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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-analyses 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 progress.[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 found 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 unchanged 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, trough 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 PPARα (peroxisome proliferators-activated receptor α) expression induced by core protein[88-91] 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 canalicula 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 syntethase, 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 RXRα (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 cells[103] 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 inflammation[35] 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/m^2 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 state[126] 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 a 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]

References

1. Romero-Gomez M. Insulin resistance and hepatitis C. *World J Gastroenterol* 2006; 12: 7075-7080.
2. Arao M, Murase K, Kusakabe A, Yoshioka K, Fukuzawa Y, Ishikawa T, Tagaya T, Yamanouchi K, Ichimiya H, Sameshima Y, et al. Prevalence of diabetes mellitus in Japanese patients infected chronically with hepatitis C virus. *J Gastroenterol* 2003; 38: 355-360.
3. Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik J, O'Rahilly S, Shore S, Tom BD, Alexander GJ. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999; 30: 1059-1063.
4. Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. *J Hepatol* 1994; 21: 1135-1139.
5. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol* 2000; 32: 209-217.
6. 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.
7. Moucari R, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, Sobesky R, Martinot-Peignoux M, Maylin S, Nicolas-Chanoine MH, 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.
8. Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, Guo L, Jacob S, Regenstein FG, Zimmerman R, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999; 29: 328-333.
9. Wang CS, Wang ST, Yao WJ, Chang TT, Chou P: Community-based study of hepatitis C virus infection and type 2 diabetes: an association affected by age and hepatitis severity status. *Am J Epidemiol* 2003; 158: 1154-1160.
10. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000; 133: 592-599.
11. Labropoulou-Karatza C, Goritsas C, Fragopanagou H, Repandi M, Matsouka P, Alexandrides T. High prevalence of diabetes mellitus among adult beta-thalassaemic patients with chronic hepatitis C. *Eur J Gastroenterol Hepatol* 1999; 11: 1033-1036.
12. Zein CO, Levy C, Basu A, Zein NN. Chronic hepatitis C and type II diabetes mellitus: a prospective cross-sectional study. *Am J Gastroenterol* 2005; 100: 48-55.
13. Fraser GM, Harman I, Meller N, Niv Y, Porath A. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. *Isr J Med Sci* 1996; 32: 526-530.
14. Simo R, Hernandez C, Genesca J, Jardi R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. *Diabetes Care* 1996; 19: 998-1000.
15. el-Zayadi AR, Selim OE, Hamdy H, Dabbous H, Ahdy A, Moniem SA. Association of chronic hepatitis C infection and diabetes mellitus. *Trop Gastroenterol* 1998; 19: 141-144.
16. Custro N, Carroccio A, Ganci A, Scafidi V, Campagna P, Di Prima L, Montalto G. Glycemic homeostasis in chronic viral hepatitis and liver cirrhosis. *Diabetes Metab* 2001; 27: 476-481.
17. Papatheodoridis GV, Chrysanthos N, Savvas S, Sevastianos V, Kafiri G, Petraki K, Manesis EK. Diabetes mellitus in chronic hepatitis B and C: prevalence and potential association with the extent of liver fibrosis. *J Viral Hepat* 2006; 13: 303-310.
18. del Olmo JA, Serra MA, Rodrigo JM. Liver cirrhosis and diabetes mellitus. *J Hepatol* 1996; 24: 645.
19. Mangia A, Schiavone G, Lezzi G, Marmo R, Bruno F, Villani MR, Cascavilla I, Fantasia L, Andriulli A. HCV and diabetes mellitus: evidence for a negative association. *Am J Gastroenterol* 1998; 93: 2363-2367.
20. Mehta SH, Brancati FL, Strathdee SA, Pankow JS, Netski D, Coresh J, Szklo M, Thomas DL. Hepatitis C virus infection and incident type 2 diabetes. *Hepatology* 2003; 38: 50-56.
21. Saxena AK, Panhotra BR. The susceptibility of patients with type-2 diabetes to hepatitis C virus infection during long-term haemodialysis. *Swiss Med Wkly* 2003; 133: 611-618.
