

Hepatitis C Virus, Insulin Resistance, and Steatosis

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Abstract

Hepatitis C virus (HCV) is one of the main causes of liver disease worldwide. Liver steatosis is a common finding in many hepatic and extrahepatic disorders, the most common being metabolic syndrome (MS). Over time, it has been shown that the frequent coexistence of these two conditions is not coincidental, since many epidemiological, clinical, and experimental studies have indicated HCV to be strongly associated with liver steatosis and numerous metabolic derangements. Here, we present an overview of publications that provide clinical evidence of the metabolic effects of HCV and summarize the available data on the pathogenetic mechanisms of this association. It has been shown that HCV infection can induce insulin resistance (IR) in the liver and peripheral tissues through multiple mechanisms. Substantial research has suggested that HCV interferes with insulin signaling both directly and indirectly, inducing the production of several proinflammatory cytokines. HCV replication, assembly, and release from hepatocytes require close interactions with lipid droplets and host lipoproteins. This modulation of lipid metabolism in host cells can induce hepatic steatosis, which is more pronounced in patients with HCV genotype 3. The risk of steatosis depends on several viral factors (including genotype, viral load, and gene mutations) and host features (visceral obesity, type 2 diabetes mellitus, genetic predisposition, medication use, and alcohol consumption). HCV-related IR and steatosis have been shown to have a remarkable clinical impact on the prognosis of HCV infection and quality of life, due to their association with resistance to antiviral therapy, progression of hepatic fibrosis, and development of hepatocellular carcinoma. Finally, HCV-induced IR, oxidative

stress, and changes in lipid and iron metabolism lead to glucose intolerance, arterial hypertension, hyperuricemia, and atherosclerosis, resulting in increased cardiovascular mortality.

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Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus belonging to the Flaviviridae family. Approximately 64–103 million people are infected with HCV worldwide, making HCV one of the major causes of chronic liver disease.¹ Acute infection may resolve spontaneously in 15%–45% of cases, but the remaining 55%–85% of infected individuals (75%–85% according to serologic surveys) fail to clear the virus and become chronically infected.^{1,2} In a significant number of patients, chronic hepatitis C (CHC) will progress to cirrhosis and hepatocellular carcinoma (HCC), which represent the end-stage HCV-related liver disease, and are among the leading causes for liver transplantation in the Western world.² Approximately 350,000 to 500,000 people die each year from hepatitis C-related liver diseases around the world.¹

The primary host cells for HCV are hepatocytes, although replication may also occur in other cell types, such as peripheral blood mononuclear cells and B and T lymphocytes.^{3,4} HCV interferes with the hepatic lipid metabolism throughout its life cycle. Viral entry into hepatocytes occurs following its binding to low-density lipoprotein receptors.^{5,6} Once internalized, HCV interferes with the host lipid metabolism for its replication and assembly, which consequently leads to hepatic steatosis. Finally, the virus is released from the hepatocyte via the very low-density lipoprotein secretion pathway.⁷

Hepatic steatosis is a condition in which there is excessive accumulation of triglycerides within the hepatocytes. The most common causes are alcohol consumption (alcoholic fatty liver disease) and insulin resistance (IR) within the metabolic syndrome (MS) (non-alcoholic fatty liver disease - NAFLD), but other causes, including malnutrition, total parenteral nutrition, severe weight loss, gastrointestinal bypasses, some inherited metabolic conditions (e.g., abetalipoproteinemia), glycogen storage diseases, lipodystrophy, alpha 1-antitrypsin deficiency, pregnancy, drugs and toxins, as well as human immunodeficiency virus (HIV) and chronic HCV infection, are also responsible for a number of cases.

NAFLD is one of the most common causes of chronic liver disease in the Western world. It represents a spectrum of

Keywords: Hepatitis C virus; Metabolic syndrome; Insulin resistance; Steatosis.

Abbreviations: CHC, chronic hepatitis C; GLUT, glucose transporter; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HOMA, homeostatic model assessment; HIV, human immunodeficiency virus; IRS, insulin receptor substrate; IR, insulin resistance; IFN α , interferon- α ; IL, interleukin; LBS, liver biopsy specimens; MS, metabolic syndrome; MTP, microsomal triglyceride transfer protein; NANB, non-A, non-B; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator activating receptor; PI3K, phosphatidylinositol 3-kinase; RBV, ribavirin; SREBP-1c, sterol regulatory element-binding protein-1c; SOCS-3, suppressor of cytokine signaling 3; SVR, sustained viral response; TNF- α , tumor necrosis factor- α ; T2DM, type 2 diabetes mellitus.

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conditions ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), where steatosis is associated with hepatic inflammation and various degrees of fibrosis and cirrhosis, which develops as a consequence of long-standing NASH.⁸ NAFLD is estimated to affect around 25%–30% of the general population, while NASH is reported in 2%–3% of the population.⁹

Strong epidemiological, biochemical, and therapeutic evidence implicate IR as the primary pathophysiological derangement and the key mechanism leading to hepatic steatosis. Indeed, NAFLD is regarded as a hepatic manifestation of the MS.

MS represents a combination of well-known and established cardiovascular disease related risk factors. Multiple definitions of MS exist with several revisions; and although criteria differ, the essential components of MS include insulin resistance/hyperglycemia, dyslipidemia, hypertension, and visceral obesity.^{10–14} These factors have a tendency of clustering together, and individuals with MS have a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality.¹⁵

Hepatic steatosis in CHC infection results from the combination of several host and viral factors that directly interfere with lipid metabolism within the hepatocytes or cause different metabolic derangements through IR. Host factors include the before mentioned components of MS, such as obesity and type 2 diabetes mellitus (T2DM); but also include alcohol consumption, medication use, and genetic predisposition (e.g., interleukin (IL) 28B polymorphism).^{16,17} Viral factors include genotype (genotype 3 causing the most pronounced steatosis), HCV RNA load, and gene mutations.^{16–18}

HCV and insulin resistance

Glucose metabolism impairment, development of IR, and T2DM can often be found accompanying CHC and is commonly measured using the homeostatic model assessment (HOMA) index. Euglycemic insulin clamp studies have shown that IR in CHC has both a hepatic and a peripheral component and induces an array of host metabolic changes.^{19,20} Besides promoting steatosis and fibrosis progression, the presence of IR has been shown to impair treatment response and, vice-versa, regress following successful treatment outcome.

Several studies have assessed IR in hepatitis C patients before and after interferon therapy. Petit *et al.* report that IR in nondiabetic HCV-infected patients was related to grading of liver fibrosis and may occur early in the course of HCV infection.²¹ In a study including 260 HCV-infected subjects, Hui *et al.* found that HCV may induce IR irrespective of the severity of liver disease and that genotype 3 had a significantly lower HOMA-IR than other genotypes.²² On the other hand, another study found that median HOMA-IR was significantly higher in patients with genotype 1 related steatosis than in those with genotype 3 related steatosis.²³ Irrespective of the genotype, higher HCV RNA levels were associated with the presence of IR and, accordingly, the severity of hepatic steatosis,^{24,25} where treatment and clearance of HCV improved IR.^{26–28} Regarding the impact of HCV infection on the development of T2DM, a meta-analysis of 34 studies found a positive correlation between HCV infection and increased risk of T2DM in comparison to the general population in both retrospective and prospective studies.²⁹ Studies investigating the association between HCV and IR, and their key findings, are summarized in Table 1.

