

## WJD 5<sup>th</sup> Anniversary Special Issues (3): Type 1 diabetes

# Hepatitis C virus infection and type 1 and type 2 diabetes mellitus

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Received: November 29, 2013 Revised: April 10, 2014

Accepted: July 12, 2014

Published online: October 15, 2014

cytokines, chemokines, and other immune-mediated mechanisms. Few data have been reported on the association of CHC and T1DM and reports on the potential association between T1DM and acute HCV infection are even rarer. A small number of studies indicate that interferon- $\alpha$  therapy can stimulate pancreatic autoimmunity and in certain cases lead to the development of T1DM. Diabetes and CHC have important interactions. Diabetic CHC patients have an increased risk of developing cirrhosis and hepatocellular carcinoma compared with non-diabetic CHC subjects. However, clinical trials on HCV-positive patients have reported improvements in glucose metabolism after antiviral treatment. Further studies are needed to improve prevention policies and to foster adequate and cost-effective programmes for the surveillance and treatment of diabetic CHC patients.

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**Key words:** Hepatitis C virus infection; Type 1 diabetes mellitus; Type 2 diabetes mellitus; Epidemiology; Pathogenesis; Prevention; Treatment

## Abstract

Hepatitis C virus (HCV) infection and diabetes mellitus are two major public health problems that cause devastating health and financial burdens worldwide. Diabetes can be classified into two major types: type 1 diabetes mellitus (T1DM) and T2DM. T2DM is a common endocrine disorder that encompasses multifactorial mechanisms, and T1DM is an immunologically mediated disease. Many epidemiological studies have shown an association between T2DM and chronic hepatitis C (CHC) infection. The processes through which CHC is associated with T2DM seem to involve direct viral effects, insulin resistance, proinflammatory

**Core tip:** Many studies have shown an association between type 2 diabetes mellitus (T2DM) and chronic hepatitis C (CHC) infection. The processes through which CHC is associated with T2DM seem to involve direct viral effects, insulin resistance, proinflammatory cytokines, and chemokines. Few data have been reported on the association of CHC and T1DM. A small number of studies indicate that interferon- $\alpha$  therapy can induce T1DM. Diabetic CHC patients have an increased risk of developing cirrhosis and hepatocellular carcinoma compared with non-diabetics. Clinical trials on hepatitis C virus-positive patients have reported improvements in glucose metabolism after antiviral treatment.

Antonelli A, Ferrari SM, Giuggioli D, Di Domenicantonio A, Ruffilli I, Corrado A, Fabiani S, Marchi S, Ferri C, Ferrannini E, Fallahi P. Hepatitis C virus infection and type 1 and type 2 diabetes mellitus. *World J Diabetes* 2014; 5(5): 586-600 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v5/i5/586.htm> DOI: <http://dx.doi.org/10.4239/wjd.v5.i5.586>

## INTRODUCTION

Hepatitis C virus (HCV) infection and diabetes mellitus (DM) are two major public health problems that cause devastating health and financial burdens worldwide<sup>[1,2]</sup>. Diabetes can be classified into two major types: type 1 (T1DM) and T2DM<sup>[3,4]</sup>. T2DM is a common endocrine disorder that encompasses multifactorial mechanisms. These mechanisms include resistance to the action of insulin, increased hepatic glucose production, and a defect in insulin secretion, all of which contribute to the development of overt hyperglycaemia<sup>[5]</sup>. T1DM is an immunologically mediated disease. Prevention and treatment of T1DM are hampered by the fact that the key immunological mechanisms of the pathogenesis of the disease are still under debate<sup>[6,7]</sup>. However, a Th1 immune response is involved in  $\beta$ -cell destruction<sup>[8]</sup> and the importance of islet autoantibodies has been highlighted<sup>[9-11]</sup>.

Chronic hepatitis C (CHC) infection has a global prevalence of 2%-3%. Approximately 170 million people are thought to be currently infected (approximately 3% of the world's population), and an additional 3-4 million are infected each year<sup>[12,13]</sup>. HCV is the main reason for liver transplantation in the developed world and the main cause of liver-related morbidity and mortality in a number of countries, including Italy. This virus is not only a frequent cause of chronic liver diseases, including hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), but it is also involved in the pathogenesis of various autoimmune and rheumatic disorders (*e.g.*, arthritis, vasculitis, sicca syndrome, porphyria cutanea tarda, lichen planus, nephropathies, and lung fibrosis) and in the development of B-cell lymphoproliferative diseases<sup>[14,15]</sup>.