22. Gowans EJ. Distribution of markers of hepatitis C virus infection throughout the body. *Semin Liver Dis* 2000; 20: 85-102.
23. Laskus T, Radkowski M, Wang LF, Vargas H, Rakela J. Search for hepatitis C virus extrahepatic replication sites in patients with acquired immunodeficiency syndrome: specific detection of negative-strand viral RNA in various tissues. *Hepatology* 1998; 28: 1398-1401.
24. Lecube A, Hernandez C, Genesca J, Esteban JI, Jardi R, Simo R. High prevalence of glucose abnormalities in patients with hepatitis C virus infection: a multivariate analysis considering the liver injury. *Diabetes Care* 2004; 27: 1171-1175.
25. Sougleri M, Labropoulou-Karatza C, Paraskevopoulou P, Fragopanagou H, Alexandrides T. Chronic hepatitis C virus infection without cirrhosis induces insulin resistance in patients with alpha-thalassaemia major. *Eur J Gastroenterol Hepatol* 2001; 13: 1195-1199.
26. Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, McCaughan GW, George J. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression [corrected]. *Gastroenterology* 2003; 125: 1695-1704.
27. Petit JM, Bour JB, Galland-Jos C, Minello A, Verges B, Guiguet M, Brun JM, Hillon P. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *J Hepatol* 2001; 35: 279-283.
28. Taura N, Ichikawa T, Hamasaki K, Nakao K, Nishimura D, Goto T, Fukuta M, Kawashimo H, Fujimoto M, Kusumoto K, et al. Association between liver fibrosis and insulin sensitivity in chronic hepatitis C patients. *Am J Gastroenterol* 2006; 101: 2752-2759.

29. Konrad T, Zeuzem S, Toffolo G, Vicini P, Teuber G, Briem D, Lormann J, Lenz T, Herrmann G, Berger A, et al. Severity of HCV-induced liver damage alters glucose homeostasis in noncirrhotic patients with chronic HCV infection. *Digestion* 2000; 62: 52-59.
30. Huang JF, Dai CY, Hwang SJ, Ho CK, Hsiao PJ, Hsieh MY, Lee LP, Lin ZY, Chen SC, Hsieh MY, et al. Hepatitis C viremia increases the association with type 2 diabetes mellitus in a hepatitis B and C endemic area: an epidemiological link with virological implication. *Am J Gastroenterol* 2007; 102: 1237-1243.
31. Hsu CS, Liu CJ, Liu CH, Wang CC, Chen CL, Lai MY, Chen PJ, Kao JH, Chen DS. High hepatitis C viral load is associated with insulin resistance in patients with chronic hepatitis C. *Liver Int* 2008; 28: 271-277.
32. Kawaguchi T, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, Nagao Y, Yanagimoto C, Hanada S, Koga H, 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.
33. Tai TY, Lu JY, Chen CL, Lai MY, Chen PJ, Kao JH, Lee CZ, Lee HS, Chuang LM, Jeng YM. Interferon-alpha reduces insulin resistance and beta-cell secretion in responders among patients with chronic hepatitis B and C. *J Endocrinol* 2003; 178: 457-465.
34. Simo R, Lecube A, Genesca J, Esteban JI, Hernandez C. Sustained virological response correlates with reduction in the incidence of glucose abnormalities in patients with chronic hepatitis C virus infection. *Diabetes Care* 2006; 29: 2462-2466.
35. Leandro G, Mangia A, Hui J, Fabris P, Rubbia-Brandt L, Colloredo G, Adinolfi LE, Asselah T, Jonsson JR, Smedile A, et al. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology* 2006; 130: 1636-1642.
36. Asselah T, Rubbia-Brandt L, Marcellin P, Negro F. Steatosis in chronic hepatitis C: why does it really matter? *Gut* 2006; 55: 123-130.
37. 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.
38. Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, Powell EE. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology* 1999; 29: 1215-1219.
39. 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.
40. Poynard T, Ratziu V, McHutchison J, Manns M, Goodman Z, Zeuzem S, Younossi Z, Albrecht J. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. *Hepatology* 2003; 38: 75-85.
41. 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.
