Metabolic and cardiovascular complications after virological cure in hepatitis C: What awaits beyond

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**Abstract**

The association between chronic hepatitis C (CHC) infection and extrahepatic manifestations (EHMs), particularly cardiometabolic diseases, has been extensively examined. However, there has still been insufficient evaluation for these EHMs after virological cure. Several multidirectional mechanisms have been proposed explaining the ability of hepatitis C virus (HCV) developing EHMs, cardiometabolic ones, as well as the effect of antiviral therapy to resolve these EHMs. Data on these manifestations after achieving sustained virologic response (SVR) are still conflicting. However, current evidence suggests that reversal of hepatic steatosis and its coexistent hypocholesterolemia after successful viral eradication led to unfavorable lipid profile, which increases cardiovascular disease (CVD) risk. Additionally, most observations showed that metabolic alterations, such as insulin resistance and diabetes mellitus (DM), undergo some degree of reduction after viral clearance. These changes seem HCV-genotype dependent. Interferon-based antiviral therapy and direct acting antiviral drugs were shown to minimize incidence of DM. Large epidemiological studies that investigated the effect of SVR on CVD showed great discrepancies in terms of results, with predominant findings indicating that CVD events decreased in patients with SVR compared to non-responders or untreated ones. In this review, we present a summary of the current knowledge regarding extrahepatic sequelae of CHC following SVR, which may have an impact on healthcare providers' clinical practice.

**Key Words:** Chronic hepatitis C; Sustained virologic response; Hepatic steatosis; Diabetes mellitus; Cardiovascular disease
INTRODUCTION

Chronic hepatitis C (CHC) infection caused by hepatitis C virus (HCV) is associated with substantial morbidity and mortality globally, affecting approximately 2.5% individuals (equivalent to 177.5 million) worldwide[1]. It is currently one of the leading etiologies for hepatocellular carcinoma (HCC) and decompensated cirrhosis requiring liver transplantation in Western countries[2,3]. The primary goal of treatment is to achieve the cure of the infection or sustained virologic response (SVR), defined as undetectable HCV RNA in the serum 12 or 24 wk after the end of treatment[4,5]. Since the introduction of first-generation direct acting antiviral agents (DAAs), boceprevir and telaprevir, in 2011, there has been a rapidly expanding population of CHC patients achieving SVR[6]. Viral eradication has been associated with marked reduction in the risk of end-stage liver disease, need for liver transplantation, and decrease in both liver-related and overall mortality[7].

Although HCV is a hepatotropic virus, for two decades several studies described the association between HCV and a heterogeneous array of extrahepatic manifestations (EHMs)[8-10] (Figure 1). Yet, the mechanism by which the virus evokes the systemic diseases remain to be elucidated. Endocrine-metabolic alterations, which are most frequently found in CHC patients, are thought to be caused by direct and indirect effects of disturbing host lipid and glucose metabolism[11,12], as well as alteration in adipokytokines released from adipose tissue[13,14]. Likewise, CHC infection has also been identified as an independent predictor for cardiovascular events such as carotid artery atherosclerosis, stroke, myocardial ischemia and heart failure, all of which are linked with poor outcomes[12]. Nevertheless, the impact on cardiovascular disease (CVD) is not fully established[15]. In clinical settings, the prognosis of CHC is not only depending on liver-related outcomes but also on extrahepatic sequelae.

Recently, much attention is drawn toward EHMs that occur following viral cure. Nonetheless, whether the development of such manifestations is a long-term consequence of the viral infection itself or an effect of HCV medications remains unknown. In this context, various reports have shown ample evidence for high prevalence of CVD and metabolic alterations such as dyslipidemia, hepatic steatosis, insulin resistance (IR), obesity and diabetes mellitus (DM)[16-19] (Table 1). While the impact of CHC infection on liver-related outcomes pre- and post-treatment has been well studied, extrahepatic sequelae, especially in post-SVR setting, are less well known. This review article highlights the current knowledge regarding the effect of SVR on EHMs.
Table 1 Summary of studies investigated cardiometabolic manifestations of chronic hepatitis C after viral cure

