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Insulin resistance, hepatic steatosis and hepatitis C: A complex relationship with relevant clinical implications

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ABSTRACT

Insulin resistance (IR) is a common pathophysiological condition where higher-than-normal concentrations of insulin are needed to maintain a normal glycemia and adequate glucose utilization in insulin target tissues. A high proportion (50-80%) of patients chronically infected with the hepatitis C virus (HCV) exhibit evidence of IR. Basic and clinical studies have disclosed a complex bidirectional relationship between IR and HCV infection that has important clinical implications. HCV infection may promote IR through direct viral-dependent mechanisms or due to activation of the inflammatory response resulting in increased production of Tumor Necrosis Factor-α and other cytokine-related molecules. These abnormalities may act synergistically with pre-existing metabolic risk factors and result in the development of hepatic steatosis and type 2 diabetes mellitus (T2DM) which are frequently found in the setting of HCV infection. Moreover, in addition to underlying metabolic abnormalities leading to its development hepatic steatosis also exhibit genotype-specific pathogenic mechanisms. A number of studies have shown that hepatic steatosis is associated to fibrosis progression in patients with HCV and that IR has a negative impact on the response rates to interferon-a-based therapy. Thus, modification of these factors through life-style changes or pharmacological agents may represent an undervalued specific target of therapy aiming to improve sustained virological response rates and reduce HCV related-morbidity and mortality.

Key words. Fatty liver. Insulin. Diabetes. Metabolic syndrome.

INTRODUCTION

Insulin resistance (IR) is a complex pathophysiological condition where higher-than-normal concentrations of insulin are needed to maintain a normal glycemia and adequate glucose utilization in insulin target tissues.[1] IR is of global importance since is closely linked to an epidemic condition such as obesity and it precedes and predicts the development of type 2 diabetes mellitus (T2DM). IR is also considered the main underlying cause of the so-called metabolic syndrome, a cluster of metabolic abnormalities that are associated to increased cardiovascular risk.[2] In the field of liver diseases, IR has reached significant notoriety as it promotes hepatic steatosis and for being considered the major underlying defect of non-alcoholic fatty liver disease (NAFLD), the most common liver disease in the West.[3-4]

IR is frequently found in patients with chronic hepatitis C (CHC).[5] Estimations from different sources indicate that roughly 50% of patients with CHC exhibit some evidence of insulin resistance.[5-6] This association is more frequent than that expected or predicted by chance and may have impact in the natural history of the disease as well as on treatment outcomes.[7-8] In addition, recent research had disclosed the existence of a complex relationship between the hepatitis C virus (HCV) infection and insulin resistance where viral-induced and host's metabolic abnormalities seem to act in a mutually reinforcing manner.[9-10] This review summarizes recent information on the intricacies and links between hepatitis C viral infection and IR. For a more detailed review of the topic the reader is referred to recent in-depth and state-of-the art papers.[5-6,10-11]

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EPIDEMIOLOGICAL ASPECTS

As mentioned before, the association of IR and CHC occurs more often than predicted by chance with figures ranging between 30 to 70%.[6-7] This was first noted in 2003 by Hui, *et al*.,[12] that compared values of fasting C peptide, serum insulin and homeostatic model assessment (HOMA-IR) in HCV infected patients and healthy volunteers showing that patients with HCV infection exhibit significantly higher levels of C peptide, fasting serum insulin and HOMA-IR compared with matched controls. High frequency of IR in HCV-infected patients has been confirmed by several studies with some differences related to the way that IR is assessed.[7,13] HOMA-IR is the most commonly used tool which has a reasonable but not perfect correlation with the gold standard tool which is the 2-step hyperinsulinemic-euglycemic clamp.[14]

IR is also likely responsible of the increased prevalence and incidence of T2DM in patients with CHC.[10,15] The reported prevalence of T2DM in non-cirrhotic patients with CHC is between 7 to 21% which is higher than that observed in other forms of chronic hepatitis or in the general population. Moreover, a prospective study showed that patients with HCV infection and a high-risk profile for developing T2DM developed the disease 11 times more frequently than those without HCV infection.[16] In line with these findings, a meta-analysis of 34 studies performed by White et al. and concluded that a significant DM risk in HCV-infected cases exists in comparison to non-infected controls in both retrospective and prospective studies.[17]

