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Infection Diseases Section *Review Article*

How Hepatitis C Virus Infection Contributes to Cardiovascular Disease: A Systematic Review

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Abstract

Hepatitis C virus (HCV) infection is a very common infection throughout the world with an estimated 200 million people infected in the world; so determination and prevention of morbidities associated with this infection is of utmost importance. 364,712 individuals who underwent investigation for potential associations between HCV infection and cardiovascular disorders in 31 studies have been reviewed in this systematic review. Only 6 out of 31 reviewed studies involving a cumulative population of 81,035 (22.2%) subjects reported a negative association between HCV infection and cardiovascular disorders. There were 2 prospective studies, both in favor of such a relation. Our data suggests that HCV has a significant effect on the development of cardiovascular diseases in the general population, either in the coronary or carotid artery. We suggest prospective cohort studies with more controlled conditions.

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Introduction

Hepatitis C virus (HCV) infection is a very prevalent chronic infection throughout the world with an estimated infection rate of about 200 million people in the world [1]. There are several transmission routes proposed by different authors for this infection including blood transfusion, injection drug use, and other parenteral exposures, but with little evidence for sexual transmission [2]. At least 75 percent of HCV infections become chronic as indicated by persistent detection of HCV RNA [3]; and this high rate of chronicity has several long-term consequences including liver failure, malignancies and extra hepatic manifestations.

Chronic infections may induce chronic inflammatory process in the human body that consequently induces atherosclerosis. HCV infection has been associated with several extra hepatic manifestations from skin and kidney to heart and brain [4]; however, cardiovascular disorders might be considered the most important of all, due to its potential ominous consequences [5]. There are several studies that have proposed HCV infection as a significant risk factor for the development of cardiovascular disorders and increased non-liver related mortality of cardiovascular events [6]. On the other hand, HCV cases may be at increased risk for cardiovascular diseases including smoking and poor nutritional statusIn this review of the literature, we tried to find the most significant studies in order to review the existing evidence in favor or against the notion that HCV infection can result in significant damage to the heart and vascular system. To

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have a better view, the article has been divided to some subheadings to more especially investigate the major vascular regions that might be affected by chronic HCV infection.

Methods

Figure 1 summarizes search strategy. To conduct our systematic review, the primary search was

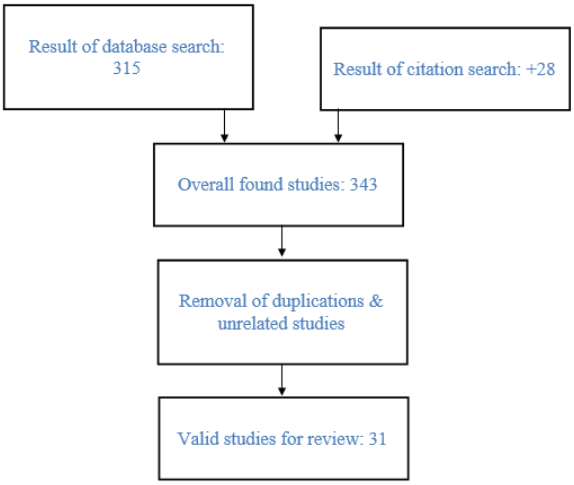

Figure 1. Searsch strategy

done using the terms "HCV" and “cardiovascular disease” as the keywords within the time-span of 1990-2013. Repeat of the search using “coronary artery disease” or “carotid artery disease” instead of “cardiovascular disease” were used to expand the search protocol. The literature search was performed using the Pubmed database, which we believe provides relatively the largest published data of the most relevant studies in the fields of microbiology and cardiovascular diseases. We also tried to boost our search searching the citations of the found articles found in Google Scholar search to find potential reports which have not been indexed in Pubmed or have not been retrieved through Pubmed search.

In our search, overall, 315 studies were found upon a search of the literature by Pubmed using the mentioned keywords and 28 more added after the search repeats. Then abstracts of the found studies were screened to find appropriate reports associated with our systematic review. A majority of the studies, despite the keywords used to finding them were not associated with our review, and we had to only include studies that satisfied our study purpose. Finally, 31 studies have been remained, and reviewed according to the following categorization of the research: HCV infection and coronary artery disease, HCV and other heart diseases, HCV infection and carotid artery disease, HCV and aortic artery disease, and HCV and cardiovascular diseases in hemodialysis patient.

