary lumen, and plaque formation (modified response-to-injury hypothesis) [14,15].

Several studies have suggested that some infectious agents may cause cellular and molecular changes that contribute to the pathogenesis of atherosclerosis. The recent identification of the possible role of viral infections and endotoxin induced acute inflammatory response (pro-inflammatory cytokines and acute phase reactants) in the initiation and maintenance of a series of inflammatory vascular events represents an interesting

development towards the better understanding of immune mediated vascular injury and premature atherosclerosis [15]. The data obtained indicate the identification of viral genomes in the atherosclerotic plaques and also pro-atherogenic effects of viral infection in cells relevant to atherogenesis (smooth muscle cells, monocyte macrophages, T cells, endothelial cells). Experimental models have also shown promotion and acceleration of atherosclerosis by infectious agents. Recent results indicate that infection by several different pathogens (Human immunodeficiency virus, Chlamydia pneumonia and hepatitis B and C viruses) can confer high risk in both early (plaque formation) and advanced atherogenesis (vascular narrowing and thrombotic occlusion).

Despite the increasing epidemiologic evidences emphasizing the pathogenic association between chronic HCV infection and coronary artery disease, there is no definite consensus regarding the pathogenic role. Up to date little data about the possible relation between HCV infection and its associated putative pathogenic processes and atherosclerosis are available. In a recent study by Alyan et al. [16], the researchers aimed to investigate the relevance of sero-positivity to HCV to the risk of coronary artery disease, the study enrolled 139 HCV sero-positive and 225 HCV sero-negative patients with angiographically documented CAD, Reardon severity score for severity of CAD was used in which the coronary circulation into eight proximal segments disease in the distal segments was not considered because of difficulty in quantifying the severity of lesions. The eight proximal segments were: the left main coronary artery; the left anterior descending artery (LAD) up to and including the origin of its second diagonal branch; the proximal third of the major septal branch of the LAD; the proximal third of the major diagonal branch of the LAD; the circumflex (CFX) artery up to and including the origin of its second obtuse marginal branch; the first third of the major obtuse marginal branch of the CFX; the right coronary artery. The percentage by which each lesion in the proximal coronary circulation narrowed the artery was assessed according to the maximal narrowing of the diameter in all projections of the artery. The extent and severity of the proximal coronary disease was assessed by assigning points to each lesion as follows: less than 50% stenosis of the luminal diameter, 1; 50-740% stenosis, 2; 75-99%, 3; and total obstruction 4.The points for each lesion in the proximal coronary circulation were summed and a coronary atherosclerosis score (CAS) obtained [58,59].

With adjustment for potential confounders the investigators found that HCV seropositivity still represented an independent risk and predictor for severity of coronary atherosclerosis as demonstrated by higher Reardon severity score with an odds ratio of 2.018 (95% confidence interval 1.575-2.579, $p<0.001$) which has been associated with a significant increase in the levels of CRP and fibrinogen in seropositive patients compared to the sero-negative control group. In another large cohort study by Butt et al. [6], 82,083 HCV-infected and 89,582 HCV-uninfected subjects were investigated for coronary artery disease and its relation to risk factors for atherosclerosis in the study population. Interestingly, the HCV-infected subjects were less likely to have hypertension, hyperlipidemia, and diabetes but were more likely to abuse alcohol and drugs and to have renal failure and anemia. HCV-infected subjects had lower mean (±:standard deviation) total plasma cholesterol (175±40.8mg/dLvs. 198±41.0mg/dL), low-density lipoprotein cholesterol (102±36.8mg/dLvs.119±38.2mg/dL), and triglyceride (144±119mg/dLvs.179±151mg/dL) levels, compared with HCV-uninfected subjects ($p<.001$ for all comparisons). In multivariable analysis, HCV infection was associated with a higher risk of CAD (hazard ratio, 1.25; 95% confidence interval, 1.20-1.30). Traditional risk factors (age, hypertension, chronic obstructive pulmonary disease, diabetes, and hyperlipidemia) were associated with a higher risk of CAD in both groups, whereas minority race and female sex were associated with a lower risk of CAD. Such conclusions have been confirmed by results from a number of late studies which potentially confirmed

that sero-positivity for HCV had a positive association with carotid artery plaque and carotid intima–media thickening compared to matching controls, independent from other risk factors for atherosclerosis and after adjustment for potential confounders like age, sex, cigarette smoking, obesity, hypertension, dyslipidemias and diabetes mellitus [12]. Furthermore, there was a clear association between CAD and pathogen burden, by serum levels of inflammatory markers and polymorphisms of the interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha genes has been reported in multiple reports [6,12,13]. Different results from late researches are displayed in Table 1.