| Ref.                          | Antiviral regimen | The studied HCV-associated cardiometabolic manifestations | Post SVR outcomes |
|-------------------------------|-------------------|----------------------------------------------------------|-------------------|
| Fernández-Rodriguez et al[28], 2006 | NA¹ | Lipid disturbances. Hepatic steatosis | Hypercholesterolemia in patients with genotype 3 No change in genotype 3 non-responders and in patients with genotype 1 regardless of response Decrease in steatosis |
| Giordanino et al[71], 2008 | IFN monotherapy or Peg-IFN + RBV (24-48 wk) | Glucose abnormalities (IFG or DM) | No significant reduction in the risk of glucose intolerance in long-term responders and non-responders |
| Arase et al[70], 2009 | IFN monotherapy or IFN + RBV | DM | Decreased incidence of DM in sustained responders. However, its development is associated with advanced liver disease |
| Corey et al[18], 2009 | NA¹ | Lipid abnormalities | Increased LDL and total cholesterol from baseline compared to non-responders Risk of CVD |
| Conjeevaram et al[67], 2011 | Peg-IFN + RBV (24-48 wk) | IR | Decreased IR |
| Kuo et al[27], 2011 | Peg-IFN + RBV (24 wk) | Change in serum lipid | Total cholesterol and triglycerides levels significantly increased No evident change in lipid profile occurred in non-SVR group |
| Aghemo et al[68], 2012 | Peg-IFN + RBV² | IR in non-diabetic CHC patients | Baseline and posttreatment HOMA-IR values were similar in SVR patients Significant increase in HOMA-IR was noted in non-SVR patients |
| Clark et al[25], 2012 | Albinterferon α-2b + RBV | Lipid abnormalities in genotypes 2,3 | Hypercholesterolemia |
| Thompson et al[66], 2012 | Albinterferon α-2b vs Peg-IFN + RBV (24-48 wk) | IR in genotypes 1,2,3 | Reduced IR in genotype 1 responders No change in genotype 1 non-responders and genotype 2 and 3 regardless of the response |
| Chang et al[29], 2014 | Peg-IFN + RBV (24/48 wk) | Lipids and IR in genotypes 2, 3 | Increased total cholesterol and triglycerides in sustained responders Decreased HOMA-IR in patients with SVR and baseline IR High HOMA-IR was found in patients without baseline IR (only in genotype 1) |
| Hsu et al[58], 2015 | Peg-IFN + RBV (16-48 wk) | Acute coronary syndrome and ischemic stroke | Improvement in both studied circulatory outcomes |
| Innes et al[89], 2015 | NA¹ | CVD | Reduced hazard and absolute risk for CVD |
| Meissner et al[24], 2015 | SOF + RBV (24 wk) | Lipid disturbances in genotype 1 | Increased LDL level and particle size and decreased triglycerides concentration and VLDL partice size irrespective to treatment response Increased intrahepatic lipid-related genes in sustained responders |
| Leone et al[72], 2016 | IFN-based regimen | DM and CVD | No significant risk reduction in DM and CVD in SVR group as opposed to non SVR |
| Yair-Sabag et al[39], 2016 | Peg-IFN + RBV (24-48 wk) | IFG and DM. Triglycerides. Hepatic steatosis | Lower IFG and DM, and higher triglycerides in sustained responders Improvement in hepatic steatosis |
| Chang et al[16], 2017 | NA¹ | Cardiovascular complications | An increased adipokine PAI-1 in SVR group, which accelerates cardiovascular risk, especially in vulnerable cases |
| Mahale et al[69], 2018 | IFN-based regimen | DM and CVD | Antiviral therapy associated with lower risk of DM and stroke whereas no significant effect on CVD |
DYSLIPIDEMIA

It has been known that HCV possesses a mutual relationship with host lipids and lipoproteins metabolisms, which the virus uses for multiple key steps in its life cycle[20,21]. HCV circulates as a lipid-rich particle, utilizing lipoprotein cell receptors to gain entry into the hepatocyte[22,23]. Within hepatocytes, it influences three mechanisms in lipid metabolism: It upregulates lipid biosynthesis, impairs
mitochondrial β-oxidation and thus lipid degradation, and reduces apolipoprotein exportation, in particular very low-density lipoprotein cholesterol (LDL), resulting in significant intracellular lipid accumulation and circulating hypocholesterolemia and hypolipoproteinemia\[13]\.

