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Systematic review: chronic viral hepatitis and metabolic derangement

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Summary

Background: The liver has a critical role in the metabolism of glucose and lipids. Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection leads to a spectrum of liver disease including chronic hepatitis, cirrhosis and hepatocellular carcinoma. Metabolic syndrome (MetS) has a rising incidence owing to an epidemic of type 2 diabetes mellitus (T2DM) and obesity. Non-alcoholic fatty liver disease is a liver manifestation of MetS and has become the most common cause of chronic liver disease worldwide.

Aim: To summarise the interplay among hepatitis viruses, MetS and its components.

Methods: We searched the literature about HBV, HCV infection, MetS, fatty liver and its components from PubMed.

Results: With respect to the viral replication cycle, lipids are important mediators between viral entry and hepatocyte in HCV infection, but not in HBV infection. Thus, HCV infection is inversely associated with hyperlipidaemia and lipid rebound occurs following sustained viral response induced by interferon-based therapy or direct antiviral agents. In addition, HCV infection is positively associated with insulin resistance, hepatic steatosis, MetS and the risk of T2DM and atherosclerosis. In contrast, HBV infection may protect infected subjects from the development of MetS and hepatic steatosis. Accumulating evidence suggests that HBV infection is inversely associated with lipid metabolism, and exhibits no conclusive association with insulin resistance or the risk of T2DM and arteriosclerosis.

Conclusions: In patients with viral hepatitis and concurrent metabolic diseases, a multidisciplinary approach should be given rather than simply antiviral treatment.

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1 | INTRODUCTION

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the two most important worldwide chronic viral hepatitis infections with 1.34 million deaths in 2015.[1] It is estimated that about 257 million persons chronically infected with HBV and approximately 71 million chronically infected with HCV globally.[1,2] HBV infection is highly prevalent in Asia-Pacific region and sub-Saharan African region.[3] In contrast, HCV infection distributes in all regions.[4] Chronic viral hepatitis infections lead to serious health problems, including chronic hepatitis, cirrhosis, hepatic failure and even hepatocellular carcinoma.[5,6] Most deaths related to viral infections are caused by end-stage liver disease and hepatocellular carcinoma. In addition, interactions among hepatitis viruses, the host and the environment affect the progression of liver diseases. Considering the host-related factors, metabolic syndrome (MetS) and associated diseases, such as obesity and insulin resistance/type 2 diabetes mellitus (T2DM), detrimentally affect the course of the disease, especially by accelerating liver fibrosis progression.[7-9]

MetS is characterised by dysglycaemia, raised blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels and obesity (particularly central adiposity).[10] It is known that MetS strongly associates with IR and frequently linked to obesity, T2DM and cardiovascular risk.[11-13] The prevalence of MetS varies among countries but markedly increases worldwide over the past few decades due to the pandemic of obesity by increase in consumption of high caloric food and sedentary lifestyles due to socioeconomic improvement.[14-16] In the adults of United States, the prevalence of MetS raised from 25.3% in 1988-1994 to 34.2% in 2007-2012.[17] The trend of increasing prevalence of MetS is also observed in Asian countries, such as Korea, Taiwan and China.[14,18] Subjects with HCV infection are also prone to develop IR, T2DM and steatosis. The replication cycle of HCV heavily depends on the pathway of lipid metabolism in hepatocytes and considerably alters host lipid haemostasis, increasing cardiovascular risk.[19-21] In contrast, studies of HBV have yielded inconclusive data on the association with hypolipidaemia.[22,23] Chronic HBV infection is not associated with, nor does it lead to, hepatic steatosis, insulin resistance or T2DM.[24] Hepatic steatosis may even promote the spontaneous clearance of hepatitis B surface antigen.[25]

Derangement of the adipokines, such as adiponectin, is frequently observed in subjects with MetS. Lower levels of adiponectin have been linked to obesity, steatosis, MetS and insulin resistance.[26] The associations of adiponectin levels with HBV and HCV infections are quite different and associated with different clinical outcomes of liver diseases.[27-32]

This comprehensive review summarises current knowledge of the associations of chronic HBV and HCV infection with metabolic derangements and extrahepatic diseases, including MetS, fatty liver, lipid metabolism, insulin resistance/T2DM, adiponectin and arteriosclerosis.

2 | CHRONIC HEPATITIS VIRAL INFECTION AND METABOLIC SYNDROME

MetS is prevalent and increases the risk of mortality, cardiovascular events and cancer development. The constellation of metabolic abnormalities of MetS includes glucose intolerance, insulin resistance, central obesity, dyslipidaemia and hypertension. The cut-offs in some components of MetS are different among available definitions and have interethnic adjustments.[33] Joint Scientific Statement in 2009 defined patients who exhibit three of the five following characteristics are diagnosed as having metabolic syndrome: abnormal waist circumference as population- and country-specific definitions, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or currently taking blood pressure-lowering agents, high-density lipoprotein of cholesterol <40 mg/dL in males or <50 mg/dL in females, fasting blood sugar ≥100 mg/dL or currently taking diabetes medications, and triglyceride ≥150 mg/dL[10] The association between viral hepatitis infections and MetS has been increasingly recognised (Table 1). In the literature, a population-based study of 53,528 subjects from Taiwan was the first to find an inverse correlation between HBV and MetS (odds ratio, 0.72, $P < .001$).[34] A population database from the United States revealed that the prevalence of MetS in the HBV population and the total population is 10.4% and 25.6%, respectively. After adjustment for confounders, this database showed an inverse association between chronic HBV infection and MetS in the general population and in men (odds ratio: 0.32 and 0.14, respectively).[35] Most previous studies have demonstrated that the prevalence of MetS was lower in the HBV population than in healthy controls, but not statistically significantly.[36-41] In contrast, a retrospective study from China found a higher prevalence of MetS in patients with chronic HBV infection than in others.[42] A recent large population-based study identified an association between chronic viral hepatitis and MetS in southern Taiwan. They found that HCV was positively associated with MetS, but HBV infection was inversely associated with MetS only for lean subjects (BMI below 24 kg/m^2).[43]

Three reviews and a meta-analysis have been published in the last 3 years. The first review found that an odds ratio of MetS risk in chronic HBV-infected patients is 0.82, but it was not statistically significant.[44] The second review covered 13 studies and a pooled analysis indicated that HBV was inversely associated with MetS with an odds ratio of 0.83 in either the East Asian or the non-East Asian region. A subgroup analysis suggested an inverse association in men and a sample population of under 45 years of age.[45] The most recently published review including 12 articles and a forest plot revealed an odds ratio of 0.8 for MetS prevalence in hepatitis B surface antigen-positive subjects compared to healthy controls.[46]

Taken together, these lines of evidence imply that the risk of MetS is not increased in HBV patients. On the contrary, HBV infection may have a protective effect against MetS. This protective effect seems to be greater in males, people under 45 years and lean subjects.

TABLE 1 A summary of studies on the association of hepatitis B virus and hepatitis C virus infection with metabolic syndrome

Author (Year)	Hepatitis virus	Study design	Subjects	Findings	Reference
Jan (2006)	HBV	Population-based cross-sectional study	53 528	There was an inverse association between MetS and HBV infection	[34]
Wong (2012)	HBV	Case series	1013	HBV infection is associated with lower prevalence of MetS.	20
Li (2013)	HBV	Case series	26 305	The prevalence of MetS was not different between HBV patients and controls.	36
Jinjuvadia (2014)	HBV	Population database	7 874 214	CHB is inverse associated with MetS.	35
Zhou (2014)	HBV	Case series	976	A positive association between HBV and MetS.	42
Chung (2014)	HBV	Hospital-based	9474	HBV infection is negative associated with MetS in men.	37
Jarcuska (2014)	HBV	Cross-sectional	855	Viral load of CHB patients with MetS was higher than those without.	38
Huang (2015)	HBV	Cross-sectional	17 030	Chronic HBV infection is inverse associated with MetS.	39
Choi (2015)	HBV	Community-based	5108	Serum HBsAg positivity is inversed associated with MetS in men.	40
Katoonizadeh (2016)	HBV	Population-based study	12 781	CHB is positive associated with MS in woman, but inverse associated with MetS in men.	41
Razi (2017)	HBV	Meta-analysis	138 994 999	CHB is associated with decreased risk of MetS.	45
Li (2017)	HBV	Meta-analysis	12 studies	Serum HBsAg positivity is inversed associated with the prevalence of MetS.	46
Kuo (2018)	HCV	Population-based study	13 428	HCV infection was positively associated with MetS	43
Banks (2017)	HCV	Retrospective observational study	476	Among chronic HCV patients, the highest risk of MetS was seen among older patients.	47
Lonardo (2009)	HCV	Case-controlled study	372	The frequency of MS in HCV-infected patients was similar to that of healthy controls and significantly lower than that seen in NAFLD patients.	49
Kuo (2016)	HCV	Population-based study	156	Higher LSM level was associated with metabolic syndrome in elderly CHC patients.	48
Yoon (2013)	HCV	Case series	104	Metabolic syndrome was significantly more prevalent in patients with CHC than in patients with CHB.	50
Dong (2018)	HCV	Retrospective observational study	1068	The presence of metabolic syndrome does not adversely affect SVR12 rates in patients treated with DAA.	51

Abbreviations: CHB, chronic hepatitis B; CHC, chronic hepatitis C; HBV, hepatitis B virus; HCV, hepatitis C virus; MetS, metabolic syndrome.

HCV is thought to induce metabolic derangements and is associated with IR, T2DM, steatosis and MetS. Insulin resistance or metabolic derangement of glucose is the central pathogenesis of both chronic hepatitis C (CHC) and MetS. HCV infection was strongly associated with MetS in a large population cohort study.[43] These two diseases have overlapping manifestations and close association. The prevalence of MetS ranges from 13.2% to 31.5% among HCV-infected patients and is higher in older subjects.[43,47] HCV-infected African Americans seem to be more prone to developing MetS than other ethnicities.[41] CHC patients who are older than 60 years have eight times the odds ratio of having MetS than those under the age of 40 years.[41] However, not all studies demonstrate the association of CHC and MetS. The presence of HCV viraemia is not found to affect the prevalence of MetS in anti-HCV antibody-positive patients.[48] One small Italian cohort study comparing the prevalence of MetS in 97 patients with HCV genotype 1/2 infection and 182 healthy controls revealed that the frequency of MetS in HCV-infected patients was similar to that of controls.[49]

CHC patients with MetS have an aggressive and severe liver disease. Fibrosis is significantly more severe in CHC patients with MetS than in those without. A study from Taiwan examined the factors associated with MetS in elderly patients with viral hepatitis in community-based population and found that higher liver stiffness value was associated with MetS.[50] The prevalence of liver cirrhosis in patients with both HCV infection and MetS was 30%, whereas it was 18.4% in patients with HCV infection alone. The effect of MetS on the response of DAA to treatment was limited. One recent study reported that MetS did not negatively affect the sustained viral response (SVR).[51]

In summary, HCV infection has been confirmed to be associated with MetS, and MS may worsen the progression of liver diseases in HCV-infected patients. Owing to the high effectiveness of DAA, the impact of viral clearance on MetS and associated diseases requires further investigation.

