Libertas Academica
FREEDOM TO RESEARCH

Open Access: Full open access to this and thousands of other papers at http://www.la-press.com.

Clinical Medicine Insights: Cardiology

Supplementary Issue: Inflammation, Atherosclerosis and Coronary Artery Disease

Atherosclerosis As a Possible Extrahepatic Manifestation of Chronic Hepatitis C Virus Infection

Nobukazu Ishizaka, Yuko Ishizaka and Minoru Yamkado

Department of Cardiology, Osaka Medical College, Osaka, Japan.

ABSTRACT: Chronic infection and associated inflammation may play a role in various unfavorable pathologic conditions, including atherosclerosis. Chronic hepatitis C virus (HCV) infection is thought to be associated with a higher prevalence of atherosclerotic vascular changes in the coronary artery, cerebrovascular artery, and carotid artery; however, little is known about the precise mechanisms by which HCV enhances atherogenic processes. Furthermore, some studies have found no association, or even an inverse association, between HCV infection and atherosclerotic vascular changes or cardiovascular events. Differences in data regarding the mode of association may be because of variations in sample size, target population, and study design. Nevertheless, physicians should be aware of cardiovascular disorders as a possible comorbidity – owing to their considerable consequences – among patients with chronic HCV infection.

KEYWORDS: hepatitis C virus, atherosclerosis, coronary artery disease

SUPPLEMENT: Inflammation, Atherosclerosis and Coronary Artery Disease

CITATION: Ishizaka et al. Atherosclerosis As a Possible Extrahepatic Manifestation of Chronic Hepatitis C Virus Infection. *Clinical Medicine Insights: Cardiology* 2014:8(S3) 1–5 doi: 10.4137/CMC.S17069.

RECEIVED: September 11, 2014. **RESUBMITTED:** October 14, 2014. **ACCEPTED FOR PUBLICATION:** October 21, 2014.

ACADEMIC EDITOR: Thomas Vanhecke, Editor in Chief

TYPE: Review

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: ishizaka@poh.osaka-med.ac.jp

Paper subject to independent expert blind peer review by minimum of two reviewers. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE).

Introduction

Chronic infection and associated inflammation may be involved in numerous unfavorable pathologic conditions, including atherosclerosis. Several studies have investigated the association between atherosclerotic disease and certain specific infectious microorganisms, such as hepatitis A virus,[1] herpes simplex virus,[2] *Chlamydia pneumoniae*,[3] and HIV[4]; however, not only do the precise mechanisms remain unclear but a controversy also exists over whether such an association really exists.[5]

It is possible that the reported results may differ according to the study design (eg, cross-sectional or longitudinal, and length of follow-up period) and/or target population (race, ethnicity, high or low risk for atherosclerosis, and sample size).[6] One of the final goals of such investigations may be to conclude whether controlling the infection of presumably infective microorganisms will effectively reduce the risk of the progression of atherosclerotic processes. Several studies have already evaluated such a possibility with both positive[7] and negative[8–10] findings. Irrespective of these efforts, the association or non-association of certain infections with atherogenesis remains obscure.[11,12]

Hepatitis C virus (HCV) is one such microorganism, chronic infection of which may or may not be associated with advanced or early stage atherosclerosis. Since the demonstration of a possible association between HCV infection and carotid atherosclerosis among the Japanese general population,[13,14] several studies have been conducted to confirm, or disprove, an independent association between HCV infection and atherosclerotic disorders, including coronary artery disease,[15] ischemic stroke,[16] and early atherosclerosis, especially among patients without advanced

liver cirrhosis. To this end, in this mini-review, we would like to discuss what has been reported about the relationship between HCV infection and atherosclerotic diseases to date, and the mechanisms by which HCV may promote atherosclerotic process, if it promotes it at all.

HCV Infection and Cardiovascular Mortality

Amin et al investigated the incidence of mortality in an Australian population diagnosed with HCV infection and found that the incidence of death related to the circulatory system, as well as all-cause death, was increased among the study subjects.[17] Guiltinan et al performed a retrospective cohort study of 10,259 HCV antibody-positive subjects and 10,259 age- and sex-matched HCV antibody-negative subjects.[18] In their study, the HCV-positive group unexpectedly had a greater risk of mortality because of cardiovascular causes with a hazard ratio of 2.21 (95% confidence interval [CI], 1.41, 3.46). In these two studies, however, whether or not the findings were because of an advancement of coronary artery atherosclerosis was not documented.