Since IR is closely linked to hepatic steatosis is also of interest to analyze the frequency of this finding in patients with HCV infection. Of note, the prevalence of hepatic steatosis is also significantly increased in HCV-infected patients compared with patients with other hepatopathies reaching figures nearer to 50% and ranging from 40% to 80%.[11] Even though hepatic steatosis is a very prevalent condition in the general population, this figure is higher than that expected by chance.[11,18] Interestingly, a consistent finding among published studies is that steatosis has a close relationship with viral genotype. Infection with genotype 3 HCV is more strongly related to steatosis than infection by non-3 genotypes, exhibiting figures of prevalence of steatosis of 70-80%,[11,19] Moreover, in genotype 3 HCV-infected patients steatosis correlates with viral load.[5] This suggests that, in the case of this genotype, viral-specific mechanisms promotes fat deposition in the liver cell.[9] On the other hand, a weaker correlation with viral load and higher values of IR parameters such as HOMA-IR index indicates that, in the setting of infection with non-3 genotypes of HCV, occurrence of steatosis is more closely linked to basal metabolic abnormalities and IR. The latter may indeed be aggravated by viral infection.[8] Thus, current evidence suggests that while HCV-associated hepatic steatosis is mainly virus-induced in genotype-3 infected patients, host-factors (mainly IR) play a major role in steatosis in non-3 genotypes.

PATHOGENETIC CONSIDERATIONS

The relationship between IR and HCV infection is complex and bidirectional (Figure 1). On one side IR, through promotion of steatosis, hepatic inflammation and a pro-fibrogenic state, might increase the chance of aggravating disease activity or determine disease progression. On the other, HCV infection itself may, through several mechanisms, induce a worsening of the insulin resistant state, promoting T2DM and hepatic derangements linked to lipotoxicity thus increasing liver injury. A brief summary of the potential mechanisms at play in this setting is provided below.

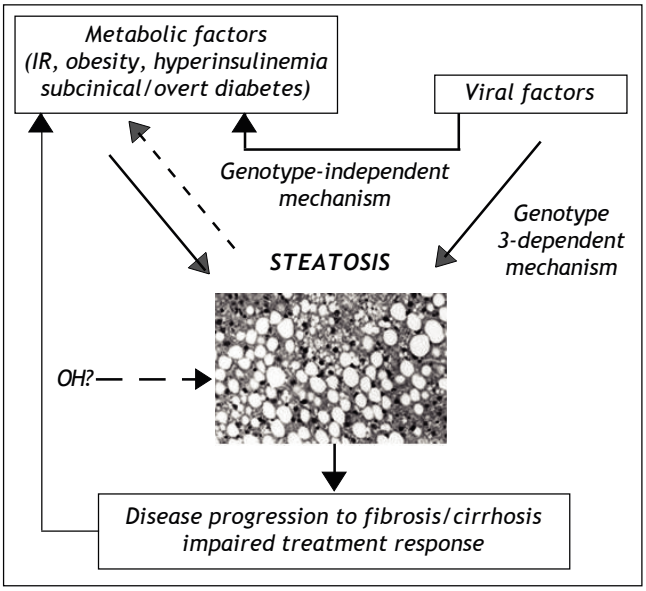

Figure 1: *Relationships between metabolic and viral factors and hepatic steatosis in the setting of chronic hepatitis C. Insulin resistance is the major determinant of steatosis and in turn is aggravated by several genotype-independent mechanisms probably related to the presence of viral proteins in the hepatocyte and due to the inflammatory response linked to viral infection. Several specific steatogenic mechanisms operate in genotype 3 infection. Alcohol consumption can also contribute to steatosis development.*

IR and HCV

IR is a complex condition which exact cause is not yet clear. It involves a disturbed action in insulin-sensitive organs such as the liver, muscle and adipose tissue.[20] Insulin effects are elicited after binding of insulin to its receptor that is linked to a complex signaling pathway that involves sequential activation of the insulin receptor substrates (IRS), phosphatidylinositol-3-kinase (PI3K), Akt and protein kinase C.[9] This cascade of events has been well characterized at the molecular level and essentially results in promotion of cellular storage of excess glucose as glycogen, suppression of gluconeogenesis and, in muscle and adipose tissue, stimulation of glucose uptake after translocation of the glucose transporter GLUT4 to the plasma membrane. IR results from defects at any level of the insulin receptor-related signaling pathway. Details of these defects are beyond the scope of this review and can be found elsewhere.[21] It is of interest however, to point out that HCV infection seems to be able of either directly induce or worsening a pre-existent IR. Compelling evidence of the latter comes from experiments involving transgenic mice showing direct effects of HCV core protein in modulating insulin signaling.[22] This effect is probably related to disturbed insulin signaling due changes in expression or activity of IRS-1.[9] Several other viral-related mechanisms such as increased HCV-core induction of the molecule suppressor of cytokine signaling 3 (SOCS-3), leading to proteasomal degradation of IRS-1 and IRS-2 have been described *in vitro*[9,11] but its importance in the clinical setting are unknown.