3 | CHRONIC HEPATITIS VIRAL INFECTION AND FATTY LIVER

Fatty liver is identified by an intrahepatic triglyceride content of more than 5% of the liver and the criterion is considered regarded as the gold standard for its diagnosis.[52] In clinical practice, fatty liver is generally diagnosed by ultrasonic examination. Proton magnetic resonance spectroscopy is a non-invasive method for measuring intrahepatic fatty content.[53] Non-alcoholic fatty liver disease (NAFLD) is known to be a common liver disease that is associated with a risk of cirrhosis or even HCC development.[54]

Using a CHB cohort with histological data, a case series study on 164 CHB patients with liver biopsy was the first to demonstrate that hepatic steatosis was associated with metabolic factors of the host rather than the virus.[55] Many subsequent studies consistently found associations of BMI and serum triglyceride level with hepatic steatosis. No association of hepatic steatosis with HBV viral load or HBeAg status was shown.[56-58] In contrast, an Indian study of 350 CHB patients found a negative association between hepatic steatosis and serum HBV DNA level.[59] A meta-analysis of 17 studies of 4100 HBV-infected patients with histological data verified a negative association between HBV viral load and hepatic steatosis. In brief, these data indicated that hepatic steatosis was positively associated with metabolic factors; however, HBV infection appeared to have a protective effect against the development of hepatic steatosis.[60]

Using ultrasonic examinations to identify fatty liver, our small-scale study of 507 subjects at a health examination centre showed that the prevalence of fatty liver and insulin resistance in CHB patients was comparable with that of healthy controls. Multivariate analysis also indicated that HBsAg-positive status was not associated with fatty liver. We concluded that HBV infection was not associated with insulin resistance or fatty liver.[61] Another study of 4365 subjects also found that the prevalence of fatty liver in an HBV-infected group was similar to that in an non-HBV-infected group (16.7% vs 18.3%).[62] However, a recent large-scale study (33 439 subjects) in Taiwan found that HBV-infected patients, especially older and obese patients, had a lower prevalence of fatty liver than the general population.[63] Furthermore, metabolic factors, such as age, body mass index, systolic blood pressure, fasting glucose and cholesterol (Chol), were positively associated with fatty liver. Positive HBsAg was negatively associated with high-density lipoprotein cholesterol (HDL-C) and fatty liver.

Using proton magnetic resonance spectroscopy to diagnose fatty liver, Wong et al prospectively enrolled 1013 subjects in Hong Kong. They found a prevalence of fatty liver of 14.3% in an HBV group and 28.6% in healthy controls (P = .003). They identified HBV infection as an independent factor associated with a lower risk of fatty liver following adjustment for demographic and metabolic factors.[23]

In brief, chronic HBV infection may be inversely associated with fatty liver. Larger cohorts or the use of highly sensitive diagnostic tools, such as proton magnetic resonance spectroscopy or histological tools, may prove the protective effect of chronic HBV infection against fatty liver in the foreseeable future.

Unlike HBV infection, HCV infection induces a derangement of lipid metabolism in hepatocyte that generates a lipid-rich environment for HCV replication. In chronic HCV infection, the prevalence of NAFLD is reportedly as high as 55%.[64] Liver steatosis is more prevalent in subjects that are infected with genotype 3 than those infected with non-genotype 3 HCV.[65,66] Genotype 3 HCV is directly linked to liver steatosis. The severity of steatosis correlates with the replication ability of HCV and improves following successful clearance of the virus.[67,68] For patients infected with other HCV genotypes, liver steatosis occurs mostly due to combination of viral and metabolic factors. Among HCV proteins, core proteins play an important pathogenic role. Impaired lipoprotein secretion by inhibition of microsomal triglyceride transfer protein, increased lipogenesis by upregulation of sterol regulatory element binding protein signalling pathway, and impaired fatty acid degradation by reducing the expression of peroxisome proliferators-activated receptor-alpha are the three main mechanisms modulated by core proteins and predispose to liver steatosis.[69,70] Other HCV proteins such as non-structure 2, non-structure 4b and non-structure 5A are also able to modulate lipogenic gene expression and thus have impact on lipid metabolism.[71,72] Several lines of evidence from in vitro studies support the genotypic difference in inducing liver steatosis and the core proteins of genotype 3 HCV may exhibit more potential to influence lipid accumulation in liver cells and regulate lipid metabolism.[73,74] Although previous transgenic mice model studies suggested that expression of HCV core or structure proteins could induce steatosis,[75,76] metabolic or genetic factors also contributed to the development of hepatic steatosis in HCV patients.[77,78] Steatosis in liver histology is one of the numerous metabolic derangements that are associated with chronic HCV infection. Other derangements such as body mass index, insulin resistance/T2DM, alcohol consumption, arterial hypertension, hypercholesterolaemia and visceral fat hypertrophy may partially predispose a subject with chronic HCV infection to the development of fatty liver.[79-83] In contrast to HCV mono-infection, dual HBV/HCV infection displays different

features. The prevalence of steatosis was similar between patients with dual HBV/HCV infection and those with HCV mono-infection, but it was lower in patients with HBV mono-infection.[84,85] However, in the subgroup of lean HBV/HCV dually infected patients with detectable HBV DNA, the prevalence of steatosis was significantly lower than the lean HCV mono-infected patients with matched HCV viraemia (15% vs 45%, $P = .02$).[84] These results indicated that HBV may interact with HCV and counteract the metabolic disarrangements caused by HCV.

NAFLD can modify the natural history of HCV infection in the progression of fibrosis. Cross-sectional studies have demonstrated that hepatic steatosis was significantly associated with fibrosis.[86,87] A longitudinal study enrolled 96 non-cirrhotic CHC patients with paired liver biopsies in an interval of 48 months apart. Worsening of fibrosis was observed in 31% of patients. Based on the status of steatosis at the first liver biopsy, the severity of hepatic steatosis was strongly related to the fibrosis progression and was the only independent factor that affects the fibrosis progression according to a multivariate analysis.[88] Another meta-analysis on 3068 CHC patients also concluded that steatosis was independently associated with fibrosis.[89] However, a study of 494 CHC patients with available liver biopsy yielded contradictory results. In that study, steatosis was associated with fibrosis based on univariate analysis, but not multivariate analysis. In a study of 136 patients with a pair of liver biopsies that were separated by 0.5-17 years, steatosis was not related to fibrosis progression.[90] These findings indicate that some non-viral factors, such as a high body mass index,[91] alcohol consumption, T2DM[92-94] and genetic polymorphism, may also predispose CHC patients to the development of steatosis.

Most of the NAFLD patients experience nutritional and metabolic disorders, such as obesity, T2DM and dyslipidaemia which may be further worsen by CHC. Therefore, lifestyle modifications and treating concomitant diseases become the fundamental and necessary modalities to achieve disease control. Lifestyle modifications involve a multi-disciplinary intervention. A combination of a low-fat (less than 10% of saturated fatty acid), hypocaloric (less than 1600 daily calories) and low carbohydrate (less than 50% of total calories) diet, and increase in physical activities or exercise to achieve an adequate body weight reduction is the key of approach.[95] A 5% of body weight reduction is necessary to get improvement of steatosis and more than 10% of reduction leads to regression of fibrosis and resolution of steatotic hepatitis.[96,97] However, adequate body weight could only be maintained in about half of people within 12 months, implying that lifestyle modifications exhibit limitation and would be a difficult issue. NAFLD and CHC share common concomitant diseases, including cardiovascular and metabolic disorders.[98] Well-controlled concomitant diseases by pharmacologic treatment are important, not only for diseases control but also for improving outcomes of associated diseases. For CHC patients with NAFLD, clearance of HCV offers benefits on reducing hepatic and extrahepatic events.[99-101] A previous study showed that steatosis is a negative predictor of SVR following interferon treatment.[69] In the current era of DAA, the very high SVR rate across various genotypes undermines the impact of steatosis on the outcome of CHC treatment. Few studies examined the changes in hepatic steatosis following DAA treatment; however, the data revealed contradictory results in hepatic steatosis following HCV clearance, as measured using a controlled attenuation parameter.[70,102,103] The long-term impact of DAA treatment on steatosis and associated features in CHC patients with SVR and should be examined in the future.

4 | CHRONIC HEPATITIS VIRAL INFECTION AND LIPID PROFILES

The liver plays a critical role in lipid metabolism, and hyperlipidaemia is a risk factor for cardiovascular disease.[104] Chronic viral hepatitis can lead to hepatic inflammation, fibrosis and even cirrhosis. Fatty acid biosynthesis has been known to contribute to the genomic replication of HCV. A recent study also revealed that fatty acid biosynthesis was associated with HBV particle production, but not through genomic replication.[105] The interplay among hepatotropic virus, liver reserve and lipid profiles is thus of interest.

Two studies from Taiwan investigated the association between HBV and lipid profiles. One revealed lower serum level of total Chol and HDL-C in patients with chronic HBV infection.[106] Another large-scale community-based study on 56,336 residents found that HBsAg-seropositive subjects had a lower prevalence of hypertriglyceridaemia and of hypercholesterolaemia.[107] Later, a study (that involved a health examination population found that HBV-infected patients had a lower incidence of hypertriglyceridaemia and hypercholesterolaemia, and higher low-density lipoprotein cholesterol (LDL-C) levels.[108] Our case-control study showed that HBV patients had a significantly higher serum adiponectin level but lower serum triglyceride (TG) and HDL-C levels than healthy controls. These differences remained unchanged for middle-age patients after modification for serum alanine aminotransferase levels. A retrospective cohort of 122 CHB patients with data on serum HBV DNA level and insulin resistance verified an inverse association of serum HBV DNA level with serum TG level, but not with insulin resistance.[22] A review article showed that in most relevant studies, the level of serum Chol was lower in CHB patients than in controls. Although serum HDL-C and LDL-C levels were lower in CHB patients than in controls, only some of the studies indicated that the difference was statistically significant. A recent meta-analysis found that the risk of hypertriglyceridaemia is 43% lower in CHB patients than in controls. These findings demonstrated that chronic HBV infection may have an inverse association with hypercholesterolaemia and hypertriglyceridaemia. Further works are needed to investigate the relationship among HBV, serum HDL-C and LDL-C levels.