By contrast, in a cross-sectional study of adults in northeast of Germany, Volzke et al reported that there was no association between serological markers of HCV infection and atherosclerotic endpoints comprising myocardial infarction, stroke, carotid intima-media thickness, carotid plaques, and stenosis.[19]

HCV Infection and Coronary Artery Disease

Whether HCV infection increases the risk of ischemic heart disease has also been investigated in several studies, with, again, both positive[15,20] and negative[21] results. On the one hand, Lin et al reported that among 5009 subjects with a mean age of 61.2 years from one community health examination in a southern village of Taiwan, HCV infection was found in 99 (1.9%) subjects, and these HCV-infected subjects had 1.76-fold increased risk of an ischemic electrocardiogram when compared with HCV non-infected subjects.[22] In addition, in a large cohort of 82,083 HCV-infected and 89,582 HCV-uninfected subjects, Butt et al reported that HCV-infected subjects had lower mean total and low-density lipoprotein (LDL) plasma cholesterol, and triglyceride levels, as compared with uninfected subjects.[23] Despite a favorable lipid profile in HCV-infected subjects, HCV infection was found to be associated with a higher risk of coronary artery disease with a hazard ratio of 1.27 (95% CI, 1.22–1.31) after adjustment of traditional risk factors.[23]

On the other hand, in a retrospective cohort with a median follow-up of 3.2 years, Forde et al found no difference in the incidence rates of myocardial infarction between HCV-infected and uninfected patients (respectively, 1.02 versus 0.92, events per 1000 person-years).[24] The prevalence of hyperlipidemia was lower among HCV-infected subjects; however, HCV infection did not have an increased hazard ratio after adjusting for potential confounders.

Furthermore, Tsui et al analyzed data from a cohort of patients with stable coronary heart disease and found that HCV-seropositive participants had higher rates of death, cardiovascular events, and hospitalization because of heart failure during the follow-up despite lower cholesterol and C-reactive protein (CRP) levels.[25] In that study, however, the association between HCV and cardiovascular outcome (cardiovascular death, myocardial infarction, or stroke) lost statistical significance after adjustment of several clinical factors (such as smoking, diabetes, hypertension) and serum lipid data. It is possible that the discrepant findings with regard to association between HCV and coronary artery disease might be, again, due to differences in the populations examined, outcomes evaluated, and confounding variables used in the multivariate analyses.[24]

Roed et al performed a systematic review of six published studies that were judged not to be heavily biased: one study suggested that HCV infection might be a protective factor against coronary artery disease, whereas the remaining five studies showed a trend toward the association of HCV with coronary artery disease.[26] The authors advocated that clinicians should be aware of the possible association between HCV and coronary artery disease, and efforts should be made to reduce cardiovascular risk factors among HCV-infected patients.

HCV Infection and Ischemic Stroke

By analyzing a community-based prospective cohort of 23,665 residents, Lee et al demonstrated that the hazard ratio of cerebrovascular death was 2.18 (95% CI, 1.50–3.16) for HCV-seropositive subjects after adjustment of conventional risk factors.[16] In their study, no specific HCV genotype was found to be more strongly (or weakly) associated with cerebrovascular death. In addition, by comparing individuals with stroke and age- and gender-matched subjects, Adinolfi et al reported that the prevalence of HCV-antibody positivity was significantly higher among patients with stroke (26.8%) than among control patients (6.6%), with an odds ratio of 2.04 after multivariate adjustment.[27] They also analyzed the prevalence of ischemic heart events among the study participants, and found that such events were significantly more prevalent among the HCV-positive patients (22%) than among the HCV-negative subjects (13%). These findings suggested that HCV infection may be associated with a higher prevalence of both cerebrovascular and ischemic heart diseases.

Liao et al compared the incidence of stroke between 4094 adults who were newly diagnosed with hepatitis C infection and 16,376 age- and sex-matched adults randomly selected from the database.[28] They reported that the cumulative risk of stroke was significantly greater for people with hepatitis C than for those without infection (2.5% vs. 1.9%, $P < 0.0001$). The adjusted hazard ratio for risk of stroke for individuals with hepatitis C infection was 1.27 (95% CI, 1.14–1.41) as compared with those people without hepatitis C infection. Hsu et al also reported that newly detected stroke was more prevalent among subjects with HCV infection as

compared with age- and sex-matched non-infected subjects with a hazard ratio of 1.23 (95% CI, 1.06–1.42; $P = 0.008$).[29] Of note, Hsu et al also investigated whether interferon-based therapy had an impact on risk of stroke among patients with chronic hepatitis C. They found that interferon-based therapy markedly reduced the risk of stroke during one to five years of follow-up for HCV patients even after adjustment of known prognostic factors (adjusted hazard ratio 0.39; 95% CI, 0.16–0.95; $P = 0.039$), suggesting the possibility that controlling HCV infection might be beneficial for stroke prevention.

