ELSEVIER

Journal of Hepatology 50 (2009) 648–651

Journal of Hepatology

www.elsevier.com/locate/jhep

Editorial

Insulin resistance in HCV mono-infected and in HIV/HCV co-infected patients: Looking to the future ☆

Calogero Cammà[1,2,*], Salvatore Petta[1]

[1]*Cattedra ed Unità Operativa di Gastroenterologia, University of Palermo, Italy*
[2]*IBIM Consiglio Nazionale delle Ricerche, Palermo, Italy*

See Articles, pages 684–692 and 712–718

Insulin resistance (IR) is defined as a condition in which higher than normal insulin concentrations are needed to achieve normal metabolic responses, or in which normal insulin concentrations fail to elicit a normal metabolic response [1]. In recent years, different lines of evidence have found that IR is a common feature in patients with chronic hepatitis C (CHC) [2], and is associated not only with host factors (visceral obesity), but also with viral ones. Clinical studies have found that HCV infection is an independent risk factor for diabetes development [3], and, in particular, that HCV-genotypes 1 (G1) and 4 are associated with IR, identifying for these genotypes a linear relation between the degree of IR and the viral load [4]. This has prompted speculation that HCV, via up-regulation of tumor necrosis factor-α (TNF-α), down-regulation of suppressor of cytokine signaling, and the protein phosphatase PPA2, is able to interfere with insulin signalling [5], in a context of complex molecular mechanisms in which primitive metabolic disorders likely play a relevant role.

The clinical relevance of IR in HCV infection arises from its ability to act as a major disease-modifier, contributing to the severity of liver damage, and to interfere with the response to antiviral therapy. The greatest evidence for a determinative role of IR in CHC comes from studies evaluating the influence of IR on fibrosis. IR can favor fibrosis progression both directly and indirectly, by inducing steatosis. IR, particularly in G1 patients, represents the pathogenetic key of liver fat accumulation [6], that is frequently reported as a factor independently associated with the severity of fibrosis in both cross-sectional [6] and cohort studies [7], via generation of lipid peroxids, stellate cell activation and collagenous deposition [8]. Similarly, several cross-sectional studies have shown that IR evaluated by both HOMA and OGIS (oral glucose insulin sensitivity), a more sensitive surrogate measure of IR), is directly associated with the severity of fibrosis in CHC patients, independently of obesity and liver steatosis [2,4,9–11].

The biological plausibility of this association resides in the ability of insulin to stimulate hepatic stellate cells and induce TNF-α and connective growth factor production [12,13]. Hui et al. [9] first identified the relation between IR and severity of fibrosis in a group of 283 patients with CHC derived from different genotypes. These data were subsequently confirmed in two large scale studies [4,10]. Moucari et al. [4] found this association in 454 non-cirrhotic HCV patients, and Cua et al. [10] identified IR as an independent risk factor for fibrosis in a cohort of 346 HCV patients, also confirming the link in the sub-groups of both G1 ($n = 186$) and genotype 3 (G3) ($n = 160$) subjects. Similarly, in a homogeneous population of 201 nondiabetic European patients with G1 CHC at low risk for the metabolic syndrome, we confirmed that the presence of IR is associated with advanced fibrosis [6], suggesting that in this context overt type 2 diabetes further increases the risk of severe fibrosis [2].

Associate Editor: M.U. Mondelli

☆ The authors declare that they do not have anything to disclose regarding funding from industries or conflict of interest with respect to this manuscript.

* Tel.: +39 091 655 2145; fax: +39 091 655 2156.
E-mail address: carlo.camma@unipa.it (C. Cammà).

