

Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C

Mohammed Eslam,* Reyes Aparcero,* Manuel Romero Gomez*

* Unit for The Clinical Management of Digestive Diseases and CIBERehd, Hospital Universitario de Valme, Sevilla, Spain.

Article commented:

Conjeevaram HS, Wahed AS, Afdhal N, Howell CD, Everhart JE, Hoofnagle JH; Virahep-C

Study Group. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. *Gastroenterology* 2011;140:469-77

Original abstract

Background & aims. Chronic hepatitis C is associated with an increased prevalence of insulin resistance, which might result from liver disease, metabolic factors, or the hepatitis C virus (HCV) itself. The effect of antiviral treatment on insulin sensitivity is not well known. We evaluated changes in insulin resistance and weight in patients with hepatitis C during and after peginterferon and ribavirin therapy. **Methods.** Virahep-C was a prospective, multi-center study of a 48-week course of combination antiviral therapy in patients infected with HCV genotype 1. Insulin resistance was estimated by the homeostasis model assessment index (HOMA2-IR) based on fasting glucose and insulin levels. **Results.** Among 341 patients, 40% had insulin resistance (HOMA2-IR > 2.0). The presence of insulin resistance was associated with increasing age, body mass index, (BMI) and fibrosis stage. Among patients with insulin resistance at the start of the trial, median decreases in HOMA2-IR values during treatment were 0.74 at 24 weeks and 0.89 at 48 weeks, whereas BMI decreased by 1.2 and 2.2 kg/m² at the same timepoints ($P < 0.001$

for all). At follow-up, HOMA2-IR and BMI levels returned toward baseline values in patients that did not respond or relapsed, but HOMA2IR values remained significantly lower in patients with sustained virological response (SVR) ($P < 0.001$), despite increases in BMI. **Conclusions.** In patients with HCV genotype 1 infections, therapy with peginterferon and ribavirin is associated with decreases in body weight and insulin resistance. Among patients with insulin resistance before treatment, resolution of HCV infection results in sustained improvements in the homeostasis model assessment index, so HCV could have a direct role in the pathogenesis of insulin resistance.

Key words. Obesity. Metabolic response. Liver disease. Clinical trial.

Abstract published under permission of Elsevier, 2011.

Comment:

There is a complex and bidirectional interaction between hepatitis C virus infection and insulin sensitivity.¹ Hepatitis C core protein promotes degradation of insulin receptor substrate-1 and induces insulin resistance. Increased insulin resistance index was associated with reduced rapid virological response^{2,3} and sustained virological response rates in patients treated with pegylated interferon and ribavirin.³⁻⁵ Moreover, hepatitis C clearance was related to improved insulin sensitivity, decreased diabetes mellitus and glucose abnormalities development during follow-up and improved insulin receptor substrate-1 and 2 expression in hepatocytes, providing strong evidence for a causal relationship between hepatitis C and glucose abnormalities.^{4,6-8} This association is also potentially imperative as it may influence decision-making about which hepatitis C patients have to be treated based on considerations other than the severity of liver disease alone. Indeed, accumula-

Correspondence and reprint request: Manuel Romero-Gómez, MD, Unit for The Clinical Management of Digestive Diseases and CIBERehd, Hospital Universitario de Valme, Ctra de Cadiz s/n, Sevilla 41014, Spain. Tel.: (+34) 955-015761 Fax: (+34) 955-015899 E-mail: mromerogomez@us.es

Manuscript received: February 28, 2011.
Manuscript accepted: March 02, 2011.

ting evidences are warning from the hepatic expression of the metabolic syndrome and insulin resistance, recently called "diabetic hepatopathy".⁹

