

Insulin resistance and steatosis in chronic hepatitis C

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Abstract

In chronic hepatitis C, insulin resistance (IR) and type 2 diabetes mellitus (DM) are more prevalent than in healthy controls or in chronic hepatitis B patients. HCV infection promotes IR mainly through increased TNF- α and cytokine suppressor (SOCS-3) production. Both events inhibit insulin receptor and IRS-1 (insulin receptor substrate) tyrosine phosphorylation. Hepatic steatosis is also 2.5 fold more frequent in hepatitis C virus (HCV) infected patients as compared to the general population. Metabolic factors play a crucial role in the etiology of hepatic steatosis genotype non-3 related, which are also the genotypes with a greater association to IR. However, genotype 3, and particularly 3a, has a greater direct steatogenic capacity, and consequently, in those patients, the association with metabolic factors is weaker. Instead, in genotype 3, steatosis associates with viral factors like viral load. Those metabolic factors influence not only the natural history of HCV infection, as well as associate to an accelerated hepatic fibrosis progression, to a worse prognosis when hepatic cirrhosis is present, namely an increased risk of hepatocellular carcinoma, and to a lower sustained viral response rate. On the other hand, in patients who achieve viral eradication, IR and hepatic steatosis may regress, and return if viral infection recurs, which once again indicates an intrinsic steatosis and IR promoter action by HCV.

Key words: Steatosis, insulin resistance, diabetes mellitus, chronic hepatitis C.

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Introduction

Chronic hepatitis C closely relates to hepatic steatosis and insulin resistance (IR)/ increased risk of type 2 diabetes mellitus (DM). Although this association may be a consequence of metabolic factors, hepatitis C virus (HCV) itself has the ability to directly promote steatosis and IR. This association is extremely important as it not only is very frequent, but it has a harmful influence in the prognosis and anti-viral treatment.

This article aims to be an in depth review of the epidemiological data of IR/DM and steatosis in chronic hepatitis C, its mechanisms, and how it influences the response to anti-viral treatment and prognosis.

Epidemiology

Insulin resistance/diabetes mellitus

The prevalence of DM in chronic hepatitis C patients is higher than the expected, having in consideration data from the general population. In patients with hepatic cirrhosis it is estimated to be 24-50%.¹⁻⁴ Hepatic cirrhosis is itself diabetogenic, however, the risk of DM in HCV related hepatic cirrhosis is 3 to 5 times greater than in other etiologies of hepatic cirrhosis, including hepatitis B virus (HBV) related.²⁻⁵ The prevalence of DM in a non cirrhotic population with chronic hepatitis C is 7.6-21%, representing a 2 to 4 fold increased risk when compared to other forms of chronic hepatitis.^{1,6-15} Only 4 studies failed to demonstrate a positive association between DM and HCV infection.¹⁶⁻¹⁹ A recent meta-analysis on 34 studies found an adjusted odds ratio of 1.67 (95% CI [1.28-2.06] relatively to non infected subjects.⁶ A follow up population study, a subset of ARIC - *Atherosclerosis Risk in Communities Study*, re-evaluated, at the end of 9 years, 1,084 patients without DM, and found that the subgroup of patients chronically infected by HCV had a 2 fold increased risk of developing DM, and that risk increased to 11 fold in high risk patients taking in consideration age and body mass index (BMI).²⁰ The opposite is also true, that is, patients with DM have a higher risk of being infected with HCV, as compared with the general population, being the prevalence of HCV seropositivity in patients with DM 4.2-10.5% in different studies.^{2,8}

This can be explained by the induction of DM by HCV, but also by a greater susceptibility of patients with DM to be infected with HCV. In fact, a recent study in patients suffering from chronic renal failure in hemodialysis showed that patients with DM had a 10 fold increased risk of HCV infection, with a higher annual seroconversion rate (11 *versus* 7%) and in a smaller time period of hemodialysis (30 *versus* 50 months).²¹

One explanation to the higher prevalence of DM could be a β -pancreatic cell dysfunction, as suggested by the fact that these patients present a blunted acute response of insulin secretion to hyperglycemia,³ and also by the presence of HCV RNA in pancreatic tissue^{22,23} which may translate a direct cytopathic effect. However, it is now more consensual to accept the development of DM as a consequence of induction of IR.