Table 1. The influence of HCV seropositivity on CVD

Authors	Study design	Samplesize 293 678 patients 98334 HCV seropositive	Findings with HCV positivity
Forde et al. [1]	Retrospective cohort	76477: 4809 HCV+; 71,668 HCV -	No association with myocardial infarction
Alyanet al. [16]	Case-control	364: 139 HCV+; 225 HCV -	Significant association with the severity of coronary atherosclerosis
Arcari et al. [60]	Case-control	582: 292 MI; 290 no MI (52 HCV+)	No association between HCV infection and MI
Younossi et al. [61]	Case-control	19 741: 173 HCV+; 19568 HCV-	HCV was associated with congestive heart failure; but not is chaemic heart disease and stroke.
Demir et al. [62]	Case-control	100: 50 HCV+;50 HCV-	Lower ratio of E/A; higher ratio of E/Em and maximum P-wave duration for HCV+ cases
Freiberg et al. [63]	Retrospective cohort	2425: 738 HIV+HCV+; 1687 HIV+HCV−	Compared to HIV+HCV- veterans, HIV+HCV+ veterans had a significantly higher adjusted risk of CAD
Butt et al. [6]	Retrospective cohort	171,665: 82,083 HCV+; 89,582	HCV infection was associated with a higher risk of CAD
Moritani et al. [64]	Case-control	1806: 31 HCV+; 1775 HCV-	No significant role for HCV on arteriosclerosis
Guiltinan et al. [65]	Retrospective cohort	20518: 10,259 HCV+; 10,259 HCV-	Cardiovascular mortality was significantly higher among the HCV

Considering the potential pathogenic role of HCV particles in promoting a chronic pro-inflammatory state involving the innate cellular and humoral immune responses with provocation of pro-inflammatory mediators and release of acute inflammatory bio-markers, the virus might effectively contribute to coronary vascular injury and ischemia. The fact that the chronic HCV infection was associated with lower levels of plasma lipids, lesser incidence of dyslipidemia, with the virus displaying an independent risk for coronary artery disease regardless of other potential risk factors for atherosclerosis in patients compared to sero-negative controls strongly potentiates the inflammatory hypothesis. For patients with HCV infection with atherosclerosis the currently identified mechanisms involve immune mediated

vascular injury either due to direct colonization of the viral pathogen in the vessel wall or stimulation of the inflammatory cascade contributing to endothelial cells activation and vessel wall infiltration by activated macrophages with vessel wall injury and plaque formation. The sharing of up-regulation of the Th1 pro-inflammatory cytokine network with a defective anti-inflammatory response in patients with coronary atherosclerosis and in patients with chronic HCV infection might be one of the possible tools by which the viral pathogen induces coronary atherosclerosis in patients with chronic HCV viremia. Rising evidences persistently emphasize such hypothesis. Despite a favorable risk profile, HCV infection is associated with a higher risk of CAD after adjustment for traditional risk factors, furthermore an increase in all- cause mortality has been observed in HCV patients with components of the metabolic syndrome [16,12,13,29].

5. CONCLUSION

The inflammatory state associated with HCV infection might contribute to an increased cardiovascular disease risk. HCV infection has been associated with metabolic complications including diabetes mellitus, the metabolic syndrome, and hepatic steatosis, all of which are important risk factors for the development of cardiovascular and peripheral vascular disease. The relationship between HCV and coronary artery disease is still lacking a lot of evidence based explanations and features one of the unmet needs requesting to be potentially addressed in future studies particularly in the era of novel therapies in patients with HCV and extrahepatic disease. The contribution of cryoglobulinemia, adhesion molecules, pro-coagulants and anti-phospholipid antibodies to the development of coronary artery disease in HCV patients remain poorly understood. A better understanding of the underlying pathogenesis might open the way for new interventional strategies in coronary artery disease with HCV infection.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Forde KA, Haynes K, Troxel AB, Trooskin S, Osterman MT, Kimmel SE, Lewis JD, Lo Re V 3rd. Risk of Myocardial Infarction Associated with Chronic Hepatitis C Virus Infection: A Population-Based Cohort Study. J Viral Hepat. 2012;19(4):271-7.
2. Alain Tedgui and Ziad Mallat. Cytokines in atherosclerosis: Pathogenic and regulatory pathways. Physiol Rev. 2006;86:515–581.
3. Mohammed RH, El Makhzangy HI. Chapter 16: Hepatitis C related Vasculitides. In Textbook: Advances in the etiology, pathogenesis and pathology of vasculitis. 2011;978-9-53307-334-7.