42. Hwang SJ, Luo JC, Chu CW, Lai CR, Lu CL, Tsay SH, Wu JC, Chang FY, Lee SD. Hepatic steatosis in chronic hepatitis C virus infection: prevalence and clinical correlation. *J Gastroenterol Hepatol* 2001; 16: 190-195.
43. 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.
44. 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.
45. Lefkowitch JH, Schiff ER, Davis GL, Perrillo RP, Lindsay K, Bodenheimer HC, Jr., Balart LA, Ortego TJ, Payne J, Dienstag JL, 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.
46. Bjornsson E, Angulo P. Hepatitis C and steatosis. *Arch Med Res* 2007; 38: 621-627.
47. Thomopoulos KC, Arvaniti V, Tsamantas AC, Dimitropoulou D, Gogos CA, Siagris D, Theocharis GJ, Labropoulou-Karatza C. Prevalence of liver steatosis in patients with chronic hepatitis B: a study of associated factors and of relationship with fibrosis. *Eur J Gastroenterol Hepatol* 2006; 18: 233-237.
48. 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.
49. Clouston AD, Jonsson JR, Purdie DM, Macdonald GA, Pandeya N, Shorthouse C, Powell EE. Steatosis and chronic hepatitis C: analysis of fibrosis and stellate cell activation. *J Hepatol* 2001; 34: 314-320.
50. 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.
51. Rubbia-Brandt L, Quadri R, Abid K, Giostra E, Male PJ, Mentha G, Spahr L, Zarski JP, Borisch B, Hadengue A, et al. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *J Hepatol* 2000; 33: 106-115.
52. Hui JM, Kench J, Farrell GC, Lin R, Samarasinghe D, Liddle C, Byth K, George J. Genotype-specific mechanisms for hepatic steatosis in chronic hepatitis C infection. *J Gastroenterol Hepatol* 2002; 17: 873-881.
53. Bedossa P, Moucari R, Chelbi E, Asselah T, Paradis V, Vidaud M, Cazals-Hatem D, Boyer N, Valla D, Marcellin P. Evidence for a role of nonalcoholic steatohepatitis in hepatitis C: a prospective study. *Hepatology* 2007; 46: 380-387.
54. Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vallee M, Heaton S, Conrad A, Pockros PJ, McHutchison JG. The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. *J Hepatol* 2004; 40: 484-490.
55. 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.
56. Castera L, Hezode C, Roudot-Thoraval F, Lonjon I, Zafrani ES, Pawlotsky JM, Dhumeaux D. Effect of antiviral treatment on evolution of liver steatosis in patients with chronic hepatitis C: indirect evidence of a role of hepatitis C virus genotype 3 in steatosis. *Gut* 2004; 53: 420-424.
57. Zaitoun AM, Al Mardini H, Awad S, Ukabam S, Makadisi S, Record CO. Quantitative assessment of fibrosis and steatosis in liver biopsies from patients with chronic hepatitis C. *J Clin Pathol* 2001; 54: 461-465.
58. Rubbia-Brandt L, Fabris P, Paganin S, Leandro G, Male PJ, Giostra E, Carlotto A, Bozzola L, Smedile A, Negro F. Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut* 2004; 53: 406-412.
59. Tsochatzis E, Papatheodoridis GV, Manesis EK, Chrysanthos N, Kafiri G, Petraki K, Hadziyannis E, Pandelidaki H, Zafiropoulou R, Savvas S, et al. Hepatic steatosis in genotype 4 chronic hepatitis C is mainly because of metabolic factors. *Am J Gastroenterol* 2007; 102: 634-641.
60. Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, Kimura S, Moriya K, Koike K. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology* 2004; 126: 840-848.
61. Knobler H, Schattner A. TNF-{alpha}, chronic hepatitis C and diabetes: a novel triad. *Qjm* 2005; 98: 1-6.
62. Maeno T, Okumura A, Ishikawa T, Kato K, Sakakibara F, Sato K, Ayada M, Hotta N, Tagaya T, Fukuzawa Y, et al. Mechanisms of increased insulin resistance in non-cirrhotic patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol* 2003; 18: 1358-1363.