HCV and hepatic steatosis

Hepatic steatosis was reported to be a histologic feature of non-A, non-B (NANB) hepatitis several years before hepatitis C testing was available, and it was considered common enough to be used as a diagnostic aid in the absence of serological diagnostic tests for hepatitis C.^{55,56} Steatosis occurs in 40%–86% of patients with chronic hepatitis C, and its frequency varies with genotype.^{16–18} As already mentioned, steatosis is more common in genotype 3 infection, where it occurs in 73% of patients, while the prevalence of steatosis in patients infected with other genotypes is around 50%.^{16–18} Infection with HCV genotype 3 is also associated with higher steatosis scores than in other genotypes, even in the absence of the metabolic risk factors associated with NAFLD, and there is a significant correlation between the degree of steatosis and the HCV RNA viral load.^{57,58} It has also been demonstrated in patients infected with HCV genotype 3 that steatosis can improve and even disappear following successful treatment with interferon (IFN) and ribavirin (RBV).⁵⁸ Recent studies investigating the role of a single-nucleotide polymorphism near the IL28B gene found that steatosis is less prevalent in carriers of the IL28B CC genotype, who also show less pronounced disturbances of lipid metabolism and a favorable response to IFN therapy.⁵⁹

Studies investigating the association between HCV and hepatic steatosis, and their key findings, are summarized in Table 2.

Pathogenesis of insulin resistance and steatosis in HCV infection

The pathogenesis of IR and steatosis in HCV infection is a very intriguing problem, and extensive research of this topic has been undertaken. Different pathogenetic mechanisms have been proposed to explain the development of IR in HCV infected patients.^{90–95}

In vitro and animal studies have greatly contributed to our understanding of both lipid and glucose metabolism alterations induced by HCV. Glucose transporter 2 (GLUT2), responsible for transporting glucose to hepatocytes, is down-regulated by the HCV core protein, while the overproduction of tumor necrosis factor alpha (TNF- α), induced by HCV infection, inhibits insulin receptor substrate (IRS) and phosphatidylinositol 3 kinase (PI3K) via suppressor of cytokine signaling (SOCS)-3. These impairments of intracellular insulin signaling could block GLUT-4 activation, reducing the uptake of glucose by cells.^{96–98}

Other cytokines besides TNF- α , such as IL-6 as well as a number of adipokines, have been shown to play a part in IR and steatosis pathogenesis of NAFLD, and evidence on their influence in HCV-induced metabolic changes continue to grow.^{99,100} HCV infection has also been suggested to cause mitochondrial dysfunction and endoplasmic reticulum impairment, while the genotype 3 HCV core protein has been shown to downregulate peroxisome proliferator activating receptor (PPAR γ) and upregulate SOCS-7, leading to further impairment of insulin signaling.^{101–103}

As for human studies, in a landmark study using liver biopsy specimens (LBS) obtained from nonobese, nondiabetic HCV-infected patients, HCV inhibited the insulin-stimulated tyrosine phosphorylation of hepatic insulin receptor substrate-1 (IRS-1), resulting in inhibition of the PI3K-Akt pathway, a key transducer of the insulin metabolic signal.^{104,105} HCV

Table 1. The association between hepatitis C virus (HCV) and insulin resistance

Methods/Study population	Findings and conclusions	Author
15 CHC patients assessed before and after IFN α therapy	Glucose tolerance improved after IFN α treatment	Tanaka <i>et al.</i> , ³⁰ 1997
13 nondiabetic CHC patients before and after IFN α therapy	HCV-induced liver injury related to deterioration of insulin sensitivity and impaired glucose homeostasis	Konrad <i>et al.</i> , ³¹ 2000
103 nondiabetic CHC patients	IR related to grading of liver fibrosis and occurred at an early stage of HCV infection	Petit <i>et al.</i> , ²¹ 2001
160 patients with CHC	Circulating insulin levels increased with fibrosis in overweight patients with CHC	Hickman <i>et al.</i> , ³² 2003
260 CHC patients	HCV may induce IR irrespective of the severity of liver disease. Genotype 3 associated with lower HOMA-IR	Hui <i>et al.</i> , ²² 2003
141 nondiabetic CHC patients	IR was significantly higher in patients with genotype 1 related steatosis than in genotype 3	Fartoux <i>et al.</i> , ²³ 2005
159 patients with CHC genotype 1 (113) and non-1 genotype (46) treated with IFN/RBV	SVR independently related to genotype, IR, and fibrosis	Romero-Gómez <i>et al.</i> , ³³ 2005
90 patients with CHC and 90 with NAFLD	Basal and postload IR were lower in CHC patients than in NAFLD	Svegliati-Baroni <i>et al.</i> , ³⁴ 2007
17 CHC patients not receiving pharmacological treatment	70% overweight or obese, 77% presented with IR	Vázquez-Vandyck <i>et al.</i> , ³⁵ 2007
89 CHC patients receiving IFN α or IFN α /RBV	HCV clearance improved IR, β -cell function, and hepatic IRS1&2 expression	Kawaguchi <i>et al.</i> , ²⁶ 2007
232 CHC and 56 HCV eradicated patients	CHC patients had higher prevalence of T2DM and IR	Imazeki <i>et al.</i> , ³⁶ 2008
162 CHC patients assessed before treatment	Higher HCV RNA levels associated with the presence of IR and hepatic steatosis	Hsu <i>et al.</i> , ²⁴ 2008
346 untreated, nondiabetic CHC patients with genotype 1 or 3	HOMA-IR rather than steatosis was independently associated with fibrosis regardless of genotype	Cua <i>et al.</i> , ³⁷ 2008
201 CHC patients with genotype 1	IR and overt diabetes were related to advanced fibrosis, regardless of steatosis	Petta <i>et al.</i> , ³⁸ 2008
82 CHC patients treated with either IFN/RBV (59) or pegylated-IFN/RBV (23)	Patients with lower HOMA-IR were more likely to achieve SVR	Poustchi <i>et al.</i> , ³⁹ 2008
34 postliver transplant patients evaluated (14 HCV positive and 20 HCV negative)	Higher IR in the HCV positive group. Higher HCV RNA levels were associated with higher HOMA-IR	Delgado-Borrego <i>et al.</i> , ⁴⁰ 2008
500 CHC patients	IR was present in 32.4% of nondiabetic CHC, associated with genotypes 1 and 4 as well as high HCV RNA levels. Fibrosis was associated with IR independent from steatosis	Moucari <i>et al.</i> , ²⁵ 2008
Meta-analysis including 34 studies of HCV infected patients	T2DM risk was higher in HCV-infected in both retrospective and prospective studies	White <i>et al.</i> , ²⁹ 2008
275 nondiabetic treatment-naïve CHC patients	IR was increased in 37% of patients, contributing to fibrosis progression, and was more prevalent in obese patients with steatosis. No connections with genotype or viremia.	Tsochatzis <i>et al.</i> , ⁴¹ 2009
28 CHC patients treated with pegylated-IFN α 2a/RBV	Disappearance of HCV RNA at 6 months after treatment independently reduced IR	Kim <i>et al.</i> , ²⁷ 2009
38 CHC patients and healthy controls	IR was positively correlated with HCV infection and liver fibrosis	Mohamed <i>et al.</i> , ⁴² 2009

(continued)

Table 1. (continued)