CHC is a multifaceted disorder that is associated with extrahepatic manifestations, including endocrinological disorders, thyroid disorders and diabetes<sup>[16,17]</sup>.

In this paper, we review the increasing evidence linking HCV infection and DM in multiple fields (epidemiology, pathogenesis, clinical aspects, prevention, and treatment).

## RELATIONSHIP BETWEEN CHC AND THE DEVELOPMENT OF T2DM

### *Origins of the hypothesis and epidemiological data in the general population*

The liver plays an important role in carbohydrate metabolism, and liver diseases such as chronic hepatitis and cirrhosis are associated with a higher prevalence of dis-

turbed glucose homeostasis, impaired glucose tolerance, and insulin resistance (IR)<sup>[18,19]</sup>, which can eventually lead to DM<sup>[20-23]</sup>. Asymptomatic, moderate serum aminotransferase elevation has frequently been found in patients with DM, particularly in those with T2DM<sup>[24,25]</sup>. This phenomenon has often been related to fatty infiltration of the liver without further investigation<sup>[26,27]</sup>. In particular, steatosis has been related to IR and T2DM, beyond intracellular fat accumulation<sup>[28]</sup>.

Liver fibrosis progression has also long been considered to be responsible for the development of IR and T2DM in patients with chronic liver diseases<sup>[29]</sup>. However, diabetes often occurs in the early stages of liver disease<sup>[30]</sup>.

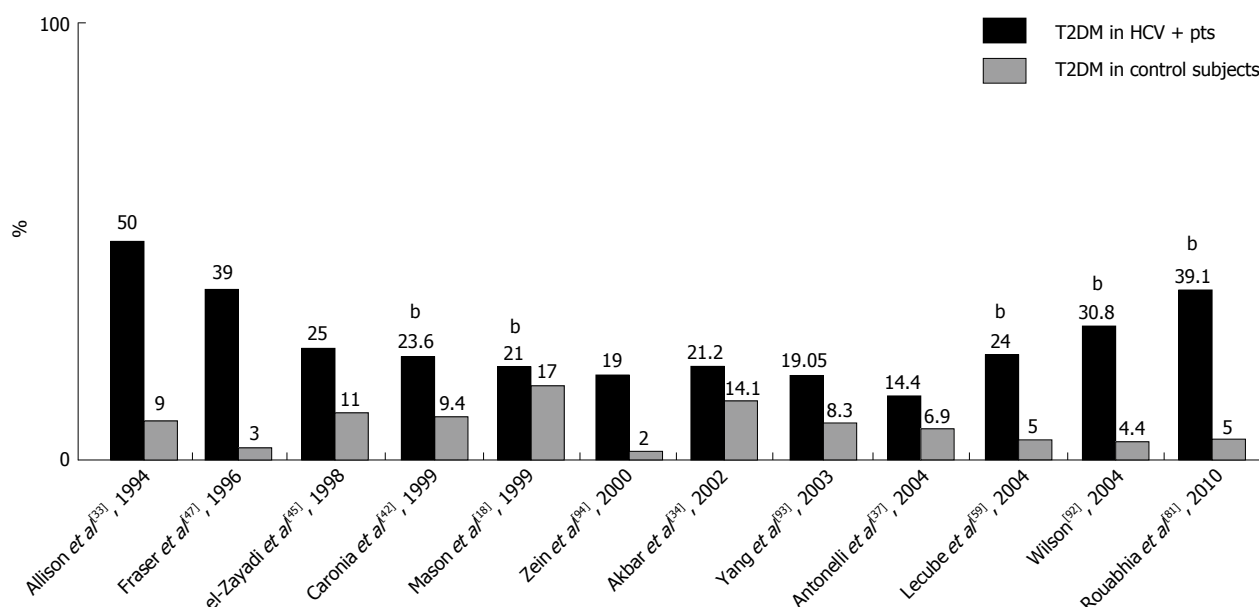
The aetiological factors that underlie the development of glucose homeostasis alterations were initially thought to be exclusively related to general long-term hepatocyte damage. However, later studies showed that patients with hepatitis B virus infection have a lower prevalence of T2DM compared with HCV-infected patients<sup>[31,32]</sup>. Thus, the question is as follows: "Does HCV infection itself have diabetogenic action?"

