

## Hepatitis C and insulin action: An intimate relationship

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Author contributions: Both authors contributed equally to this work.

Conflict-of-interest statement: None of the authors has any conflict of interest.

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Received: July 6, 2015

Peer-review started: July 11, 2015

First decision: September 16, 2015

Revised: December 10, 2015

Accepted: December 29, 2015

Article in press: January 4, 2016

Published online: January 18, 2016

### Abstract

Chronic hepatitis C virus (HCV) infection has been shown to be linked to a higher prevalence of type 2 diabetes compared with the general population or with patients with chronic hepatitis B infection and diabetes is the most common extra-hepatic manifestation of HCV. The HCV-diabetes association is due to insulin resistance (IR) that occurs early in the course of the

disease even in patients without or with minimal fibrosis. The mechanisms for HCV-induced IR are only partly understood and include a direct inhibitory effect of HCV on insulin signaling pathway. IR in chronic HCV results in an increased progression rate of hepatic fibrosis, cirrhosis and hepatocellular carcinoma. Some but not all studies found that IR reduces the response rate to interferon/ribavirin therapy. Whether IR affects the response to the new direct-acting antiviral treatments is still unknown.

**Key words:** Hepatitis C; Type 2 diabetes; Antiviral therapy; Insulin resistance; Insulin signaling

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**Core tip:** Chronic hepatitis C virus (HCV) infection is associated with a higher prevalence of diabetes as compared to either the general population or patients with chronic hepatitis B infections. HCV hepatitis is linked to insulin resistance (IR) early in the disease course, mediated partly by direct inhibitory effect of the viral proteins on insulin signaling. The presence of IR is associated with an increased rate of disease progression to fibrosis, cirrhosis and hepatocellular carcinoma. Interferon and ribavirin treatment of HCV hepatitis may be less successful in the presence of IR. The effect of IR on the new direct-acting antiviral treatment is unclear.

Knobler H, Malnick S. Hepatitis C and insulin action: An intimate relationship. *World J Hepatol* 2016; 8(2): 131-138 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i2/131.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i2.131>

### INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major healthcare problem worldwide with between 130-170 million people infected<sup>[1,2]</sup>. In addition, there are extra-

hepatic manifestations of HCV infection including mixed cryoglobulinemia, thyroid disorders and other autoimmune-mediated diseases<sup>[3]</sup>, but several studies published since 1994 provide evidence that diabetes mellitus (DM) maybe the most common extra-hepatic disease associated with chronic HCV.

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## THE ASSOCIATION BETWEEN HCV AND DIABETES

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The first studies that demonstrated an association between HCV and DM evaluated patients at advanced stage of liver disease necessitating liver transplantation and revealed that diabetes occurred in 50% and 62% of patients whose liver failure was HCV-related compared to 9% in patients whose liver failure was related to other causes<sup>[4,5]</sup>. These unexpected results were confirmed by studies from many parts of the world demonstrating that the increased prevalence of diabetes in HCV patients is unique and is significantly different compared to hepatitis B virus (HBV) infection<sup>[6-8]</sup>.

Many of these additional studies, however, also included patients with cirrhosis - a condition that by itself is known to lead to impaired glucose tolerance<sup>[9,10]</sup>.

### **Diabetes in non-cirrhotic HCV patients**

In order to avoid the confounding effect of cirrhosis on glucose metabolism, we designed a study conducted in patients without liver cirrhosis that included 45 patients with chronic HCV, 88 patients with chronic HBV infection and 90 healthy individuals<sup>[11]</sup>. Diabetes status was based on an oral glucose tolerance test (OGTT). We found that 33% of HCV patients had type 2 diabetes compared to 12% of patients with chronic HBV infection and 6% of a healthy control cohort. We have reported that HCV patients with diabetes had a higher incidence of a family history of diabetes as compared to HCV patients without diabetes ( $P < 0.001$ ). In addition on comparing liver biopsies from HCV patients with diabetes to those with HCV and no diabetes there was a significantly higher inflammatory activity, fibrosis grade and more steatosis.