In cases of HCV infection, the replication cycle of HCV is strongly associated with human lipid metabolism and entry, replication and assembly require host lipids, lipoproteins and apolipoproteins.[109] Existing evidence indicates that HCV controls the host factor diacylglycerol acyltransferase-1 to promote the biogenesis of lipid droplets, and the HCV core protein recruit non-structure 5A

that carries HCV RNA from the replication complex on the endoplasmic reticulum-derived membranous web to lipid droplets.[110,111] Simultaneously, the enveloped viral particles may be packaged into endoplasmic reticulum luminal lipid droplets in the very low-density lipoprotein cholesterol (VLDL) precursor[112] and secreted into circulation via the VLDL-dependent pathway as lipo-viral particles.[113]

HCV infection alters many aspects of the relationship between the liver function and lipoprotein homeostasis, including by impairing the VLDL-releasing pathway, which is one of the causal mechanisms of hepatic lipid accumulation, dyslipidaemia and hypobetalipoproteinaemia.[9] The HCV core and non-structure 5A proteins interact with apolipoprotein (apo)A,[114] apoAII[115] and apoE,[116,117] and so might play roles in liver steatosis, mediated by the derangement of lipid metabolism. The HCV lipo-viral particles contain increased levels of apoC-III that may inhibit the activity of lipoprotein lipase, disturbing the intravascular catabolism of TG-rich lipoproteins.[118] Moreover, the profiles of serum lipids, such as TG, Chol, LDL-C and HDL-C, were reduced in patients with acute[119,120] and chronic HCV infection.[121-123] An increasing body of evidence demonstrated that HCV may modulate lipid metabolism[124,125] and promote the synthesis of saturated fatty acids by controlling the enzymes in the lipid synthesis pathway.[126,127] Supplementation with poly-unsaturated free fatty acids counteracts HCV-induced lipid alterations and inhibits HCV infection.[128] These results indicated that HCV may take over the lipid biosynthesis machinery and make the lipid environment more favourable conducive to virus infection.

Earlier studies already suggested that interferon-based antiviral therapy could reverse the hypocholesterolaemia induced by HCV. In the era of DAA, increased levels of Chol and LDL-C follow the clearance of HCV has been reported. Our study investigating the dynamic changes of the loading capacities of VLDL and LDL-C following DAA treatment revealed that the TG and Chol loading capacities in VLDL and the Chol loading capacity in LDL-C rapidly increased following SVR.[129] These results indicated that large amounts of lipids released from the liver into blood circulation may increase levels of Chol and LDL-C, resulting in the hydrolysis of TG. However, studies on the long-term dynamics of lipid profile following SVR and the effects on clinical outcomes, especially cardiovascular events, must be conducted afterwards.

5 | CHRONIC HEPATITIS VIRAL INFECTION WITH INSULIN RESISTANCE AND DIABETES MELLITUS

The liver has insulin receptors and plays a role in glucose homeostasis. Insulin resistance is considered to be a cause of both MetS and NAFLD. However, the relationship between chronic HBV infection and insulin resistance is not fully understood. Our previous works demonstrated that insulin resistance did not differ between HBV patients and healthy controls. According to multivariate linear regression, carrying HBV was not associated with insulin resistance and hepatic steatosis. A study of 7880 adults from Korea yielded inconsistent results, showing chronic HBV infection was associated with insulin resistance, based on both HOMA-insulin resistance and the quantitative insulin check index after adjustments were made for age, gender, BMI and the alcohol consumption.[130] Therefore, further studies are needed to confirm the association of chronic HBV infection with insulin resistance.

Regarding the relationship between HBV and DM, a cross-sectional study of 835 Asian Americans and Pacific islanders found that the prevalence of DM was significantly higher in Asian American HBV carriers than controls, but not in Pacific islander HBV carriers.[131] Our previous study on 1223 adults from Taiwan found that the prevalence of DM among HBV carriers was comparable to that among non-HBV controls. Among 296 non-diabetic subjects, the 10-year incidence of DM and glucose intolerance did not differ between these two groups, suggesting asymptomatic HBV infection did not increase the risk of T2DM.[132] A population-based cohort study with a large sample and 20 years of observations yielded consistent findings. The incidence of DM among HBV carriers was comparable to that among non-HBV controls, indicating that HBV may have no effect on DM development.[133] However, a meta-analysis of 15 studies showed that the prevalence of T2DM among HBV carriers is 1.33 times than that among controls. They concluded that the risk of T2DM was increased in chronically HBV-infected patients, but more data are required to reach a definite conclusion.[134] Owing to these controversial results, the association among HBV, insulin resistance and T2DM remains inconclusive.

Unlike HBV infection, HCV-infected subjects are at a higher risk of developing insulin resistance. The odds ratio of insulin resistance among these subjects is approximately 2.2-3.0 times that of healthy volunteers, and the prevalence of insulin resistance is 22.5%-62% among HCV-infected subjects.[134-141] Similarly, the odds ratio of developing T2DM in HCV-infected subjects is about 1.2-1.7 and the prevalence is 18%-35%.[142,143] The impairment of glucose metabolism in HCV-infected patients may be associated with a higher risk of worsening liver fibrosis, steatosis, HCC and resistance to antiviral treatment.[144]

Several possible mechanisms are involved in the development of HCV-induced insulin resistance (Figure 1). Impairment of glucose uptake arises from suppression of glucose transporters 1 and 2 in HCV-infected cells and interferon treatment can restore glucose transporters expression.[145] Glucose transporters are responsible for glucose transport into hepatocytes. HCV also induces the overproduction of tumour necrosis factor alpha, which can block glucose transporters activity and reduce the uptake of glucose by hepatocytes.[146,147] In HCV core-transgenic mice livers and HCV core-transfected human hepatoma cells, the HCV core up-regulated suppressor of cytokine signalling 3 and caused the ubiquitination of insulin receptor substrate 1 and 2. The HCV core also suppressed the insulin-induced phosphorylation of phosphatidylinositol 3-kinase and protein kinase B (also known as Akt), leading to impaired the activity of insulin.[148]

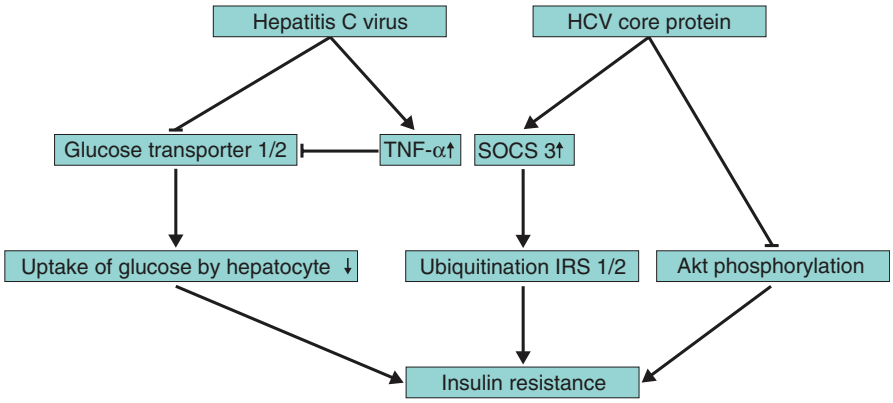

FIGURE 1 Illustration of the possible mechanisms of insulin resistance induced by HCV. TNF-α, tumour necrosis factor alpha; SOCS, suppressor of cytokine signalling; IRS, insulin receptor substrate; Akt, phosphatidylinositol 3-kinase and protein kinase B.

Many studies found an independent association of insulin resistance with the progression of hepatic fibrosis and the occurrence of HCC.[143,149-154] Insulin resistance also impairs the response to interferon treatment.[144,155,156] However, the clearance of HCV by interferon therapy improves insulin resistance[157-159] and prevents insulin resistance development after 2 years following SVR. Non-SVR patients had a higher risk of *de novo* insulin resistance than SVR patients (17% vs 7%, $P = .007$). A meta-analysis of the association of SVR with extrahepatic diseases of CHC revealed that SVR reduced the risk of insulin resistance at follow-up (odds ratio: 0.42, 95% CI 0.33-0.53) and had a significant protective effect against the incidence of new-onset T2DM (odds ratio: 0.34, 95% CI 0.21-0.56).[160] In the era of DAA, the very high SVR rate causes doubt on whether insulin resistance could affect antiviral response. In contrast, insulin resistance significantly improved quickly when SVR is achieved.[160] Additionally, for patients with T2DM, SVR leads to better glycaemic control at 12-week post-treatment than before DAA treatment is commenced.[129,161,162] Dawood et al. further indicated that 26.7% of patients had to decrease the dose of antidiabetic treatment because of better glycaemic control.[163] In addition, the improvement of insulin resistance is also observed in patients achieving SVR. These results suggest the long-term benefits of insulin resistance and T2DM control generally follow HCV clearance by DAA treatment. However, the treating physicians should be cautious that some degree of insulin resistance may remain in patients with advanced fibrosis.[164]

6 | CHRONIC HEPATITIS VIRAL INFECTION AND ADIPONECTIN

Adiponectin is one of three adipocytokines and is the most abundant. It is a protein hormone that is produced by adipose tissue and is responsible for the regulation of carbohydrate and lipid metabolism. Once it has bound to receptors of hepatocytes, adiponectin triggers signal transduction pathways that influence lipid synthesis or fatty acid oxidation. Three isoforms of adiponectin, with a high molecular weight, a medium molecular weight and a low molecular weight, are produced through post-translation modification. The biological functions of adiponectin, include anti-inflammation, anti-fibrosis, anti-oxidation, immunomodulation and others.[165-167] Obesity is associated with reduced adiponectin levels and a low level of adiponectin is a risk factor for the development of T2DM and MetS. Table 2 presents the relationship between HBV/HCV infection and adiponectin level.