Since the discovery of HCV in 1989, attention has been paid to the association of CHC with the development of DM. Additionally from 1994<sup>[33]</sup> until now, several epidemiological studies on the seroprevalence of HCV have shown higher prevalences in diabetic patients than in controls (Figure 1). Moreover, analyses have shown a higher prevalence of DM in patients who are seropositive for HCV than in controls without HCV infection.

To analyse the epidemiological data, we searched for published studies in the PubMed database, covering the period from 1994 to December 2012. The literature search was performed using combinations of the terms "diabetes", "diabetes mellitus", "type 2 diabetes mellitus", "T2DM", "type 2 DM", "non-insulin dependent diabetes", or "NIDDM"; "hepatitis", "hepatitis C", "hepatitis C virus", "HCV", "HVC", or "chronic hepatitis"; and "risk", "risk factor", "case-control", "cohort", "clinical trial", "cross sectional", "epidemiology", "observational", "meta-analysis", "systematic review", or "review". For epidemiological studies, we only searched human studies and publications in English and Italian, the languages understood by the authors.

The data represent a very heterogeneous population regarding gender, age, and ethnic group. Globally, approximately seventy studies are in agreement with an association<sup>[18,26,30-96]</sup>, although not all of them have shown significant data. However, some of the non-significant data may be attributed to small sample sizes and other methodological factors (Figure 1).

Certain negative data that are not in agreement with an association between HCV infection and T2DM have also been reported<sup>[97-104]</sup>. However, the number of published epidemiological studies that are in agreement with the association between HCV infection and T2DM is higher than the number of studies in disagreement with this hypothesis.



**Figure 1** Patients seropositive for hepatitis C virus show a higher prevalence of diabetes mellitus than healthy controls. Twelve representative epidemiological studies demonstrated a relationship between HCV infection and the development of type 2 diabetes mellitus (T2DM). Analyses have shown a higher prevalence of diabetes mellitus in patients who are seropositive for HCV than in controls. <sup>b</sup> $P < 0.001$ , T2DM in HCV+ pts vs T2DM in control subjects. HCV+: Hepatitis C virus-infected; pts: Patients.

## HCV INFECTION AND T2DM ASSOCIATION: PATHOGENESIS

### Direct effects of HCV and IR

HCV is hepatotropic and noncytopathic; nevertheless, its genome has been identified in a number of tissues beyond the liver, including pancreatic acinar cells and epithelial cells of the pancreatic duct<sup>[105,106]</sup>. Although post-mortem studies have revealed that HCV replicates in the pancreas<sup>[107]</sup> and animal models have suggested a direct effect of HCV infection on IR in the liver<sup>[108]</sup>, the evidence is scanty.

Of interest are the roles of structural and non-structural HCV proteins. HCV has an RNA genome of 9.6 kb that encodes approximately 3010 amino acids and is translated into structural (core, E1, and E2) and non-structural (NS3-NS5B) proteins. These proteins play a role in the development of IR and oxidative stress *via* reactive oxygen species at the cellular level<sup>[109-113]</sup>. The HCV core protein, alone or in combination with other viral proteins, increases phosphorylation of insulin receptor substrate-1 (IRS-1), which is the basis of IR<sup>[114-116]</sup>. Phosphorylated IRS-1 activates phosphatidylinositol 3-kinase (PI3K)<sup>[117,118]</sup>, and the activation of PI3K and one of its downstream targets, Akt, is essential for most of the metabolic effects of insulin<sup>[119-126]</sup>. Therefore, defects at the level of the association of PI3K with IRS-1 and a lack of PI3K activation may contribute to IR and the increased prevalence of diabetes in HCV-infected patients. Indeed, this mechanism ultimately promotes glucose transporter-4 translocation to the plasma membrane to enhance glucose uptake<sup>[127,128]</sup>. Within the IR mechanism impairment of the activation of Akt/PKB is the key step that can inhibit glucose uptake<sup>[30,129,130]</sup>.