The study by Conjeevaram, *et al.*,¹⁰ addressed the effect of hepatitis C virus eradication on insulin resistance index. In a large cohort of 341 patients infected with genotype 1, peginterferon plus ribavirin therapy was associated with falling body weight and HOMA-IR, and these changes were more evident in patients with pre-existing insulin resistance before treatment. Resolution of hepatitis C infection resulted in sustained improvement in the HOMA-IR. Our group,⁴ in a cohort of 50 patients with chronic hepatitis C treated with pegylated interferon/ribavirin combination, HOMA1-IR was measured at the start, at 24 weeks of therapy and at 24 week follow-up after stopping therapy. We showed no improvement in HOMA values among non-responders and although HOMA index decreased in the responder group at 24 weeks, at 24 week follow-up the values returned to baseline among the relapser group, whereas in patients who achieved SVR, mean HOMA value was significantly lower compared to baseline. In 89 Japanese patients eradication of hepatitis C led to improvement of HOMA scores and intrahepatic expression of IRS-1 and IRS-2.⁶ Similar results in HOMA score changes were reported in a separate cohort including 181 genotype 4 patients.⁷ Thus, this study including the largest cohort confirmed previous results. Moreover, the study confirmed that baseline insulin resistance was associated with body mass index, triglycerides, fibrosis and steatosis and the sole factor associated with HOMA decline during and after therapy was baseline HOMA index demonstrating the higher HOMA the better decline, supporting the idea that the impact of HOMA on hepatitis C clearance was more evident in difficult to treat cohorts.¹¹ Interestingly, 55% of patients reached normal insulin sensitivity between sustained responders at the end-of-follow-up, quite similar to the percentage of patients receiving peginterferon plus ribavirin and metformin¹² at week 24 of therapy suggesting that in more than a half of patients insulin resistance was strongly related to hepatitis C.

A interesting point was the author's choice to use HOMA2-IR model for assessment of IR, instead of the widely used model HOMA1-IR. In the light of these complex interplay relationship between insulin resistance and hepatitis C, the methods of measurement of insulin sensitivity gained more focus. Insulin resistance can be evaluated either by direct measurement of insulin-mediated glucose uptake (IMGU) or, alternatively, by surrogate esti-

mation of IR. In the view of that, direct method is technically challenging.¹³ Focus has been directed on the simple and accessible measurement method for the evaluation of insulin sensitivity. To date, HOMA-IR has been the widely used model. HOMA is one of a family of "paradigm models". This model is a structural computer model of the glucose insulin feedback system in the homeostatic state. The model consists of a number of nonlinear empirical equations describing the functions of organs and tissues involved in glucose regulation. HOMA1-IR was the first developed in 1985 by Matthews, *et al.*,¹⁴ $HOMA1-IR = (\text{glucose} \times \text{insulin})/22.5$. While; HOMA2IR is the correctly solved computer model,¹⁵ has a nonlinear solution. This updated version of the HOMA model accounts for variations in hepatic and peripheral glucose resistance, the insulin secretion curve has been modified to allow for an increase in insulin secretion in response to a plasma glucose concentration of $> 10 \text{ mmol/l}$ (180 mg/dL).¹⁶ This version incorporates an estimate of proinsulin secretion into the model and thus allows the use of either total (radioimmunoassay [RIA]) or specific insulin assays. Renal glucose losses have also been included in the model, thus allowing its use in hyperglycemic subjects.¹⁸ However, HOMA2IR still has the inconvenience that only a specific range of values are acceptable for calculation. In clinical practice, this limitation makes difficult the management of insulin results outside the limits and the need for a computer to run the program.¹⁷ HOMA2-IR was calculated using the computer-based solution of the model provided by the Diabetes Trials Unit, Oxford Center for Diabetes, Endocrinology and Metabolism found at the website: (<http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/history.php>). Up to date, there are no current clinical guidelines can answer many of the important concerns: the accurate method for assessment of insulin resistance, the optimal cut-off and the method of interpretation of HOMA, in the view of its complex interplay with many factors. Although theoretically the performance of HOMA2-IR seems to be better than the original one HOMA1-IR, the available data from the clinical studies failed to find that. In a Brazilian study, the HOMA1-IR showed an area under the receiver operating curve (AUC) higher than the area verified for the HOMA2-IR computer model, as discriminators of metabolic syndrome, but this difference did yielded statistical significance.¹⁸ In another study, HOMA1 and HOMA-2 measures identified similar patterns of increasing IR in the both older and younger people.¹⁹ Two recent studies confirmed HOMA1 and HOMA-2 were significantly asso-

ciated with metabolic syndrome (odds ratio 5.7 and 4.2, respectively),²⁰ and ROC curve for diagnosis of the metabolic syndrome showed that AUC for the HOMA1 and 2 methods were 0.741 and 0.680, respectively.²¹ Lastly, Conjeevaram et al used a cutoff value (> 2) for identifying insulin resistance, which is the same cutoff value used with HOMA1-IR. Although, there are no established reference values for assessing IR, using HOMA2-IR, the limited available data in the literature refer to that the cut-off value to detect impaired insulin sensitivity using HOMA2-IR is lower than that of HOMA1-IR and cutoff value has ranged from 1.4 to 1.8.²⁰⁻²²

This study opens future challenges. It is still unknown whether insulin resistance in hepatitis C setting invariably induces its deleterious effect metabolic syndrome-mediated only or it may be induced due to purely virus-induced insulin resistance, without the remaining constellation of cytokine changes that accompany the metabolic syndrome. This distinction may be especially crucial when antiviral therapy has to be undertaken; because here therapy should be aimed at correcting insulin resistance may need to be tolerated according to the underlying molecular mechanisms, which may differ according to the viral genotype and the presence or absence of metabolic syndrome.