Several studies have linked successful HCV eradication with rebound rise in lipid levels. Meissner et al\[24\], who investigated the influence of DAAs, sofosbuvir and ribavirin, on serum lipid profiles and intrahepatic lipid-related genes expression in patients with genotype 1 CHC, reported that serum LDL level and molecular size increased early in therapy, whereas triglycerides concentration and very low-density lipoprotein cholesterol (VLDL) particle size decreased concomitantly, irrespective of treatment outcome. This observation likely reflects a direct effect on lipid metabolism associated with the inhibition of HCV replication\[24\]. This notion was further supported in several reports. Clark et al\[25\], used cholesterol metabolites as an indicator to evaluate the impact of HCV on lipid metabolism. In this study, genotype 3 but not genotype 2 showed a selected interference with late cholesterol synthesis pathway, resulting in hypocholesterolemia. However, this interference was resolved after SVR. Another Japanese study that included 100 subjects showed early rebound (within 28 d) in LDL level in CHC patients who underwent interferon-free DAA treatment. However, the elevation was regimen-specific, more prominent in the group who received daclatasvir and asunaprevir for 24 wk than in those received ledipasvir and sofosbuvir for 12 wk\[26\]. In addition, many reports correlated the rebound in lipid profile with treatment response status\[27-29\]. This was clearly demonstrated by Corey et al\[18\], which conducted a 2 steps study to evaluate the relationship between CHC infection and its treatment with lipid levels. After confirming that HCV infection is associated with significantly lower LDL concentrations in the first step, they found that remarkable hyperlipidemia was developed in patients who achieved viral clearance, compared to non-responders or those who relapsed. In the same context, some studies have further investigated the role HCV genotype on post-SVR hypercholesterolemia. In a study that included 215 patients, Fernández-Rodríguez et al\[28\] observed that increased serum cholesterol levels were associated with genotype 3 in patients who achieved SVR. In contrast, un-changed serum cholesterol figures were noted in genotype 3 non-responders and genotype 1 regardless of response\[28\]. Although the reversal of both hepatic steatosis and hypolipidemia has been reported only in genotype 3 in this study, there is accumulating evidence demonstrating that the reversal of hypolipidemia is not HCV-genotype specific\[29,30\].
Many reports proposed that atherosclerotic CVD risk increases after successful eradication of HCV due to the unfavorable lipid profile, which is a result of reversed hypolipidemia, represented in high serum LDL and small dense LDL. The latter has greater atherogenic potential and is a better marker for prediction of CVD than LDL[31,32]. The important question at this point is whether these patients require lipid-lowering treatment. According to the National Cholesterol Education Program Adult Treatment Plan Guideline III, patients should be put on lipid lowering agents for: (1) an LDL >100 mg/dL, if they have coronary heart disease or its equivalents[1]; (2) an LDL >130 mg/dL, if they have two or more major coronary heart disease risk factors[2]; and (3) an LDL >190 mg/dL, with none or one major risk factor[33]. Corey and his colleagues have found that 13% of their studied cohort had post-SVR LDL levels requiring lipid lowering therapy as these patients had values > 130 mg/dL plus presence of two or more major coronary heart disease risk factors. Nonetheless, before antiviral therapy, none of these patients had LDL readings requiring medications. Post-treatment lipid profile deterioration may reach clinically meaningful level requiring the consideration for cholesterol lowering therapy.