63. Lecube A, Hernandez C, Genesca J, Simo R. Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: A case-control study. *Diabetes Care* 2006; 29: 1096-1101.

64. Hotamisligil GS. The role of TNFalpha and TNF receptors in obesity and insulin resistance. *J Intern Med* 1999; 245: 621-625.
65. Kawaguchi T, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T, Taniguchi E, Kumemura H, Hanada S, Maeyama 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.
66. 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.
67. Pazienza V, Clement S, Pugnale P, Conzelman S, Foti M, Mangia A, Negro F. The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. *Hepatology* 2007; 45: 1164-1171.
68. Haruta T, Uno T, Kawahara J, Takano A, Egawa K, Sharma PM, Olefsky JM, Kobayashi M. A rapamycin-sensitive pathway down-regulates insulin signaling via phosphorylation and proteasomal degradation of insulin receptor substrate-1. *Mol Endocrinol* 2000, 14: 783-794.
69. Rui L, Yuan M, Frantz D, Shoelson S, White MF. SOCS-1 and SOCS-3 block insulin signaling by ubiquitin-mediated degradation of IRS1 and IRS2. *J Biol Chem* 2002; 277: 42394-42398.
70. Bernsmeier C, Duong FH, Christen V, Pugnale P, Negro F, Terracciano L, Heim MH. Virus-induced over-expression of protein phosphatase 2A inhibits insulin signalling in chronic hepatitis C. *J Hepatol* 2008; 49: 429-440.
71. Abid K, Pazienza V, de Gottardi A, Rubbia-Brandt L, Conne B, Pugnale P, Rossi C, Mangia A, Negro F. An *in vitro* model of hepatitis C virus genotype 3a-associated triglycerides accumulation. *J Hepatol* 2005; 42: 744-751.
72. Moriya K, Yotsuyanagi H, Shintani Y, Fujie H, Ishibashi K, Matsuura Y, Miyamura T, Koike K. Hepatitis C virus core protein induces hepatic steatosis in transgenic mice. *J Gen Virol* 1997; 78 (Pt 7): 1527-1531.
73. Chang ML, Chen JC, Yeh CT, Sheen IS, Tai DI, Chang MY, Chiu CT, Lin DY, Bissell DM. Topological and evolutional relationships between HCV core protein and hepatic lipid vesicles: studies in vitro and in conditionally transgenic mice. *World J Gastroenterol* 2007; 13: 3472-3477.
74. Hope RG, McLauchlan J. Sequence motifs required for lipid droplet association and protein stability are unique to the hepatitis C virus core protein. *J Gen Virol* 2000; 81: 1913-1925.
75. Boulant S, Montserret R, Hope RG, Ratinier M, Targett-Adams P, Lavergne JP, Penin F, McLauchlan J. Structural determinants that target the hepatitis C virus core protein to lipid droplets. *J Biol Chem* 2006; 281: 22236-22247.
76. Hourioux C, Patient R, Morin A, Blanchard E, Moreau A, Trassard S, Giraudeau B, Roingeard P. The genotype 3-specific hepatitis C virus core protein residue phenylalanine 164 increases steatosis in an *in vitro* cellular model. *Gut* 2007; 56: 1302-1308.
77. Perlemuter G, Sabile A, Letteron P, Vona G, Topilco A, Chretien Y, Koike K, Pessayre D, Chapman J, Barba G, 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.
78. Mirandola S, Realdon S, Iqbal J, Gerotto M, Dal Pero F, Bortoletto G, Marcolongo M, Vario A, Datz C, Hussain MM, et al. Liver microsomal triglyceride transfer protein is involved in hepatitis C liver steatosis. *Gastroenterology* 2006; 130: 1661-1669.
79. Lin MC, Gordon D, Wetterau JR. Microsomal triglyceride transfer protein (MTP) regulation in HepG2 cells: insulin negatively regulates MTP gene expression. *J Lipid Res* 1995; 36: 1073-1081.
80. Au WS, Kung HF, Lin MC. Regulation of microsomal triglyceride transfer protein gene by insulin in HepG2 cells: roles of MAPKerk and MAPKp38. *Diabetes* 2003; 52: 1073-1080.