### **Large cohort studies evaluating the relationship between HCV and diabetes**

The National Health and Nutrition Examination Survey (NHANES III) evaluated 9841 community-dwelling subjects and found that 8% of this population had type 2 diabetes and 2% were anti-HCV positive. The odds ratio (OR) for type 2 DM in those over 40 years of age after adjusting for sex, body mass index (BMI), ethnicity, poverty index, and previous drug or alcohol use was 3.77 (95%CI: 1.80-7.87)<sup>[12]</sup>. There was no increased risk for DM in those with chronic HBV infection. Although liver biopsies were not performed in these patients, there were no clinical signs of chronic liver disease. A large study of consecutive chronic HCV patients from Spain, found a 3-fold increase in the prevalence of glucose abnormalities in non-cirrhotic HCV+ compared

with HCV- subjects<sup>[13]</sup> but not in cirrhotic patients. Furthermore, multivariate analysis of chronic HCV patients without cirrhosis found that HCV infection was an independent determinant of glucose abnormalities, OR of 4.26 (95%CI: 2.03-8.93). In the Atherosclerosis Risk in Communities study, with a follow-up of 9-years pre-existing HCV infection was found to be a significant risk factor for developing diabetes in aged patients or those with a high BMI. This finding was strikingly robust with a relative hazard of 11.58 (95%CI: 1.39-96.6)<sup>[14]</sup>. Two meta-analyses including 47 cross-sectional and cohort studies found that HCV was associated with DM with an OR of 1.7<sup>[15,16]</sup> with an excess risk observed in comparison to HBV-infected controls.

However a recent additional report based on NHANES data 1999-2010 survey evaluated 15128 participants with known HCV and glucose status and did not find an association between HCV status and diabetes/pre-diabetes<sup>[17]</sup>. The reasons for this discrepancy are not entirely clear however the number of patients who were HCV positive was relatively small (1.7% were anti-HCV+ and 1.1% were HCV RNA+) and OGTT was not performed. Another factor that can reduce the strength of the association between HCV infection and diabetes in this recent United States survey is the increase within the rate of obesity and consequently obesity-induced diabetes that may dilute the effect of HCV.

Taken together, the vast majority of studies suggest that chronic hepatitis C is specifically associated with type 2 diabetes and the association is strongest in patients with additional risk factors such as older age and positive family history of diabetes implying that HCV leads to diabetes particularly in susceptible hosts.

### **Interferon-induced diabetes**

Interferon treatment that was until recently the cornerstone of HCV treatment was shown to induce a distinct form of diabetes. However this is a relatively rare complication that in contrast to the common form of HCV-related type 2 diabetes described above, has an abrupt onset, necessitates insulin treatment from onset and is mediated by an autoimmune process manifested by a very high titer of pancreatic autoantibodies<sup>[18]</sup>.

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## PATHOGENESIS OF HEPATITIS C ASSOCIATED DIABETES

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### **HCV and insulin resistance**

There is substantial evidence that insulin resistance (IR), that has a pivotal role in the pathogenesis of type 2 diabetes, develops early in the course of HCV infection<sup>[19-21]</sup>. A study of 260 subjects with HCV with assorted stages of fibrosis compared with 137 healthy volunteer in which IR was measured by the homeostasis model assessment-IR (HOMA-IR), found significant IR even in the sub-group of 121 patients with only stage 0 or 1 of hepatic fibrosis. However, although IR was detected even in subjects with minimal or no fibrosis,

more advanced fibrosis was associated with increased HOMA-IR<sup>[19]</sup>. Other studies confirmed these findings and showed a correlation between the degree of fibrosis and IR<sup>[20,22]</sup>. By using the gold standard measurement of IR, the hyperinsulinemic - euglycemic clamp it was shown that IR occurred mainly in the periphery, *i.e.*, in muscles and not in the liver and was related to viral load but not to liver fat content<sup>[23]</sup>. The notion that HCV has a direct effect on insulin sensitivity that is not mediated by virus-induced steatosis is also supported by a transgenic mice model which expresses the HCV core protein in the liver. IR was detected as early as 1 mo of age while hepatic steatosis developed after 3 mo<sup>[24]</sup>. In a landmark study, Aytug *et al*<sup>[25]</sup> evaluated liver specimens obtained from non-obese non-diabetic HCV patients compared to controls and their data not only confirmed the existence of HCV-induced IR but also revealed a specific impairment of insulin - stimulated IRS-1/PI3 kinase signaling pathway in HCV patients, a pathway that is responsible for insulin metabolic effects.