0168-8278/$36.00 © 2009 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.jhep.2009.01.003

Several recent studies have underscored the role of IR in the development of advanced disease in HCV-infected patients. First, IR was reported to be associated with the presence of esophageal varices in a cohort of 104 patients with HCV-related Child-Pugh A cirrhosis [14], suggesting the ability of insulin to interfere with both fixed (architectural disturbances) and dynamic (functional alterations) components of portal hypertension. Second, type 2 diabetes, the advanced expression of IR, was identified as an independent risk factor for hepatocellular carcinoma (HCC) in patients with HCV infection [15], in keeping with the potential role of insulin and IGF-1 in the carcinogenesis. Finally, steatosis, a manifestation of IR, was independently associated with HCC in patients with CHC in both cross-sectional [16] and cohort studies [17].

A correct evaluation of the role of IR in CHC needs further attention, considering the potential use of insulin sensitizing drugs (metformin, glitazones) in the management of CHC, though caution is necessary. Two placebo-controlled trials in NASH patients showed that pioglitazone is able to improve fibrosis [18,19]. In the same clinical setting, similar results have been reported by Bugianesi et al using metformin for one year [20]. By contrast, a recent randomized placebo controlled trial in which NAFLD patients received metformin for six months only, did not confirm a significative histological improvement [21].Unfortunately, all data on HCV patients originate from cross-sectional papers, and the lack of prospective studies remains an important limit in the assessment of the role of IR in fibrosis progression over time. At present, the use of metformin or glitazones in HCV patients to improve liver fibrosis cannot be recommended, and long-term, prospective, randomized trials are eagerly awaited. Conversely, evidence of the role of IR in the development of both portal hypertension (PH) and HCC is weak, and comes from isolated reports for PH [14] or studies measuring surrogate markers of IR for HCC [15–17].

Contrasting data exist on the role of IR as a predictor of sustained virological response (SVR) in the setting of both HCV mono-infected and HIV/HCV co-infected subjects. Romero-Gomez et al. [22] observed that IR impaired SVR to peginterferon plus ribavirin in 159 HCV mono-infected patients (mean age 41 years; 71% G1), and similar results were reported for obese patients with HCV G2 or G3 infection in a paper recently published in the Journal [23]. In addition, Conjeevaram et al. [24] confirmed the independent association between IR and SVR rate in G1 African-American and White-American infected patients with a mean HOMA value ranging from 3.5 to 6.8. However, the evidence in the literature is not unequivocal. As in recent reports [25,26], we could not confirm a significant reduction in the response to combination therapy in subjects with IR. In our setting [6], moderate/severe steatosis, but not IR, was associated with a low likelihood of SVR in G1 HCV patients, emphasizing the importance of the degree of steatosis in interferon unresponsiveness.

In this issue of the Journal, Dai et al. [27] report that in Asiatic patients with G1 CHC, IR, but not steatosis, was an independent predictor of poor response to antiviral treatment. A methodological issue of the current study is the potential limitation of the generalizability of its results to different populations and settings, given that the results were obtained in normal-weight Taiwanese patients with normal cholesterol and triglyceride levels, and low prevalence of steatosis (26%), all suggesting a low risk for the metabolic syndrome. It should also be remarked that this study included an easy-to-treat population with low mean viral load (500,000 UI/ml), low prevalence of steatosis and severe (F3–F4) hepatic fibrosis (14%). It should also be emphasized that in Taiwanese patients, a population at high likelihood of response to combination treatment, G1-infected subjects achieved an SVR of 65% with a short course 24-week therapy.

In the same issue of the Journal, Merchante and colleagues [28] demonstrate in a retrospective study that IR, assessed by the HOMA, is not a significant predictor of SVR to pegylated interferon plus ribavirin in a cohort of 155 HIV/HCV co-infected patients at high prevalence of IR. This study identifies HCV genotype, viral load and baseline LDL cholesterol levels as independent predictors of SVR. Unfortunately, a methodological issue of the study arises in the lack of data on steatosis as a potential predictor of SVR. In the setting of HIV/HCV co-infected patients, after the introduction of antiretroviral agents, the resulting reduction in morbidity and mortality has been accompanied to some degree by the development of significant metabolic and morphological changes [29]. Specifically, IR and diabetes have been found much more common than in age- and BMI-matched non-HIV controls [30]. The principal actor in these metabolic alterations is thought to be HIV therapies. Mitochondrial toxicity, alterations in adipose expression of genes involved in adipocyte differentiation and lipid metabolism, increased levels of proinflammatory cytokines and reduction of adiponectin have been forwarded as the most important putative pathophysiological mechanisms involved in these alterations [29].