With respect to the relationship between adiponectin and HBV treatment, our earlier study revealed that adiponectin levels tended to decrease in the responders of CHB patients upon interferon-alpha treatment for 24 weeks, but an insulin suppression test revealed improved insulin resistance.[168] Another study revealed that a marked decline in adiponectin level after antiviral therapy is associated with a reduction of fibrosis using either interferon or lamivudine.[169]

One of our previous studies showed that CHB patients had significantly higher serum adiponectin levels than healthy controls, but lower TG and HDL-C levels.[22] Our subsequent study also found that serum adiponectin level was associated with serum HBsAg and HBV DNA.[170]

Regarding the relationship among adiponectin, liver fibrosis and steatosis, a study revealed that adiponectin level was positively correlated with the severity of liver fibrosis. Another study on adiponectin levels in different cases of chronic liver disease found a positive association with the severity of fibrosis in CHB and male CHC patients. No relationship among steatosis, necroinflammation and adiponectin level existed.[26] Nevertheless, a study from China presented a different finding that serum adiponectin was inversely associated with steatosis in CHB patients.[27]

TABLE 2 Comparison of metabolic derangements between chronic HBV and HCV infection

	HBV	HCV
Metabolic syndrome	↓	↑
Fatty liver	↓	↑
Hyperlipidaemia	↓	↓
Insulin resistance	NA	↑
Diabetes mellitus	NA	↑
Adiponectin	↑	↓
Atherosclerosis	NA	↑

Considering cirrhosis and HCC, one of our studies revealed that CHB patients had a significantly lower serum adiponectin level than patients with cirrhosis or HCC. Multivariate analysis found that high serum adiponectin was associated with the development of HCC, suggesting serum adiponectin level was correlated with the progression of HBV-related liver disease.[171] We also confirmed that a higher serum adiponectin level was associated with a dose-dependent increased risk of HCC.[172]

These lines of evidence suggested that serum adiponectin was not only associated with chronic HBV infection but also with the progression of HBV-related liver disease, including fibrosis, cirrhosis and especially the development of HCC, probably due to the deteriorating liver reserve.

As mentioned earlier, the HCV replication cycle depends strongly on the lipids in hepatocytes. Lower levels of adiponectin have been linked to steatosis, MetS, insulin resistance and poor responses to interferon therapy in CHC patients.[28-31] Although a study investigating the level of adiponectin in CHC patients shows controversial results compared to healthy controls,[173] lines of evidence from other studies conclusively demonstrate the negative correlation between adiponectin level and steatosis in CHC patients.[174-176] Of note, genotype 3 exhibits lower level of adiponectin than other HCV genotypes.[176] Adiponectin level has been demonstrated to be negatively associated with insulin resistance in CHC patients with MetS.[177] CHC patients with MetS have low adiponectin levels than those without MetS. These results were confirmed by Aksõz et al, in which chronic HCV infection did not affect adiponectin concentration in the absence of metabolic disorders.[178] Moreover, adiponectin levels are not associated with HCV RNA levels, suggesting the impact of HCV infection on adiponectin levels may not be directly caused by virus itself but by metabolic or hepatic alterations after HCV infection.[179,180]

The reduced expression level of adiponectin in CHC patients with steatosis may relate to tumour necrosis factor alpha.[181,182] This finding was confirmed by a study by Zografos et al, showing that low adiponectin and high tumour necrosis factor alpha levels were associated with hepatic steatosis.[31] Peroxisome proliferator-activated receptor alpha also play a role in steatosis. Lines of evidence reveal that HCV core proteins suppress the hepatic expression of peroxisome proliferator-activated receptor alpha and then affect the ability of adiponectin to normally function in lipid metabolism, and subsequently results in reduced fatty acid oxidation, which produces a predisposition to lipid accumulation in hepatocytes.[183] The hypoadiponectinaemia can be reversed by administering a peroxisome proliferator-activated receptor alpha agonist.[184,185] Oxidative stress against HCV also plays a role.[186] Reactive oxygen species induced by HCV activates nuclear factor kappa-light-chain-enhancer of activated B cells that subsequently increases the expression of many cytokines, including tumour necrosis factors and IL-6, and then downregulates adiponectin.[187]

Although there is association of hypoadiponectinaemia with steatosis in CHC patients, those with significant inflammation or fibrosis had hyperadiponectinaemia.[188,189] A case-controlled study further showed that HCV-related HCC patients had a higher level of adiponectin than those without HCC and healthy controls.[190] Since adiponectin may also enhance T-cell-dependent cytokines production,[28] the complex interactions among adiponectin, metabolic disarrangements and immune responses would contribute to the heterogeneous features of adiponectin in CHC patients and further studies are needed to address this interesting and important issue.

A few studies reported the changes of adiponectin levels upon antiviral treatment. A lower adiponectin level was a negative predictive factor of achieving SVR in interferon-based therapy.[31,180,191] A decrease in adiponectin level is observed only in CHC patients who have achieved SVR. In the era of DAA, studies on the dynamics of adiponectin levels and responses to treatment are still lacking. Based on the dramatic changes in lipid profiles following eradication of HCV, the adiponectin level after viral clearance may provide new insights to lipid metabolism in liver cells.

7 | CHRONIC HEPATITIS VIRAL INFECTION AND ARTERIOSCLEROSIS

Chronic infection has been proposed to be linked with atherosclerosis, which increases the risk of cardiovascular disease. Whether chronic HBV infection is associated with atherosclerosis is thus of interest.

Using coronary angiography, two studies found that the percentage of patients with coronary arterial disease who are HBV-seropositive is similar to that of those without that disease.[192,193] Using carotid duplex or pulse wave velocity, two cross-sectional studies showed HBV carriers were not associated with a higher risk of arteriosclerosis than non-HBV infected controls.[194,195] Some studies yielded conflicting results. A small case-control study using carotid intima-media thickness, an early index of atherosclerosis, revealed that NASH, HBV and HCV were associated with early arteriosclerosis, independent of potential confounders.[196] In contrast, a study using the Taiwan national insurance database found that HBV was associated with a reduced risk of acute ischaemic stroke.[197] A recent meta-analysis revealed that HBV tended to promote atherosclerosis-associated disease, but not significantly so.[198] Therefore, the relationship between HBV and atherosclerosis requires further clarification.

A recent cohort study compared the cardiovascular outcomes and all-cause mortality rates within 13 years between chronic HBV and HCV-infected patients. Arterial events included acute coronary syndrome, peripheral artery disease and acute ischaemic stroke. The study concluded that chronically HCV-infected patients had a higher risk of arterial events and all-cause mortality than chronically HBV-infected patients.[199]

Chronic HCV infection causes a chronic systemic inflammation status that is triggered and maintained by HCV proteins. Oxidative stress,[200] the induction of pro-atherogenic cytokines and chemokines,[201] the direct atherogenic effect of HCV replication in carotid plaques[202] and metabolic factors that are related to HCV infection, including steatosis, insulin resistance and T2DM,[182,203] all contribute

to the process of arteriosclerosis which increases the risk of cardiovascular events in CHC patients.

In addition to hepatic diseases, extrahepatic manifestations that are related to HCV infection are clinically associated with an increased risk of organ dysfunction. Of these, cardiovascular diseases are important manifestations that worsen outcomes for CHC patients. A community-based prospective cohort study in Taiwan found that the hazard ratio for occurrence of cerebrovascular death and circulatory diseases was 2.18 (95% CI:1.50-3.16) and 1.50 (95% CI:1.10-2.03) for anti-HCV-seropositives, respectively.[19,20] In a large meta-analysis that compared the risk of cardiovascular diseases in 297,613 HCV patients with that in 557,814 uninfected controls, the odds ratio of cardio-cerebrovascular disease was 1.428 (95% CI: 1.214-1.681) for HCV patients. A sub-analysis also demonstrated that HCV infection increased the risk of coronary artery disease (odds ratio: 1.382; 95% CI: 1.103-1.732) and of cerebrovascular disease (odds ratio: 1.485; 95% CI: 1.079-2.044).[204]

A few studies addressed the association between cardiovascular risk and DAA treatment. A recent retrospective, a case-controlled study involved 4436 pegylated interferon/ribavirin-treated and 12 667 DAA-treated CHC patients. Treatment with pegylated interferon and ribavirin (hazard ratio, 0.78; 95% CI, 0.71-0.85) or a DAA regimen (0.57; 95% CI, 0.51-0.65) was associated with a significantly lower risk of a cardiovascular event than that associated with no treatment.[205] However, findings regarding vascular parameters following SVR that is achieved by DAA are inconsistent. One recent study measured and compared the intima thickness of the carotid artery at baseline and that 9-12 months after the end of treatment.[206] It enrolled 182 DAA-treated CHC patients and all achieved SVR. The intima thickness significantly decreased (0.94 ± 0.29 mm vs 0.81 ± 0.27, $P < .001$) and a significant reduction in the prevalence of carotid thickening from baseline to follow-up was observed (42.8% vs 17%, $P < .001$). A study from Japan provided contradictory results. It measured intima thickness following DAA treatment and found that the maximal intima thickness was higher after 1 year of treatment than the baseline value. The authors observed that a small dense LDL-C was associated with the increase in intima thickness.[207] Another report found a significant improvement of tricuspid annular plane systolic excursion and lateral E' velocity relative to baseline values, following SVR to DAA in HCV cirrhotic patients.[208] Central artery stiffness was also increased following HCV clearance as a result of DAA treatment and was related to an increase in LDL-C.[209] Long-term results addressing these paradoxical findings in terms of vascular parameters and the risk of cardiovascular events following viral clearance would be worth investigating.

8 | CONCLUSIONS

It is clear that different hepatitis viruses have different effects on metabolic factors and hepatic/extrahepatic diseases. Both chronic HBV and HCV infection are inversely associated with hyperlipidaemia. Chronic HCV infection is positively associated with fatty liver and MetS, but chronic HBV infection may protect against them. Chronic HCV infection is associated with insulin resistance and an increased risk of T2DM or atherosclerosis, but no similar conclusion can be drawn with respect to chronic HBV infection. Serum adiponectin level is increased in HBV-infected patients, but any such change in HCV-infected patients remains controversial. The complex interplay among viral hepatitis, metabolic factors and diseases deserves further studies. In clinical practice, the treating physicians should pay attention to chronic viral hepatitis patients with concomitant metabolic disorders and implement a multidisciplinary approach, including life-style modification and body weight reduction, instead of simple antiviral therapy. In addition, management of metabolic diseases is also mandatory to prevent the progression of liver disease and improve the adverse outcomes of associated diseases.

