# HCV and Diabetes Mellitus: Considerations About Effects of Interferon Therapy

Laura Reynaud*, Maria A. Carleo, Maria Talamo and Guglielmo Borgia

*Department of Public Medicine and Social Security, Section of Infectious Disease, Center for Basic and Clinical Immunology Research (CISI)-University of Naples "Federico II", Italy*

**Abstract:** Nowadays HCV-related chronic hepatitis represents one of the main challenge for infectious diseases for many reasons: the dimension of the phenomenon, as millions of patients are afflicted with this pathology in the world, the dramatic consequences on the quality of their life, the economic and sanitary efforts sustained by the society, but also the stimulating results in therapeutic approach due to the introduction of interferons in monotherapy first and association therapy (IFN plus ribavirin) later in modern protocols. The results obtained with these therapies are very encouraging even if medical doctors and patients know very well that this therapy is related to some side effects that grow dramatically in number with the progression of scientific knowledge. The Authors review the literature on the relationship among HCV, IFN therapy and diabetes to understand better damages and benefits of this long debated matter and possibly add their contribution to clinical and therapeutic strategies.

**Keywords:** Hepatitis C virus, diabetes mellitus, interferon.

## INTRODUCTION

We know that it is possible to distinguish type 1 and type 2 diabetes mellitus (DM), different in their pathogenic mechanisms.

Type 1 diabetes mellitus is related to immune-mediated damage to pancreatic beta-islet cells, even if genetic predisposition and environmental factors are necessary for its development. It is characterized by islet infiltration of T-lymphocytes and monocytes and by hyper-expression of Major Histocompatibility Complex (MHC) class I antigens [1].

Type 2 diabetes mellitus is related to peripheral insulin resistance (IR), obesity, hyperinsulinemia [2].

## METHODOLOGY

The Authors review the literature of last eleven years on the relationship among HCV, IFN therapy and diabetes.

## HCV AND DIABETES MELLITUS

It is frequent to observe glucose intolerance or diabetes mellitus in course of chronic liver disease; some studies have demonstrated a strong correlation between Hepatitis C Virus (HCV) and type 2 diabetes mellitus and, in some cases, genotype 2a has been found to be specifically linked with diabetes.

Mason *et al.* have found, by means of multivariate analysis, that HCV infection and age but not cirrhosis are independent predictors of diabetes [3, 4].

Nevertheless, recent literature data report, in HCV-infected patients with chronic hepatitis and normal transaminases, a fivefold higher prevalence of diabetes than in anti-HCV negative patients and conclude that correlation starts at early stages of hepatic disease [5, 6].

The most accredited mechanism by which HCV determines type 2 diabetes mellitus is insulin-resistance syndrome likely to be related to steatosis, hyper-production of pro-inflammatory cytokines or to the direct involvement of HCV in insulin signalling pathway [6-9].

Tumor necrosis factor (TNF)-α has also been suggested as possible link between diabetes and HCV [10].

The relationship among HCV, steatosis and IR is genotype specific: Fartoux *et al.* show that steatosis and fibrosis are more frequent and severe in patients infected with genotype 3 than in those infected with genotype 1, while host factors such as age, disease duration, alcohol consumption, Body Max Index (BMI), serum ALT activity, Homeostasis model assessment index [HOMA index: method to calculate insulin resistance = fasting serum insulin (μU/ml)x serum glucose (mMol/L)/22.5] and histological activity score are not different in the two groups. In genotype 1 patients age, BMI, HOMA IR and hepatic iron concentration were significantly linked with the degree of steatosis.

HOMA IR and viral load were the only variable independently related to fatty liver in genotype 1 and genotype 3 infected patients respectively.

Steatosis is genotype 3 mediated by a cytopathic mechanism while IR is responsible for the development of steatosis in genotype 1 viral infected patients, a sort of cascade mechanism in which IR determines an increased circulating insulin causing steatosis, a risk factor for fibrosis.

All these considerations seem very interesting for the therapeutic approach regarding, for example, lifestyle changes (weight loss, abolition of alcohol consumption, cardio-vascular control) and metformin or peroxisome proliferator activated receptor γ-agonists assumption [11-17].

*Address correspondence to this author at the Department of Public Medicine and Social Security - Section of Infectious Disease (Ed. 18), University of Naples "Federico II", Via Sergio Pansini, 5, 80131 Naples, Italy; Tel: +390817463086; Fax: +390817463094; E-mail: reynaud@unina.it

1874-1436/07 

## INTERFERONS AND DIABETES: A REVIEW

Interferons (IFN) are natural molecules with antiviral, antiproliferative and immunomodulatory effects, which are usually employed in the therapy of malignancies and chronic viral hepatitis.