The detailed molecular events leading to IR in HCV-infected patients are, however, unclear. Recent evidence supports the existence of a significant extrahepatic component of HCV-induced IR. Thus, the molecular pathogenesis of the glucose metabolism disturbances observed in hepatitis C is much more complex than expected<sup>[131]</sup>.

Recently, Eslam *et al.*<sup>[132]</sup> showed that polymorphisms in the IFNL3 (IL28B) region are associated with spontaneous and treatment-induced recovery from HCV infection. Furthermore, circumstantial evidence suggests a link between single-nucleotide polymorphisms in IFNL3 and lipid metabolism, steatosis, and IR in CHC. The emerging picture suggests that the responder genotypes of IFNL3 polymorphisms are associated with higher serum lipid levels and less frequent steatosis and IR<sup>[132]</sup>.

### HCV-induced immune responses; cytokines, chemokines-mediated effects

Viral innate immune evasion strategies and human genetic determinants underlie the transition of acute HCV infection into viral persistence and chronic infection. Host genetic factors can influence both the outcome of the infection and the response to antiviral therapy. Recent insights into how HCV regulates immune signalling within the liver reveal a complex interaction of the patient's genetic background with viral and host factors related to the innate immune triggering and control that dictate the outcome of HCV infection and immunity<sup>[133]</sup>.

Beyond the direct effects of HCV on IRS-1/PI3K, the HCV core protein may induce IR indirectly *via* stimulation of the secretion of proinflammatory cytokines<sup>[115]</sup>. In patients with CHC, most likely due to HCV-induced inflammation, there is hypersecretion of insulin-resistant proinflammatory cytokines such as interleukin (IL)-6 and

tumour necrosis factor (TNF)- $\alpha$ <sup>[134-138]</sup>. Proinflammatory cytokines also upregulate suppressors of cytokine signalling proteins as part of a negative feedback loop to attenuate cytokine signalling<sup>[139,140]</sup>. This phenomenon may contribute to increased gluconeogenesis due to a lack of Akt-mediated inhibition of phosphoenolpyruvate carboxykinase gene expression. In this context, it is interesting to note that leptin can modulate the action of insulin in liver cells by antagonising insulin-stimulated IRS-1 tyrosine phosphorylation, increasing phosphoenolpyruvate carboxykinase gene expression, and decreasing glucokinase expression, which results in increased gluconeogenesis<sup>[141]</sup>. Together with the increase in gluconeogenesis, the enhanced production and accumulation of lipids mediated by inhibition of the AMP-activated protein kinase occur after HCV infection<sup>[142]</sup>. Additionally TNF- $\alpha$  plays a role in lipid metabolism. Indeed, the lipolysis-stimulating effect of TNF- $\alpha$  leads to increased serum levels of free fatty acids, which reduces insulin sensitivity<sup>[143,144]</sup>.

Cytokines are intercellular mediators involved in viral control and in the liver damage induced by infection with HCV. The complex cytokine network that operates during the initial infection allows the coordinated, effective development of both the innate and the adaptive immune responses. However, HCV interferes with cytokines at various levels and escapes the immune response by inducing a Th2/T cytotoxic 2 cytokine profile. The inability to control infection leads to the recruitment of inflammatory infiltrates into the liver parenchyma by interferon (IFN)- $\gamma$ -inducible CXC chemokine ligand (CXCL)9, CXCL10, and CXCL11, which result in sustained liver damage and eventually liver cirrhosis. The most important systemic HCV-related extrahepatic diseases (mixed cryoglobulinemia, lymphoproliferative disorders, thyroid autoimmune disorders, and T2DM) are associated with complex dysregulation of the cytokine/chemokine network, involving proinflammatory and Th1 chemokines<sup>[145,146]</sup>.

## HCV-INFECTED PATIENTS WITH T1DM

Few data on this association have been reported, and published studies have shown only small proportions of CHC patients positive for one or more markers of pancreatic autoimmunity<sup>[18,147-150]</sup>.