In fact, chronically HCV infected subjects present a 3 fold increased risk of IR and glucose metabolism impairment,^{24,25} with IR occurring in very early stages of hepatic lesion (fibrosis stage 0 or 1),²⁶ with a worsening tendency as hepatic fibrosis progresses.^{7,12,26-29} IR severity can be genotype specific, although the different studies are not consensual in that regard: some authors found a greater IR severity in genotype 1 and 4 as compared to genotype 3,^{7,26} others in genotype 2a as compared to genotype 1,⁸ and others failed to find an association with genotype.^{5,30} Two levels of evidence suggest a causal relation between HCV infection and DM: an association between IR severity and DM with higher viral load,^{7,30,31} and an improvement in IR after a sustained viral response (SVR) to anti-viral treatment as opposite to an un-

changed IR in non responders, despite a decrease in BMI.³²⁻³⁴

Steatosis

Although the estimated prevalence of hepatic steatosis in the general population is 20%, in patients with chronic hepatitis C it may vary from 40-80%, depending on alcohol consumption, obesity, diabetes and other risk factors to fatty liver.³⁵⁻⁴³ If all steatogenic co-factors are excluded, the prevalence of steatosis remains 50% (although present in less than 30% of the hepatocytes in about two thirds of the patients),^{38,40} resulting in a 2.5 fold increased prevalence as compared with the general population and other forms of chronic liver disease,⁴⁴⁻⁴⁶ particularly HBV infection, in which the prevalence of steatosis is 18%.⁴⁷ In chronic hepatitis C, although hepatic steatosis can be related to metabolic factors like obesity, dyslipidaemia and DM,^{38-42,48,49} as much as one third of the patients with steatosis do not have any metabolic impairment.⁴⁴ Also, steatosis is more frequent in HCV as compared to HBV infected subjects, even after adjustment to BMI. As shown in Table I.³⁷

Several lines of evidence suggest that steatosis can be attributed to HCV infection. Steatosis is more frequent in association to genotype 3a as compared to other genotypes (74 *versus* 50%),^{26,39,43,48,50-54} which suggests that some sequences of viral genome may be involved in the intracellular lipid accumulation. On the other hand, in genotype 3 infection, steatosis correlates to viral load^{39,40,43,54} and can revert after effective treatment but

Table I. Factors associated to hepatic steatosis in chronic hepatitis C.

Reference	Number of patients	Steatosis (% of patients)	Association to Steatosis					
			Host factors			Viral factors		
			BMI	Alcohol	DM	Genotype	Viral load	Fibrosis
Leandro 2006 ³⁵	3,068	51	yes	yes	yes	yes, 3	NA	yes
Rubbia-Brandt 2004 ⁵⁸	755	42	yes	yes	NA	yes, 3	NA	yes, 3
Patton 2004 ⁵⁴	574	48	yes	NA	NA	yes, 3	yes	yes, 1
Poynard 2003 ⁴⁰	1,428	65	yes	NA	NA	yes, 3	yes, 3	yes
Asselah 2003 ¹⁴²	290	46	yes	no	NA	yes, 3	NA	no
Castera 2003 ¹⁴³	96	54	yes	no	NA	yes, 3a	no	yes
Monto 2002 ⁴⁸	297	58	yes	no	yes	yes, 3a	no	no
Serfaty 2002 ¹⁴⁴	142	42	yes	no	no	yes, 3a	NA	no
Hui 2002 ⁵²	124	73	yes	yes	NA	yes, 3	NA	no
Westin 2002 ¹⁴⁵	98	42	yes	no	NA	yes, 3a	NA	yes
Ong 2001 ¹⁴⁶	170	53	yes	no	no	NA	NA	yes
Hwang 2001 ⁴²	106	52	yes	NA	NA	no	no	yes
Adinolfi 2001 ³⁹	180	48	yes, 1	NA	NA	yes, 3a	yes, 3a	yes
Rubbia-Brandt 2000 ⁵¹	101	41	NA	NA	NA	yes, 3a	yes	yes
Hourigan 1999 ³⁸	148	61	yes	no	no	yes, 3a	yes	yes
Giannini 1999 ¹⁴⁷	172	70	NA	NA	NA	no	NA	yes
Czaja 1998 ³⁷	60	52	yes	NA	yes	NA	NA	NA
Mihm 1997 ⁵⁰	86	86	NA	NA	NA	yes, 3a	NA	yes
Wong 1996 ¹⁴⁸	200	38	NA	NA	NA	NA	NA	yes
Fiore 1996 ⁴¹	121	60	yes	yes	no	NA	NA	yes