HCV infection and coronary artery disease

Coronary artery disease (CAD) is one of the major causes of mortality in all human populations especially in the industrialized countries; and therefore detection of its risk factors and preventing populations from them seem to be the most fundamental endeavors that should be considered to attenuate health burden imposed by CAD. There are several studies investigating potential correlation between HCV infection and coronary artery diseases. In a recent study from the UK, Forde *et al.* [7] conducted a retrospective cohort study in The Health Improvement Network, from 1996 through 2008, including patients with at least 18 years of age and 6 months of follow-up. 4809 HCV-infected individuals were compared to 71,668 age and sex matched patients without HCV. During a median follow-up of 3.2 years, HCV infection was not associated with an increased risk of incident myocardial infarction (MI) (adjusted HR, 1.10; 95% confidence interval [CI], 0.67-1.83) [7]. In an interesting case-control study on 139 HCV seropositive and 225 HCV seronegative patients with angiographically documented CAD, Alyan *et al.* [8] found that HCV seropositivity represented an independent predictor for severity of coronary atherosclerosis demonstrated by higher Reardon severity score [OR 2.01; 95% CI 1.57-2.58]. A case-control study on US army personnel including 292 myocardial infarction (MI) patients and 290 control individuals, with no history of myocardial infarction (noMI) revealed no association

between HCV seropositivity and acute myocardial infarction [adjusted relative risk, 0.94; 95% CI, 0.52–1.68) [9]. In a large survey conducted based on data retrieved from the National Health and Nutrition Examination Surveys (NHANES) collected between 1999 and 2010 were used to determine the impact of HCV infection on cardiovascular disease [10]. Of 19 741 participants, 173 (0.88%) were positive for HCV RNA (HCV+). In multivariate analysis, HCV was independently associated with congestive heart failure but not with ischemic heart disease and stroke [10]. A case control study involving 50 anti-HCV antibody positive cases and 50 negative controls and performed transthorasic echocardiography on all participants [11]. They found that cases had lower ratio of E/A; but higher ratio of E/Em and maximum P-wave duration [11]. In a study on 8579 veterans, during the median 7.3 years of follow-up, there were 194 coronary heart disease (CHD) events and 1186 deaths. Compared with HIV+HCV- Veterans, HIV+HCV+ Veterans had a significantly higher adjusted risk of CHD regardless of whether death was treated as a censored event [adjusted HR, 1.93; 95% CI, 1.02 to 3.62] or a competing risk [adjusted HR, 1.46; 95% CI, 1.03 to 2.07] [12]. Another large cohort study on 82,083
HCV-infected and 89,582 HCV-uninfected veterans showed that, in multivariable analysis, HCV infection was associated with a higher risk of CHD (HR, 1.25; 95% CI, 1.20-1.30] [13]. A case-control study on 1806 healthy individuals, 31 of which HCV infected showed that HCV infection has no significant effect on the development of arteriosclerosis [14]. A retrospective cohort study of 10,259 HCV antibody-positive allogeneic blood donors from 1991 to 2002 and 10,259 HCV antibody-negative donors matched for demographic data showed that cardiovascular mortality was significantly higher among the HCV seropositive donors (HR, 2.21, 95% CI, 1.41, 3.46) [15].
Table 1 summarizes data of studies reviewed in this section.

HCV and other heart diseases

In a case-control study by El-Waseef *et al.* [16] performed echocardiography of left ventricular function in 80 multitransfused children aged 3 to 15 years with no clinical evidence of heart failure, and compared the results between HCV positive and negative individuals [16].

Table 1. Effects of HCV infection on coronary artery disease

Author	Study methodology	Sample size	Findings regarding HCV positivity
Forde et al. [7]	Retrospective cohort	76477: 4809 HCV+; 71,668 HCV -	No association with myocardial infarction
Alyan *et al. [8]*	Case-control	364: 139 HCV+; 225 HCV -	Significant association with the severity of coronary atherosclerosis
Arcari et al. [9]	Case-control	582: 292 MI; 290 noMI (52 HCV+)	No association between HCV infection and MI
Younossi et al. [10]	Case-control	19 741: 173 HCV+; 19568 HCV-	HCV was associated with congestive heart failure; but not ischaemic heart disease and stroke.
Demir et al. [11]	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. [12]	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. [13]	Retrospective cohort	171,665: 82,083 HCV+; 89,582	HCV infection was associated with a higher risk of CAD
Moritani et al. [14]	Case-control	1806: 31 HCV+; 1775 HCV-	No significant role for HCV on arterosclerosis
Guiltinan et al. [15]	Retrospective cohort	20518: 10,259 HCV+; 10,259 HCV-	Cardiovascular mortality was significantly higher among the HCV
Total		293 678: 98334 HCV+	