Even rarer are reports on the potential association between autoimmune diabetes and acute HCV infection. Only two cases have been described in the literature<sup>[151,152]</sup>. Several mechanisms have been postulated to initiate the process. Even if HCV can infect extrahepatic tissue in patients with hepatitis C<sup>[16,107,153]</sup>, no direct involvement of HCV in the onset of T1DM has been clarified yet. Nevertheless, the direct destruction of  $\beta$ -cells by viral infection could be a good explanation. Beyond the undemonstrated direct mechanisms, HCV infection surely initiates an immune reaction against  $\beta$ -cells or causes an acceleration of diabetes onset when an immune reaction against  $\beta$ -cells is already present. Some authors have also suggested the in-

volvement of a process of molecular mimicry as a trigger of HCV-related autoimmunity<sup>[154,155]</sup>. Indeed, glutamic acid decarboxylase (GAD) 65 shares amino acid sequence similarities with antigenic regions of the HCV polyprotein<sup>[156]</sup>. Of interest, HCV/self-homologous autoantigenic regions are also mimicked by other microbial agents. Such mimics may give rise to  $\beta$ -cell autoimmunity through a multiple-hit mechanism of molecular mimicry<sup>[154,155,157]</sup>. Cross-reactive immunity does not exclude the possible involvement of additional factors, such as proinflammatory cytokines, which may act in concert, leading to the development and/or maintenance of pancreatic autoimmunity during acute HCV infection<sup>[156]</sup>. Another possibility is the induction of antibody reactivity against GAD and the development of full-blown diabetes, mediated by IL-18 and other proinflammatory cytokines. In particular, IL-18 is presumed to play a pathogenetic role in T1DM, specifically because this cytokine appears to be involved in acceleration of the development of overt disease<sup>[152,158-160]</sup>. IL-18 can induce both Th1 and Th2 responses, depending on the surrounding cytokines<sup>[161]</sup>, and this cytokine plays a pathogenic role in several diseases<sup>[161]</sup>, including acute hepatic injury<sup>[162]</sup>. Other proinflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , which are elevated in patients with acute hepatitis<sup>[163]</sup>, can also induce autoimmune diabetes<sup>[164-167]</sup>.

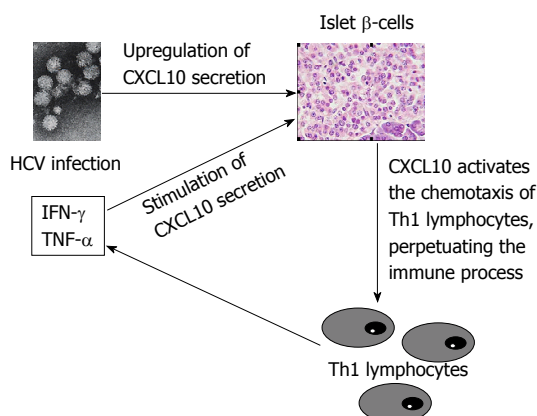
## OTHER IMMUNE ASPECTS OF HCV ASSOCIATED WITH T1DM OR T2DM

Immune aspects have been reported in both T1DM and T2DM, and based on the immunology, it is clear that the lines separating T1DM from latent autoimmune diabetes in adults (LADA) and T2DM are not well delineated<sup>[10,11,16,37,145,168-170]</sup>.

The type of diabetes manifested by patients with CHC is not classical T2DM, and the labelling of HCV patients as having T2DM is purely conventional and possibly inaccurate. The lines separating T1DM from LADA and T2DM are fading away as new pathogenetic information is obtained<sup>[170]</sup>.