Methods/Study population	Findings and conclusions	Author
14 patients with CHC (without MS) and 7 healthy controls	HCV infection was associated with peripheral and hepatic IR	Vanni <i>et al.</i> , ¹⁹ 2009
170 HCV mono-infected nad 170 HIV/HCV co-infected patients	IR was associated with liver fibrosis and steatosis in HCV mono-infected.	Halfon <i>et al.</i> , ⁴³ 2009
96 CHC non-genotype 3 patients with advanced fibrosis treated with pegylated-IFN/RBV	HCV suppression was correlated with improvement in IR independent from potential confounders	Delgado-Borrego <i>et al.</i> , ²⁸ 2010
188 patients in with different stages of HCV infection	IR, regardless of presence of T2DM, was significantly associated with HCC in patients with CHC	Hung <i>et al.</i> , ⁴⁴ 2010
40 CHC genotype 1 patients enrolled in a study of danoprevir	HOMA-IR improvement was correlated with a decrease in viral load	Moucarri <i>et al.</i> , ⁴⁵ 2010
92 untreated consecutive male CHC patients	IR was detected in 63 (69%) patients. IR was associated with steatosis.	Ahmed <i>et al.</i> , ⁴⁶ 2011
1,038 treatment-naive CHC patients enrolled in albinterferon alpha-2b vs. pegylated-IFN α 2a study	SVR was independently associated with significant reduction in HOMA-IR in patients with genotype 1, not in genotypes 2 or 3	Thompson <i>et al.</i> , ⁴⁷ 2012
50 noncirrhotic, nondiabetic CHC patients (27 untreated, 23 treated with pegylated-IFN/RBV)	IR was not strongly associated with SVR. HCV therapy may improve IR regardless of virologic response	Brandman <i>et al.</i> , ⁴⁸ 2012
140 CHC patients treated with pegylated-IFN α 2a/RBV for 48 weeks	SVR was significantly lower in the IR-HCV group compared with the non-IR-HCV. Plasma insulin levels and HOMA-IR were decreased significantly in patients with SVR	Ziada <i>et al.</i> , ⁴⁹ 2012
431 CHC patients receiving pegylated-IFN α 2a/RBV or pegylated-IFN α 2b/RBV	SVR prevented development of <i>de novo</i> IR in nondiabetic patients with CHC	Aghemo <i>et al.</i> , ⁵⁰ 2012
155 anti-HCV positive patients without T2DM, hypercortisolism, thyroid disease, hyperlipidemia or infective diseases	79 (51%) patients had elevated HOMA-IR	Kiran <i>et al.</i> , ⁵¹ 2013
102 nondiabetic and non-cirrhotic CHC patients (69% genotype 1)	25% of subjects had IR. HCV viral load and genotype did not influence IR	Mukhtar <i>et al.</i> , ⁵² 2013
30 CHC patients and 8 healthy controls underwent a fasting test	9 CHC patients had elevated HOMA-IR. Total ketone body change rate was lower in CHC patients. Mitochondrial β -oxidation impairment due to HCV infection suggested	Sato <i>et al.</i> , ⁵³ 2013
44 treatment naive patients with genotype 1 or 3	IR was found in 27 (61%) and significant steatosis in 37 (84%) patients. No difference in IR between genotypes. IR associated with higher levels of liver fibrosis and steatosis.	Péres <i>et al.</i> , ⁵⁴ 2013

CHC, chronic hepatitis C; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HOMA, homeostatic model assessment; HIV, human immunodeficiency virus; IFN α , interferon- α ; IRS, insulin receptor substrate; IR, insulin resistance; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; SVR, sustained viral response; T2DM, type 2 diabetes mellitus.

core protein was thus shown to impair hepatocyte insulin signaling by increasing cytokine production, predominantly TNF- α , activating SOCS, and inhibiting IRS through several mechanisms.

All these mechanisms are probably responsible for hepatic IR. However, there is also evidence of significant peripheral IR in HCV infection. Milner *et al.*, using a hyperinsulinemic-euglycemic clamp, found no difference in hepatic glucose production and nonesterified free fatty acids suppression with insulin between CHC patients and controls, suggesting IR is predominantly in muscles.²⁰ Vanii *et al.* approximated the

contribution of peripheral IR in CHC to reach 80%.¹⁹ The role of liver-derived circulating factors (hepatokines), as possible mediators of the liver-muscle crosstalk, has yet to be fully elucidated.¹⁰⁶

The development of steatosis is also probably a result of several mechanisms. Both HCV induced and host related IR as well as metabolic factors are important for its development; it is also, however, a consequence of derangements of lipid metabolism caused directly by HCV.¹⁶

The influence of HCV on cholesterol and lipogenesis pathways of hepatocytes is a crucial part of its life cycle. HCV core

Table 2. The association between HCV and hepatic steatosis

Methods/Study population	Findings and conclusions	Authors
240 LBS from patients with acute hepatitis A (86 patients), B (78 patients), and NANB (76 patients)	Steatosis was found in 26% of NANB hepatitis patients compared to 10% of hepatitis A and 6% of B patients	Kryger <i>et al.</i> , ⁶⁰ 1982
181 LBS from 94 patients with chronic NANB hepatitis	Microvesicular steatosis was found in 59% of patients and was considered a typical sign of the chronic NANB	Wiese <i>et al.</i> , ⁵⁶ 1985
LBS from 39 patients with chronic NANB hepatitis during evaluation and follow-up	Fatty metamorphosis noted in 20 (51%) patients	Di Bisceglie <i>et al.</i> , ⁶¹ 1991
LBS from 50 patients with CHC and 21 patients with autoimmune chronic hepatitis	Steatosis was more common in patients with CHC (72% vs. 19%)	Bach <i>et al.</i> , ⁶² 1992
54 LBS from 45 patients with CHC	Fatty change present in 29/54 (54%) specimens	Scheuer <i>et al.</i> , ⁶³ 1992
LBS from 358 anti-HCV positive patients	Steatosis was a prominent feature in patients with chronic HCV infection	Giusti <i>et al.</i> , ⁶⁴ 1993
Comparison of 317 HCV and 299 HBV LBS	Large-droplet fat droplets more likely to be seen in HCV	Lefkowitz <i>et al.</i> , ⁶⁵ 1993
LBS from 55 asymptomatic anti-HCV positive blood donors	Steatosis present in 47%	McMahon <i>et al.</i> , ⁶⁶ 1994
LBS from 148 patients with chronic hepatitis of which 121 (81.8%) were HCV-positive	Steatosis found in 60% of HCV-positive and in 52% of HCV-negative patients. No significant association between steatosis and HCV was found	Fiore <i>et al.</i> , ⁶⁷ 1996
LBS from 90 patients with CHC compared according to genotype	Steatosis was more prevalent in patients with HCV genotype 3a compared to genotypes 1a or 1b	Mihm <i>et al.</i> , ⁶⁸ 1997
LBS from 60 CHC patients compared to 18 patients with chronic hepatitis B and 41 with nonalcoholic steatohepatitis	Fat deposition occurred more often in patients with CHC than in chronic hepatitis B (52% versus 22%)	Czaja <i>et al.</i> , ⁶⁹ 1998
LBS from 43 CHC patients	Steatosis was observed in 21 (48.8%) patients	Fujie <i>et al.</i> , ⁷⁰ 1999
LBS from 148 CHC untreated patients	91 patients (61%) had steatosis of various grade	Hourigan <i>et al.</i> , ⁷¹ 1999
LBS from 101 HCV-infected patients without other risk factors for a fatty liver	Steatosis was found in 41 (40.6%) patients. HCV genotype 3 was associated with higher steatosis scores	Rubbia-Brandt <i>et al.</i> , ⁵⁷ 2000
LBS from 170 CHC patients	Steatosis was found in 90 (52.9%) patients	Ong <i>et al.</i> , ⁷² 2001
LBS from 180 consecutive CHC patients and 41 additional subjects with a known duration of infection	86 (48%) patients showed steatosis. Genotype 3a was associated with a higher prevalence	Adinolfi <i>et al.</i> , ⁷³ 2001
LBS from 100 male patients with untreated noncirrhotic CHC	Hypobetalipoproteinemia and genotype 3 were associated with steatosis in CHC patients	Serfaty <i>et al.</i> , ⁷⁴ 2001
Pre- and post-treatment LBS from 28 HCV genotype 1 and 34 genotype 3 patients	Steatosis was initially present in 16 (57%) patients with HCV genotype 1 and 21 (62%) patients with genotype 3. Achieving SVR greatly reduced steatosis in genotype 3 patients, but not in genotype 1	Kumar <i>et al.</i> , ⁷⁵ 2002
LBS from 97 CHC patients	Steatosis was present in 171 patients (57.6%) with BMI and genotype 3a as independent predictors	Monto A <i>et al.</i> , ⁷⁶ 2002
Paired LBS from 98 CHC patients prior to antiviral treatment	41 (42%) showed signs of steatosis. Prevalence and grade of steatosis were strongly associated with HCV genotype 3	Westin <i>et al.</i> , ⁷⁷ 2002
LBS from 124 CHC patients	90 (73%) specimens showed signs of steatosis. Genotype 3 was associated with increased steatosis grade	Hui <i>et al.</i> , ⁷⁸ 2002