NA = not available, BMI = body mass index, DM = diabetes mellitus.

reoccurs in re-infection,^{40,55,56} the same having not been verified in the other genotypes.^{38,40,43} Also, the localization of steatosis, particularly in genotype 3 infected patients, is predominantly in periportal zone (acinar 1) and not in centrilobular zone (acinar 3) more typical of metabolic associated steatohepatitis.⁵⁷

It is now accepted that in chronic hepatitis C, there can occur two types of steatosis, a "metabolic" steatosis, that is consequence of metabolic factors like alcohol consumption and risk factors of non alcoholic fatty liver (the most important ones being obesity, visceral fat and IR); and a viral steatosis that may result from a direct viral cytopathic effect. The former associates to genotype 1, 2 and 4^{39,48,58,59} and do not revert after anti-viral treatment.⁴⁰ The latter associates to genotype 3 and does not relate to BMI or IR.⁵³ However, even the "metabolic" steatosis can be partially an indirect consequence of viral infection, since HCV induces a metabolic deregulation with IR.

Pathogenesis

IR occurs very early in HCV infection, in parallel with an elevation in TNF- α levels.⁶⁰⁻⁶³ TNF- α induces IR through the inhibition of insulin receptor and IRS-1 (insulin receptor substrate) tyrosine phosphorylation,^{61,64} impairing the signaling pathway which would lead to the translocation of GLUT4 to the cell surface membrane, diminishing the cellular glucose uptake.

HCV also directly promotes IR through the proteasomal degradation of IRS-1.^{65,66} The molecular mechanism that leads to IRS-1 degradation varies according to genotype.⁶⁷ Genotype 1 promotes the expression of SOCS-3 (suppressor of cytokine signaling 3), a negative regulator of insulin signaling, which acts through the IRS-1 ubiquitination, targeting it to proteasomes where it is destroyed. Genotype 1b also diminishes IRS-1 levels, through the activation of mTOR (mammalian target of rapamycin) which induces serine/threonine phosphorylation, redistribution and proteasomal degradation of IRS-1.⁶⁸ Genotype 3 promotes SOCS 7 expression,⁶⁹ with a mechanism of IRS-1 degradation similar to that induced by SOCS 3; it also inhibits PPAR- γ , further worsening IR.⁶⁷

Lastly, HCV induces protein phosphatase 2A expression, through an endoplasmic reticulum stress response pathway, which dephosphorylates PkB/Akt (a main enzyme in the insulin signaling pathway), and thereby lowers its kinase activity.⁷⁰

HCV infection can indirectly promote the development of hepatic steatosis, but it is itself steatogenic. All genotypes are steatogenic, however genotype 3 is three times more potent.⁷¹ In fact, animal models with transgenic mice showed that the core protein can induce the appearance of lipid droplets.⁷² More recently, *in vitro* and *in vivo* studies showed a topological relation, with the core protein being localized in the membrane of

those lipidic vesicles.⁷³ We already know what sequences in core protein are essential to that preferential localization.^{74,75} One possible molecular explanation to a greater steatogenic property of genotype 3, could be a phenylalanine residue at position 164 in core protein domain II, instead of tyrosine like in other genotypes, what translates in a higher affinity to lipids.⁷⁶

Steatosis can be induced in 3 ways: decreasing the lipids export by hepatocytes, decreasing fatty acids consumption (that is its oxidation) or increasing de novo synthesis.

Decreased hepatocyte lipid export is a consequence of a decreased assembly of triglycerides in VLDL (very low density lipoproteins) particles and its secretion. Animal models and studies in humans, demonstrated that core protein inhibits microsomal triglyceride transfer protein (MTP) activity,⁷⁷ an enzyme that transfers lipids to endoplasmic reticulum, allowing its association to B apolipoprotein and triglycerides rich VLDL assembly. That inhibition occurs in all genotypes, however it is more potent with genotype 3;⁷⁸ in genotype 1 and 2 infected patients, the decreased MTP activity seems to be a consequence of a reduced transcription induced by IR and hyperinsulinism. In fact, insulin inhibits MTP expression through a MAP-Kerk (mitogen-activated extracellular signal-regulated protein kinase) pathway.^{79,80} In accordance to MTP dysfunction, HCV infected patients with severe steatosis present decreased cholesterol and apo B plasma levels.^{81,82}