INF therapy can produce a lot of systemic side effects that include a flu-like syndrome, hematological abnormalities, cardiovascular and central nervous symptoms, gastrointestinal symptoms, diabetes mellitus, autoimmune disorders, pulmonary dysfunction, depression and retinopathy [18, 19].

In course of interferon therapy, the cumulative incidence of all autoimmune disorders is described between 1 and 3%; the frequency of glucose intolerance is estimated about 0,1-0,6%, while insulin dependent diabetes mellitus (IDDM) with anti-pancreatic islet cell (ICA) antibody or anti-glutamic acid decarboxylase (GAD) are described as rare cases [18-20].

Uto *et al.* describe a case of IDDM with various autoantibodies including anti-insulin receptor antibody (AIRA) [19].

Three are the possible mechanisms supposed to explain the effects of α-IFN on pancreatic dysfunction in patients suffering from HCV infection: 1) viral dsRNA should induce apoptosis in pancreatic β-cells and also production of α-INF, directly cytotoxic to pancreatic β-cells; 2) α-IFN should activate apoptosis through oligoadenylate synthase -RnaseL and the protein kinase R; 3) INF should increase regulatory hormone secretion, such as growth hormone, glucagon and injure glucose tolerance [20, 21].

Thirty six cases of α-IFN IDDM had been reported up to 2006 [20, 22]. In 2003 Fabris *et al.* reviewed thirty-one cases of DM in course of IFN therapy. Twenty-five of these patients were afflicted with chronic C hepatitis, three with chronic B hepatitis, three with cancer, one of whom was also infected with HIV.

Nine patients were treated with α-interferon plus ribavirin, one patient with α-interferon and interleukin-2, one patient with α- and β-interferon, one with β-interferon alone, the remaining with α-interferon monotherapy.

Family predisposition for IDDM and non insulin dependent diabetes mellitus (NIDDM) was positive in three cases and six cases respectively, sixteen of them had negative family history for diabetes while there were no data for six patients.

At the moment of diagnosis eleven patients were positive for ICA, two for IA (insulin antibody)-Abs, eighteen for GAD-Abs; Human Leukocyte Antigen (HLA) haplotypes for the study of susceptibility to IDDM were detected in sixteen of the eighteen cases studied.

Unfortunately neither these data of literature include the total number of treated patients in considered temporal interval, nor the information regarding viral genotype is available.

According to the conclusions of this work: a small number of patients afflicted with chronic C hepatitis is positive for pancreatic autoimmunity markers; they are at relative risk of developing DM if treated with alpha interferon; only a few patients develop de novo pancreatic autoimmunity and fall in the group at risk of developing DM; a timely suspension of α-IFN therapy is rarely accompanied by regression of clinical DM.

This report confirm that IDDM, in course of α-IFN therapy, is a rare event; IFN seems to play a trigger effect on IDDM onset so as it can also amplify thyroid autoimmune response in predisposed subjects [1, 23-27].

In the latest years, the onset of diabetes has also been observed in course of therapy with pegylated α-interferon (Peg-α-IFN), a new progress in the therapeutic approach to chronic viral hepatitis.

Recent data from international literature report almost six cases of IDDM: one of these patients, reported by Jabr *et al*, had a history of HIV/HCV coinfection while another patient, described by Soultati *et al*, developed double side effects: diabetic ketoacidosis and tyro-toxicosis (a condition characterized by circulating thyroid hormones increase and a series of symptoms and signs such as tachycardia, diarrhea, anxiety) in course of association therapy with Peg-α-IFN plus ribavirin [20, 28-31].

We can conclude that Peg-α-IFN shares the autoimmunity triggering role with classical α-IFN [20].

Romero-Gòmez *et al.* (2005) studied the rate of sustained virological response (SVR) to Peg-α-IFN plus ribavirin in 159 chronic HCV patients, concluding that IR, fibrosis and genotype are independent predictors of the response to antiviral therapy, that is IR impairs SVR [32].

Konishi *et al.* examined the influence of DM on the outcome of IFN-α2b plus ribavirin therapy in a cohort of 110 patients with chronic C hepatitis: sex, age, BMI, alanineaminotransferase levels, HCV-RNA titer, and HCV genotype did not differ between the patients with or without DM, while HCV genotype 1 and the presence of DM were independently associated with SVR, to say that DM reduces the response to IFN [33].