(continued)

Table 2. (continued)

Methods/Study population	Findings and conclusions	Authors
Paired LBS (mean interval time of 48 months) were evaluated in 96 patients with CHC	Steatosis was initially found in 51 (54%) of patients. Worsening of steatosis was observed in 34% of patients, stability in 50%, and improvement in 16%	Castéra <i>et al.</i> , ⁷⁹ 2003
LBS from 1,428 treatment naïve patients were assessed at baseline and 24 weeks after treatment with peginterferon or interferon α -2b and ribavirin	At baseline, steatosis was present in 935 of 1428 patients (65%), including 175 of 210 patients (83%) with genotype 3 versus 760 of 1218 (62%) with other genotypes. Steatosis was associated with genotype 3, fibrosis and lower SVR	Poynard <i>et al.</i> , ⁵⁶ 2003
LBS from 290 CHC patients	135 patients (46.6%) had steatosis, and it was associated with HCV genotype 3, higher grade of necroinflammation, and higher BMI	Asselah <i>et al.</i> , ⁸⁰ 2003
LBS from 755 CHC patients	Steatosis was found in 315 (42%) and fibrosis in 605 patients. Steatosis was independently associated with fibrosis, genotype 3, BMI, ongoing alcohol abuse and age	Rubbia-Brandt <i>et al.</i> , ⁸¹ 2004
LBS from 574 CHC patients	Steatosis was present in 277 (48%) of patients. Severity of steatosis was associated with BMI, HCV genotype 3, age, and duration of infection	Patton <i>et al.</i> , ⁸² 2004
Paired LBS (median interval of 61 months) from 135 untreated CHC patients with a METAVIR score of A1F1 or lower on first liver biopsy	Steatosis was the only independent factor predictive of progression of fibrosis regardless of genotype	Fartoux <i>et al.</i> , ⁸³ 2005
LBS from two cohorts with a total of 325 genotype 1 HCV infected patients were analyzed for the presence and severity of steatosis in relation to the rs12979860 polymorphism at the IL28B locus	Steatosis was found in 67.4% (89/132) of IL28B non-CC patients compared to 39.6% (19/48) of CC patients	Tilman <i>et al.</i> , ⁵⁹ 2011
LBS from 92 untreated males with CHC	Steatosis was found in 54% of patients and was associated with IR	Ahmed <i>et al.</i> , ⁴⁶ 2011
LBS from 152 liver transplant recipients with HCV followed up for a median of 2.09 years	Steatosis was frequent (29.6%) in the early post-transplant period and its presence within the first year carried a higher risk of fibrosis progression	Brandman <i>et al.</i> , ⁸⁴ 2011
LBS from 148 CHC patients	Steatosis was found in 40 patients (27%). No correlation with fibrosis or response to combined antiviral therapy was found	Rafi <i>et al.</i> , ⁸⁵ 2011
LBS from 50 HCV positive patients	28 (56%) patients had steatosis, and it was associated with age and triglycerides levels	Ouakaa-Kchaou <i>et al.</i> , ⁸⁶ 2011
LBS from 50 patients with HCV genotype 2 and 256 with HCV genotype 3	Steatosis was present in 72% of patients. Advanced liver fibrosis and hepatic steatosis were more common in HCV genotype 3	Melo <i>et al.</i> , ⁸⁷ 2014
LBS from 330 patients with chronic hepatitis (66 HBV, 198 HCV, and 66 HBV-HCV co-infected)	Steatosis prevalence was comparable between the HBV-HCV co-infected and HCV groups (47.0% vs 49.5%, respectively). HBV group showed lowest steatosis rates (33.3%)	Zampino R <i>et al.</i> , ⁸⁸ 2014
110 HBV infected, 111 HCV infected and 136 NAFLD patients were evaluated using steatosis biomarkers (SteatoTest > 0.38 as a surrogate for steatosis > 5%)	Prevalence of steatosis was 21% in chronic hepatitis B, 43% in CHC and 82% in NAFLD patients	Pais <i>et al.</i> , ⁸⁹ 2015

BMI, body mass index; CHC, chronic hepatitis C; HBV, hepatitis B virus; HCV, hepatitis C virus; LBS, liver biopsy specimens; NANB, non-A, non-B; NAFLD, non-alcoholic fatty liver disease; SVR, sustained viral response; IR, insulin resistance.

protein plays a major role in the replication process by inducing accumulation of lipid droplets as well as lipogenic gene and protein activity, consequently manifesting as hepatic steatosis.¹⁰⁷ Main mechanisms of HCV-induced hepatic steatosis include promotion of lipogenesis, impairment of mitochondrial lipid oxidation, and decreased microsomal triglyceride transfer protein (MTTP) activity.^{108,109}

The activity of the HCV core protein decreases the expression and activity of the nuclear PPAR- α/γ , which, besides being strongly involved in lipid and lipoprotein metabolism, seem to have a protective effect against hepatic inflammation and fibrosis. The analysis of PPAR- α expression in LBS of 86 untreated patients with HCV and controls found it to be deeply impaired.¹¹⁰ The HCV core protein also induces hepatic fat accumulation by activating the sterol regulatory element-binding protein-1c (SREBP-1c), a transcription factor regulating lipogenesis.¹¹¹ A study in transgenic mice expressing the full HCV protein repertoire showed maturational activation and nuclear translocation of SREBP-1c, resulting in increased lipogenic enzyme transcription.¹¹² The factors involved in pathogenesis of metabolic changes in HCV infection as well as clinical outcomes are shown in Fig. 1.

Clinical consequences of hepatitis C associated steatosis and IR

The presence of both steatosis and IR in CHC may affect fibrosis and therapy outcomes as well as promote atherosclerosis and hepatic malignancy.

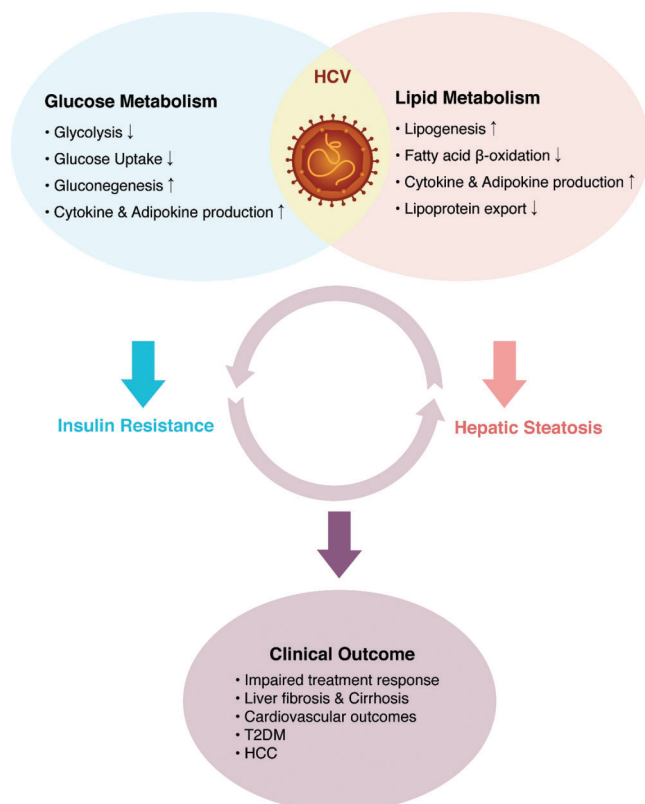


Fig. 1. Pathogenic effects and outcomes of HCV infection.