### IR and HCV genotypes

The relationship between IR and HCV genotype is still controversial. In a study of Hui *et al*<sup>[19]</sup> patients with genotype 3 had significantly lower HOMA-IR compared with other genotypes and this association remained significant even after adjusting for other variables. In another large study of 275 non-diabetic treatment-naïve HCV patients, HOMA-IR was significantly higher in non-3 genotype compared with genotype 3. However in non-obese patients with minimal fibrosis, using a cut-off level of HOMA > 3 as indicating IR, there was no significant effect of genotypes<sup>[26]</sup>. In another smaller study of 44 patients that used a cut-off level of HOMA  $\geq$  2 as indicating IR, the prevalence of IR was similarly high, 65% and 57% in genotype 1 and genotype 3, respectively<sup>[27]</sup>. However it is important to emphasize that the usage of these HOMA-IR criteria to define IR is problematic since there are no acceptable absolute cut-off levels.

### The underlying mechanisms for HCV-induced IR

**Tumor necrosis factor alpha:** The role of the cytokine tumor necrosis factor alpha (TNF- $\alpha$ ) in HCV-induced IR is supported by several studies (for review<sup>[28]</sup>). TNF- $\alpha$  producing cells, the majority of which are derived from macrophage/Kupfer cell lineage, are increased in HCV infection; and TNF- $\alpha$  activation was found to be significantly associated with the inflammatory process<sup>[29]</sup>. TNF- $\alpha$  also has an important inhibitory role on the insulin signaling pathway and the mechanism is mediated by activating serine/threonine (Ser/Thr) kinases that phosphorylate the insulin receptor substrate (IRS) protein, and uncoupling it from both upstream and downstream effectors<sup>[30]</sup>. TNF- $\alpha$  induces IR also by indirect mechanisms such as increasing lipolysis leading to increased serum free fatty acids and regulating expression of several adipocyte genes that modulate insulin sensitivity<sup>[31]</sup>. TNF- $\alpha$  binds to two distinct cell

surface receptors, TNFR-1 and TNFR-2 that undergo proteolytic cleavage producing soluble receptors sTNFR1 and sTNFR2. Serum levels of TNF- $\alpha$  and sTNFR were increased in HCV-infected patients compared with controls<sup>[32]</sup>. When serum sTNFR were measured in non-cirrhotic HCV patients with and without diabetes, non-HCV patients with type 2 diabetes and controls, a marked increase of sTNFR was found in the HCV-diabetes<sup>+</sup> group compared to HCV patients without diabetes, and non-HCV patients with type 2 DM<sup>[33]</sup>. A significant correlation was found between the degree of liver inflammation and sTNFR<sup>[29]</sup>. The role of TNF- $\alpha$  in HCV-induced IR is supported by the finding that anti TNF- $\alpha$  antibody administration restored insulin sensitivity in a transgenic mice model that specifically expressed the HCV core protein in the liver<sup>[24]</sup>.

However, increased levels of TNF- $\alpha$  are also present in other chronic liver diseases and thus cannot fully account for the unique association between HCV and IR. Therefore direct effects of HCV proteins on insulin signaling have been also considered.

### Direct effects of HCV proteins on insulin signaling

In human hepatoma cells, HCV core protein up-regulates suppressor cytokine signaling (SOCS)-3, which is known to inhibit insulin signaling by causing ubiquitination of IRS1 and IRS2 proteins<sup>[34]</sup>. These defects were not detected in SOCS3<sup>-/-</sup> mouse embryonic fibroblasts cells or in the presence of an inhibitor of proteasomal proteolysis<sup>[34]</sup>. We have reported several impairments of the insulin signaling cascade linked to the proteasomal degradation of IRS-1 protein<sup>[35]</sup>. Additionally we found that the core protein impaired insulin ability to inhibit the expression of the target gene insulin growth factor binding protein-1.

HCV can also inhibit insulin signaling by dephosphorylation of AKT involving the endoplasmic reticulum stress signal inducing over-expression of protein phosphatase 2A<sup>[36]</sup>. Taken together these data imply a direct effect of HCV core protein in inhibiting insulin signaling pathway.

## DOES ERADICATION OF HCV AMELIORATE IR?

A recent study of 8 normoglycemic men with chronic HCV infection that used the hyperinsulinemic-euglycemic clamp that provides a direct measurement of peripheral insulin sensitivity, showed that viral clearance led to improvement in glycemic control and to insulin sensitivity that become comparable to 15 matched HCV-negative controls<sup>[37]</sup>. A larger earlier study, using the surrogate marker HOMA-IR also showed that in HCV patients who were sustained responders HOMA-IR decreased while in it did not change in nonresponders and relapsers<sup>[38]</sup>. However, another study showed that HCV therapy improved IR regardless of virologic response but the repose was greatly influenced by BMI

changes and interferon use making data interpretation difficult<sup>[39]</sup>.