Simò *et al.* (2006) decided to compare the incidence of glucose abnormalities in HCV infected patients with or without SVR after antiviral therapy.

They observed that clearance of HCV significantly reduces the development of glucose abnormalities in chronic C hepatitis afflicted patients. Obviously this conclusion is a further confirmation that HCV infection causes IDDM [6].

In recent literature it has also been described a case of resolution of pre-existing type 2 DM in a patient with chronic HCV infection, which did not respond to IFN therapy [22].

## DISCUSSION

According to international literature we propose that all patients afflicted with chronic C hepatitis undergo a complete screening for autoimmune markers including those regarding the predisposition to IDDM (ICA, IA GAD-Abs, and if possible HLA haplotypes too) before, during and after IFN therapy.

We also suggest a screening for risk factors of metabolic syndrome before IFN therapy.

Moreover we think that the usual patients' counseling would include information about the possible developing of DM in course of IFN therapy.

In fact, the subject should be informed about the risk that DM could impair effectiveness of IFN therapy, that a recovery is possible even in case of non response to IFN therapy and also that SVR is shown to ameliorate glucose abnormalities.

Moreover if either genetic predisposition or environmental factors or host factors are positive for the risk of developing DM, we suggest to act on modifiable life style: body weight loss (in particular for type 2 diabetes), correct alimentary approach, physical activities, patient education. This attitude will have very important consequences on the patient's life: in fact beside the direct role played by HCV and IFN, the weight loss would positively influence IR and glucose homeostasis. We agree that there are obstacles due to the high costs of laboratory screening and counseling but we wonder whether these expenses will be really larger than the management of a diabetic subject during their whole life. According to WHO, direct health care costs of diabetes range from 2.5% to 15% of annual health care budgets, depending on local diabetes prevalence and the sophistication of the treatment available.

## REFERENCES


[1] Fabris, P.; Floreani, A.; Tositti, G.; Vergani, D.; De Lalla, F.; Betterle, C. *Aliment. Pharmacol. Ther.,* **2003**, *18,* 549-558.

[2] Mason, A.; Nair, S. *AJG*, **2003**, *98,* 243-246.

[3] Tai, T.Y.; Lu, J.Y.; Chen, C.L.; Lai, M.Y.; Chen, P.J.; Kao, J.H.; Lee, C.Z.; Lee, H.S.; Chuang, L.M.; Jeng, Y.M. *J. Endocrinol.,* **2003**, *178,* 457-465.

[4] Hadziyannis, S.; Karamanos, B. *Hepatology*, **1999**, *29(2),* 604-605.

[5] Lecube, A.; Hernàndez, C.; Genescà, J.; Esteban, J.I.; Jardì, R.; Simò, R. *Diabetes Care*, **2004**, *27,* 1171-1175.

[6] Simò, R.; Lecube, A.; Genescà, J.; Esteban, J.I.; Hernàndez, C. *Diabetes Care,* **2006**, *29,* 2462-2466.

[7] Lecube, A.; Hernàndez, C.; Genescà, J.; Simò, R. *Diabetes Care,* **2006**, *29,* 1096-1101.

[8] Shintani Y.; Fujie, H.; Miyoshi, H.; Tsutsumi, T.; Tsukamoto, K.; Kimura, S.; Moriya, K.; Koike, K. *Gastroenterology,* **2004**, *126,* 840-848.

[9] Perrella, A.; Borgia, G.; Reynaud, R.; Borrelli, F.; Di Sirio, S.; Grattacaso, S.; Perrella, O. *Gastroenterology,* **2004**, *127,*1279-1280.

[10] Knobler, H.; Schattner, *A. J. Med.,* **2005**, *98,* 1-6.

[11] Zekry, A.; Mc Hutchinson, J.G.; Diehl, A.M. *Gut,* **2005**, *54,* 903-906.

[12] Fartoux, L.; Poujol-Robert, A.; Guèchot, J.; Wendum, D.; Poupon, R.; Serfaty, L. *Gut,* **2005**, *54,* 1003-1008.

[13] Mello, V.; Cruz, T.; Nuñez, G.; Simões, M.T.; Ney-Oliveira, F.; Braga, H.; Araújo, C.; Cunha, S.; Schinoni, M.I.; Cruz, M.; Parana, R. *J. Med. Virol.,* **2006**, *78,* 1406-1410.