Liver fibrosis severity and progression are associated with hepatic steatosis and can be used as a clinically relevant parameter regarding starting and prioritizing treatment in CHC patients.^{77,82,113,114}

IR, independent of other factors, is significantly associated with HCC development in patients with CHC.⁴⁴

Of further clinical relevance, primarily in areas where IFN-free regimens with direct-acting antivirals are not yet the standard of care, is the fact that IR has been shown to affect negatively responses to IFN treatment, effectively lowering sustained viral response (SVR) rates irrespective of genotype.¹¹⁵

A review by Negro lists a number of conflicting studies regarding the impact of chronic HCV infection on cardiovascular morbidity.¹¹⁶ It is not yet clear if the reported conditions and observations, such as increased incidence of coronary artery disease, stroke rate, and carotid plaque formation, are a result of a systemic chronic inflammation, direct viral action, or a consequence of IR.

The intricacies of the pathogenesis of IR, hepatic steatosis, and metabolic syndrome are not yet fully understood, and the fact that HCV is able to induce such changes and play a part in such a complex interplay of metabolic processes means it should remain an important focus of research, even as new therapies promise to make hepatitis C an easily manageable condition.

Conclusions

Many epidemiological, clinical, and experimental studies have shown that HCV infection is strongly associated with liver steatosis, IR, and the development of T2DM. Our overview of available clinical data further establishes this premise and, with very few exceptions, shows the presence and strength of this association across various groups of patients, providing a strong foothold for future consideration of this topic. The severity of hepatic steatosis in CHC arises from the combination of several host features (like visceral obesity, genetic predisposition, medication use, and alcohol consumption) and viral factors (including genotype, viral load, and gene mutations), which interfere with lipid metabolism within the hepatocytes or promote IR in the liver and peripheral tissues.

The presence and severity of HCV associated steatosis and IR impact liver fibrosis severity and progression, lower rates of response to interferon-based therapy, promote HCC development, and probably increase cardiovascular morbidity.

The recognition of the link between HCV, steatosis, and MS is important for improved patient treatment and care, and many unresolved issues make it an intriguing area of future research.

Conflict of interest

None

Author contributions

Concept and literature search (DK and LVJ), drafting the manuscript (DK, LVJ and SS), and critical revision with intellectual content (LVJ, MD, MVS, IBC).

References

- [1] www.who.int/mediacentre/factsheets/fs164/en/, accessed July 2015.
- [2] Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology* 2002;36: S21–S29. doi: 10.1002/hep.1840360704.

- [3] Revie D, Salahuddin SZ. Human cell types important for hepatitis C virus replication in vivo and in vitro: old assertions and current evidence. *Virology* 2011;8:346. doi: 10.1186/1743-422X-8-346.
- [4] Castillo I, Rodríguez-Inigo E, Bartolome J, de Lucas S, Ortiz-Movilla N, Carreno V, *et al*. Hepatitis C virus replicates in peripheral blood mononuclear cells of patients with occult hepatitis C virus infection. *Gut* 2005;54:682–685. doi: 10.1136/gut.2004.057281.
- [5] Zhu YZ, Qian XJ, Zhao P, Qi ZT. How hepatitis C virus invades hepatocytes: the mystery of viral entry. *World J Gastroenterol* 2014;20:3457–3467. doi: 10.3748/wjg.v20.i13.3457.
- [6] Li HC, Lo SY. Hepatitis C virus: Virology, diagnosis and treatment. *World J Hepatol* 2015;7:1377–1389. doi: 10.4254/wjh.v7.i10.1377.
- [7] Bartenschlager R, Penin F, Lohmann V, André P. Assembly of infectious hepatitis C virus particles. *Trends Microbiol* 2011;19:95–103. doi: 10.1016/j.tim.2010.11.005.
- [8] Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Shimazaki M, *et al*. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005;143:722–728. doi: 10.7326/0003-4819-143-10-200511150-00009.
- [9] Adams LA, Lindor KD. Nonalcoholic fatty liver disease. *Ann Epidemiol* 2007;17:863–869. doi: 10.1016/j.annepidem.2007.05.013.
- [10] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539–553. doi: 10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S.
- [11] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–3421.
- [12] Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109:433–438. doi: 10.1161/01.CIR.0000111245.75752.C6.
- [13] Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet* 2005;366:1059–1062. doi: 10.1016/S0140-6736(05)67402-8.
- [14] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al*. 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; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644.
- [15] Sundström J, Risérus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. *BMJ* 2006;332:878–882. doi: 10.1136/bmj.38766.624097.1F.
- [16] Cheng F-K F, Torres DM, Harrison SA. Hepatitis C and lipid metabolism, hepatic steatosis, and NAFLD: still important in the era of direct acting antiviral therapy? *J Viral Hepat* 2014;21:1–8. doi: 10.1111/jvh.12172.
- [17] Lonardo A, Adinolfi LE, Restivo L, Ballestri S, Romagnoli D, Baldelli E, *et al*. Pathogenesis and significance of hepatitis C virus steatosis: An update on survival strategy of a successful pathogen. *World J Gastroenterol* 2014;20:7089–7103. doi: 10.3748/wjg.v20.i23.7089.
- [18] Asselah T, Rubbia-Brandt L, Marcillan P, Negro F. Steatosis in chronic hepatitis C: why does it really matter? *Gut* 2006;55:123–130. doi: 10.1136/gut.2005.069757.