They found that HCV positive children represented a significantly higher rate of systolic dysfunction, but diastolic dysfunction was equally observed between the two groups [16]. In a cohort of patients with stable CAD, Tsui *et al.* [17] examined the association between HCV seropositivity and risk for the following outcomes: death, cardiovascular (CV) events, and heart failure events. 8.6% participants were found to be seropositive for HCV, and after adjustments, HCV remained significantly associated with an increased risk for heart failure events [HR=2.13; 95% CI: 1.19-3.80][17]. Genetic factors have also been accused of playing major roles in the HCV-associated cardiovascular diseases. Shichi *et al.* [18] showed that DPB1*0401 and DPB1*0901 were significantly associated with increased risk to HCV-associated hypertrophic cardiomyopathy either in dominant model [OR, 3.94, 95% CI, 1.19, 13.02] and in recessive model [OR, 9.85, 95% CI, 1.83, 53.04], respectively [18]. Another study finding a low HCV infection rate among idiopathic dilated cardiomyopathy patients suggested that HCV infection has no effect on the development of idiopathic cardiomyopathy [19]. Similar findings have been reported by Dalekos *et al.* that reported no clinical or subclinical evidence for cardiomyopathy in HCV infected patients, and no HCV seropositive case represented cardiomyopathy in their series [20]. Another study comparing the prevalence of HCV infection in patients with and without cardiomyopathy also reported alike data; although in the latter study, authors reported that among patients with dilated cardiomyopathy, HCV infection was independently associated with larger LV end-systolic dimension [21]. HCV infection has also been associated with elevated levels of cardiac troponins I & T and N-terminal pro-brain natriuretic peptide, suggestive of persistent myocardial injury due to HCV infection [22]. A multicenter population-based study from Japan reported 10.6% prevalence rate for hypertrophic cardiomyopathy and 6.3% for dilated cardiomyopathy in a population-based study; both were significantly higher than that found in their general population (2.4%) [23]. Moreover, HCV seropositivity was significantly higher in patients suffering from hypertrophic cardiomyopathy than those with dilated cardiomyopathy [23]. In a case-control study comparing the prevalence of HCV infection between hypertrophic cardiomyopathy and ischemic heart disease, Matsumori *et al.* [24] reported a significantly higher infection rate in the cardiomyopathy patients than the latter group (17% vs. 2.5%, respectively) [24]. Maruyama *et al.* [25] in a study on 217 consecutive cases of chronic HCV infection without overt heart disease reported that abnormal ECG was found in 9% of the patients with HCV while abnormal myocardial injury severity score was found in 87% of the HCV infected individuals [25]. Moreover, after interferon therapy, myocardial injury severity score was improved in patients with sustained virologic response while it worsened with the reappearance of HCV RNA in relapsers, and in non-responders, it did not change with interferon therapy [25]. Table 2 summarizes data of the reviewed studies.

HCV infection and carotid artery disease

Miyajima *et al.* [26] in a population-based study of 1908 inhabitants of a Japanese town evaluated carotid intima-media thickness (IMT) found that compared to HCV negative patients and those with transient infection, patients with chronic HCV infection had significant decrease in IMT, suggestive of mild atherosclerosis associated with the infection [26]. In a case-control study of 803 subjects (326 liver biopsy-proven chronic HCV infected & 477 matched healthy controls), chronic HCV infected patients had a higher prevalence of carotid atherosclerosis than controls and this significance levels was also available among younger subjects [27]. In a case-control study involving 1297 participants (329 chronic HCV, 173 with transient infection and 795 never infected), patients with chronic infection had an independently significant increased IMT compared to never infected individuals [0.70 (0.67 to 0.73)] [28]. An interesting study from Italy investigating the pathogenesis of HCV-induced carotid atherosclerosis, detected HCV RNA or its replicative intermediates in the carotid plaque tissues from anti-HCV-positive patients, but did not detect it within the nine carotid plaque tissues obtained from anti-HCV-negative patients [29]. This finding is highly suggestive of a direct impact of HCV infection within the arterial walls [29]. In another study by the same authors, Boddi *et al.* [30]

Table 2. Effects of HCV infection on heart diseases other than coronary artery disease