[14] D'Souza, R.; Sabini, C.A.; Foster, G.R. *Am. J. Gastroenterol.,* **2005**, *100,* 1-7.

[15] Tarantino, G.; Conca, P.; Sorrentino, P.; Ariello, M. *J. Gastroenterol. Hepatol.,* **2006**, *21,* 1266-8.

[16] Pazienza, V.; Clément, S.; Pugnale, P.; Conzelman, S.; Foti, M.; Mangia, A.; Negro, F. *Hepatology,* **2007**, *45,* 1164-1171.

[17] Walsh, M.J.; Jonsson, J.R.; Richardson, M.M.; Lipka, G.M.; Purdie, D.M.; Clouston, A.D.; Powell, E.E. *Gut,* **2006**, *55,* 529-535.

[18] Fattovich, G.; Giustina, G.; Favarato, S.; Ruol, A.; Investigators of the Italian Association for the Study of the Liver. *J. Hepatol.,* **1996**, *24,* 38-47.

[19] Uto, H.; Matsuoka, H.; Murata, M.; Okamoto, T.; Miyata, Y.; Hori, T.; Ido, A.; Hirono, S.; Hayashi, K.; Tsubouchi, H. *Diabetes Res. Clin. Pract.,* **2000**, *49,* 101-106.

[20] Soultati, A.S.; Dourakis, S.P.; Alexopoulou, A.; Deutsch, M.; Archimandritis, A.J. *World J. Gastroenterol.,* **2007**, *13,* 1292-1294.

[21] Devendra, D.; Eisenbarth, G.S. *Clin. Immunol.,* **2004**, *111,* 225-233.

[22] Tahrani, A.; Bowler, L.; Singh, P.; Coates, P. *Eur. J. Gastroenterol. Hepatol.,* **2006**, *18(3),* 291-293.

[23] Fabris, P.; Betterle, C.; Greggio, N.A.; Zanchetta, R.; Bosi, E.; Biasin, M.R.; de Lalla, F. *J. Hepatol.,* **1998**, *28,* 514-517.

[24] Wesche, B.; Jaeckel, E.; Trautwein, C.; Wedemeyer, H.; Falorni, A.; Frank, H.; von zur Mühlen, A.; Manns, M.P.; Brabant, G. *Gut,* **2001**, *48,* 378-383.

[25] Bosi, E.; Minelli, R.; Bazzigaluppi, E.; Salvi, M. *Diabetic Med.,* **2001**, *18,* 329-332.

[26] Betterle, C.; Fabris P, Zanchetta R, Pedini B, Tositti G, Bosi E, de Lalla F. *Diabetes Care,* **2000**, *23(8),* 1177-1181.

[27] Pellicano, R.; Smedile, A.; Peyre, S.; Astegiano, M.; Saracco, G.; Bonardi, R.; Rizzetto, M. *Minerva Gastroenterol e Dietol.,* **2005**, *51,* 55.

[28] Jabr, F.I.; Maria, M.D. *Am. J. Med.,* **2003**, *115,* 158-159.

[29] Tosone, G.; Borgia, G.; Gentile, I.; Cerini, R.; Conte, M.C.; Orlando, R.; Piazza, M. *Acta Diabetol.,* **2007**, *44,* 167-169.

[30] Cozzolongo, R.; Betterle, C.; Fabris, P.; Paola, A.M.; Lanzilotta, E.; Manghisi, O.G. *Eur. J. Gastroenterol. Hepatol.,* 2006, *18,* 689-92.

[31] Primo, V.J. *Gastroenterol. Hepatol.,* **2004**, *27,* 69.

[32] Romero-Gòmez, M.; Del Mar Viloria, M.; Andrade, R.J.; Salmerón, J.; Diago, M.; Fernández-Rodríguez, C.M.; Corpas, R.; Cruz, M.; Grande, L.; Vázquez, L.; Muñoz-De-Rueda, P.; López-Serrano, P.; Gila, A.; Gutiérrez, M.L.; Pérez, C.; Ruiz-Extremera, A.; Suárez, E.; Castillo, J. *Gastroenterology,* **2005**, *128,* 636-641.

[33] Konishi, I.; Horiike, N.; Hiasa, Y.; Tokumoto, Y.; Mashiba, T.; Michitaka, K.; Miyake, Y.; Nonaka, S.; Joukou, K.; Matsuura, B.; Onji, M. *Hepatol. Res.,* **2007**, *37,* 331-6.


Received: October 23, 2007 Revised: November 19, 2007 Accepted: November 23, 2007