- [19] Vanni E, Abate ML, Gentilcore E, Hickman I, Gambino R, Cassader M, *et al*. Sites and mechanisms of insulin resistance in nonobese, nondiabetic patients with chronic hepatitis C. *Hepatology* 2009;50:697–706. doi: 10.1002/hep.23031.
- [20] Milner KL, van der Poorten D, Trenell M, Jenkins AB, Xu A, Smythe G, *et al*. Chronic hepatitis C is associated with peripheral rather than hepatic insulin resistance. *Gastroenterology* 2010;138:932–941. doi: 10.1053/j.gastro.2009.11.050.
- [21] Petit JM, Bour JB, Galland-Jos C, Minello A, Verges B, Guiguet M, *et al*. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *J Hepatol* 2001;35:279–283. doi: 10.1016/S0168-8278(01)00143-X.
- [22] Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, *et al*. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterology* 2003;125:1695–1704. doi: 10.1053/j.gastro.2003.08.032.
- [23] Fartoux L, Poujol-Robert A, Guéchet J, Wendum D, Poupon R, Serfaty L. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut* 2005;54:1003–1008. doi: 10.1136/gut.2004.050302.
- [24] Hsu C-S, Liu C-J, Liu C-H, Wang C-C, Chen C-L, Lai M-Y, *et al*. High hepatitis C viral load is associated with insulin resistance in patients with chronic hepatitis C. *Liver Int* 2008;28:271–277. doi: 10.1111/j.1478-3231.2007.01626.x.
- [25] Mouchari R, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, *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. doi: 10.1053/j.gastro.2007.11.010.
- [26] Kawaguchi T, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, *et al*. Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *Am J Gastroenterol* 2007;102:570–576. doi: 10.1111/j.1572-0241.2006.01038.x.
- [27] Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, Jeon WK, *et al*. Clearance of HCV by Combination Therapy of Pegylated Interferon alpha-2a and Ribavirin Improves Insulin Resistance. *Gut Liver* 2009;3:108–115. doi: 10.5009/gnl.2009.3.2.108.
- [28] Delgado-Borrego A, Jordan SH, Negre B, Healey D, Lin W, Kamegaya Y, *et al*. Reduction of insulin resistance with effective clearance of hepatitis C infection: results from the HALT-C trial. *Clin Gastroenterol Hepatol* 2010;8:458–462. doi: 10.1016/j.cgh.2010.01.022.
- [29] White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: A systematic review and meta-analysis. *J Hepatol* 2008;49:831–844. doi: 10.1016/j.jhep.2008.08.006.
- [30] Tanaka H, Shiota G, Kawasaki H. Changes in glucose tolerance after interferon-alpha therapy in patients with chronic hepatitis C. *J Med* 1997;28:335–346.
- [31] Konrad T, Zeuzem S, Vicini P, Toffolo G, Briem D, Lormann J, *et al*. Evaluation of factors controlling glucose tolerance in patients with HCV infection before and after 4 months therapy with interferon-alpha. *Eur J Clin Invest* 2000;30:111–121. doi: 10.1046/j.1365-2362.2000.00608.x.
- [32] Hickman IJ, Powell EE, Prins JB, Clouston AD, Ash S, Purdie DM, *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. doi: 10.1016/S0168-8278(03)00463-X.
- [33] Romero-Gómez M, Del Mar Viloria M, Andrade RJ, Salmerón J, Diago M, Fernández-Rodríguez CM, *et al*. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005;128:636–641.
- [34] Svegliati-Baroni G, Bugianesi E, Bouserhal T, Marini F, Ridolfi F, Tarsetti F, *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. doi: 10.1136/gut.2006.107946.
- [35] Vázquez-Vanduyck M, Roman S, Vázquez JL, Huacuja L, Khalsa G, Troyo-Sanromán R, *et al*. Effect of Breathwalk on body composition, metabolic and mood state in chronic hepatitis C patients with insulin resistance syndrome. *World J Gastroenterol* 2007;13:6213–6218. doi: 10.3748/wjg.13.6213.
- [36] Imazeki F, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H. Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients. *Liver Int* 2008;28:355–362. doi: 10.1111/j.1478-3231.2007.01630.x.
- [37] Cua IH, Hui JM, Kench JG, George J. Genotype-specific interactions of insulin resistance, steatosis, and fibrosis in chronic hepatitis C. *Hepatology* 2008;48:723–731. doi: 10.1002/hep.22392.
- [38] Petta S, Cammà C, Di Marco V, Alessi N, Cabibbi D, Caldarella R, *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. doi: 10.1111/j.1572-0241.2008.01813.x.
- [39] Poustchi H, Negro F, Hui J, Cua IH, Brandt LR, Kench JG, *et al*. Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol* 2008;48:28–34. doi: 10.1016/j.jhep.2007.07.026.
- [40] Delgado-Borrego A, Liu YS, Jordan SH, Agrawal S, Zhang H, Christofi M, *et al*. Prospective study of liver transplant recipients with HCV infection: evidence for a causal relationship between HCV and insulin resistance. *Liver Transpl* 2008;14:193–201. doi: 10.1002/lt.21267.
- [41] Tsochatzidis E, Manolakopoulos S, Papatheodoridis GV, Hadziyannis E, Triantos C, Zisimopoulos K, *et al*. Serum HCV RNA levels and HCV genotype do not affect insulin resistance in nondiabetic patients with chronic hepatitis C: a multicentre study. *Aliment Pharmacol Ther* 2009;30:947–954. doi: 10.1111/j.1365-2036.2009.04094.x.
- [42] Mohamed HR, Abdel-Azziz MY, Zalata KR, Abdel-Razik AM. Relation of insulin resistance and liver fibrosis progression in patients with chronic hepatitis C virus infection. *Int J Health Sci (Qassim)* 2009;3:177–186.
- [43] Halfon P, Pénaranda G, Carrat F, Bedossa P, Boulière M, Ouzan D, *et al*. Influence of insulin resistance on hepatic fibrosis and steatosis in hepatitis C virus (HCV) mono-infected compared with HIV-HCV co-infected patients. *Aliment Pharmacol Ther* 2009;30:61–70. doi: 10.1111/j.1365-2036.2009.03995.x.
- [44] Hung CH, Wang JH, Hu TH, Chen CH, Chang KC, Yen YH, *et al*. Insulin resistance is associated with hepatocellular carcinoma in chronic hepatitis