Author	Study methodology	Sample size	Findings regarding HCV positivity
El-Waseef *et al.* [16]	Case-control	80; 25 HCV+; 65 HCV-	Systolic dysfunction was significantly more prevalent among HCV+; diastolic dysfunction was no different.
Tsui *et al. [17]*	Case-control	981: 84 HCV+; 897 HCV-	In multivariate analysis, HCV remained significant associate of heart failure
Shichi *et al.* [18]	Case-control	170: 38 HCV+HCM; 132 HC	HCV-associated hypertrophic cardiomyopathy was dependent on the patients genetics
Reis *et al.* [19]	Case-control	105: 34 DCM; 32 ICM; 39 Chagas-CM (1 HCV+)	Only 2.9% (1/34) of DCM patients were HCV carriers
Dalekos *et al.* [20]	Observational	157: 102 HCV+; 55 DCM	None of HCV+ patients had DCM; none of DCM patients had HCV
Kawai *et al. [21]*	Prospective cohort	148 hemodialysis patients: 49 HCV+	Multivariate analysis demonstrated HCV infection as an independent determinant of worsening of carotid-femoral pulse wave velocity
Matsumori *et al.* [22]	Case-control	1355 heart failure: 59 HCV+; 1296 HCV-	Elevated levels of cardiac troponins I & T and N-terminal pro-brain natriuretic peptide, suggestive of persistent myocardial injury due to HCV
Matsumori *et al.* [23]	Case-control	11,967: 650 HCV+; 11317 HCV-	HCV was more prevalent in HCM than DCM; but in both HCV was more common than in that in the general population
Matsumori *et al.* [24]	Case-control	75; 35 HCM; 40 IHD (7 HCV+)	HCV was significantly more prevalent in HCM than in IHD
Maruyama *et al.* [25]	Observational	217 HCV+	87% had abnormal myocardial scintigraphy; HCV therapy was associated with improvement in myocardial injury severity score
Total		15255: 1232 HCV+	

investigated the prevalence and severity of IMT in carotid artery by high-resolution B-mode ultrasonography in 31 HCV seropositive (HCV+) and in 120 matched HCV seronegative (HCV-) controls. The prevalence of an IMT > 1 mm was significantly higher in HCV+ than in HCV negative patients and HCV positivity was significantly associated with >1 mm IMT in multivariate regression analysis [30]. In another case-control study, Targher *et al.* [31] demonstrated that IMT was significantly increased in HCV infected patients compared to controls, but this increase was significantly lower than that in patients with non-alcoholic steatohepatitis (NASH) [31]. In a cross-sectional population-based study of 4784 subjects, Ishizaka *et al.* [32] reported that HCV seropositivity was found to be independently associated with an increased risk of carotid-artery plaque [OR 1.92 [95% CI 1.56-2.38]] and carotid IMT [2.85 [2.28-3.57]] after adjustment for confounding risk factors [32]. Sawayama *et al.* [33] prospectively investigated the impact of lipid lowering agents on the progression or regression of carotid IMT and found that although HCV negative patients showed a significant reduction of Max-IMT the rate of decrease in the Max-IMT of HCV infected patients was low; their findings suggests that HCV can also prevent beneficial effects of endeavors attenuating traditional risk factors [33]. Ishizaka *et al.* [34] studied 1992 patients (1.3% positive for HCV core protein) and found that carotid artery plaque was positive in 24% of HCV negative patients while the rate was 64% in the core protein-negative subjects; multivariate logistic regression analysis confirmed this association [OR 5.61 (95% CI 2.06-15.26)][34]. Petta *et al.* [35] conducted a prospective cohort study on 174 biopsy proven HCV infected cases and 174 HCV negative controls demonstrated that carotid plaques were significantly more frequently available HCV infected patients than control patients (42% vs. 23%, respectively). Moreover, HCV infected patients had a significantly larger IMT compared to control patients [35]. A population-based cohort study on 4094 HCV infected patients and 16,376 HCV negative individuals during 96,752 person-years of follow-up, reported that stroke events was significantly more commonly

observed in the HCV infected patients (2.5% vs. 1.9%, respectively; HR, 1.27 (95%CI, 1.14 to 1.41) [36]. Lee *et al.* [37] in a community-based prospective cohort study of 23 665 residents, 255 cerebrovascular deaths were happened during 382 011 person-years of follow-up. After adjustments for several conventional risk factors, the risk of cerebrovascular death for HCV seropositive patients was significantly higher than that in HCV seronegative subjects [HR 2.18 (95%CI, 1.50 to 3.16] [37]. Table 3 summarizes data of studies evaluating effects of HCV infection on cardiovascular diseases.

HCV and aortic artery disease

There are just a limited number of studies investigating the potential effects of HCV infection on aortic artery disorders. Matsumae *et al.* [38] investigated carotid-femoral pulse wave velocity (cfPWV) as a surrogate of aortic stiffness in a cohort of hemodialysis patients and after 3 years of follow up, they found that HCV was among the independent correlates of rapid progression of cfPWV and aortic stiffness. Consistent to this study, Oyake *et al.* [39] in a prospective cohort study on 94 outpatient hemodialysis patients reported that HCV-positive patients had higher aortic cfPWV compared to HCV-negative patients.