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REFER ENCES

1. *Global Hepatitis Report 2017*. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
2. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol*. 2017;2:161-176.
3. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg sero- prevalence and endemicity. *Vaccine*. 2012;30:2212-2219.
4. Liaw YF. Antiviral therapy of chronic hepatitis B: opportunities and challenges in Asia. *J Hepatol*. 2009;51:403-410.
5. Chan HL, Sung JJ. Hepatocellular carcinoma and hepatitis B virus. *Semin Liver Dis*. 2006;26:153-161.
6. Hwang SJ. Hepatitis C virus infection: an overview. *J Clin Microbiol Immunol Infect*. 2001;34:227-234.
7. Shyu YC, Huang TS, Chien CH, Yeh CT, Lin CL, Chien RN. Diabetes poses a higher risk of hepatocellular carcinoma and mortality in patients with chronic hepatitis B: a population-based cohort study. *J Viral Hepat*. 2019;26:718-726. https://doi.org/10.1111/jvh.13077.

8. Yen YH, Chang KC, Tsai MC, et al. Elevated body mass index is a risk factor associated with possible liver cirrhosis across different etiologies of chronic liver disease. *J Formos Med Assoc*. 2018;117:268-275.
9. Li X, Gao Y, Xu H, Hou J, Gao P. Diabetes mellitus is a significant risk factor for the development of liver cirrhosis in chronic hepatitis C patients. *Sci Rep*. 2017;7:9087.
10. Alberti KG, Eckel RH, Grundy SM, et al.; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; Internatnal Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640-1645.
11. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444:881-887.
12. Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. *Diabetes Care*. 2008;31:1898-1904.
13. Benetos A, Thomas F, Pannier B, Bean K, Jégo B, Guize L. All-cause and cardiovascular mortality using the different definitions of metabolic syndrome. *Am J Cardiol*. 2008;102:188-191.
14. Ranasinghe P, Mathangasinghe Y, Jayawardena R, Hills AP, Misra A. Prevalence and trends of metabolic syndrome among adults in the asia-pacific region: a systematic review. *BMC Public Health*. 2017;17:101.
15. Borch-Johnsen K. The metabolic syndrome in a global perspective. The public health impact—secondary publication. *Dan Med Bull*. 2007;54:157-159.
16. Pitsavos C, Panagiotakos D, Weinem M, Stefanadis C. Diet, exercise and the metabolic syndrome. *Rev Diabet Stud*. 2006;3:118-126.
17. Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, national health and nutrition examination survey, 1988–2012. *Prev Chronic Dis*. 2017;14:E24.
18. Lee SE, Han K, Kang YM, et al.;Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Trends in the prevalence of metabolic syndrome and its components in South Korea: Findings from the Korean National Health Insurance Service Database (2009–2013). *PLoS ONE*. 2018;13:e0194490.
19. Schaefer EA, Chung RT. HCV and host lipids: an intimate connection. *Semin Liver Dis*. 2013;33:358-368.
20. Lee MH, Yang HI, Lu SN, et al.; R.E.V.E.A.L.-HCV Study Group. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis*. 2012;206:469-477.
21. Lee M-H, Yang H-I, Wang C-H, et al. Hepatitis C virus infection and increased risk of cerebrovascular disease. *Stroke*. 2010;41:2894-2900.
22. Hsu C-S, Liu C-H, Wang C-C, et al. Impact of hepatitis B virus infection on metabolic profiles and modifying factors. *J Viral Hepat*. 2012;19:e48-e57.
23. Chiang CH, Lai JS, Hung SH, Lee LT, Sheu JC, Huang KC. Serum adiponectin levels are associated with hepatitis B viral load in overweight to obese hepatitis B virus carriers. *Obesity (Silver Spring)*. 2013;21:291-296.
24. Wong V-S, Wong G-H, Chu W-W, et al. Hepatitis B virus infection and fatty liver in the general population. *J Hepatol*. 2012;56:533-540.
25. Chu CM, Lin DY, Liaw YF. Does increased body mass index with hepatic steatosis contribute to seroclearance of hepatitis B virus (HBV) surface antigen in chronic HBV infection? *Int J Obes (Lond)*. 2007;31:871-875.
26. Frankenberg ADV, Reis AF, Gerchman F. Relationships between adiponectin levels, the metabolic syndrome, and type 2 diabetes: a literature review. *Arch Endocrinol Metab*. 2017;61:614-622.
27. Tsochatzis E, Papatheodoridis GV, Hadziyannis E, et al. Serum adipokine levels in chronic liver diseases: association of resistin levels with fibrosis severity. *Scand J Gastroenterol*. 2008;43:1128-1136.
28. Wu D, Li H, Xiang G, et al. Adiponectin and its receptors in chronic hepatitis B patients with steatosis in china. *Hepat Mon*. 2013;13:e6065.
29. Palmer C, Hampartzoumian T, Lloyd A, Zekry A. A novel role for adiponectin in regulating the immune responses in chronic hepatitis C virus infection. *Hepatology*. 2008;48:374-3384.
30. Derbala M, Rizk N, Al-Kaabi S, et al. Adiponectin changes in HCV-Genotype 4: Relation to liver histology and response to treatment. *J Viral Hepat*. 2009;16:689-696.
31. Jonsson JR, Moschen AR, Hickman IJ, et al. Adiponectin and its receptors in patients with chronic hepatitis C. *J Hepatol*. 2005;43:929-936.
32. Zografos TA, Liaskos C, Rigopoulou EI, et al. Adiponectin: a new independent predictor of liver steatosis and response to IFN-alpha treatment in chronic hepatitis C. *Am J Gastroenterol*. 2008;103:605-614.
33. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415-1428.
34. Jan C-F, Chen C-J, Chiu Y-H, et al. A population-based study investigating the association between metabolic syndrome and hepatitis B/C infection (Keelung Community-based Integrated Screening study No. 10. *Int J Obes (Lond)*. 2006;30:794-799.
35. Jinjuvadia R, Liangpunsakul S. Association between metabolic syndrome and its individual components with viral hepatitis B. *Am J Med Sci*. 2014;347:23-27.
36. Li WC, Lee YY, Chen I-C, Sun C, Chiu FH, Chuang CH. Association between the hepatitis B and C viruses and metabolic diseases in patients stratified by age. *Liver Int*. 2013;33:1194-1202.
37. Chung TH, Kim MC, Kim CS. Association between hepatitis B surface antigen seropositivity and metabolic syndrome. *Korean J Fam Med*. 2014;35:81-89.
38. Jarcuška P, Janicko M, Kružliak P, et al. Hepatitis B virus infection in patients with metabolic syndrome: a complicated relationship. Results of a population based study. *Eur J Intern Med*. 2014;25:286-291.
39. Huang CY, Lu CW, Liu YL, Chiang CH, Lee LT, Huang KC. Relationship between chronic hepatitis B and metabolic syndrome: a structural equation modeling approach. *Obesity (Silver Spring)*. 2016;24:483-489.
40. Choi JS, Han KJ, Lee S, et al. Serum HBV surface antigen positivity is associated with low prevalence of metabolic syndrome in Korean adult men. *J Epidemiol*. 2015;25:74-79.
41. Katoonizadeh A, Ghoroghi S, Sharafkhah M, et al. Chronic hepatitis B infection is not associated with increased risk of vascular mortality while having an association with metabolic syndrome. *J Med Virol*. 2016;88:1230-1237.
42. Zhou Y, Cui Y, Deng H, Yu J. Association between hepatitis B virus infection and metabolic syndrome: a retrospective cohort study in Shanghai, China. *BMC Public Health*. 2014;14:516.
43. Kuo YH, Kee KM, Wang JH, et al. Association between chronic viral hepatitis and metabolic syndrome in southern Taiwan: a large population-based study. *Aliment Pharmacol Ther*. 2018;48:993-1002.
44. Wang CC, Tseng TC, Kao JH. Hepatitis B virus infection and metabolic syndrome: fact or fiction? *J Gastroenterol Hepatol*. 2015;30:14-20.
45. Razi B, Alizadeh S, Omidkhoda A, Imani D, Rezaei R. Association of chronic hepatitis B infection with metabolic syndrome and its components: Meta-analysis of observational studies. *Diabetes Metab Syndr*. 2017;11(Suppl 2):S939-S947.