Other important aspect of the relation between IR and HCV infection is the role of hepatic and systemic inflammation. It has been suggested that increased levels of pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF-α), IL-6 and leptin, and reduced levels of adiponectin may directly contribute to the occurrence of HCV-related IR.[6] Although there is *in vitro* evidence in support of this view (i.e. TNF- α interferes with insulin signaling in the liver by inducing serine phosphorylation of IRS-1 and hypophosphorylation of IRS-2), a direct proof of this has been difficult in the clinical setting due to the presence of many confounders.[9,23]

Steatosis and HCV

fat accumulation in the liver cell (steatosis) can occur by many mechanisms. The commonest causes are linked to alcohol consumption and metabolic derangements, mainly IR, seen in overweight and obese people with IR and/or diabetes. The latter condition (which is termed NAFLD) encompasses a pathological spectrum from simple steatosis to an inflammatory form of the disease termed nonalcoholic steatohepatitis (NASH). While simple steatosis has a benign clinical course NASH patients are deemed at high-risk for developing more advanced fibrosis, cirrhosis and hepatocellular carcinoma.[24-25]

NAFLD pathogenesis may involve a two-step process. The first and obligatory phase, is the development of IR that has a central role in triglyceride accumulation in liver cells.[26] In the setting of IR, uninhibited lipolysis occurs in adipose tissue determining a fatty acid overflow to the liver. After their uptake by hepatocytes, fatty acids are utilized for triglyceride synthesis.[27-28] In addition, compensatory hyperinsulinemia present in IR contributes to stimulate *de novo* lipogenesis in the liver cell contributing to steatosis. The second step, which occurs only in a proportion of NAFLD subjects, is hepatic inflammation and triggering of local fibrogenesis. The underlying mechanisms that determine that some individuals with simple steatosis evolve toward NASH remain unknown. However, inflammatory events occurring in the adipose tissue are key initial events in promotion IR through adipokine imbalance and fatty acid-induced oxidative stress are considered among the main culprits.[27]

Being both common entities in the general population, NAFLD and HCV infection can clearly coexist. Since HCV infection may aggravate IR, which is the main cause of NAFLD, it is difficult to quantitate the contribution of each condition in a given patient. Some authors have proposed that NAFLD or NASH can be diagnosed on histological basis in the setting of concomitant HCV infection.[29] However, this is controversial and difficult due to lack of information on cut-offs for the degree of steatosis and the fact that some histological findings can be present in both conditions. In spite of that, it has been estimated that 10% of patients with HCV display features of NASH.[8] As mentioned before, the close association of steatosis with HCV genotype 3 infection suggests that direct viral-related steatogenic mechanisms are at play in this setting. In the case of non-3 genotypes, pre-existing IR drives steatosis development and worsening of IR due to HCV infection can either increase the degree of steatosis or determine progression to NASH. Some of the proposed specific mechanisms involved in the pathogenesis of steatosis in the context of HCV infection are shown in table 1.

Table 1. Potential mechanisms involved in the development of hepatic steatosis in the setting of HCV infection.*

1. **Direct viral-related mechanisms.**
   - HCV core protein inhibition of microsomal triglyceride transfer protein activity resulting in decreased VLDL secretion and intracellular accumulation of lipids.
   - Impaired expression and transcriptional activity of PPAR-a resulting in reduced mitochondrial oxidation of fatty acids.
   - Induction of SREBP-1 expression and transcriptional activity promoting hepatic lipogenesis.
   - Down-regulation of PPAR-γ mRNA.
2. **Exacerbation of Insulin Resistance.**
   - Increased levels of pro-inflammatory cytokines (i.e.TNF-α).
   - Viral Interference of the IRS-1 pathway.
   - Viral-induced oxidative stress.

* Viral-related mechanisms are mainly at play in HCV gentotype-3 infection. HCV: Hepatitis C virus. VLDL: very low density lipoprotein. PPAR: peroxisome proliferator-activated receptor. SREBP: Sterol regulatory element binding protein. TNF: tumor necrosis factor. IRS-1: insulin receptor substrate-1.

CLINICAL IMPLICATIONS

The clinical implications of the presence of IR and steatosis in patients with CHC have become evident in many studies that consistently showed that these co-factors are related to both a poorer response to antiviral therapy and disease progression.[19,30-32] Current data on the topic is summarized below.

The negative impact of IR on achieving sustained viral response (SVR, defined as undetectable HCV RNA 24 weeks after completing treatment) after standard antiviral therapy (Pegylated interferon plus ribavirin) in patients with CHC has been demonstrated in several studies. Romero-Gómez, *et al.*, [33] showed marked differences in the rates of SVR in HCV infected patients with and without IR, assessed by HOMA-IR. In this study, 23 of 70 (32.8%) patients with genotype 1 CHC and IR (HOMA-IR > 2) achieved a SVR vs. 26 of 43 (60.5%) genotype 1 CHC patients without IR. These results has been confirmed by other authors (34-37) and extended to non-1 genotypes.[38] Thus, since IR is an independent predictor of treatment response, HOMA-IR could help to predict treatment outcome in a given patient.