All the current available data raise one important question: is IR, or the underlying steatosis, the cause of low SVR?

The role of insulin sensitizers in mono-infected cases is a matter of debate. In a recent trial, [31] pioglitazone treatment associated with PEG-IFN plus RBV in patients who were previously non-responders to standard therapy failed to elicit a satisfactory virological response after 12 weeks of retreatment. Similar negative results were reported by Romero-Gomez et al. [32] in a randomized double-blinded trial, evaluating the efficacy of metformin with PEG-IFN plus RBV for 48 weeks in a

cohort of 123 naïve G1 CHC patients with IR. These negative results do not confirm a direct interaction between IR and low SVR, though a more prolonged correction of IR, preceding the onset of antiviral therapy, might be necessary to improve the SVR rate.

Regarding the role of steatosis as a predictor of SVR, no studies have evaluated the potential effectiveness of fatty liver correction in increasing the likelihood of response. To correct steatosis, the antiviral therapy should be preceded by effective lifestyle changes and long-term use of insulin sensitizing drugs, though this strategy could also fail in the presence of other cofactors, and of steatogenic viral factors. Experimental and clinical evidence suggests that HCV G3 is directly able to induce steatosis [5], but similar effects may also be produced by G1 HCV [5]. There is also evidence of an association between retinol binding protein 4 (RBP4) and steatosis in G1 CHC patients, largely independent of IR and metabolic factors, pointing to a possible direct viral involvement in RBP4 abnormalities [33]. In this setting, the correction of metabolic factors might not necessarily result in an improved SVR rate, due to the persistence of viral steatogenic mechanisms.

Concerning the issue of IR or steatosis as predictors of SVR, we believe the available evidence is insufficient to give a definitive answer both in mono- and co-infected patients. In fact, when a significant heterogeneity in baseline characteristics of patients is found between different studies, caution must be exercised when comparing results. Considering different geographical and clinical settings, it is reasonable to speculate that both IR and steatosis could play an important role in the achievement of an SVR.

In conclusion, the question of IR in both HCV mono- and HIV/HCV co-infected subjects is far from settled. The promotion of diet and life-style changes remains mandatory, considering that weight loss can improve liver fibrosis in HCV mono-infected persons [34], but pharmacological treatment of IR cannot be recommended on the basis of available studies. What has been learned about HCV and IR interaction in HCV mono-infected patients could be probably applied in the setting of HIV/HCV co-infected subjects, given that retroviral therapy represents a further risk factor for IR development, though, again, further data are needed.

Acknowledgement

The authors thank Giulio Marchesini for relevant, helpful discussion and insight.

References

[1] Bugianesi E, McCullough AJ, Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. Hepatology 2005;42:987–1000.

[2] Petta S, Cammà C, Marco VD, Alessi N, Cabibi 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.

[3] Wang CS, Wang ST, Yao WJ, Chang TT, Chou P. Hepatitis C virus infection and the development of type 2 diabetes in a community-based longitudinal study. Am J Epidemiol 2007;166:196–203.

[4] Moucari 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.

[5] Negro F. Insulin resistance and HCV: will new knowledge modify clinical management? J Hepatol 2006;45:514–519.

[6] Cammà C, Bruno S, Di Marco V, Di Bona D, Rumi M, Vinci M, et al. Insulin resistance is associated with steatosis in nondiabetic patients with genotype 1 chronic hepatitis C. Hepatology 2006;43:64–71.