4. Shah PK. Link between infection and atherosclerosis: Who are the culprits: viruses, bacteria, both, or neither? Circulation. 2001;103:5–6.
5. Kiechl S, Egger G, Mayr M, et al. Chronic infections and the risk of carotid atherosclerosis: Prospective results from a large population study. Circulation. 2001;103:1064–70.
6. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. CID. 2009;49.
7. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med. 1999;340:115–126.
8. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: From pathophysiology to practice. Journal of the American College of Cardiology. 2009;54(23):2129–2138.
9. Libby P, Paul M. Ridker, Attilio Maseri. Inflammation and atherosclerosis. Circulation. 2002;105:1135-1143.
10. Jonasson L, Holm J, Skalli O, Bondjers G, Hansson G. Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. Atherosclerosis. 1986;6:131–138.
11. Hartvigsen K, Chou MY, Hansen MF, et al. The role of innate immunity in atherogenesis. J Lipid Res. 2009;50:388–393.
12. Vassalle C, Masini S, Bianchi F, Zucchelli GC. Evidence for association between hepatitis C virus seropositivity and coronary artery disease. Heart. 2004;90(5):565–566.
13. Ishizaka N, Ishizaka Y, Takahashi E, et al. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. Lancet. 2002;359:133–5.
14. Subbotin VM. Neovascularization of coronary tunica intima (DIT) is the cause of coronary atherosclerosis. Lipoproteins invade coronary intima via neovascularization from adventitial vasa vasorum, but not from the arterial lumen: a hypothesis. Theor Biol Med Model. 2012;9:11.
15. Khan BZ, Akhtar B, Bhatti T, Khawaja A. Hepatitis-C virus infection, enhancing silent epedemic of coronary artery disease. Pakistan Heart Journal. 2007;40(1-2):24-28.
16. Alyan O, Kacmaz F, Ozdemir O, Deveci B, Astan R, Celebi AS, Ilkay E. Hepatitis C infection is associated with increased coronary artery atherosclerosis defined by modified Reardon severity score system. Circ J. 2008;72(12):1960-5.
17. Packard RS, Andrew MD, Lichtman H, Libby P. Innate and Adaptive Immunity in Atherosclerosis. SeminImmunopathol. 2009;31(1):5.
18. Weyand CM, Younge BR, Goronzy JJ. T cells in arteritis and atherosclerosis. Curr Opin Lipidol. 2008;469–477.
19. Saadoun D, Bieche I, Maisonobe T, et al. Involvement of chemokines and type 1cytokines in the pathogenesis of hepatitis C virus-associated mixed cryoglobulinemia vasculitis neuropathy. Arthritis Rheum. 2005; 52:2917–25.
20. Saadoun D, Boyer O, Trebeden-Negre H, et al. Predominance of type 1 (Th1) cytokine production in the liver of patients with HCV-associated mixed cryoglobulinemia vasculitis. J Hepatol. 2004;41:1031-7.
21. Napoli J, Bishop GA, McCaughan GW. Increased intrahepatic messenger RNA expression of interleukins 2, 6 and 8 in hepatic cirrhosis. Gastroenterology. 1994;107(3):789-98.
22. Kaplanski G, Maisonobe T, Marin V, et al. Vascular cell adhesion molecule-1 (VCAM-1) plays a central role in the pathogenesis of severe forms of vasculitis due to hepatitis C-associated mixed cryoglobulinemia. J Hepatol. 2005;42:334-340.