46. Li Y, Zhao Y, Wu J. Serum HBV surface antigen positivity is associated with low prevalence of metabolic syndrome: a meta-analysis. *PLoS ONE*. 2017;12:e0177713.
47. Banks DE, Bogler Y, Bhuket T, Liu B, Wong RJ. Significant disparities in risks of diabetes mellitus and metabolic syndrome among chronic hepatitis C virus patients in the U.S. *Diabetes Metab Syndr*. 2017;11(Suppl 1):S153-S158.
48. Kuo Y-H, Tsai M-C, Kee K-M, ,et, al. Associated factors for metabolic syndrome in the older adults with chronic virus hepatitis in the community. *PLoS ONE*. 2016;11:e0155544.
49. Lonardo A, Ballestri S, Adinolfi LE, et al. Hepatitis C virus-infected patients are 'spared' from the metabolic syndrome but not from insulin resistance. A comparative study of nonalcoholic fatty liver disease and hepatitis C virus-related steatosis. *Can J Gastroenterol*. 2009;23:273-278.
50. Yoon H, Lee JG, Yoo JH, et al. Effects of metabolic syndrome on fibrosis in chronic viral hepatitis. *Gut Liv*. 2013;7:469-474.
51. Dong TS, Aby ES, Benhammou JN, et al. Metabolic syndrome does not affect sustained virologic response of direct-acting antivirals while hepatitis C clearance improves hemoglobin A1c. *World J Hepatol*. 2018;10:612-621.
52. Hashimoto E, Tokushige K, Farrell GC. Histological features of nonalcoholic fatty liver disease: what is important? *J. Gastroenterol Hepatol*. 2012;27:5-7.
53. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. *J Hepatol*. 2009;51:433-445.
54. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology*. 2010;51:1972-1978.
55. Altlparmak E, Koklu S, Yalinkilic M, et al. Viral and host causes of fatty liver in chronic hepatitis B. *World J Gastroenterol*. 2005;11:3056-3059.
56. Minakari M, Molaei M, Shalmani HM, et al. Liver steatosis in patients with chronic hepatitis B infection: host and viral risk factors. *Eur J Gastroenterol Hepatol*. 2009;21:512-516.
57. Peng D, Han Y, Ding H, Wei L. Hepatic steatosis in chronic hepatitis B patients is associated with metabolic factors more than viral factors. *J Gastroenterol Hepatol*. 2008;23:1082-1088.
58. Shi JP, Fan JG, Wu R, Gao XQ, Zhang L, Wang H. Prevalence and risk factors of hepatic steatosis in patients with chronic hepatitis B. *Zhonghua Gan Zang Bing Za Zhi*. 2008;16:519-523.
59. Sakhuja P, Kumar A, Hissar S, et al. Steatosis in chronic hepatitis B: prevalence and correlation with biochemical, histologic, viral, and metabolic parameters. *Indian J Pathol Microbiol*. 2011;54:454-459.
60. Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. *J Gastroenterol Hepatol*. 2011;26:1361-1367.
61. Wang CC, Hsu CS, Liu CJ, Kao JH, Chen DS. Association of chronic hepatitis B virus infection with insulin resistance and hepatic steatosis. *J Gastroenterol Hepatol*. 2008;23:779-782.
62. Xu QH, Jie YS, Shu X, Chen LB, Cao H, Li G. Relationship of fatty liver with HBV infection, hyperlipidemia and abnormal alanine aminotransferase. *Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi*. 2009;23:141-143.
63. Cheng Y-L, Wang Y-J, Kao W-Y, et al. Inverse Association between hepatitis B virus infection and fatty liver disease: a large-scale study in populations seeking for check-up. *PLoS ONE*. 2013;8:e72049.
64. Lonardo A, Loria P, Adinolfi LE, Carulli N, Ruggiero G. Hepatitis C and steatosis: a reappraisal. *J Viral Hepat*. 2006;13:73-80.
65. Rubbia-Brandt L, Fabris P, Paganin S, et al. Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut*. 2004;53:406-412.
66. Sharma P, Balan V, Hernandez J, et al. Hepatic steatosis in hepatitis C virus genotype 3 infection: does it correlate with body mass index, fibrosis, and HCV risk factors? *Dig Dis Sci*. 2004;49:25-29.
67. Negro F. Steatosis and insulin resistance in response to treatment of chronic hepatitis C. *J Viral Hepat*. 2012;19(Suppl 1):42-47.
68. Bochud P-Y, Cai T, Overbeck K, ,et, al.;Hepatitis C Cohort Study Group. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. *J Hepatol*. 2009;51:655-666.
69. Abenavoli L, Masarone M, Peta V, et al. Insulin resistance and liver steatosis in chronic hepatitis C infection genotype 3. *World J Gastroenterol*. 2014;20:15233-15240.
70. Chang ML. Metabolic alterations and hepatitis C: from bench to bedside. *World J Gastroenterol*. 2016;22:1461-1476.
71. Oem J-K, Jackel-Cram C, Li Y-P, et al. Activation of sterol regulatory element-binding protein 1c and fatty acid synthase transcription by hepatitis C virus non-structural protein 2. *J Gen Virol*. 2008;89:1225-1230.
72. Kim K, Kim KH, Ha E, Park JY, Sakamoto N, Cheong J. Hepatitis C virus NS5A protein increases hepatic lipid accumulation via induction of activation and expression of PPARgamma. *FEBS Lett*. 2009;583:2720-2726.
73. Abid K, Pazienza V, de Gottardi A, et al. An in vitro model of hepatitis C virus genotype 3a-associated triglycerides accumulation. *J Hepatol*. 2005;42:744-751.
74. Del Campo JA, Romero-Gómez M. Steatosis and insulin resistance in hepatitis C: a way out for the virus? *World J Gastroenterol*. 2009;15:5014-5019.
75. Matsuura Y, Miyamura T, Koike K, et al. Hepatitis C virus core protein induces hepatic steatosis in transgenic mice. *J Gen Virol*. 1997;78:1527-1531.
76. Naas T, Ghorbani M, Alvarez-Maya I, et al. Characterization of liver histopathology in a transgenic mouse model expressing genotype 1a hepatitis C virus core and envelope proteins 1 and 2. *J Gen Virol*. 2005;86:2185-2196.
77. Reddy KR, Govindarajan S, Marcellin P, et al. Hepatic steatosis in chronic hepatitis C: baseline host and viral characteristics and influence on response to therapy with peginterferon alpha-2a plus ribavirin. *J Viral Hepat*. 2008;15:129-136.
78. Petta S, Rosso C, Leung R, et al. Effects of IL28B rs12979860 CC genotype on metabolic profile and sustained virologic response in patients with genotype 1 chronic hepatitis C. *Clin Gastroenterol Hepatol* 2013;11:311-317.e1.
79. Rubbia-Brandt L, Quadri R, Abid K, et al. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *J Hepatol*. 2000;33:106-115.
80. Hickman IJ, Powell EE, Prins JB, et al. In overweight patients with chronic hepatitis C, circulating insulin is associated with hepatic fibrosis: implications for therapy. *J Hepatol*. 2003;39:1042-1048.
81. Shintani Y, Fujie H, Miyoshi H, et al. Hepatitis C virus infection and diabetes: Direct involvement of the virus in the development of insulin resistance. *Gastroenterology*. 2004;126:840-848.
82. Lonardo A, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology*. 2004;126:586-597.
83. Adinolfi LE, Restivo L, Zampino R, Lonardo A, Loria P. Metabolic alterations and chronic hepatitis C: treatment strategies. *Expert Opin Pharmacother*. 2011;12:2215-2234.
84. Goossens N, de Vito C, Mangia A, et al.; BOSTIC Study Group. Effect of hepatitis B virus on steatosis in hepatitis C virus co-infected subjects: a multi-centre study and systematic review. *J Viral Hepat*. 2018;25:920-929.

85. Zampino R, Coppola N, Cirillo G, et al. Insulin resistance and steatosis in HBV-HCV co-infected patients: role of PNPLA3 polymorphisms and impact on liver fibrosis progression. *World J Hepatol*. 2014;6:677-684.
86. Hwang S-J, Luo J-C, Chu C-W, et al. Hepatic steatosis in chronic hepatitis C virus infection: prevalence and clinical correlation. *J Gastroenterol Hepatol*. 2001;16:190-195.
87. Wyatt J, Baker H, Prasad P, Gong YY, Millson C. Steatosis and fibrosis in patients with chronic hepatitis C. *J Clin Pathol*. 2004;5:402-406.
88. Castéra L, Pawlotsky JM, Dhumeaux D. Worsening of steatosis and fibrosis progression in hepatitis C. *Gut*. 2003;52:1531.
89. Leandro G, Mangia A, Hui J, et al. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology*. 2006;130:1636-1642.
90. Perumalswami P, Kleiner DE, Lutchman G, et al. Steatosis and progression of fibrosis in untreated patients with chronic hepatitis C infection. *Hepatology*. 2006;43:780-787.
91. Hourigan LF, Macdonald GA, Purdie D, et al. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology*. 1999;29:1215-1219.
92. Monto A, Alonzo J, Watson JJ, Grunfeld C, Wright TL. Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol. *Hepatology*. 2002;36:729-736.
93. Hu K-Q, Kyulo NL, Esrailian E, et al. Overweight and obesity, hepatic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States. *J Hepatol*. 2004;40:147-154.
94. Adinolfi LE, Ingrosso D, Cesaro G, et al. Hyperhomocysteinemia and the MTHFR C677T polymorphism promote steatosis and fibrosis in chronic hepatitis C patients. *Hepatology*. 2005;41:995-1003.
95. Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. *World J Gastroenterol*. 2018;24:3361-3373.
96. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology*. 2015;149:367-378.
97. Sung KC, Ryu S, Lee JY, Kim JY, Wild SH, Byrne CD. Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. *J Hepatol*. 2016;65:791-797.
98. Harrison S, Brunt E, Qazi R, et al. Effect of significant histologic steatosis or steatohepatitis on response to antiviral therapy in patients with chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2005;3:604-609.
99. Kim D, Li AA, Perumpail BJ, et al. Changing trends in etiology-based and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. *Hepatology*. 2019;69:1064-1074.
100. El-Serag HB, Christie IC, Puenpatom A, Castillo D, Kanwal F, Kramer JR. The effects of sustained virological response to direct-acting anti-viral therapy on the risk of extrahepatic manifestations of hepatitis C infection. *Aliment Pharmacol Ther*. 2019;49:1442-1447.
101. Mahale P, Engels EA, Li R, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. *Gut*. 2018;67:553-561.
102. Tada T, Kumada T, Toyoda H, et al. Viral eradication reduces both liver stiffness and steatosis in patients with chronic hepatitis C virus infection who received direct-acting anti-viral therapy. *Aliment Pharmacol Ther*. 2018;47:1012-1022.
103. Rout G, Nayak B, Patel AH, et al. Therapy with oral directly acting agents in hepatitis C infection is associated with reduction in fibrosis and increase in hepatic steatosis on transient elastography. *J Clin Exp Hepatol*. 2019;9:207-214.
104. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. *Prim Care*. 2013;40:195-211.
105. Okamura H, Nio Y, Akahori Y, et al. Fatty acid biosynthesis is involved in the production of hepatitis B virus particles. *Biochem Biophys Res Commun*. 2016;475:87-92.
106. Su TC, Lee YT, Cheng TJ, Chien HP, Wang JD. Chronic hepatitis B virus infection and dyslipidemia. *J Formos Med Assoc*. 2004;103:286-291.
107. Chen J-Y, Wang J-H, Lin C-Y, et al. Lower prevalence of hypercholesterolemia and hyperglyceridemia found in subjects with seropositivity for both hepatitis B and C strains independently. *J Gastroenterol Hepatol*. 2010;25:1763-1768.
108. Liu PT, Hwang AC, Chen JD. Combined effects of hepatitis B virus infection and elevated alanine aminotransferase levels on dyslipidemia. *Metabolism*. 2013;62:220-225.
109. Popescu CI, Riva L, Vlaicu O, Farhat R, Rouillé Y, Dubuisson J. Hepatitis C virus life cycle and lipid metabolism. *Biology (Basel)*. 2014;3:892-921.
110. Miyanari Y, Atsuzawa K, Usuda N, et al. The lipid droplet is an important organelle for hepatitis C virus production. *Nat Cell Biol*. 2007;9:1089-1097.
111. Masaki T, Suzuki R, Murakami K, et al. Interaction of hepatitis C virus nonstructural protein 5A with core protein is critical for the production of infectious virus particles. *J Virol*. 2008;82:7964-7976.
112. Huang H, Sun F, Owen DM, et al. Hepatitis C virus production by human hepatocytes dependent on assembly and secretion of very low-density lipoproteins. *Proc Natl Acad Sci U S A*. 2007;104:5848-5853.
113. André P, Komurian-Pradel F, Deforges S, et al. Characterization of low- and very-low-density hepatitis C virus RNA-containing particles. *J Virol*. 2002;76:6919-6928.
114. Shi ST, Polyak SJ, Tu H, Taylor DR, Gretch DR, Lai MM. Hepatitis C virus NS5A colocalizes with the core protein on lipid droplets and interacts with apolipoproteins. *Virology*. 2002;292:198-210.
115. Sabile A, Perlemuter G, Bono F, et al. Hepatitis C virus core protein binds to apolipoprotein AII and its secretion is modulated by fibrates. *Hepatology*. 1999;30:1064-1076.
116. Benga WJ, Krieger SE, Dimitrova M, et al. Apolipoprotein E interacts with hepatitis C virus nonstructural protein 5A and determines assembly of infectious particles. *Hepatology*. 2010;51:43-53.
117. Cun W, Jiang J, Luo G. The C-terminal alpha-helix domain of apolipoprotein E is required for interaction with nonstructural protein 5A and assembly of hepatitis C virus. *J Virol*. 2010;84:11532-11541.
118. Sun H-Y, Lin C-C, Lee J-C, et al. Very low-density lipoprotein/lipo-viro particles reverse lipoprotein lipase-mediated inhibition of hepatitis C virus infection via apolipoprotein C-III. *Gut*. 2013;62:1193-1203.
119. Arain SQ, Talpur FN, Channa NA. A comparative study of serum lipid contents in pre and post IFN-alpha treated acute hepatitis C patients. *Lipids Health Dis*. 2015;14:117.
120. Corey KE, Kane E, Munroe C, Barlow LL, Zheng H, Chung RT. Hepatitis C virus infection and its clearance alter circulating lipids: implications for long-term follow-up. *Hepatology*. 2009;50:1030-1037.
121. Li JH, Qian Lao X, Tillmann HL, et al. Interferon-lambda genotype and low serum low-density lipoprotein cholesterol levels in patients with chronic hepatitis C infection. *Hepatology*. 2010;51:1904-1911.
122. Jármay K, Karácsony G, Nagy A, Schaff Z. Changes in lipid metabolism in chronic hepatitis C. *World J Gastroenterol*. 2005;11:6422-6428.
123. Negro F, Sanyal AJ. Hepatitis C virus, steatosis and lipid abnormalities: clinical and pathogenic data. *Liver Int*. 2009;29(Suppl 2):26-37.
124. Rojas Á, del Campo JA, Maraver M, et al. Hepatitis C virus infection alters lipid metabolism depending on IL28B polymorphism