HCV and cardiovascular diseases in hemodialysis patients

Renal failure patients are at a significant risk for cardiovascular diseases [40] and HCV infection might be able to sharpen this risk enhancement even more. In a case-control study by Yelken *et al.* [41] investigated coronary flow reserve (CFR) by transthoracic Doppler echocardiography, as a marker of endothelial dysfunction and carotid IMT measures in 26 non-diabetic HCV positive hemodialysis patients and 26 HCV-negative controls. HCV-positive dialysis patients represented lower CFR measurement than their HCV-negative counterparts, suggestive of a significant impact of HCV infection on the cardiovascular risk enhancement in hemodialysis patients [41]. In another case-control study of larger sample size,

Table 3. Effects of HCV infection on carotid artery disease

Author	Study methodology	Sample size	Findings regarding HCV positivity
Miyajima [26]	Case-control	1908: 1780 HCV-; 88 transient infection; 40 chronic HCV infection	IMT was reduced in the group with chronic infection, with a significant intergroup difference
Adinolfi et al. [27]	Case-control	803: 326 HCV+; 477 HC*	Higher prevalence of carotid atherosclerosis in HCV+
Mostafa [28]	Case-control	1297: 329 chronic HCV+; 173 transient infect; 795 HCV-	Increased IMT was detected in chronic HCV than never infected controls
Boddi et al. [29]	Case-control	7 HCV+ carotid plaques; 9 HCV- plaques	HCV RNA was significantly found in carotid plaques of HCV seropositive
Boddi et al. [30]	Case-control	151: 31 HCV+; 120 HCV-	The prevalence and severity of carotid IMT was significantly higher in HCV+
Targher et al. [31]	Case-control	180: 60 NASH; 60 HCV+; 60 HC	HCV was independent confounder of carotid IMT in multivariate analysis
Ishizaka et al. [32]		4784: 104 HCV+; 4680 HCV-	HCV associated with carotid plaque
Sawayama et al. [33]	Case-control	165 hyperlipidemic: 25 HCV+	HCV negative patients showed significant decrease in Max-IMT significantly more than HCV+
Ishizaka et al. [34]	Case-control	1992: 496 carotid plaque; 1496 no plaque (25 HCV+)	24% of HCV- vs. 64% of HCV positive patients had carotid plaque
Petta et al. [35]	Case-control	348: 174 HCV+; 174 HC	Carotid plaques were both more prevalent and more prominent in the HCV+ subjects
Liao et al. [36]	Case-control	20470: 4094 HCV+; 16,376 HCV-	Stroke events was more prevalent in HCV+
Lee et al. [37]	Prospective cohort	23 665: 255 cerebrovascular death (1154 HCV+)	Cerebrovascular deaths was significantly more common in HCV+
Total		55779: 6304 HCV+ cases	

* HC: healthy control

Caliskan *et al.* [42] investigated a cohort of 72 hemodialysis patients (36 HCV-positive and 36 - negative controls) but found no significant difference between the two groups regarding the carotid IMT, carotid plaque score and brachial artery endothelium-dependent dilatation [41]. Adam et al. [43] enrolled 37 HCV positive and 30 HCV negative hemodialysis patients found no association between HCV positivity and arterial stiffness. Knoll et al. [44] in a retrospective cohort study of 58 HCV positive renal failure patients, and found that HCV positive dialysis patients who had not undergone renal transplantation (though eligible) had a significantly higher mortality rate than those received renal allograft [44]. Two studies by Matsumae et al. [38] and Oyake *et al.* [39] have been described earlier in the previous section.

Conclusion

Aside from renal disease patients, overall 364,712 individuals who underwent investigation for any potential association between HCV infection and cardiovascular disorders in 31 studies have been reviewed in this systematic review. Only 6 out of 31 reviewed studies involving a cumulative population of 81,035 (22.2%) subjects reported a negative association between HCV infection and cardiovascular disorders. There were 2 prospective studies, both in favor of a significant relation between HCV infection and cardiovascular disease. Our data suggests that HCV have a significant effect on the development of cardiovascular diseases in the general population, either in the coronary artery or carotid artery. There is data scarcity on the impact of HCV infection on aortic atherosclerosis in the general population, and both of the available studies are on renal disease patients. In renal disease patients, similar findings to the general population have been reported, suggesting a significant relationship between HCV infection and cardiovascular diseases. We suggest prospective cohort studies with more controlled conditions.

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