HCV Infection and Carotid Atherosclerosis

Several studies have examined whether there is an association between HCV infection and carotid atherosclerosis. For example, Ishizaka et al showed that the prevalence of carotid plaque was higher among subjects who were positive for HCV-antibody or HCV core antigen than among control subjects.[13,14] Although some studies reported similar observations, others demonstrated conflicting results.[30] For example, Kiechl et al examined five-year changes in carotid atherosclerosis by high-resolution duplex scanning, and found a strong association between the development of new atherosclerotic lesions and respiratory, urinary, and other types of chronic infectious illness, including infections of *C. pneumoniae*; however, HCV seropositivity was found to be unrelated to early stage atherogenesis.[31] In a population-based study, Miyajima et al demonstrated, in reverse, that patients with chronic HCV infection had significantly decreased carotid intima-media thickness as compared with non-infected subjects.[32]

In 2010, Aslam et al undertook a systematic review of the literature to study the association between HCV and carotid atherosclerotic plaques[33]; overall, 11 studies were selected for detailed review.[13,14,19,30,34–39] Among a total of 12,265 patients, 655 were found to be HCV positive. There were no differences in the baseline characteristics of patients according to HCV infection status. However, HCV-positive patients were more likely to have a carotid plaque than HCV-negative patients (48.2% vs. 20.7%, $P = 0.05$). Aslam et al advocated the necessity of long-term large-scale prospective studies to further confirm the association between HCV status and carotid atherosclerosis. By analyzing carotid artery morphology among 174 patients with G1 chronic hepatitis C patients that were consecutively biopsy-proven, Petta et al. found that carotid plaques were more prevalently found in HCV-infected patients compared with 41.9% vs. 22.9%, $P < 0.001$).[40] They also found that the presence of advanced hepatic fibrosis identifies a subgroup of patients with G1 chronic hepatitis C who are at higher risk of developing atherosclerotic lesions.

It is known that HCV infection is often associated with a favorable lipoprotein profile.[41] It was recently shown that carotid intima-media thickness did not differ according to HCV infection status; however, after adjustment of cardiovascular risk factors, individuals with chronic HCV infection had increased intima-media thickness as compared with individuals who had never been infected, suggesting a direct infection on intima-media thickening.[42]

HCV Infection and Aortic Stiffness

Tomiyama et al analyzed 7514 subjects who underwent annual health checkups, including pulse wave velocity (PWV), and showed that HCV seropositivity was a significant factor for PWV independent of known atherosclerotic risk factors.[43] By analyzing the data from 148 patients on hemodialysis, Matsumae et al reported that HCV infection, as well as ankle-brachial blood pressure index and LDL cholesterol/high-density lipoprotein cholesterol, was a determinant of worsening carotid-femoral PWV.[44] Oyake et al showed that, among 94 outpatients undergoing chronic hemodialysis, blood pressure, hemoglobin A1c, and HCV viremia were found to be independent determinants of high PWV.[45] These findings suggest that chronic HCV infection may promote arterial stiffening.

Association between HCV Infection and Chronic Kidney Disease

Chronic kidney disease is a condition defined as moderate decline in renal function and/or increase in urinary albumin excretion. Recent studies have shown that not only proteinuria but also decreased renal function, even before end-stage renal disease requiring chronic hemodialysis, is associated with increased cardiovascular events.[46,47]

In a cross-sectional study in which data were analyzed from a large-scale community examination of 54,966 adults for HCV infection in an endemic area in Taiwan, Lee et al showed that HCV infection was an independent risk factor for both proteinuria and low glomerular filtration rate.[48] In addition, by following up subjects who had the first-time diagnosis of HCV between 1999 and 2006, Chen showed that the frequency of chronic kidney disease was 1.66-fold higher in the HCV than in the non-HCV cohort (5.46 vs. 3.43 per 1000 person-years) with a significantly greater adjusted hazard ratio of 1.28 (95% CI, 1.12–1.46).[49]