and viral genotype and modulates gene expression in vivo and in vitro. *J Viral Hepat*. 2014;21:19-24.
125. Yamaguchi A, Tazuma S, Nishioka T, et al. Hepatitis C virus core protein modulates fatty acid metabolism and thereby causes lipid accumulation in the liver. *Dig Dis Sci*. 2005;50:1361-1371.
126. Moriya K, Todoroki T, Tsutsumi T, et al. Increase in the concentration of carbon 18 monounsaturated fatty acids in the liver with hepatitis C: analysis in transgenic mice and humans. *Biochem Biophys Res Commun*. 2001;281:1207-1212.
127. Miyoshi H, Moriya K, Tsutsumi T, et al. Pathogenesis of lipid metabolism disorder in hepatitis C: polyunsaturated fatty acids counteract lipid alterations induced by the core protein. *J Hepatol*. 2011;54:432-438.
128. Leu G-Z, Lin T-Y, Hsu JTA. Anti-HCV activities of selective polyunsaturated fatty acids. *Biochem Biophys Res Commun*. 2004;318:275-280.
129. Sun HY, Cheng PN, Tseng CY, Tsai WJ, Chiu YC, Young KC. Favouring modulation of circulating lipoproteins and lipid loading capacity by direct antiviral agents grazoprevir/elbasvir or ledipasvir/sofosbuvir treatment against chronic HCV infection. *Gut*. 2018;67:1342-1350.
130. Lee JG, Lee S, Kim YJ, et al. Association of chronic viral hepatitis B with insulin resistance. *World J Gastroenterol*. 2012;18:6120-6126.
131. Li-Ng M, Tropp S, Danoff A, Bini EJ. Association between chronic hepatitis B virus infection and diabetes among Asian Americans and Pacific Islanders. *Dig Liver Dis*. 2007;39:549-556.
132. Huang Z-S, Huang T-S, Wu T-H, Chen M-F, Hsu C-S, Kao J-H. Asymptomatic chronic hepatitis B virus infection does not increase the risk of diabetes mellitus: A ten-year observation. *J Gastroenterol Hepatol*. 2010;25:1420-1425.
133. Spradling PR, Simons B, Narayanan M, et al. Incidence of diabetes mellitus in a population-based cohort of persons with chronic hepatitis B virus infection. *J Viral Hepat*. 2013;20:510-513.
134. Cai C, Zeng J, Wu H, et al. Association between hepatitis B virus infection and diabetes mellitus: a meta-analysis. *Exp Ther Med*. 2015;10:693-698.
135. Shaheen M, Echeverry D, Oblad MG, Montoya MI, Teklehaimanotn S, Akhtar AJ. Hepatitis C, metabolic syndrome, and inflammatory markers: results from the Third National health and Nurition Examination Survey [NHANES III]. *Diabetes Res Clin Pract*. 2007;75:320-326.
136. Park SK, Cho YK, Park JH, et al. Change of insulin sensitivity in hepatitis C patients with normal insulin sensitivity: a 5-year prospective follow-up study variation of insulin sensitivity in HCV patients. *Intern Med J*. 2010;40:503-511.
137. Duseja A, Dhiman RK, Chawla Y, et al. Insulin resistance is common in patients with predominantly genotype 3 chronic hepatitis C. *Dig Dis Sci*. 2009;54:1778-1782.
138. Huang JF, Chuang WL, Yu 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;25:299-305.
139. 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.
140. Veldt BJ, Chen W, Heathcote EJ, et al. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology*. 2008;47:1856-1862.
141. Dai C-Y, Yeh M-L, Huang C-F, et al. Chronic hepatitis C infection is associated with insulin resistance and lipid profiles. *J Gastroenterol Hepatol*. 2015;30:879-884.
142. Wang CS, Wang ST, Yao WJ, Chang TT, Chou P. Hepatitis C virus infection and the development of type 2 diabetes in a community-based longitudinal study. *Am J Epidemiol*. 2007;166:196-203.
143. Moucari R, Asselah T, Cazals–Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology*. 2008;134:416-423.
144. El-Zayadi AR, Anis M. Hepatitis C virus induced insulin resistance impairs response to antiviral therapy. *World J Gastroenterol*. 2012;18:212-224.
145. Kasai D, Adachi T, Deng L, et al. HCV replication suppresses cellular glucose uptake through down-regulation of cell surface expression of glucose transporters. *J Hepatol*. 2009;50:883-894.
146. Banerjee S, Saito K, Ait-Goughoulte M, Meyer K, Ray RB, Ray R. Hepatitis C virus core protein upregulates serine phosphorylation of insulin receptor substrate-1 and impairs the downstream akt/protein kinase B signaling pathway for insulin resistance. *J Virol*. 2008;82:2606-2612.
147. Nkontchou G, Bastard J-P, Ziol M, et al. Insulin resistance, serum leptin, and adiponectin levels and outcomes of viral hepatitis C cirrhosis. *J Hepatol*. 2010;53:827-833.
148. Kawaguchi T, Yoshida T, Harada M, et al. Hepatitis C virus down-regulates insulin. receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol*. 2004;165:1499-1508.
149. Petta S, Cammà C, Marco VD, et al. Insulin resistance and diabetes increase fibrosis in the liver of patients with genotype 1 HCV infection. *Am J Gastroenterol*. 2008;103:1136-1144.
150. Hui JM, Sud A, Farrell GC, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterology*. 2003;125:1695-1704.
151. Patel K, Thompson AJ, Chuang WL, et al. Insulin resistance is independently associated with significant hepatic fibrosis in Asian chronic hepatitis C genotype 2 or 3 patients. *J Gastroenterol Hepatol*. 2011;26:1182-1188.
152. Svegliati-Baroni G, Bugianesi E, Bouserhal T, et al. Post-load insulin resistance is an independent. predictor of hepatic fibrosis in virus C chronic hepatitis and in non-alcoholic fatty liver disease. *Gut*. 2007;56:1296-1301.
153. Salmon D, Bani-Sadr F, Loko M-A, et al. Insulin resistance is associated with a higher risk of hepatocellular carcinoma in cirrhotic HIV/HCV-co-infected patients: results from ANRS CO13 HEPAVIH. *J Hepatol*. 2012;56:862-868.
154. Huang Y-W, Yang S-S, Fu S-C, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis C patients with new-onset diabetes: a nationwide cohort study. *Hepatology*. 2014;60:807-814.
155. D'Souza R, Sabin CA, Foster GR. Insulin resistance plays a significant role in liver fibrosis in chronic hepatitis C and in the response to antiviral therapy. *Am J Gastroenterol*. 2005;100:1509-1515.
156. Abd El-Wahab EW, Mikheal A, Sidkey F, Shatat HZ. Insulin resistance as a predictor of early virologic response to HCV therapy among chronic HCV Egyptian patients. *J Med Virol*. 2015;87:428-440.
157. Chien CH, Lin CL, Hu CC, Chang JJ, Chien RN. Clearance of hepatitis C virus improves insulin resistance during and after peginterferon and ribavirin therapy. *J Interferon Cytokine Res*. 2015;35:981-989.
158. Butt AA, Umbleja T, Andersen JW, Sherman KE, Chung RT; ACTG A5178 Study Team. Impact of peginterferon alpha and ribavirin treatment on. lipid profiles and insulin resistance in Hepatitis C virus/HIV-coinfected persons. *Clin Infect Dis*. 2012;55:631-638.
159. Aghemo A, Prati GM, Rumi MG, et al. Sustained virological response. prevents the development of insulin resistance in patients with chronic hepatitis C. *Hepatology*. 2012;56:1681-1687.
160. Cacoub P, Desbois AC, Comarmond C, Saadoun D. Impact of sustained virological response on the extrahepatic manifestations of chronic hepatitis C: a meta-analysis. *Gut*. 2018;67:2025-2034.
161. Ciancio A, Bosio R, Bo S, et al. Significant improvement of glycemic control in diabetic patients with HCV infection responding to direct-acting antiviral agents. *J Med Virol*. 2018;90:320-327.
162. Hum J, Jou JH, Green PK, et al. Improvement in glycemic control of type 2 diabetes after successful treatment of hepatitis C virus. *Diabetes Care*. 2017;40:1173-1180.