23. Boyle JJ, Weissberg PL, and Bennett MR. Tumor necrosis factor-alpha promotes macrophage-induced vascular smooth muscle cell apoptosis by direct and autocrine mechanisms. Arterioscler Thromb Vasc Biol. 2003;23:1553–1558.
24. Parks WC, Wilson CL, and Lopez-Boado YS. Matrix metalloproteinases as modulators of inflammation and innate immunity. Nat Rev Immunol. 2004;4:617–629.
25. Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kappa B by Toll-like receptor 3. Nature. 2001;413:732–738.
26. Monaco C, Andreakos E, Kiriakidis S, Mauri C, Bicknell C, Foxwell B, Cheshire N, Paleolog E, Feldmann M. Canonical pathway of nuclear factor kappa B activation selectively regulates proinflammatory and prothrombotic responses in human atherosclerosis. Proc Natl Acad Sci U S A. 2004;101:5634–9.
27. Kaptoge S. et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: An individual participant meta-analysis. Lancet. vol. 2010;375(9709):132–140.
28. Wenliang Che, Buchun Zhang, Wenling Liu, YidongWei, Yawei Xu, Dayi Hu. Association between high-sensitivity C-reactive protein and N-terminal Pro-B-type natriuretic peptide in patients with hepatitis C virus infection. Mediators of Inflammation. 2012;1-6.
29. Danesh J, Wheeler JG, Hirschfield JM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350:1387–1397.
30. Bassan R, Potsch A, Maisel A, et al. B-type natriuretic peptide: a novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. European Heart Journal. 2005;26(3):234–240.
31. Sabatine MS, Morrow DA, De Lemos JA, et al. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. Journal of the American College of Cardiology. 2004;44(10):1988–1995.
32. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. New England Journal of Medicine. 2004;350(7):655–663.
33. Antonelli A, Ferri C, Ferrari SM, et al. High levels of circulating N-terminal pro-brain natriuretic peptide in patients with hepatitis C. Journal of Viral Hepatitis. 2010;17(12):851–853.
34. Matsumori A, Shimada T, Chapman NM, Tracy SJ, Mason JW. Myocarditis and heart failure associated with hepatitis C virus infection. Journal of Cardiac Failure. 2006;12(4):293–298.
35. Machida K, Cheng KTH, Sung VML, Levine AM, Foung S, Lai MC. Hepatitis C virus induces toll-like receptor 4 expression, leading to enhanced production of beta interferon and interleukin-6. Journal of Virology. 2006;866–874.
36. Howell J, Angus P, Gow P, Visvanathan K. Toll-like receptors in hepatitis C infection: Implications for pathogenesis and treatment. Journal of Gastroenterology and Hepatology. 2013;28:766–776.
37. Xu XH, Shah PK, Faure E, Equils O, Thomas L, Fishbein MC, Luthringer D, Xu XP, Rajavashisth TB, Yano J, Kaul S, Arditi M. Toll-like receptor-4 is expressed by macrophages in murine and human lipid-rich atherosclerotic plaques and up regulated by oxidized LDL. Circulation. 2001;104:3103–8.
38. Akira S, Takeda K, Kaisho T. Toll-like receptors: Critical proteins linking innate and acquired immunity. Nat. Immunol. 2001;2:675–680.
39. Burzyn D, Rassa JC, Kim D, Nepomnaschy I, Ross SR, Piazzon I. Toll-like receptor 4-dependent activation of dendritic cells by a retrovirus. J. Virol. 2004;78:576–584.