Possible Mechanisms to Explain the Observed Link

Several factors might mediate the link, if present at all, between HCV infection and atherogenesis.[50] These include disrupted iron homeostasis, increased oxidative stress,[51] induction of hepatic steatosis leading to aggravated insulin sensitivity and other related metabolic abnormalities,[52] activation of immunological and/or inflammatory processes and associated cytokine imbalance,[53,54] and in situ viral replications.[36,55]

There may be receptors for HCV entry in cerebrovascular endothelial cells, and HCV RNA has been observed in brain tissue from infected individuals.[56] In addition, Boddi et al demonstrated that HCV RNA was present within carotid plaques.[55] Although not fully proven, these findings collectively suggest that active local infection of HCV may have an impact on the pathology of arterial wall cells.

Conclusion

Herein we have described several studies that had tried to clarify the association or non-association between HCV infection and atherosclerotic disease; however, the results do not seem to be uniform. On the other hand, owing to their considerable consequences, cardiovascular disorders are not a negligible comorbidity among patients with chronic HCV infection.[57] Furthermore, interferon/ribavirin combination therapy, which is effective for HCV eradication, may lead to an unfavorable lipid.[58] In order to minimize the risk of vascular events, it is necessary to control atherogenic risk factors among HCV-infected patients, regardless of the mode of association between HCV and atherogenesis–that is, causal, resultant, or by chance.