81. Petit JM, Benichou M, Duvillard L, Jooste V, Bour JB, Minello A, Verges B, Brun JM, Gambert P, Hillon P. Hepatitis C virus-associated hypobetalipoproteinemia is correlated with plasma viral load, steatosis, and liver fibrosis. *Am J Gastroenterol* 2003; 98: 1150-1154.
82. Serfaty L, Andreani T, Giral P, Carbonell N, Chazouilleres O, Poupon R. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. *J Hepatol* 2001; 34: 428-434.
83. Fernandez-Checa JC, Garcia-Ruiz C, Colell A, Morales A, Mari M, Miranda M, Ardite E. Oxidative stress: role of mitochondria and protection by glutathione. *Biofactors* 1998; 8: 7-11.
84. Okuda M, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM, Weinman SA. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology* 2002; 122: 366-375.
85. Negro F. Mechanisms and significance of liver steatosis in hepatitis C virus infection. *World J Gastroenterol* 2006; 12: 6756-6765.
86. Napolitano M, Giuliani A, Alonzi T, Mancone C, D'Offizi G, Tripodi M, Bravo E. Very low density lipoprotein and low density lipoprotein isolated from patients with hepatitis C infection induce altered cellular lipid metabolism. *J Med Virol* 2007; 79: 254-258.
87. Moriya K, Fujie H, Shintani Y, Yotsuyanagi H, Tsutsumi T, Ishibashi K, Matsuura Y, Kimura S, Miyamura T, Koike K. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. *Nat Med* 1998; 4: 1065-1067.
88. Dharancy S, Malapel M, Perlemuter G, Roskams T, Cheng Y, Dubuquoy L, Podevin P, Conti F, Canva V, Philippe D, et al. Impaired expression of the peroxisome proliferator-activated receptor alpha during hepatitis C virus infection. *Gastroenterology* 2005; 128: 334-342.
89. Cheng Y, Dharancy S, Malapel M, Desreumaux P. Hepatitis C virus infection down-regulates the expression of peroxisome proliferator-activated receptor alpha and carnitine palmitoyl acyl-CoA transferase 1A. *World J Gastroenterol* 2005; 11: 7591-7596.
90. Yamaguchi A, Tazuma S, Nishioka T, Ohishi W, Hyogo H, Nomura S, Chayama K. Hepatitis C virus core protein modulates fatty acid metabolism and thereby causes lipid accumulation in the liver. *Dig Dis Sci* 2005; 50: 1361-1371.
91. de Gottardi A, Pazienza V, Pugnale P, Bruttin F, Rubbia-Brandt L, Juge-Aubry CE, Meier CA, Hadengue A, Negro F. Peroxisome proliferator-activated receptor-alpha and -gamma mRNA levels are reduced in chronic hepatitis C with steatosis and genotype 3 infection. *Aliment Pharmacol Ther* 2006; 23: 107-114.
92. Su AI, Pezacki JP, Wodicka L, Brideau AD, Supekova L, Thimme R, Wieland S, Bukh J, Purcell RH, Schultz PG, et al. Genomic analysis of the host response to hepatitis C virus infection. *Proc Natl Acad Sci USA* 2002; 99: 15669-15674.
93. Kim KH, Hong SP, Kim K, Park MJ, Kim KJ, Cheong J. HCV core protein induces hepatic lipid accumulation by activating SREBP1 and PPARgamma. *Biochem Biophys Res Commun* 2007; 355: 883-888.
94. Fukasawa M, Tanaka Y, Sato S, Ono Y, Nitahara-Kasahara Y, Suzuki T, Miyamura T, Hanada K, Nishijima M: Enhancement of de novo fatty acid biosynthesis in hepatic cell line Huh7 expressing hepatitis C virus core protein. *Biol Pharm Bull* 2006; 29: 1958-1961.
95. Jackel-Cram C, Babiuk LA, Liu Q. Up-regulation of fatty acid synthase promoter by hepatitis C virus core protein: genotype-3a core has a stronger effect than genotype-1b core. *J Hepatol* 2007, 46:999-1008.