- C infection. *World J Gastroenterol* 2010;16:2265–2271. doi: 10.3748/wjg.v16.i18.2265.
- [45] Moucari R, Forestier N, Larrey D, Guyader D, Couzigou P, Benhamou Y, *et al*. Danoprevir, an HCV NS3/4A protease inhibitor, improves insulin sensitivity in patients with genotype 1 chronic hepatitis C. *Gut* 2010;59:1694–1698. doi: 10.1136/gut.2010.219089.
- [46] Ahmed AM, Hassan MS, Abd-Elsayed A, Hassan H, Hasanain AF, Helmy A. Insulin resistance, steatosis, and fibrosis in Egyptian patients with chronic Hepatitis C virus infection. *Saudi J Gastroenterol* 2011;17:245–251. doi: 10.4103/1319-3767.82578.
- [47] Thompson AJ, Patel K, Chuang W-L, Lawitz EJ, Rodriguez-Torres M, Rustgi VK, *et al*. Viral clearance is associated with improved insulin resistance in genotype 1 chronic hepatitis C but not genotype 2/3. *Gut* 2012;61:128–134. doi: 10.1136/gut.2010.236158.
- [48] Brandman D, Bacchetti P, Ayala CE, Maher JJ, Khalili M. Impact of Insulin Resistance on HCV Treatment Response and Impact of HCV Treatment on Insulin Sensitivity Using Direct Measurements of Insulin Action. *Diabetes Care* 2012;35:1090–1094. doi: 10.2337/dc11-1837.
- [49] Ziada DH, El Saadany S, Enaba M, Ghazy M, Hasan A. The interaction among insulin resistance, liver fibrosis and early virological response in Egyptian patients with chronic hepatitis C. *Can J Gastroenterol* 2012;26:325–329.
- [50] Aghemo A, Prati GM, Rumi MG, Soffredini R, D'Ambrosio R, Orsi E, *et al*. Sustained virological response prevents the development of insulin resistance in patients with chronic hepatitis C. *Hepatology* 2012;56:1681–1687. doi: 10.1002/hep.25867.
- [51] Kiran Z, Zuberi BF, Anis D, Qadeer R, Hassan K, Afsar S. Insulin resistance in non-diabetic patients of chronic Hepatitis C. *Pakistan Journal of Medical Sciences* 2013;29:201–204.
- [52] Mukhtar NA, Bacchetti P, Ayala CE, Melgar J, Christensen S, Maher JJ, *et al*. Insulin Sensitivity and Variability in Hepatitis C Virus Infection Using Direct Measurement. *Digestive diseases and sciences* 2013;58:1141–1148. doi: 10.1007/s10620-012-2438-3.
- [53] Sato C, Saito T, Misawa K, Katsumi T, Tomita K, Ishii R, *et al*. Impaired mitochondrial β -oxidation in patients with chronic hepatitis C: relation with viral load and insulin resistance. *BMC Gastroenterology* 2013;13:112. doi: 10.1186/1471-230X-13-112.
- [54] Pères DP, Cheinquer H, Wolf FH, Cheinquer N, Falavigna M, Pères LD. Prevalence of insulin resistance in chronic hepatitis C genotype 1 and 3 patients. *Ann Hepatol* 2013;12:871–875.
- [55] Dienes HP, Popper H, Arnold W, Lobeck H. Histologic observations in human hepatitis non-A, non-B. *Hepatology* 1982;2:562–571. doi: 10.1002/hep.1840020509.
- [56] Wiese M, Haupt R. Histomorphologic picture of chronic non-A, non-B hepatitis. *Dtsch Z Verdau Stoffwechsellkr* 1985;45:101–110.
- [57] Rubbia-Brandt L, Quadri R, Abid K, Giostra E, Zarski JP, Spahr L, *et al*. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *J Hepatol* 2000;33:106–115. doi: 10.1016/S0168-8278(00)80166-X.
- [58] Poynard T, Ratziu V, McHutchison J, Manns M, Goodman Z, Albrecht J, *et al*. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. *Hepatology* 2003;38:75–85. doi: 10.1053/jhep.2003.50267.
- [59] Tillmann HL, Patel K, Muir AJ, Guy CD, Li JH, Lao XQ, *et al*. Beneficial IL28B genotype associated with lower frequency of hepatic steatosis in patients with chronic hepatitis C. *J Hepatol* 2011;55:1195–1200. doi: 10.1016/j.jhep.2011.03.015.
- [60] Kryger P, Christoffersen P. Light microscopic morphology of acute hepatitis non-A, non-B. A comparison with hepatitis type A and B. *Liver* 1982;2:200–206. doi: 10.1111/j.1600-0676.1982.tb00197.x.
- [61] Di Bisceglie AM, Goodman ZD, Ishak KG, Hoofnagle JH, Melpolder JJ, Alter HJ. Long-term clinical and histopathological follow-up of chronic posttransfusion hepatitis. *Hepatology* 1991;14:969–974. doi: 10.1002/hep.1840140603.
- [62] Bach N, Thung SN, Schaffner F. The histological features of chronic hepatitis C and autoimmune chronic hepatitis: a comparative analysis. *Hepatology* 1992;15:572–577. doi: 10.1002/hep.1840150403.
- [63] Scheuer PJ, Ashrafzadeh P, Sherlock S, Brown D, Dusheiko GM. The pathology of hepatitis C. *Hepatology* 1992;15:567–571. doi: 10.1002/hep.1840150402.
- [64] Giusti G, Pasquale G, Galante D, Russo M, Sardaro C, Gallo C, *et al*. Clinical and histological aspects of chronic HCV infection and cirrhosis. *Hepato-gastroenterology* 1993;40:365–369.
- [65] Lefkowitz JH, Schiff ER, Davis GL, Perrillo RP, Lindsay K, Bodenheimer HC Jr, *et al*. Pathological diagnosis of chronic hepatitis C: a multicenter comparative study with chronic hepatitis B. The Hepatitis Interventional Therapy Group. *Gastroenterology* 1993;104:595–603.
- [66] McMahon RFT, Yates AJ, McLindon J, Babbs C, Lovej EM, Warnes TW. The histopathological features of asymptomatic hepatitis C virus-antibody positive blood donors. *Histopathology* 1994;24:517–524. doi: 10.1111/j.1365-2559.1994.tb00569.x.
- [67] Fiore G, Fera G, Napoli N, Vella F, Schiraldi O. Liver steatosis and chronic hepatitis C: a spurious association? *Eur J Gastroenterol Hepatol* 1996;8:125–129. doi: 10.1097/00042737-199602000-00006.
- [68] Mihm S, Fayyazi A, Hartmann H, Ramadori G. Analysis of histopathological manifestations of chronic hepatitis C virus infection with respect to virus genotype. *Hepatology* 1997;25:735–739. doi: 10.1002/hep.510250340.
- [69] Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Host- and disease-specific factors affecting steatosis in chronic hepatitis C. *J Hepatol* 1998;29:198–206. doi: 10.1016/S0168-8278(98)80004-4.
- [70] Fujie H, Yotsuyanagi H, Moriya K, Shintani Y, Tsutsumi T, Takayama T, *et al*. Steatosis and intrahepatic hepatitis C virus in chronic hepatitis. *J Med Virol* 1999;59:141–145. doi: 10.1002/(SICI)1096-9071(199910)59:2<141::AID-JMV3>3.0.CO;2-5.
- [71] Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, *et al*. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology* 1999;29:1215–1219. doi: 10.1002/hep.510290401.
- [72] Ong JP, Younossi ZM, Speer C, Olano A, Gramlich T, Boparai N. Chronic hepatitis C and superimposed nonalcoholic fatty liver disease. *Liver* 2001;21:266–271. doi: 10.1034/j.1600-0676.2001.021004266.x.
- [73] Adinolfi LE, Gambardella M, Andreato A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001;33:1358–1364. doi: 10.1053/jhep.2001.24432.
- [74] Serfaty L, Andreani T, Giral P, Carbonell N, Chazouillères O, Poupon R. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. *J Hepatol* 2001;34:428–434. doi: 10.1016/S0168-8278(00)00036-2.
- [75] Kumar D, Farrell GC, Fung C, George J. Hepatitis C virus genotype 3 is cytopathic to hepatocytes: Reversal of hepatic steatosis after sustained therapeutic response. *Hepatology* 2002;36:1266–1272. doi: 10.1053/jhep.2002.36370.
- [76] 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. doi: 10.1053/jhep.2002.35064.
- [77] Westin J, Nordlinder H, Lagging M, Norkrans G, Wejstål R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *J Hepatol* 2002;37:837–842. doi: 10.1016/S0168-8278(02)00299-4.
- [78] Hui JM, Kench J, Farrell GC, Lin R, Samarasinghe D, Liddle C, *et al*. Genotype-specific mechanisms for hepatic steatosis in chronic hepatitis C infection. *J Gastroenterol Hepatol* 2002;17:873–881. doi: 10.1046/j.1440-1746.2002.02813.x.
- [79] Castéra L, Hézode C, Roudot-Thoraval F, Bastie A, Zafrani ES, Pawlotsky JM, *et al*. Worsening of steatosis is an independent factor of fibrosis progression in untreated patients with chronic hepatitis C and paired liver biopsies. *Gut* 2003;52:288–292. doi: 10.1136/gut.52.2.288.
- [80] Asselah T, Boyer N, Guimont MC, Cazals-Hatem D, Tubach F, Nahon K, *et al*. Liver fibrosis is not associated with steatosis but with necroinflammation in French patients with chronic hepatitis C. *Gut* 2003;52:1638–1643. doi: 10.1136/gut.52.11.1638.
- [81] Rubbia-Brandt L, Fabris P, Paganin S, Leandro G, Male PJ, Giostra E. Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut* 2004;53:406–412. doi: 10.1136/gut.2003.018770.
- [82] Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vallée M, *et al*. The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. *J Hepatol* 2004;40:484–490. doi: 10.1016/j.jhep.2003.11.004.
- [83] Fartoux L, Chazouillères O, Wendum D, Poupon R, Serfaty L. Impact of steatosis on progression of fibrosis in patients with mild hepatitis C. *Hepatology* 2005;41:82–87. doi: 10.1002/hep.20519.
- [84] Brandman D, Pingitore A, Lai JC, Roberts JP, Ferrell L, Bass NM, *et al*. Hepatic steatosis at 1 year is an additional predictor of subsequent fibrosis severity in liver transplant recipients with recurrent hepatitis C virus. *Liver Transpl* 2011;17:1380–1386. doi: 10.1002/lt.22389.
- [85] Rafi H, Kabbaj N, Salihoun M, Amrani L, Acharki M, Guedira M, *et al*. Influence of steatosis on progression of fibrosis and virological response in chronic hepatitis C cases. *Arab J Gastroenterol* 2011;12:136–138. doi: 10.1016/j.ajg.2011.07.003.
- [86] Ouakaa-Kchaou A, Gargouri D, Kochlef A, Debiche A, Elloumi H, Ghouma M, *et al*. Steatosis in chronic hepatitis C: prevalence and predictive factors. *Tunis Med* 2011;89:830–836.
- [87] Melo IC, Ferraz ML, Perez RM, Emori CT, Uehara SN, de Carvalho-Filho RJ, *et al*. Do differences exist between chronic hepatitis C genotypes 2 and 3? *Rev Soc Bras Med Trop* 2014;47:143–148. doi: 10.1590/0037-8682-0269-2013.
- [88] Zampino R, Coppola N, Cirillo G, Boemio A, Minichini C, Marrone A, *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. doi: 10.4254/wjh.v6.i9.677.