Author Contributions

Conceived the concepts: NI, MY. Wrote the first draft of the manuscript: NI. Contributed to the writing of the manuscript: NI, YI. Agree with manuscript results and conclusions: NI, YI, MY. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Prasad A, Zhu J, Halcox JP, Waclawiw MA, Epstein SE, Quyyumi AA. Predisposition to atherosclerosis by infections: role of endothelial dysfunction. *Circulation*. 2002;106:184–90.
2. Mendy A, Vieira ER, Gasana J. Seropositivity to herpes simplex virus type 2, but not type 1 is associated with premature cardiovascular diseases: a population-based cross-sectional study. *Atherosclerosis*. 2013;231:18–21.
3. Jitsuiki K, Yamane K, Nakajima M, et al. Association of *Chlamydia pneumoniae* infection and carotid intima-media wall thickness in Japanese Americans. *Circ J*. 2006;70:815–9.
4. Ng B, Macpherson P, Haddad T, Dwivedi G. Heart failure in HIV infection: focus on the role of atherosclerosis. *Curr Opin Cardiol*. 2014;29(2):174–9.
5. Laek B, Szklo M, McClelland RL, et al. The prospective association of *Chlamydia pneumoniae* and four other pathogens with development of coronary artery calcium: the multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis*. 2013;230:268–74.
6. Sander D, Winbeck K, Klingelhofer J, Etgen T, Conrad B. Progression of early carotid atherosclerosis is only temporarily reduced after antibiotic treatment of *Chlamydia pneumoniae* seropositivity. *Circulation*. 2004;109:1010–15.
7. Sander D, Winbeck K, Klingelhofer J, Etgen T, Conrad B. Reduced progression of early carotid atherosclerosis after antibiotic treatment and *Chlamydia pneumoniae* seropositivity. *Circulation*. 2002;106:2428–33.
8. Anderson JL, Muhlestein JB, Carlquist J, et al. Randomized secondary prevention trial of azithromycin in patients with coronary artery disease and serological evidence for *Chlamydia pneumoniae* infection: The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study. *Circulation*. 1999;99:1540–7.
9. Zahn R, Schneider S, Frilling B, et al. Antibiotic therapy after acute myocardial infarction: a prospective randomized study. *Circulation*. 2003;107:1253–9.
10. Jaff MR, Dale RA, Creager MA, et al. Anti-chlamydial antibiotic therapy for symptom improvement in peripheral artery disease: prospective evaluation of rifalazil effect on vascular symptoms of intermittent claudication and other endpoints in *Chlamydia pneumoniae* seropositive patients (PROVIDENCE-1). *Circulation*. 2009;119:452–8.
11. Lockhart PB, Bolger AF, Papapanou PN, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation*. 2012;125:2520–44.
12. Hyvarinen K, Mantyla P, Buhlin K, et al. A common periodontal pathogen has an adverse association with both acute and stable coronary artery disease. *Atherosclerosis*. 2012;223:478–84.
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. Ishizaka Y, Ishizaka N, Takahashi E, et al. Association between hepatitis C virus core protein and carotid atherosclerosis. *Circ J*. 2003;67:26–30.
15. Vassalle C, Masini S, Bianchi F, Zucchelli GC. Evidence for association between hepatitis C virus seropositivity and coronary artery disease. *Heart*. 2004;90:565–6.
16. Lee MH, Yang HI, Wang CH, et al. Hepatitis C virus infection and increased risk of cerebrovascular disease. *Stroke*. 2010;41:2894–900.
17. Amin J, Law MG, Bartlett M, Kaldor JM, Dore GJ. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. *Lancet*. 2006;368:938–45.
18. Guiltinan AM, Kaidarova Z, Custer B, et al. Increased all-cause, liver, and cardiac mortality among hepatitis C virus-seropositive blood donors. *Am J Epidemiol*. 2008;167:743–50.
19. Volzke H, Schwahn C, Wolff B, et al. Hepatitis B and C virus infection and the risk of atherosclerosis in a general population. *Atherosclerosis*. 2004;174:99–103.
20. Butt AA, Fultz SL, Kwoh CK, Kelley D, Skanderson M, Justice AC. Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology*. 2004;40:115–9.
21. Arcari CM, Nelson KE, Netski DM, Nieto FJ, Gaydos CA. No association between hepatitis C virus seropositivity and acute myocardial infarction. *Clin Infect Dis*. 2006;43:e53–6.
22. Lin MS, Guo SE, Chen MY, et al. The impact of hepatitis C infection on ischemic heart disease via ischemic electrocardiogram: a cross-sectional observational study. *Am J Med Sci*. 2013 ;347(6):478–84.
23. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis*. 2009; 49:225–32.
24. Forde KA, Haynes K, Troxel AB, et al. Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study. *J Viral Hepat*. 2012;19:271–7.
25. Tsui JI, Whooley MA, Monto A, Seal K, Tien PC, Shlipak M. Association of hepatitis C virus seropositivity with inflammatory markers and heart failure in persons with coronary heart disease: data from the Heart and Soul study. *J Card Fail*. 2009;15:451–6.
26. Roed T, Lebech AM, Kjaer A, Weis N. Hepatitis C virus infection and risk of coronary artery disease: a systematic review of the literature. *Clin Physiol Funct Imaging*. 2012;32:421–30.
27. Adinolfi LE, Restivo L, Zampino R, et al. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis*. 2012;221:496–502.
28. Liao CC, Su TC, Sung FC, Chou WH, Chen TL. Does hepatitis C virus infection increase risk for stroke? A population-based cohort study. *PLoS One*. 2012;7:e31527.
29. Hsu CS, Kao JH, Chao YC, et al. Interferon-based therapy reduces risk of stroke in chronic hepatitis C patients: a population-based cohort study in Taiwan. *Aliment Pharmacol Ther*. 2013;38:415–23.
30. Bilora F, Rinaldi R, Boccioletti V, Petrobelli F, Girolami A. Chronic viral hepatitis: a prospective factor against atherosclerosis. A study with echo-color Doppler of the carotid and femoral arteries and the abdominal aorta. *Gastroenterol Clin Biol*. 2002;26:1001–4.
31. 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.
32. Miyajima I, Kawaguchi T, Fukami A, et al. Chronic HCV infection was associated with severe insulin resistance and mild atherosclerosis: a population-based study in an HCV hyperendemic area. *J Gastroenterol*. 2013;48:93–100.
33. Aslam F, Alam M, Lakkis NM. Hepatitis C and carotid atherosclerosis: a retrospective analysis. *Atherosclerosis*. 2010;209:340–3.
34. Fukui M, Kitagawa Y, Nakamura N, Yoshikawa T. Hepatitis C virus and atherosclerosis in patients with type 2 diabetes. *JAMA*. 2003;289:1245–6.
35. Targher G, Bertolini L, Padovani R, Rodella S, Arcaro G, Day C. Differences and similarities in early atherosclerosis between patients with non-alcoholic steatohepatitis and chronic hepatitis B and C. *J Hepatol*. 2007;46:1126–32.
36. Boddi M, Abbate R, Chellini B, et al. HCV infection facilitates asymptomatic carotid atherosclerosis: preliminary report of HCV RNA localization in human carotid plaques. *Dig Liver Dis*. 2007;39(suppl 1):S55–60.
37. Bilora F, Campagnolo E, Rinaldi R, Rossato A, Arzenton M, Petrobelli F. Carotid and femoral atherosclerosis in chronic hepatitis C: a 5-year follow-up. *Angiology*. 2008;59:717–20.
38. Caliskan Y, Oflaz H, Pusuroglu H, et al. Hepatitis C virus infection in hemodialysis patients is not associated with insulin resistance, inflammation and atherosclerosis. *Clin Nephrol*. 2009;71:147–57.
39. Tien PC, Schneider MF, Cole SR, et al. Association of hepatitis C virus and HIV infection with subclinical atherosclerosis in the women's interagency HIV study. *AIDS*. 2009;23:1781–4.
40. Petta S, Torres D, Fazio G, et al. Carotid atherosclerosis and chronic hepatitis C: a prospective study of risk associations. *Hepatology*. 2012;55:1317–23.
41. Dai CY, Chuang WL, Ho CK, et al. Associations between hepatitis C viremia and low serum triglyceride and cholesterol levels: a community-based study. *J Hepatol*. 2008;49:9–16.