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## THE EFFECT OF IR AND DIABETES ON THE CLINICAL OUTCOME OF HCV

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The link between HCV infection and IR and diabetes is complex. IR appears at an early stage of chronic HCV infection as discussed above and results in an increased rate of progression of hepatic fibrosis and the complications of cirrhosis including hepatocellular carcinoma (HCC)<sup>[40]</sup>.

IR is also related to obesity and type 2 diabetes and both of these conditions are known to be risk factors for HCC leading to about 2-fold increased prevalence<sup>[41,42]</sup>. The rise in HCV infection and HCV-induced IR together with increased obesity-induced IR may partly explain the marked increase in HCC in the last decades<sup>[43]</sup>.

The compensatory hyperinsulinemia that occurs in IR can lead to fibrogenesis. In human hepatic stellate cells (HSC), incubation with insulin and insulin growth factor (IGF)-1 led to increased HSC proliferation and type 1 collagen gene expression<sup>[44]</sup>. The increased IGF-1 levels that occur in the IR state is also one of the mechanisms for IR-associated malignancy and particularly HCC and changes in the expression pattern of IGF system components were found in human hepatoma cell lines and in animal models<sup>[45]</sup>.

In a recent systemic review of 14 studies including 3695 participants with HCV infection, the relative risk for fibrosis was 2.26 (95%CI: 1.52-3.06) for genotype 1, but the association was not significant for genotype 3<sup>[46]</sup>. HCV is also intimately related to hepatic steatosis<sup>[47,48]</sup> and steatosis is much more common in patients infected with HCV than in other liver diseases. This association is most marked for genotype 3<sup>[49]</sup>. Steatosis is also linked to HCC and in two lines of transgenic mice expressing the HCV core protein, HCC developed within fat-containing adenomas<sup>[50]</sup>.

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## THE EFFECT OF IR AND DIABETES ON THE RESPONSE TO THERAPY

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It has been shown that patients with high IR have a slower rate of decline in the viral load of HCV RNA compared to patients with low IR, even in the first 24 h of treatment<sup>[51]</sup>. In addition, there is an association between a high degree of IR and a low rate of rapid viral response in genotypes 1<sup>[52]</sup>, 3<sup>[53]</sup> and 4<sup>[54]</sup>. Several studies have shown that IR is associated with a higher likelihood of not achieving sustained virological response (SVR)<sup>[52-56]</sup>. A study from Spain of 159 patients with chronic HCV hepatitis found that those with a SVR had lower baseline HOMA scores compared to those patients who did not achieve a SVR<sup>[57]</sup>. The Virahep-C study which included both Caucasian and African-Americans found that IR and interferon dose were negatively associated with SVR<sup>[56]</sup>. The patients in this study had a high degree of obesity

and IR as compared to other published reports. These studies have used HOMA to assess insulin sensitivity, a surrogate measure of IR although this technique is less precise than more direct measurements such as the insulin suppression test<sup>[58]</sup>. Furthermore IR can change over time with in patients with chronic HCV infection<sup>[59]</sup>. When IR was directly assessed by means of an insulin suppression test in a cohort of 50 non-cirrhotic, non-diabetic patients with chronic HCV infection, SVR was not associated with insulin sensitivity<sup>[39]</sup>. The steady state plasma glucose level decreased during anti-viral therapy but was not statistically significant between those patients achieving SVR and those not achieving SVR during and after treatment<sup>[39]</sup>. IR often progresses to diabetes but in a study that evaluated SVR and the development of diabetes or impaired glucose tolerance, no such correlation was found during a median follow up of 8 years<sup>[60]</sup>. In 2011, two meta-analyses were published that examined the effect of IR on SVR including fourteen studies with more than 2700 patients<sup>[61,62]</sup>. The studies that did not find an association between IR and SVR had a baseline HOMA value of less than 3 and a low prevalence of advanced fibrosis. This suggests that the HOMA value may be predictive of response to antiviral treatment in those patients with advanced liver disease. These inconsistent data may be partly due the interplay between the baseline characteristics of the patients and the effect of the HCV virus on insulin sensitivity. Notably, about 25%-30% of the United States population have metabolic features of HCV-independent IR<sup>[63]</sup>.