- [89] Pais R, Rusu E, Zilisteanu D, Ciciu A, Micu L, Voiculescu M, Poynard T, Ratziu V. Prevalence of steatosis and insulin resistance in patients with chronic hepatitis B compared with chronic hepatitis C and non-alcoholic fatty liver disease. *Eur J Intern Med* 2015;26:30–36. doi: 10.1016/j.ejim.2014.12.001.
- [90] Mangia A, Ripoli M. Insulin resistance, steatosis and hepatitis C virus. *Hepatol Int* 2013;7:S782–S789. doi: 10.1007/s12072-013-9460-1.
- [91] Kawaguchi Y, Mizuta T. Interaction between hepatitis C virus and metabolic factors. *World J Gastroenterol* 2014;20:2888–2901. doi: 10.3748/wjg.v20.i11.2888.
- [92] Bose SK, Ray R. Hepatitis C virus infection and insulin resistance. *World J Diabetes* 2014;5:52–58. doi: 10.4239/wjd.v5.i1.52.
- [93] Vanni E, Abate ML, Gentilcore E, Hickman I, Gambino R, Cassader M, *et al*. Sites and mechanisms of insulin resistance in nonobese, nondiabetic patients with chronic hepatitis C. *Hepatology* 2009;50:697–706. doi: 10.1002/hep.23031.
- [94] Vespasiani-Gentilucci U, Gallo P, De Vincentis A, Galati G, Picardi A. Hepatitis C virus and metabolic disorder interactions towards liver damage and atherosclerosis. *World J Gastroenterol* 2014;20:2825–2838. doi: 10.3748/wjg.v20.i11.2825.
- [95] Adinolfi LE, Zampino R, Restivo L, Lonardo A, Guerrera B, Marrone A, *et al*. Chronic hepatitis C virus infection and atherosclerosis: Clinical impact and mechanisms. *World J Gastroenterol* 2014;20:3410–3417. doi: 10.3748/wjg.v20.i13.3410.
- [96] Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, Kimura S, *et al*. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology* 2004;126:840–848. doi: 10.1053/j.gastro.2003.11.056.
- [97] Romero-Gómez M. Insulin resistance and hepatitis C. *World J Gastroenterol* 2006;12:7075–7080.
- [98] Banerjee A, Meyer K, Mazumdar B, Ray RB, Ray R. Hepatitis C virus differentially modulates activation of forkhead transcription factors and insulin-induced metabolic gene expression. *J Virol* 2010;84:5936–5946. doi: 10.1128/JVI.02344-09.
- [99] Cua IH, Hui JM, Bandara P, Kench JG, Farrell GC, McCaughan GW, *et al*. Insulin resistance and liver injury in hepatitis C is not associated with virus-specific changes in adipocytokines. *Hepatology* 2007;46:66–73. doi: 10.1002/hep.21703.
- [100] Stojšavljević S, Gomercić Palčić M, Virović Jukić L, Smircić Duvnjak L, Duvnjak M. Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol* 2014;20:18070–18091. doi: 10.3748/wjg.v20.i48.18070.
- [101] Bugianesi E, Salamone F, Negro F. The interaction of metabolic factors with HCV infection: does it matter? *J Hepatol* 2012;56:S56–S65. doi: 10.1016/S0168-8278(12)60007-5.
- [102] Brault C, Levy PL, Bartosch B. Hepatitis C virus-induced mitochondrial dysfunction. *Viruses* 2013;5:954–980. doi: 10.3390/v5030954.
- [103] Yao W, Cai H, Li X, Li T, Hu L, Peng T. Endoplasmic reticulum stress links hepatitis C virus RNA replication to wild-type PGC-1 α /liver-specific PGC-1 α upregulation. *J Virol* 2014;88:8361–8374. doi: 10.1128/JVI.01202-14.
- [104] Aytug S, Reich D, Sapiro LE, Bernstein D, Begum N. Impaired IRS-1/PI3-kinase signaling in patients with HCV: a mechanism for increased prevalence of type 2 diabetes. *Hepatology* 2003;38:1384–1392. doi: 10.1053/jhep.2003.09012.
- [105] Kawaguchi T, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T, *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. doi: 10.1016/S0002-9440(10)63408-6.
- [106] Peyrou M, Bourgoin L, Poher AL, Altirriba J, Maeder C, Caillon A, *et al*. Hepatic PTEN deficiency improves muscle insulin sensitivity and decreases adiposity in mice. *J Hepatol* 2015;62:421–429. doi: 10.1016/j.jhep.2014.09.012.
- [107] Masaki T, Suzuki R, Murakami K, Aizaki H, Ishii K, Murayama A, *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. doi: 10.1128/JVI.00826-08.
- [108] Perlemuter G, Sabile A, Letteron P, Vona G, Topilco A, Chrétien Y, *et al*. Hepatitis C virus core protein inhibits microsomal triglyceride transfer protein activity and very low density lipoprotein secretion: a model of viral-related steatosis. *FASEB J* 2002;16:185–194. doi: 10.1096/fj.01-0396com.
- [109] Amako Y, Munakata T, Kohara M, Siddiqui A, Peers C, Harris M. Hepatitis C virus attenuates mitochondrial lipid β -oxidation by downregulating mitochondrial trifunctional-protein expression. *J Virol* 2015;89:4092–4101. doi: 10.1128/JVI.01653-14.
- [110] Dharancy S, Malapel M, Perlemuter G, Roskams T, Cheng Y, Dubuquoy L, *et al*. Impaired expression of the peroxisome proliferator-activated receptor α during hepatitis C virus infection. *Gastroenterology* 2005;128:334–342. doi: 10.1053/j.gastro.2004.11.016.
- [111] McPherson S, Jonsson JR, Barrie HD, O'Rourke P, Clouston AD, Powell EE. Investigation of the role of SREBP-1c in the pathogenesis of HCV-related steatosis. *J Hepatol* 2008;49:1046–1054. doi: 10.1016/j.jhep.2008.06.022.
- [112] Lerat H, Kammoun HL, Hainault I, Mérour E, Higgs MR, Callens C, *et al*. Hepatitis C virus proteins induce lipogenesis and defective triglyceride secretion in transgenic mice. *J Biol Chem* 2009;284:33466–33474. doi: 10.1074/jbc.M109.019810.
- [113] Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001;33:1358–1364. doi: 10.1053/jhep.2001.24432.
- [114] Cholet F, Noursbaum JB, Richecoeur M, Oger E, Cauvin JM, Lagarde N, *et al*. Factors associated with liver steatosis and fibrosis in chronic hepatitis C patients. *Gastroenterol Clin Biol* 2004;28:272–278. doi: 10.1016/S0399-8320(04)94918-4.
- [115] Eslam M, Aparcero R, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, *et al*. Meta-analysis: insulin resistance and sustained virological response in hepatitis C. *Aliment Pharmacol Ther* 2011;34:297–305. doi: 10.1111/j.1365-2036.2011.04716.x.
- [116] Negro F. Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. *J Hepatol* 2014;61:S69–78. doi: 10.1016/j.jhep.2014.08.003.