96. Tsutsumi T, Suzuki T, Shimoike T, Suzuki R, Moriya K, Shintani Y, Fujie H, Matsuura Y, Koike K, Miyamura T. Interaction of hepatitis C virus core protein with retinoid X receptor alpha modulates its transcriptional activity. *Hepatology* 2002; 35: 937-946.
97. Andre P, Komurian-Pradel F, Deforges S, Perret M, Berland JL, Sodoyer M, Pol S, Brechot C, Paranhos-Baccala G, Lotteau V. Characterization of low- and very-low-density hepatitis C virus RNA-containing particles. *J Virol* 2002; 76:6919-6928.
98. Monazahian M, Bohme I, Bonk S, Koch A, Scholz C, Grethe S, Thomssen R. Low density lipoprotein receptor as a candidate receptor for hepatitis C virus. *J Med Virol* 1999; 57: 223-229.
99. Agnello V, Abel G, Elfahal M, Knight GB, Zhang QX. Hepatitis C virus and other flaviviridae viruses enter cells via low density lipoprotein receptor. *Proc Natl Acad Sci USA* 1999; 96: 12766-12771.

100. Petit JM, Minello A, Duvillard L, Jooste V, Monier S, Texier V, Bour JB, Poussier A, Gambert P, Verges B, et al. Cell surface expression of LDL receptor in chronic hepatitis C: correlation with viral load. *Am J Physiol Endocrinol Metab* 2007; 293: E416-420.
101. Petta S, Camma C, Marco VD, Alessi N, Cabibi D, Caldarella R, Licata A, Massenti F, Tarantino G, Marchesini G, 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.
102. Muzzi A, Leandro G, Rubbia-Brandt L, James R, Keiser O, Malinverni R, Dufour JF, Helbling B, Hadengue A, Gonvers JJ, et al. Insulin resistance is associated with liver fibrosis in non-diabetic chronic hepatitis C patients. *J Hepatol* 2005; 42: 41-46.
103. Svegliati-Baroni G, Ridolfi F, Di Sario A, Casini A, Marucci L, Gaggiotti G, Orlandoni P, Macarri G, Perego L, Benedetti A, et al. Insulin and insulin-like growth factor-1 stimulate proliferation and type I collagen accumulation by human hepatic stellate cells: differential effects on signal transduction pathways. *Hepatology* 1999; 29: 1743-1751.
104. Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, Conti M, Huet S, Ba N, Buffet C, et al. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. *Hepatology* 2001; 34: 738-744.
105. Paradis V, Dargere D, Vidaud M, De Gouville AC, Huet S, Martinez V, Gauthier JM, Ba N, Sobesky R, Ratziu V, et al. Expression of connective tissue growth factor in experimental rat and human liver fibrosis. *Hepatology* 1999; 30: 968-976.
106. Abou-Shady M, Friess H, Zimmermann A, di Mola FF, Guo XZ, Baer HU, Buchler MW. Connective tissue growth factor in human liver cirrhosis. *Liver* 2000; 20: 296-304.
107. Fartoux L, Chazouilleres 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.
108. Kurosaki M, Matsunaga K, Hirayama I, Tanaka T, Sato M, Komatsu N, Umeda N, Hosokawa T, Ueda K, Tsuchiya K, et al. The presence of steatosis and elevation of alanine aminotransferase levels are associated with fibrosis progression in chronic hepatitis C with non-response to interferon therapy. *J Hepatol* 2008; 48: 736-742.
109. Walsh MJ, Vanags DM, Clouston AD, Richardson MM, Purdie DM, Jonsson JR, Powell EE. Steatosis and liver cell apoptosis in chronic hepatitis C: a mechanism for increased liver injury. *Hepatology* 2004; 39: 1230-1238.
110. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Haruna Y, Imano E, Suzuki M, Kanda T, Kawano S, Hiramatsu N, et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. *Am J Gastroenterol* 2006; 101: 70-75.
111. Sigal SH, Stanca CM, Kontorinis N, Bodian C, Ryan E. Diabetes mellitus is associated with hepatic encephalopathy in patients with HCV cirrhosis. *Am J Gastroenterol* 2006; 101: 1490-1496.