42. Mostafa A, Mohamed MK, Saeed M, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. *Gut*. 2010;59: 1135–40.
43. Tomiyama H, Arai T, Hirose K, Hori S, Yamamoto Y, Yamashina A. Hepatitis C virus seropositivity, but not hepatitis B virus carrier or seropositivity, associated with increased pulse wave velocity. *Atherosclerosis*. 2003;166:401–3.
44. Matsumae T, Ueda K, Abe Y, Nishimura S, Murakami G, Saito T. What factors accelerate aortic stiffening in hemodialysis patients? An observational study. *Hypertens Res*. 2010;33:243–9.
45. Oyake N, Shimada T, Murakami Y, et al. Hepatitis C virus infection as a risk factor for increased aortic stiffness and cardiovascular events in dialysis patients. *J Nephrol*. 2008;21:345–53.
46. Perkovic V, Verdon C, Ninomiya T, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. *PLoS Med*. 2008;5:e207.
47. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–305.
48. Lee JJ, Lin MY, Yang YH, Lu SN, Chen HC, Hwang SJ. Association of hepatitis C and B virus infection with CKD in an endemic area in Taiwan: a cross-sectional study. *Am J Kidney Dis*. 2010;56:23–31.
49. Chen YC, Lin HY, Li CY, Lee MS, Su YC. A nationwide cohort study suggests that hepatitis C virus infection is associated with increased risk of chronic kidney disease. *Kidney Int*. 2013 ;85:1200–7.
50. Zampino R, Marrone A, Restivo L, et al. Chronic HCV infection and inflammation: clinical impact on hepatic and extra-hepatic manifestations. *World J Hepatol*. 2013;5:528–40.
51. Yadav D, Hertan HI, Schweitzer P, Norkus EP, Pitchumoni CS. Serum and liver micronutrient antioxidants and serum oxidative stress in patients with chronic hepatitis C. *Am J Gastroenterol*. 2002;97:2634–9.
52. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology*. 2001;33:1358–64.
53. Jacobson Brown PM, Neuman MG. Immunopathogenesis of hepatitis C viral infection: Th1/Th2 responses and the role of cytokines. *Clin Biochem*. 2001;34:167–71.
54. Oliveira CP, Kappel CR, Siqueira ER, et al. Effects of hepatitis C virus on cardiovascular risk in infected patients: a comparative study. *Int J Cardiol*. 2013;164:221–6.
55. Boddi M, Abbate R, Chellini B, et al. Hepatitis C virus RNA localization in human carotid plaques. *J Clin Virol*. 2010;47:72–5.
56. Fletcher NF, Wilson GK, Murray J, et al. Hepatitis C virus infects the endothelial cells of the blood-brain barrier. *Gastroenterology*. 2012;142(634–43):e636.
57. Karbasi-Afshar R, Adibi P, Khedmat H, Jalali A. How hepatitis C virus infection contributes to cardiovascular disease: a systematic review. *Intern J Travel Med Global Health*. 2013;1:55–64.
58. Tada S, Saito H, Ebinuma H, et al. Treatment of hepatitis C virus with peg-interferon and ribavirin combination therapy significantly affects lipid metabolism. *Hepatol Res*. 2009;39:195–9.