40. Morris DR, Moxon JV, Biros E, Krishna SM, Golledge J. Meta-analysis of the association between transforming growth factor-beta polymorphisms and complications of coronary heart disease. PLoS One. 2012;7(5):e37878.
41. Sakaguchi S. Regulatory T cells: key controllers of immunologic self-tolerance. Cell. 2000;101:455-8.
42. Malek TR. The main function of IL-2 is to promote the development of T regulatory cells. J Leukoc Biol. 2003;74:961–965.
43. Massague J, Wotton D. Transcriptional control by the TGFbeta/ Smad signaling system. EMBO J. 2000;19:1745–1754.
44. Amandine Verga-Gérard, Marine Porcherot, Laurène Meyniel-Schicklin, Patrice André, Vincent Lotteau, Laure Perrin-Cocon. Hepatitis C virus/human interactome identifies SMURF2 and the viral protease as critical elements for the control of TGF-β signaling. Published online before print June 18; 2013. doi: 10.1096/fj.
45. Lebastchi AH, Qin L, Khan SF, Zhou J, Geirsson A, Kim RW, Li W, Tellides G. Activation of human vascular cells decreases their expression of transforming growth factor-beta. Atherosclerosis. 2011;219(2):417–424.
46. Lonardo A, Adenolfi LE, Restivo L, Ballestri S, Romagnoli D, et al. Pathogenesis and significance of hepatitis C virus steatosis: An update on survival strategy of a successful pathogen. World J of Gastroenterol. 2014;20(23):7089-7103.
47. Rafiq N, Stepanova M, Lam B, Younossi Z. Type 2 diabetes (DM), obesity and hypertension (HTN) are associated with mortality in hepatitis C (HCV) patients. 44th Annual Meeting of the European Association for the Study of the Liver (EASL 2009) April 22-26, 2009, Copenhagen, Denmark.
48. Huang JF, Chuang WL, Yu ML, Yu SH, Huang CF, Huang CI, Yeh ML, et al. Hepatitis C virus infection and metabolic syndrome-a community-based study in an endemic area of Taiwan. Kaohsiung J Med Sci. 2009;25(6):299-305.
49. Sheikh MY, Choi J, Qadri I, Friedman JE, Sanyal AJ. Hepatitis C virus infection: molecular pathways to metabolic syndrome. Hepatology. 2008;47(6):2127-33.
50. Shimizu Y, Hishiki T, Ujino S, Sugiyama K, Funami K, Shimotohno K. Lipoprotein component associated with hepatitis C virus is essential for virus infectivity. Curr Opin Virol. 2011;1(1):19-26.
51. Huang H, Sun F, Owen DM, Li W, Chen Y, Gale M, Jr, Ye J. Hepatitis C virus production by human hepatocytes dependent on assembly and secretion of very low-density lipoproteins. Proc Natl Acad Sci USA. 2007;104:5848–5853.
52. Andre P, Komurian-Pradel F, Deforges S, Perret M, Berland JL, Sodoyer M, Pol S, Brechot C, Paranhos-Baccala G, Lotteau V. Characterization of low-and very-low-density hepatitis C virus RNA-containing particles. J Virol. 2002;76:6919–6928.
53. Bartosch B, Dubuisson J. Recent advances in hepatitis C virus cell entry. Viruses. 2010; 2:692–709.
54. Gulam H Syed, Yutaka Amako, Aleem Siddiqui. Hepatitis C Virus hijacks host lipid metabolism. Trends Endocrinol Metab. 2010;21(1):33.
55. Targett-Adams P, Boulant S, Douglas MW, McLauchlan J. Lipid metabolism and HCV infection. Viruses. 2010;2(5):1195–1217.
56. Su TC, Lee YT, Cheng TJ, Chien HP, Wang JD. Chronic hepatitis B virus infection and dyslipidemia. J Formos Med Assoc. 2004;103(4):286-91.
57. Olanta Zuwała-Jagiello, Monika Pazgan-Simon, Krzysztof Simon, Maria Warwas. Picolinic acid in patients with chronic hepatitis C infection: A preliminary report. Mediators of Inflammation. Online. 2012;1-10. Article ID 762863.
58. Jenkins PJ, Harper RW, Nestel PJ. Severity of coronary atherosclerosis related to lipoprotein concentration. Br Med J. 1978;2:388-91.

59. Reardon MF, Nestel PJ, Craig IH, Harper RW. Lipoprotein predictors of the severity of coronary artery disease in men and women. Circulation. 1985;71:881-8.
60. Arcari CM, Nelson KE, Netski DM, Nieto FJ, Gaydos CA. No association between hepatitis C vi-russeropositivity and acute myocardial infarction. Clin Infect Dis. 2006;43(6):e53-6.
61. Younossi ZM, Stepanova M, Nader F, Younossi Z, Elsheikh E. Associations of chronic hepatitis C with metabolic and cardiac outcomes. Aliment Pharmacol Ther. 2013;37(6):647-52. doi: 10.1111/apt.12234.
62. Demir M, Demir C. Effect of hepatitis C virus infection on the left ventricular systolic and diastolic functions. South Med J. 2011;104(8):543-6. doi: 10.1097/SMJ.0b013e31822462e2.
63. Freiberg MS, Chang CC, Skanderson M, McGinnis K, Kuller LH, Kraemer KL, Rimland D, Goetz MB, Butt AA, Rodriguez Barradas MC, Gibert C, Leaf D, Brown ST, Samet J, Kazis L, Bryant K, Justice AC. Veterans aging cohort study. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. Circ Cardiovasc Qual Outcomes. 2011;4(4):425-32. doi: 10.1161/CIRCOUTCOMES.110.957415.
64. Moritani M, Adachi K, Arima N, Takashima T, Miyaoka Y, Niigaki M, Furuta K, Sato S, Kinoshita Y. A study of arteriosclerosis in healthy subjects with HBV and HCV infection. J Gastroenterol. 2005;40(11):1049-53.
65. Guiltinan AM, Kaidarova Z, Custer B, Orland J, Strollo A, Cyrus S, Busch MP, Murphy EL. Increased all-cause, liver, and cardiac mortality among hepatitis C virus-seropositive blood donors. Am J Epidemiol. 2008;167(6):743-50. doi: 10.1093/aje/kwm370.

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