In summary, this study adds evidence to the role of hepatitis C on insulin resistance and how curing hepatitis C insulin sensitivity improves. This bidirectional correlation between hepatitis C and insulin resistance, metabolic syndrome and type 2 diabetes remain a major concern and attract our attention to this evolving challenge.²²

CONFLICT OF INTEREST

None Financial support: None Potential competing interests: None

REFERENCES

- Romero-Gomez M. Insulin resistance and Hepatitis C. *World J Gastroenterol* 2006; 12: 7075-80.
- Grasso A, Malfatti F, De Leo P, et al. Insulin resistance predicts rapid virological response in non-diabetic, non-cirrhotic genotype 1 HCV patients treated with peginterferon alpha-2b plus ribavirin. *J Hepatol* 2009; 51: 984-90.
- Khattab M, Eslam M, Sharwae MA, et al. Insulin resistance predicts rapid virologic response to peginterferon/ribavirin combination therapy in hepatitis C genotype 4 patients. *Am J Gastroenterol* 2010; 105: 1970-7.
- Romero-Gomez M, Del Mar Viloria M, Andrade RJ, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005; 128: 636-41.
- Poustchi H, Negro F, Hui J, 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.
- Kawaguchi T, Ide T, Taniguchi E, 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: 570-6.
- Chehadeh W, Abdella N, Ben-Nakhi A, et al. Risk factors for the development of diabetes mellitus in chronic hepatitis C virus genotype 4 infection. *J Gastroenterol Hepatol* 2009; 24: 42-8.
- Romero-Gomez M, Fernández-Rodríguez CM, Andrade RJ, et al. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. *J Hepatol* 2008; 48: 721-7.
- Arab JP, Ramírez C, Arrese M. Early warning of liver disease in diabetics. *Ann Hepatol* 2010; 9: 307-9.
- Conjeevaram HS, Wahed AS, Afzal N, Howell CD, Everhart JE, Hoofnagle JH; Virahep-C Study Group. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. *Gastroenterology* 2011; 140: 469-77.
- Romero Gómez M. Insulin resistance and sustained virological response in hepatitis C: From bench to bedside. *Liver Int* 2011; 51: 1-3.
- Romero-Gómez M, Diago M, Andrade RJ, Calleja JL, Salmerón J, Fernández-Rodríguez CM, et al. Treatment of insulin resistance with metformin in naïve genotype 1 chronic hepatitis C patients receiving peginterferon alfa-2a plus ribavirin. *Hepatology* 2009; 50: 1702-8.
- DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; 237: 214-3.
- Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412-19.
- Levy JC, Matthews DR, Hermans MP: Correct homeostasis model assessment (HOMA) evaluation uses the computer program (Letter). *Diabetes Care* 1998; 21: 2191-2.
- Rudenski AS, Matthews DR, Levy JC, Turner RC: Understanding "insulin resistance": both glucose resistance and insulin resistance are required to model human diabetes. *Metabolism* 1991; 40: 908-917.
- Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; 27: 1487-95.
- Geloneze B, Vasques AC, Stabe CF, Pareja JC, Rosado LE, Queiroz EC, Tambascia MA. BRAMS Investigators. HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome: Brazilian Metabolic Syndrome Study (BRAMS). *Arq Bras Endocrinol Metabol* 2009; 53: 281-7.
- Chang AM, Smith MJ, Bloem CJ, Galecki AT, Halter JB, Supiano MA. Limitation of the homeostasis model assessment to predict insulin resistance and beta-cell dysfunction in older people. *J Clin Endocrinol Metab* 2006; 91: 629-34.
- Safar FH, Mojiminiyi OA, Al-Rumaih HM, Diejomaoh MF. Computational methods are significant determinants of the associations and definitions of insulin resistance using the homeostasis model assessment in women of reproductive age. *Clin Chem* 2011; 57: 279-85.
- Mojiminiyi OA, Abdella NA. Effect of homeostasis model assessment computational method on the definition and associations of insulin resistance. *Clin Chem Lab Med* 2010; 48: 1629-34.
- Eslam M, Khattab MA, Harrison SA. Insulin resistance and hepatitis C: an evolving story. *Gut* 2011; (in press).