HEPATIC STEATOSIS

Hepatic steatosis is a frequent histological liver finding in patients with CHC[34]. Since HCV is known to hijack lipid metabolic pathways for virion maturation and secretion, several possible mechanisms of HCV-induced liver steatosis have been suggested. HCV induces lipogenesis by increasing intrahepatic fat milieu through sterol regulatory element binding protein 1c, which is a protein that overexpresses LDL receptors which in turn facilitates fatty acid uptake by hepatocytes, leading to higher intrahepatic fat content[35]. In contrast, HCV inhibits lipolysis by disturbing mitochondrial β-oxidation[36], either directly by the virus itself or indirectly via downregulation of the enzyme carnitine palmitoyltransferase-1, which regulates fatty acids oxidation[37,38]. These two mechanisms further potentiated by HCV-induced IR[39]. Moreover, HCV core protein suppresses the activity of microsomal triglyceride transfer protein, which is used for the assembly and secretion of VLDL, resulting in increased intracytoplasmic lipid droplets and therefore steatosis[40]. Miyoshi et al[41], who studied the role of HCV core protein in development of steatosis in HCV genotype 2, revealed that core protein activates the enzyme 5-7 desaturase, fatty acid metabolizing enzyme, and therefore leads to accumulation of triglycerides. This lipid metabolism disorder was also associated with mitochondrial dysfunction[41].

Hepatic steatosis is commonly reported among patients with HCV genotype 1 and genotype 3. Its occurrence in the latter has been correlated mainly to the previously mentioned mechanisms. Therefore, resolution of steatosis observed after successful viral eradication suggests a direct steatogenic pathway for HCV genotype 3[42]. This hypothesis was backed in a study of patients treated with interferon-based regimen, in which 91% of genotype 3 patients and only 43% of other genotypes have had their steatosis improved after viral cure[43]. Kumar et al[44], have also observed similar findings when steatosis was profoundly reduced in genotype 3 patients post-SVR, while no change irrespective of the treatment response occurred in genotype 1. Although development of fatty liver was associated with viral characteristics in genotype 3 (viral steatosis), the condition in genotype 1 corresponded to metabolic features such as glucose level and IR (metabolic steatosis). This observation suggests that in patients with genotype 1, factors other than the viral features play an essential role in the development of hepatic steatosis[28].

After achieving SVR with antiviral therapy, reversal of steatosis is the most common reported outcome, which was seen in several studies[17,27,28,39]. However, recent reviews showed contradictory findings[45,46]. In a prospective study that investigated the prevalence of hepatic steatosis and fibrosis in patients with CHC post-SVR, steatosis prevalence found to be 47.5%, almost as same as the pre-treatment figure (50%). Besides, overall average fibrosis score was reduced after viral clearance. Nevertheless, patients who had steatosis have maintained clinically significant fibrosis scores, compared to those without fatty liver[46]. In another study included 49 patients aimed to evaluate the impact of DAAs on glucose and lipid homeostasis, controlled attenuation parameter values were markedly increased at the end of follow up compared to baseline. More importantly, this finding was independent of weight gain, since no change in body mass index (BMI) was observed over time[45].
Patients with CHC and viral-induced hepatic steatosis have been shown to have worse hepatic outcomes in pre-treatment setting[47]. Nonetheless, a recent study depicts that presence of post-SVR steatosis does not carry a better risk profile[48]. In this study, which aimed to assess the effect of steatosis on HCC and all-cause mortality in CHC patients post-SVR, presence of fatty liver was associated with a considerable 7.5-fold increase in both primary endpoints[48]. Furthermore, there is also a substantially higher risk of EHMs, particularly CVD, after amelioration of steatosis post-SVR[17]. These findings combined highlight the importance of hepatic steatosis as a major risk factor for poor outcome and warrant a special consideration of screening and follow-up in this population.