[7] 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.

[8] Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. J Clin Invest 2004;114:147–152.

[9] 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.

[10] Cua IHY, Hui JM, Kench JG, George J. Genotype-specific interactions of insulin resistance, steatosis, and fibrosis in chronic hepatitis C. Hepatology 2008;48:723–731.

[11] 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.

[12] Svegliati-Baroni G, Ridolfi F, Di Sario A, Casini A, Marucci L, Gaggiotti G, 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.

[13] Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, 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.

[14] Cammà C, Petta S, Di Marco V, Bronte F, Ciminnisi S, Licata G, et al. Insulin resistance is a risk factor for esophageal varices in HCV cirrhosis. Hepatology 2009;49:195–203.

[15] El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4:369–380.

[16] Ohata K, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, et al. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. Cancer 2003;97:3036–3043.

[17] Pekow JR, Bhan AK, Zheng H, Chung RT. Hepatic steatosis is associated with increased frequency of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. Cancer 2007;109:2490–2496.

[18] Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135:1176–1184.

[19] Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with non-alcoholic steatohepatitis. N Engl J Med 2006;355:2297–2307.

[20] Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin

versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol 2005;100:1082–1090.
[21] Haukeland JW, Konopski Z, Loberg EM, Haaland TK, von Wolkmann HL, Raschpichler G, et al. A randomized, placebo controlled trial with metformin in patients with NAFLD. Hepatology 2008;48:62.
[22] 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.
[23] 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.
[24] Conjeevaram HS, Kleiner DE, Everhart JE, Hoofnagle JH, Zacks S, Afdhal NH, et al. Race, insulin resistance and hepatic steatosis in chronic hepatitis C. Hepatology 2007;45:80–87.
[25] Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vallee 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.
[26] Poynard T, Ratziu V, McHutchison J, Manns M, Goodman Z, Zeuzem S, 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.
[27] Dai C-Y, Huang J-F, Hsieh M-Y, Hou N-J, Lin Z-Y, Chen S-C, et al. Insulin resistance predicts response to peginterferon-alpha/ribavirin combination therapy in chronic hepatitis C patients. J Hepatol 2009;50:712–718.
[28] Merchante N, de los Santos-Gil I, Merino D, González-Serrano M, Mira JA, Sanz-Sanz J, et al. Insulin resistance is not a relevant predictor of sustained virological response to pegylated interferon plus ribavirin in HIV/HCV-coinfected patients. J Hepatol 2009;50:684–692.
[29] Mallewa JE, Wilkins E, Vilar J, Mallewa M, Doran D, Back D, et al. HIV-associated lipodystrophy: a review of underlying mechanisms and therapeutic options. J Antimicrob Chemother 2008;62:648–660.
[30] Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicentre AIDS cohort study. Arch Int Med 2005;165:1179–1184.
[31] Overbeck K, Genné D, Golay A, Negro F. Swiss Association for the Study of the Liver (SASL). Pioglitazone in chronic hepatitis C not responding to pegylated interferon-alpha and ribavirin. J Hepatol 2008;49:295–298.
[32] Romero-Gomez M, Diago M, Andrade RJ, Calleja JL, Salmeron J, Fernandez-Rodriguez CM, et al. Metformin with peginterferon alfa2a and ribavirin in the treatment of naive genotype 1 chronic epatiti C patients with insulin resistance (TRIC-1): final results of a randomized and double-blinded trial. Hepatology 2008;48:LB6.
[33] Petta S, Cammà C, Di Marco V, Alessi N, Barbaria F, Cabibi D, et al. Retinol-binding protein 4: a new marker of virus-induced steatosis in patients infected with HCV genotype 1. Hepatology 2008;48:28–37.
[34] Hickman IJ, Clouston AD, MacDonald GA, Purdie DM, Prins JB, Ash S, et al. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. Gut 2002;51:89–94.