112. Thuluvath PJ. Higher prevalence and severity of hepatic encephalopathy in patients with HCV cirrhosis and diabetes mellitus: is presence of autonomic neuropathy the missing part of the puzzle? *Am J Gastroenterol* 2006; 101: 2244-2246.
113. Camma C, Petta S, Di Marco V, Bronte F, Ciminnisi S, Licata G, Peralta S, Simone F, Marchesini G, Craxi A. Insulin resistance is a risk factor for esophageal varices in hepatitis C virus cirrhosis. *Hepatology* 2008.
114. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; 126: 460-468.
115. Kumar D, Farrell GC, Kench J, George J. Hepatic steatosis and the risk of hepatocellular carcinoma in chronic hepatitis C. *J Gastroenterol Hepatol* 2005; 20: 1395-1400.
116. Ohata K, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, Abiru S, Nakagawa Y, Shigeno M, Miyazoe S, et al. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer* 2003; 97: 3036-3043.
117. Tanaka A, Uegaki S, Kurihara H, Aida K, Mikami M, Nagashima I, Shiga J, Takikawa H. Hepatic steatosis as a possible risk factor for the development of hepatocellular carcinoma after eradication of hepatitis C virus with antiviral therapy in patients with chronic hepatitis C. *World J Gastroenterol* 2007; 13: 5180-5187.
118. Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. *Hepatology* 2003; 38: 639-644.
119. McCullough AJ. Obesity and its nurturing effect on hepatitis C. *Hepatology* 2003; 38: 557-559.
120. Harrison SA, Brunt EM, Qazi RA, Oliver DA, Neuschwander-Tetri BA, Di Bisceglie AM, Bacon BR. 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.
121. Soresi M, Tripi S, Franco V, Giannitrapani L, Alessandri A, Rappa F, Vuturo O, Montalto G. Impact of liver steatosis on the antiviral response in the hepatitis C virus-associated chronic hepatitis. *Liver Int* 2006; 26: 1119-1125.
122. Rodriguez-Torres M, Rios-Bedoya CF, Ortiz-Lasanta G, Purcell-Arevalo D, Marxuach-Cuetara A, Jimenez-Rivera J. Weight affect relapse rates in latinos with genotype 2/3 chronic hepatitis C (CHC) treated with peg IFN alfa-2a (Pegasys) 180 mcg/week and 800 mg daily of ribavirin for 24 weeks. *J Med Virol* 2008; 80: 1576-1580.
123. Hickman IJ, Clouston A, Macdonald GA, Purdie D, Prins JB, Ash S, Jonsson JR, Powell EE. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis. *Gut* 2002; 51: 89-94.
124. Tarantino G, Conca P, Ariello M, Mastrolia M. Does a lower insulin resistance affect antiviral therapy response in patients suffering from HCV related chronic hepatitis? *Gut* 2006; 55: 585.
125. Charlton MR, Pockros PJ, Harrison SA. Impact of obesity on treatment of chronic hepatitis C. *Hepatology* 2006; 43: 1177-1186.
126. Jonsson JR, Barrie HD, O'Rourke P, Clouston AD, Powell EE. Obesity and steatosis influence serum and hepatic inflammatory markers in chronic hepatitis C. *Hepatology* 2008; 48: 80-87.
127. Correia ML, Haynes WG. Leptin, obesity and cardiovascular disease. *Curr Opin Nephrol Hypertens* 2004; 13: 215-223.
128. Kamal SM, Fehr J, Roesler B, Peters T, Rasenack JW. Peginterferon alone or with ribavirin enhances HCV-specific CD4 T-helper 1 responses in patients with chronic hepatitis C. *Gastroenterology* 2002; 123: 1070-1083.
129. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology* 2004; 40: 46-54.
130. Anty R, Gelsi E, Giudicelli J, Marine-Barjoan E, Gual P, Benzaken S, Saint-Paul MC, Sadoul JL, Huet PM, Tran A. Glucose intolerance and hypoadiponectinemia are already present in lean patients with chronic hepatitis C infected with genotype non-3 viruses. *Eur J Gastroenterol Hepatol* 2007; 19: 671-677.