**INSULIN RESISTANCE & DIABETES MELLITUS**

Based on multiple epidemiological studies, metabolic alterations such as IR, DM, and metabolic syndrome are frequent comorbidities in patients with CHC, as opposed to controls[19,49]. The rationale behind this association is still not completely understood but it could be attributed to the presence of liver disease, metabolic characteristics such as obesity, or the inflammatory process induced by HCV infection. HCV has been found to modulate insulin signaling pathways although the precise molecular mechanism of HCV-mediated IR is not fully understood. In two mouse-model experimental studies, HCV core protein was found to play a major role in the development of IR[50,51] particularly through PA28γ gene-dependent pathway[50]. HCV genotypes 1, 2 and 4[52] and genotypes 1 and 4[53] were noticed to have higher IR compared to genotype 3[52] and genotypes 2 and 3[53], respectively. Oxidative stress and proinflammatory cytokines were also found to play a role in de novo IR[54,55]. The disruption in glucose and lipid metabolism associated with IR[56] leads to evolution of hepatic steatosis and development of DM. Among subjects with chronic liver disease, the prevalence of DM in CHC patients prior to treatment varies from 13.6% to 67.4%, which is higher than that reported in individuals with other etiologies, such as chronic hepatitis B[57]. Furthermore, a case-control study demonstrated that the presence of CHC was associated with an over 11-fold increase in risk of developing DM over a follow-up period of 9 years[58]. DM seems to have a bidirectional relationship with HCV, in which the latter causes IR while DM is linked with more aggressive course of HCV-related outcomes such as progressive fibrosis[49,59,60], and increased risk of cirrhosis and HCC[61,62]. All the above conditions make patients with CHC more susceptible to have metabolic syndrome[63]. However, due to the hypolipidemia caused by HCV infection[64], which does not fit the traditional diagnostic criteria, a peculiar type of metabolic syndrome known as hepatitis C-associated dysmetabolic syndrome has been defined[63,65].

There is frequent evidence that have showed a beneficial effect of antiviral therapy using interferon-based regimens on IR in long-term HCV responders. Thompson et al[66], who studied 1038 non-diabetic patients, concluded that IR was substantially decreased in HCV-genotype 1 responders but not in genotype 1 non-responders or those with genotype 2 or 3 irrespective of treatment outcome. This finding was independent of any changes in BMI. Similar findings were also reported in a prospective study[29]. In the Virahep-C, a prospective multicenter study, an improvement in the homeostatic model assessment for IR (HOMA-IR) was observed 24 wk after treatment completion among HCV genotype 1 patients who had IR prior to therapy[57]. Nonetheless, Aghemo et al[68], who enrolled 384 non-diabetic patients with HCV genotypes 1 and 4 failed to display any differences in HOMA-IR values between baseline and 24 wk post-SVR. All the above findings indicate that longer follow-up may be needed to better assess glucose metabolism disturbances after HCV viral clearance with interferon-based regimens, especially in HCV genotype 1 patients. Paradoxically, in a head-to-head comparison of 178 subjects with HCV genotype 1 and 4 between interferon-based antiviral therapy and DAAs to assess metabolic outcomes, there was a significant elevation in HOMA-IR in those who have taken interferon-based regimen[31].

In addition to its effect on IR, antiviral therapy has been thought to decrease incidence of post-SVR hyperglycemia and DM. Interferon-based regimens have been studied extensively and they are usually associated with a decreased incidence of DM in non-diabetic patients with CHC after elimination of HCV[69]. However, several studies have emphasized the beneficial role of attaining SVR, which lessens glucose metabolism abnormalities induced by HCV infection[10,39,70]. Other studies could not detect any significant differences between treatment responders and non-
CARDIOVASCULAR DISEASE

CHC infection has been linked to an array of EHMs, including an increased risk of CVD[76-79]. Several direct and indirect HCV pro-atherogenic mechanisms have been postulated. HCV is assumed to play a direct role in the development of arterial atherosclerosis by inducing endothelial dysfunction, likely through interleukin 1β[80], a pro-inflammatory cytokine. Likewise, it has been observed that HCV has the ability to live and replicate inside carotid plaques[81], which further supports an immediate pro-atherogenic effect. Moreover, chronic inflammation and oxidative stress that are caused by structural and non-structural viral proteins have also been shown to trigger plaque formation[80]. In a multicenter Italian study that evaluated the effect of attaining SVR using DAAs on subclinical carotid arteriosclerosis compared to an untreated cohort, ultrasonographic carotid measurements showed a significant reduction in mean carotid intima-media thickness in treatment group at the end of follow-up compared to baseline (from 0.94 mm to 0.81 mm, P < 0.001). No significant changes in the intima-media thickness were found in the control group. The BMI of these patients did not change during follow-up, while a significant increase in serum cholesterol levels was observed. The study concluded that eradication of HCV by DAAs led to an amelioration in carotid atherosclerosis, particularly intima-media thickness. Furthermore, HCV can also induce atherosclerosis indirectly since it is associated with an increased risk of metabolic syndrome components, including IR, DM, and hepatic steatosis, which are well-known predisposing factors for CVD[82-84]. On the other hand, some studies have failed to show any significant association between HCV and cardiovascular events[85,86].