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## TARGETING IR AS PART OF HCV TREATMENT

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In view of the link between IR and the progression of HCV hepatitis and the possible influence of IR on treatment, attention has been drawn to improving the metabolic factors related to IR before or during anti-viral treatment.

### *Lifestyle modification*

A 24 wk lifestyle and dietary intervention was shown to reduce BMI and HOMA in obese patients with chronic HCV hepatitis<sup>[64]</sup>. A 3-mo trial of a low calorie diet before starting anti-viral therapy has been shown to result in a higher end-of- treatment viral response in patients with type 1 chronic HCV hepatitis together with an improvement in IR.

### *Metformin*

Metformin is an insulin sensitizer that mainly decreases hepatic glucose production. An attempt to add metformin to treatment with peg-interferon-2a and ribavirin led to decreased HOMA-IR and viral load, together with an improvement in the SVR, but this effect was observed only in females<sup>[65]</sup>. In another study metformin administration led to an increase in SVR in both male and female HCV patients with genotype 1 treated by

pegylated interferon and ribavirin<sup>[66]</sup>.

### Thiazolidinediones

Thiazolidinediones produce an increase in insulin sensitivity *via* activation of the peroxisome proliferator-activated receptor- $\gamma$  in adipocytes and skeletal muscle<sup>[67]</sup>. Pioglitazone has been shown to produce an increase in SVR in patients with genotype 4 and IR but not in patients with genotype 1<sup>[68]</sup>. Another study of pioglitazone added to pegylated interferon-2a and ribavirin in non-diabetic HCV patients who previously did not respond to this treatment and who had HOMA > 2, was terminated after none of the first five patients achieved a 12 wk viral response, despite an improvement in IR in some of them<sup>[69]</sup>.

In a recent small study of patients with HCC, in a sub-group analysis of diabetic over-weight patients, the addition of pioglitazone to curative treatment resulted in reduced HCC recurrence<sup>[70]</sup>.

## THE EFFECT OF DIABETES ON THE RESPONSE TO THE DIRECT-ACTING ANTI-VIRAL TREATMENTS

The recently approved sofosbuvir, simeprevir, ledipasvir, and the combination of paritaprevir, ombitasvir and dasabuvir have ushered in the era of interferon-free therapy for HCV hepatitis. These direct-acting anti-viral treatments (DAA) achieve SVRs of more than 90% for most treatment groups<sup>[71]</sup>. With such an effective treatment available it is likely that the effect of IR will be less evident. However, a recent preliminary report suggests that metabolic factors such as diabetes and hyperlipidemia still compromise the effect of DAA treatment. This was based on the results of a recent study that examined SVR at 12-wk in 54 non-Caucasian populations in the United States, 65% of whom were Hispanic and 24% had diabetes. SVR in this study was 81% which is lower than the rate reported in previous studies. A pre-treatment glucose level of less than 126 mg/dL was shown to be linked to a higher rate of SVR<sup>[72]</sup>. Further studies are needed to evaluate the effect of IR and diabetes on the response to DAA treatment.

Although the future of treatment of HCV hepatitis will undoubtedly be oral, once-daily pangenotypic therapy with a nearly 100% SVR, in 2015 there is still a place for treatment of HCV hepatitis with interferon-containing regimens.

For patients with genotypes 2-6 peginterferon and ribavirin is still effective treatment. For patients with genotype 2, 24 wk of treatment is sufficient and an SVR of 85%-90% is achieved<sup>[73]</sup>. Interferon has an important role in the treatment of genotype 3, including a regimen with sofosbuvir<sup>[74]</sup>, and in the treatment of genotype 4 with an SVR of 43%-70% and 60%-85% SVR for genotype 6<sup>[75]</sup>.

In addition for many economically-constrained health services and patients who are self-funding, the

cost of the DAAs is prohibitive, and treatment with interferon will remain an option for the near future<sup>[76]</sup>.

## CONCLUSION

IR is intimately related to HCV infection based on numerous studies in animal models and humans resulting in increased prevalence of type 2 diabetes in HCV patients. The underlying mechanisms are only partly understood and recent data suggest a direct inhibitory effect of the virus on insulin signaling pathway. IR was shown by several, but not all studies, to have a deleterious effect on the clinical course of chronic HCV infection and the inconsistency maybe explained by differences in the baseline characteristics of the patients. Small studies suggest that life-style intervention and metformin may increase SVR rate but further studies are needed to confirm these findings. The effect of IR in the DAA drugs era is still unclear.

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