Other animal models propose an inhibition of VLDL secretion by a different mechanism, oxidative stress dependent. Oxygen reactive species are a consequence of mitochondrial respiratory chain impairment, when a small proportion of electron efflux interacts with oxygen molecules before reaching the cytochrome oxidase complex.⁸³ Core protein may accumulate in mitochondria, impairing electron transport and thus increasing the production of oxygen reactive species.⁸⁴ Oxidative stress leads to cellular damage through lipids and structural proteins peroxidation, disturbing the cellular traffic apparatus and VLDL secretion.⁸⁵ Recently a study suggested that HCV can impair the lipid cellular metabolism, through a modification in the response to VLDL and LDL. In fact, Napolitano et al. demonstrated an impaired metabolic response to VLDL and LDL isolated from patients infected with HCV, with a slower VLDL catabolism, which can result in a higher VLDL-LDL switch in circulation. They also showed a higher LDL catabolism with subsequent intracellular lipid accumulation leading to steatosis. The mechanism of response modulation to VLDL/LDL still needs to be explained, but it can be a consequence of a direct binding between HCV and lipoproteins or a modification in their molecular composition.⁸⁶

A second steatogenic pathway is **decreased fatty acids consumption**, through mitochondrial beta-oxidation inhibition. In fact, core protein may induce structural changes in mitochondria membranes, with subsequent

derangement of lipid β -oxidation, promoting steatosis.⁸⁷ More recently, it has also been demonstrated a diminished PPAR α (peroxisome proliferators-activated receptor α) expression induced by core protein⁸⁸⁻⁹¹ which is more potent with genotype 3 as compared to genotype 1.⁹¹ PPAR- α is a nuclear receptor that regulates the transcription of several major genes in the lipids metabolism, for instance CPT1A (mitochondrial carnitine palmitoyl acyl-CoA transferase 1), which is a rate limiting enzyme in the mitochondrial β -oxidation mediating the entry of fatty acids in the mitochondria; ACOX (acyl-CoA oxidase), the main enzyme in mitochondrial β -oxidation; and Mdr2, a transport protein in canalicular membranes which controls biliary phospholipids secretion. Several experimental models showed a diminished PPAR- α expression and transcriptional activity, with a decreased CPT1A and ACOX expression with decreased fatty acids oxidation, as well as a decreased Mdr2 expression with a potential decrease in phospholipids associated fatty acids biliary excretion.⁸⁸⁻⁹¹

A third steatogenic mechanism is the promotion of de novo fatty acids synthesis. A chimpanzee animal model showed an early SREBP-1c (sterol regulatory element binding protein signaling pathway) expression induction after HCV infection.⁹² SREBP-1c is a transcriptional factor that regulates several genes in lipid metabolism, namely fatty acids synthetase, acetyl-CoA carboxylase and stearoyl-CoA desaturase, key lipogenic enzymes which are also overexpressed in HCV infection.⁹³⁻⁹⁵ Additionally, core protein also binds to DNA-binding domain of RXR α (retinoid X receptor α – a nuclear receptor that regulates several genes involved in cellular lipids synthesis), increasing its transcriptional activity.⁹⁶

Interestingly, hepatic steatosis may promote viral replication. HCV may associate to LDL in lipo-viral particles that circulate in blood stream.⁹⁷ Therefore, LDL receptors allow HCV cellular intake,⁹⁸⁻¹⁰⁰ and VLDL/LDL plasma levels may regulate HCV binding to its target by competitive inhibition. So, when HCV promotes lower VLDL plasma levels, it enhances its cellular dissemination.⁴⁴

Consequences in the prognosis of chronic hepatitis C

IR favors fibrosis progression in chronic hepatitis C.^{26,101,102} Hyperinsulinism, IR related, directly activates stellate cells¹⁰³ and, in association to hyperglycemia, it increases connective tissue growth factor (CTGF),¹⁰⁴ a key cytokine in hepatic fibrogenesis.^{105,106} Steatosis also relates to more advanced fibrosis^{35,38,48,58} and to accelerated fibrosis progression,^{39,107,108} in such a way that some authors suggest treating HCV infected patients with evidence of hepatic steatosis, even if they only present mild inflammatory activity. Steatosis may sensitize the liver to inflammation³⁵ and apoptosis, and subsequently enhance

fibrosis.¹⁰⁹ In fact, a recent study showed that hepatic steatosis associates to higher programmed cell death by apoptosis with stellate cells activation.¹⁰⁹