Several studies have shown that either antiviral therapy or the attainment of SVR minimize CVD risk[87-90]. However, the results are rather controversial. Butt et al[87], who studied the effect of antiviral therapy, interferon- or DAAs-based regimens, on CVD risk found that the incidence of CVD in treatment arm was 7.2% in comparison with 13% in control group, regardless of the antiviral regimen. Treatment with DAAs was superior to interferon-based regimen, with a hazard ratio (HR) of 0.57 (95% CI: 0.51-0.65) and HR 0.78 (95% CI: 0.71-0.85), respectively. SVR was also associated with lower risk of incident CVD events HR 0.87 (95% CI: 0.77-0.98). In a nation-wide cohort study on Taiwanese residents with HCV who had received interferon-based regimens compared to an untreated cohort, antiviral therapy was associated with lower risks of acute coronary syndrome and ischemic stroke, with HR 0.77 (95% CI: 0.62-0.97) and HR 0.62 (95% CI: 0.46-0.83), respectively. This risk reduction was not observed in subjects who had insufficient treatment course (< 16 wk)[88]. Further supporting data was observed in a study comprising 3385 HCV patients, which found that SVR was associated with a lower relative hazard reduction and absolute risk reduction for CVD[89]. However, some epidemiological studies have found contradictory findings. A large retrospective cohort study which enrolled 160875 subjects was aimed to investigate the impact of successful viral eradication on a variety of EHMs. In terms of CVD risk, the study concluded that SVR was associated with a diminished risk for stroke HR 0.84 (95% CI: 0.74-0.94), but not for CVD aHR 1.12 (95% CI: 0.81-1.56), when
compared to the untreated cohort [65]. From the same perspective, a negative result was also reported by Leone et al [72], who studied the influence of SVR on EHMs. The researchers did not find any significant cardiovascular risk reduction in SVR group compared to non-SVR, with HR 1.14 (95% CI: 0.57-2.3). Despite disparities in the findings across individual studies, a meta-analysis including 53841 patients demonstrated that SVR significantly reduces CVD risk, with a pooled of HR 0.76 (95% CI: 0.61-0.94) [31].

Apart from the direct treatment effect on CVD risk, therapeutic changes on other EHMs may also play role in the development of atherosclerotic events. Deteriorated lipid profile after HCV clearance has been shown to predispose patients to an elevated risk of CVD [31]. In a study of 617 patients with a mean follow-up of 26.8 mo, Huang et al [31] investigated whether deterioration of lipid profile post-SVR increased the risk of cardio-cerebral disease. Five patients developed cardio-cerebrovascular events (3 CVD and 2 cerebrovascular disease) over 1376 person-years. An LDL surge >40% was found to be the only predictor of these vascular events, with a HR of 15.44 (95% CI: 1.73-138.20) [31]. Evidence on risk of CVD in CHC pre- or post-treatment remains controversial. Nonetheless, most of the literature indicates that achieving SVR via antiviral therapy is associated with a significant risk reduction.

CONCLUSION

EHMs including cardiometabolic conditions are commonly seen among patients with CHC infection. Data on these conditions after elimination of HCV is inconsistent. However, the predominant evidence in the literature suggests that viral clearance using antiviral therapy leads to deterioration in lipid profile, reduction in the incidence of metabolic alteration such as IR, DM, and hepatic steatosis, and improvement in cardio-cerebral disease. Five patients developed cardio-cerebrovascular events (3 CVD and 2 cerebrovascular disease) over 1376 person-years. An LDL surge >40% was found to be the only predictor of these vascular events, with a HR of 15.44 (95% CI: 1.73-138.20) [31]. Evidence on risk of CVD in CHC pre- or post-treatment remains controversial. Nonetheless, most of the literature indicates that achieving SVR via antiviral therapy is associated with a significant risk reduction.

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