IR has been also associated to fibrosis in CHC patients.[39-40] However, it is its main consequence steatosis, the feature that has been found more consistently associated to disease progression in patients with CHC.[11] Studies including paired biopsies provide stronger evidence in this regard.[32,41-42] More recently, these results were confirmed by analysis of data from the HALT-C Trial cohort.[43-44] In this study involving more than 1000 patients, hepatic steatosis was a strong and independent predictor of fibrosis not related to other laboratory markers for liver disease severity. A number of mechanisms can account for the profibrogenic effects of IR and steatosis.[19,45]

Another important clinical implication of IR in CHC is the strong relationship of IR and T2DM development.[15] Cross-sectional and longitudinal studies support the notion that HCV infection determines an excess in the risk of developing T2DM, particularly in those with known risk factors.[15-16] More recently the relationships between HCV infection, T2DM and hepatocellular carcinoma have gained significant attention given the rise of liver cancer in the United States.[46-47] Interestingly, it has been shown that IR is somewhat modified by treatment and that the incidence of T2DM in patients achieving SVR is significantly lower than that seen in non-responders.[48]

PERPECTIVES FOR CLINICAL MANAGEMENT

Available data on the complex relationship between IR and CHC offers some opportunities for clinical intervention. This includes active management of body weight and specific pharmacological treatment of IR and/or hepatic steatosis.

Although it has been shown that weight reduction may have impact on both liver histology and biochemistry in patients with CHC,[49-50] interventions aiming to modify body weight before treatment have not been formally tested in large-scale trials. Thus, we do not known if patients that lose weight and introduce lifestyle changes have a different natural history that those that do not follow these general recommendations. However, analysis of outcomes in the HALT-C trial provides strong evidence about the benefits of weight loss in overweig-

ht or obese patients with CHC.[44] In this study, patients that lost more than 5% of the baseline weight showed significant decrease in both hepatic steatosis and inflammation. As for the potential impact of weight loss on the response to antiviral treatment, no large prospective studies have been conducted. Only a small study reported by Tarantino, *et al.*, [51] showed that a strict low calorie diet for three months, aiming to achieve a 10% reduction in body mass index before starting treatment, indeed determined higher rates of response to peginterferon plus ribavirin therapy. It is therefore appropriate to specifically counsel those CHC patients who are overweight or obese aiming to lose at least 5% of their basal weight in order to potentially improve the response to antiviral therapy.[52] Joint work of hepatologists with a multidisciplinary obesity management-team could increase chances of a successful response in this setting.

Management of IR with insulin sensitizing agents aiming to increase the chances of responding to treatment is another recently explored possibility.[19] However, available data is limited in this regard. The INSPIRED-HCV study[53] considered administration of pioglitazone to HCV infected patients that did not respond to standard treatment. This trial was prematurely terminated due to lack of efficacy. However, the dose of pioglitazone (15mg/d) and the difficult-to-treat patients included in the trial limit the interpretation of results. Other attempts of improving treatment response with pioglitazone have been reported. One study published only in abstract form showed that in genotype-1 patients naïve to treatment 30 mg/d of pioglitazone showed a significantly increased occurrence of a rapid virological response.[54] Unfortunately, SVR were not reported. In other preliminary study, Conjeevaram et al. showed that although pioglitazone treatment led to a significant reduction in IR and reversal of hepatic steatosis in HCV genotype-1 patients with IR, SVR was similar in treated and non-treated patients.[55] Another recent study from Egypt involving HCV infected genotype 4 patients showed positive results.[56] More recently, an interesting case-report suggest that sequential, rather than concomitant, administration of pioglitazone with antiviral therapy could be more effective in achieving response to treatment.[57] Finally, the addition of metformin to standard antiviral treatment was studied in a prospective, multicentered, randomized, double-blinded, placebo-controlled trial in 19 Spanish hospitals.[58] Although there was a trend to achieve a higher SVR in metformin treated patients the study failed to show a statistically significant difference between arms. Clearly, additional studies on the role of adding insulin sensitizing agents to standard antiviral treatment are warranted.

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ABBREVIATIONS: USED IN THIS PAPER:

IR: Insulin resistance; HCV: hepatitis C virus; T2DM: type 2 diabetes mellitus; NAFLD: non-alcoholic fatty liver disease; CHC; chronic hepatitis C; HOMA-IR: homeostatic model assessment; IRS: insulin receptor substrates; IL: interleukin; TNF: tumor necrosis factor; NASH: Nonalcoholic steatohepatitis; SVR: sustained viral response.

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