DM associates to a decreased life expectancy in cirrhotic patients,¹¹⁰ as well as an earlier progression to more severe hepatic encephalopathy.¹¹¹ The mechanism that favors encephalopathy is still not known, but it may be dependent on diabetes-related autonomic neuropathy and subsequent constipation and/or impairment in ammonia metabolism.¹¹² A recent study also demonstrated IR as a risk factor to portal hypertension and the development of esophageal varices.¹¹³ In fact, the authors found that HOMA-IR index higher than 3.5 was a good predictor of esophageal varices presence, with an AUC 0.80.

DM is a risk factor for the development of hepatocellular carcinoma.¹¹⁴ Regarding a possible association between hepatic steatosis and hepatic carcinogenesis, different studies show opposite results.¹¹⁵⁻¹¹⁷

Treatment implications

Obesity and steatosis decrease anti-viral treatment response.^{40,54,118-122} However, that negative influence seems to be limited to metabolic steatosis and not to viral one, since genotype 3 associated steatosis does not seem to change the response to anti-viral treatment.⁴⁰ Patients with BMI higher than 30 kg/m² have a 4 fold lower chance of sustained viral response.¹¹⁸ A pilot study showed that weight loss, even if mild, associates to an improvement not only in steatosis, but also in fibrosis, in patients with chronic hepatitis C, after as little as 3 months.^{123,124}

There are 3 mechanisms which may explain why obesity compromises anti-viral treatment response. First, obesity may interfere with interferon bio-availability. In fact, subcutaneous administration of pegylated interferon in obese patients may decrease its absorption as a consequence of defective subcutaneous lymph drainage, leading to lower plasma levels.¹²⁵

Another proposed mechanism is obesity as a pro-inflammatory state¹²⁶ with a negative influence in immune response to therapy. Several adipokines may have a major role in that immune deregulation. Leptine is an adipocyte secreted cytokine that is increased in obesity. However, in obesity, despite there is hyperleptinemia, there is also resistance to leptin actions.¹²⁷ Leptine has a pro-inflammatory action promoting Th1 immune response, which is believed to be essential in achieving a sustained response to interferon. Therefore, leptin resistance may have a negative influence in anti-viral treatment.¹²⁸ Another important cytokine is adiponectin, which has an anti-inflammatory activity antagonizing TNF- α ,¹²⁹ being decreased in obesity and HCV infection.^{130,131} On the contrary, TNF- α not only has a pro-inflammatory activity, as directly promotes IR, and inversely correlates to anti-viral treatment response.¹³²

Lastly, obesity promotes IR, which is known to associate to a negative influence in anti-viral treatment response.¹³³⁻¹³⁵ In fact, Romero-Gómez et al. showed 33% sustained viral response rate in genotype 1 in patients with IR, as opposed to 66% in patients without IR.¹³⁶ Also, Poustchi et al. found a 6.5 times lower sustained viral response in patients with IR.¹³⁵ The association between IR and no response to anti-viral treatment may be due to a SOCS-3 activation, which not only promotes IR, but also inhibits STAT-1 (signal transducer and activator of transcription).¹³⁷ After α interferon binds to its receptor, it activates tyrosine kinases that phosphorylate STAT-1, promoting its migration to the nucleus, where it regulates several anti-viral genes transcription. SOCS-3 protein inhibits that tyrosine phosphorylation, thus inhibiting α interferon action.¹³⁸

We still do not know whether treating IR actually translates in a better response to α interferon. At the moment, patients should be advised to change to healthier life styles that promote less IR, as weight loss and physical exercise; however medication with insulin sensitizer agents in this context still do not have an evidence based fundament,¹³⁹ although a small retrospective study suggests that a better glycemic control may improve survival in these patients.¹⁴⁰ However, a pilot study in previously non responders to standard anti-viral therapy with IR, showed no benefit of a triple therapy with pioglitazone.¹⁴¹

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