163. Dawood AA, Nooh MZ, Elgamal AA. Factors associated with improved glycemic control by direct-acting antiviral agent treatment in Egyptian type 2 diabetes mellitus patients with chronic hepatitis C genotype 4. *Diabetes Metab J*. 2017;41:316-321.
164. Adinolfi LE, Nevola R, Guerrera B, et al. Hepatitis C virus clearance by direct-acting antiviral treatments and impact on insulin resistance in chronic hepatitis C patients. *J Gastroenterol Hepatol*. 2018;33:1379-1382.
165. Masaki T, Chiba S, Tatsukawa H, et al. Adiponectin protects LPS-induced liver injury through modulation of TNF-alpha in KK-Ay obese mice. *Hepatology*. 2004;40:177-184.
166. Handy JA, Saxena NK, Fu P, et, al. Adiponectin activation of AMPK disrupts leptin-mediated hepatic fibrosis via suppressors of cytokine signaling (SOCS-3). *J Cell Biochem*. 2010;110:1195-1207.
167. Kamada Y, Tamura S, Kiso S, et al. Enhanced carbon tetrachloride-induced liver fibrosis in mice lacking adiponectin. *Gastroenterology*. 2003;125:1796-1807.
168. Lu J-Y, Chuang L-M, Yang W-S, et al. Adiponectin levels among patients with chronic hepatitis B and C infections and in response to IFN-alpha therapy. *Liver Int*. 2005;25:752-759.
169. Hui CK, Zhang HY, Lee NP, et al.; Kong Liver Fibrosis Study Group. Serum adiponectin is increased in advancing liver fibrosis and declines with reduction in fibrosis in chronic hepatitis B. *J Hepatol*. 2007;47:191-202.
170. Hsu C-S, Liu W-L, Chao Y-C, et al. Adipocytokines and liver fibrosis stages in patients with chronic hepatitis B virus infection. *Hepatol Int*. 2015;9:231-242.
171. Liu C-J, Chen P-J, Lai M-Y, et al. High serum adiponectin correlates with advanced liver disease in patients with chronic hepatitis B virus infection. *Hepatol Int*. 2009;3:364-370.
172. Chen C-L, Yang W-S, Yang H-I, et al. Plasma adipokines and risk of hepatocellular carcinoma in chronic hepatitis B virus-infected carriers: a prospective study in Taiwan. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1659-1671.
173. Carvalho RF, Atta AM, de Oliveira IS, et al. Adiponectin levels and insulin resistance among patients with chronic hepatitis C. *Acta Trop*. 2018;178:258-263.
174. Petit J-M, Minello A, Jooste V, et al. Decreased plasma adiponectin concentrations are closely related to steatosis in hepatitis C virus-infected patients. *J Clin Endocrinol Metab*. 2005;90:2240-2243.
175. Ashour E, Samy N, Sayed M, Imam A. The relationship between serum adiponectin and steatosis in patients with chronic hepatitis C genotype-4. *Clin Lab*. 2010;56:103-1310.
176. Durante-Mangoni E, Zampino R, Marrone A, et al. Hepatic steatosis and insulin resistance are associated with serum imbalance of adiponectin/tumour necrosis factor-alpha in chronic hepatitis C patients. *Aliment Pharmacol Ther*. 2006;24:1349-1357.
177. Grigorescu M, Radu C, Crişan D, et al. Metabolic syndrome, insulin resistance and adiponectin level in patients with chronic hepatitis C. *J Gastrointestin Liver Dis*. 2008;17:147-154.
178. Aksõz K, Unsal B, Kirci A, et al. The relationship between chronic HCV infection and the level of plasma adiponectin. *Turk J Gastroenterol*. 2008;19:254-257.
179. Cua IHY, Hui JM, Bandara P, et al. Insulin resistance and liver injury in hepatitis C is not associated with virus-specific changes in adipocytokines. *Hepatology*. 2007;46:66-73.
180. Chang ML, Kuo CJ, Pao LH, Hsu CM, Chiu CT. The evolving relationship between adiponectin and insulin sensitivity in hepatitis C patients during viral clearance. *Virulence*. 2017;8:1255-1264.
181. Zhang L, Sugiyama T, Murabayashi N, et al. The inflammatory changes of adipose tissue in late pregnant mice. *J Mol Endocrinol*. 2011;47:157-165.
182. Durante-Mangoni E, Zampino R, Marrone A, et al. Hepatic steatosis and insulin resistance are associated with serum imbalance of adiponectin/tumour necrosis factor- alpha in chronic hepatitis C patients. *Aliment Pharmacol Ther*. 2006;24:1349-1357.
183. Dharancy S, Malapel M, Perlemuter G, et al. Impaired expression of the peroxisome proliferator-activated receptor alpha during hepatitis C virus infection. *Gastroenterology*. 2005;128:334-342.
184. Bajaj M, Suraamornkul S, Piper P, et al. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. *J Clin Endocrinol Metab*. 2004;89:200-206.
185. Díez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. *Eur J Endocrinol*. 2003;148:293-300.
186. De Maria N, Colantonl A, Fagiuoli S, et al. Association between reactive oxygen species and disease activity in chronic hepatitis C. *Free Radic Biol Med*. 1996;21:291-295.
187. Peta V, Torti C, Milic N, Focà A, Abenavoli L. Adiponectin serum level in chronic hepatitis C infection and therapeutic profile. *World J Hepatol*. 2015;7:44-52.
188. Restivo L, Zampino R, Guerrera B, Ruggiero L, Adinolfi LE. Steatosis is the predictor of relapse in HCV genotype 3- but not 2-infected patients treated with 12 weeks of pegylated interferon-α-2a plus ribavirin and RVR. *J Viral Hepat*. 2012;19:346-352.
189. Corbetta S, Redaelli A, Pozzi M, et al. Fibrosis is associated with adiponectin resistance in chronic hepatitis C virus infection. *Eur J Clin Invest*. 2011;41:898-905.
190. Khattab MA, Eslam M, Mousa YI, et al. Association between metabolic abnormalities and hepatitis C-related hepatocellular carcinoma. *Ann Hepatol*. 2012;11:487-494.
191. Khattab MA, Eslam M, Shatat M, et al. Changes in adipocytokines and insulin sensitivity during and after antiviral therapy for hepatitis C genotype 4. *J Gastrointestin Liver Dis*. 2012;21:59-65.
192. Amirzadegan A, Davoodi G, Boroumand MA, Darabyan S, Dehkordi MR, Goodarzynejad H. Association between hepatitis B surface antibody seropositivity and coronary artery disease. *Indian J Med Sci*. 2007;61:648-655.
193. Tong DY, Wang XH, Xu CF, Yang YZ, Xiong SD. Hepatitis B virus infection and coronary atherosclerosis: results from a population with relatively high prevalence of hepatitis B virus. *World J Gastroenterol*. 2005;11:1292-1296.
194. Moritani M, Adachi K, Arima N, et al. A study of arteriosclerosis in healthy subjects with HBV and HCV infection. *J Gastroenterol*. 2005;40:1049-1053.
195. Yang K-C, Chen M-F, Su T-C, et al. Hepatitis B virus seropositivity is not associated with increased risk of carotid atherosclerosis in Taiwanese. *Atherosclerosis*. 2007;195:392-397.
196. 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;46:1126-1132.
197. Tseng CH, Muo CH, Hsu CY, Kao CH. Association of hepatitis B virus infection With decreased ischemic stroke. *Acta Neurol Scand*. 2016;134:339-345.
198. Li CG, Liao SJ, Que JL, Liu KJ, Wang HY, Yu J. The relationship between exposure to hepatitis B virus and increased atherosclerosis-associated morbidity-a meta-analysis. *Kardiol Pol*. 2018;76:119-124.
199. Wu V-C, Chen T-H, Wu M, et al. Comparison of cardiovascular outcomes and all-cause mortality in patients with chronic hepatitis B and C: a 13-year nationwide population-based study in Asia. *Atherosclerosis*. 2018;269:178-184.
200. Adinolfi LE, Zampino R, Restivo L, et al. Chronic hepatitis C virus infection and atherosclerosis: clinical impact and mechanisms. *World J Gastroenterol*. 2014;20:3410-3417.
201. 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;5:528-540.

202. Boddi M, Abbate R, Chellini B, et al. Hepatitis C virus RNA localization in human carotid plaques. *J Clin Virol*. 2010;47:72-75.
203. 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.
204. Ambrosino P, Lupoli R, Di Minno A, et al. The risk of coronary artery disease and cerebrovascular disease in patients with hepatitis C: A systematic review and meta-analysis. *Int J Cardiol*. 2016;221:746-754.
205. Butt AA, Yan P, Shuaib A, Abou-Samra AB, Shaikh OS, Freiberg MS. Direct-acting antiviral therapy for HCV infection is associated with a reduced risk of cardiovascular disease events. *Gastroenterology*. 2019;156:987-996.
206. Petta S, Adinolfi LE, Fracanzani AL, et al. Hepatitis C virus eradication by direct-acting antiviral agents improves carotid atherosclerosis in patients with severe liver fibrosis. *J Hepatol*. 2018;69:18-24.
207. Ichikawa T, Miyaaki H, Miuma S, et al. Carotid intima-media thickness and small dense low-density lipoprotein cholesterol increase after one year of treatment with direct-acting antivirals in patients with hepatitis C virus infection. *Intern Med*. 2019;58:1209-1215. https://doi.org/10.2169/internalmedicine.1514-18.
208. Novo G, Macaione F, Giannitrapani L, et al. Subclinical cardiovascular damage in patients with HCV cirrhosis before and after treatment with direct antiviral agents: a prospective study. *Aliment Pharmacol Ther*. 2018;48:740-749.
209. Cheng PN, Chen JY, Chiu YC, Chiu HC, Tsai LM. Augmenting central arterial stiffness following eradication of HCV by direct acting antivirals in advanced fibrosis patients. *Sci Rep*. 2019;9(1):1426. https://doi.org/10.1038/s41598-018-378294

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