131. Wang AY, Hickman IJ, Richards AA, Whitehead JP, Prins JB, Macdonald GA. High molecular weight adiponectin correlates with insulin sensitivity in patients with hepatitis C genotype 3, but not genotype 1 infection. *Am J Gastroenterol* 2005; 100: 2717-2723.
132. Larrea E, Garcia N, Qian C, Civeira MP, Prieto J. Tumor necrosis factor alpha gene expression and the response to interferon in chronic hepatitis C. *Hepatology* 1996; 23: 210-217.
133. 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.
134. Chu CJ, Lee SD, Hung TH, Lin HC, Hwang SJ, Lee FY, Lu RH, Yu MI, Chang CY, Yang PL, et al. Insulin resistance is a major determinant of sustained virological response in genotype 1 chronic hepatitis c patients receiving peginterferon Alpha-2b plus ribavirin. *Aliment Pharmacol Ther* 2008.

135. Poustchi H, Negro F, Hui J, Cua IH, Brandt LR, Kench JG, George J. Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol* 2008; 48: 28-34.
136. Romero-Gomez M, Del Mar Viloria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, Corpas R, Cruz M, Grande L, Vazquez L, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005; 128: 636-641.
137. Walsh MJ, Jonsson JR, Richardson MM, Lipka GM, Purdie DM, Clouston AD, Powell EE. Non-response to antiviral therapy is associated with obesity and increased hepatic expression of suppressor of cytokine signalling 3 (SOCS-3) in patients with chronic hepatitis C, viral genotype 1. *Gut* 2006; 55: 529-535.
138. Song MM, Shuai K. The suppressor of cytokine signaling (SOCS) 1 and SOCS3 but not SOCS2 proteins inhibit interferon-mediated antiviral and antiproliferative activities. *J Biol Chem* 1998; 273: 35056-35062.
139. Lonardo A, Carulli N, Loria P. HCV and diabetes. A two-question-based reappraisal. *Dig Liver Dis* 2007; 39: 753-761.
140. Kwon SY, Kim SS, Kwon OS, Kwon KA, Chung MG, Park DK, Kim YS, Koo YS, Kim YK, Choi DJ, et al. Prognostic significance of glycaemic control in patients with HBV and HCV-related cirrhosis and diabetes mellitus. *Diabet Med* 2005; 22: 1530-1535.
141. Overbeck K, Genne D, Golay A, Negro F. Pioglitazone in chronic hepatitis C not responding to pegylated interferon-alpha and ribavirin. *J Hepatol* 2008; 49: 295-298.
142. Asselah T, Boyer N, Guimont MC, Cazals-Hatem D, Tubach F, Nahon K, Daikha H, Vidaud D, Martinot M, Vidaud M, et al. Liver fibrosis is not associated with steatosis but with necroinflammation in French patients with chronic hepatitis C. *Gut* 2003; 52: 1638-1643.
143. Castera L, Hezode C, Roudot-Thoraval F, Bastie A, Zafrani ES, Pawlotsky JM, Dhumeaux D. 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.
144. Serfaty L, Poujol-Robert A, Carbonell N, Chazouilleres O, Poupon RE, Poupon R. Effect of the interaction between steatosis and alcohol intake on liver fibrosis progression in chronic hepatitis C. *Am J Gastroenterol* 2002; 97: 1807-1812.
145. Westin J, Nordlinder H, Lagging M, Norkrans G, Wejstal R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *J Hepatol* 2002; 37: 837-842.
146. 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.
147. Giannini E, Ceppa P, Botta F, Fasoli A, Romagnoli P, Cresta E, Venturino V, Risso D, Celle G, Testa R. Steatosis and bile duct damage in chronic hepatitis C: distribution and relationships in a group of Northern Italian patients. *Liver* 1999; 19: 432-437.
148. Wong VS, Wight DG, Palmer CR, Alexander GJ. Fibrosis and other histological features in chronic hepatitis C virus infection: a statistical model. *J Clin Pathol* 1996; 49: 465-469.