Three studies have reported<sup>[37,38,171]</sup> that HCV patients with T2DM are leaner than T2DM controls and show significantly lower low-density lipoprotein-cholesterol levels and systolic and diastolic blood pressures. Furthermore, patients with HCV-associated mixed cryoglobulinaemia (MC + HCV) and T2DM had non-organ-specific autoantibodies more frequently (34% *vs* 18%, respectively) than did non-diabetic MC + HCV patients<sup>[37]</sup>. An immune-mediated mechanism for MC + HCV-associated diabetes has been postulated<sup>[37]</sup>, and a similar pathogenesis might be involved in diabetes in HCV patients. This hypothesis is strengthened by the finding that autoimmune phenomena are more common in T2DM patients than previously thought<sup>[10]</sup>. However, as the prevalence of classic  $\beta$ -cell autoimmune markers is not increased in HCV patients<sup>[70]</sup>, other immune phenomena might be involved<sup>[168]</sup>. Chemokines could be important in this context. In fact, in children with newly





**Figure 2** Potential regulation of the endocrine manifestations of hepatitis C virus infection in islet  $\beta$ -cells. Hepatitis C virus (HCV) infection may act by upregulating CXCL10 gene expression and the subsequent secretion of this chemokine by islet  $\beta$ -cells. These events lead to the recruitment of Th1 lymphocytes that secrete interferon (IFN)- $\gamma$  and tumour necrosis factor (TNF)- $\alpha$ , which induce chemokine secretion by islet  $\beta$ -cells, thus perpetuating the immune cascade. This cascade may lead to the appearance of autoimmune thyroid disorders in genetically predisposed subjects.

diagnosed T1DM, raised serum CXCL10 and normal chemokine (C-C motif) ligand 2 concentrations signal a predominantly Th1-driven autoimmune process, which shifts toward Th2 immunity 2 years after diagnosis<sup>[172]</sup>.

Based on the abovementioned concepts, HCV infection of  $\beta$ -cells<sup>[106]</sup> may act by upregulating CXCL10 gene expression and secretion (as previously shown in human hepatocytes<sup>[173]</sup>) and recruiting Th1 lymphocytes that secrete IFN- $\gamma$  and TNF- $\alpha$ , which induce CXCL10 secretion by  $\beta$ -cells and thus perpetuate the immune cascade. This cascade may lead to the appearance of  $\beta$ -cell dysfunction in genetically predisposed subjects (Figure 2). Recently, certain studies have confirmed this hypothesis, demonstrating higher serum levels of CXCL10 in HCV patients with T2DM than in those without<sup>[16,169]</sup>.

## T1DM AND T2DM IN HCV-INFECTED PATIENTS TREATED WITH IFN- $\alpha$

An important research area concerns the relationship between diabetes and IFN- $\alpha$  therapy in HCV-infected patients. In particular, studies have shown a high prevalence of markers of pancreatic autoimmunity in HCV-positive patients after or during IFN- $\alpha$  therapy, most likely due to the immunostimulatory effects of this cytokine. Indeed, IFN- $\alpha$  has antiviral, antiproliferative, and immunomodulatory activities<sup>[174]</sup>. Thus, in predisposed individuals, IFN- $\alpha$  can either induce a diabetogenic process or accelerate a diabetogenic process that is already underway<sup>[18,175,176]</sup>. For this reason, islet cell autoantibodies and GADAb should be investigated before and during IFN treatment to identify subjects who are at high risk of developing T1DM<sup>[177-180]</sup>. A small number of patients can develop *de novo* pancreatic autoimmunity and fall into a group of patients at risk of developing DM. In general, patients who are initially positive for organ-specific auto-

antibodies (in particular, thyroid- and pancreas-specific autoantibodies) and those who seroconvert seem to be at high risk of developing clinical autoimmune disease after treatment with IFN- $\alpha$ <sup>[181]</sup>. Timely suspension of IFN- $\alpha$  therapy is rarely accompanied by regression of clinical DM. No correlation has been documented between the response to antiviral therapy and the development of DM.

IFN- $\alpha$  increases HLA class I antigen expression and natural killer cell and T cell activities, and this cytokine may be an important cofactor in the development of a Th1 immune reaction. This reaction can contribute to the development of autoimmune disease by the activation of CD4+ lymphocytes that secrete IL-2, IFN- $\gamma$  and TNF- $\beta$ . These cytokines help in the generation of CD8+ cytotoxic T cells<sup>[182]</sup>. In addition to its immunomodulatory properties, IFN- $\alpha$  can also increase IR and induce hyperglycaemia<sup>[183-188]</sup>. Fabris *et al.*<sup>[189]</sup> documented the first case of T1DM development during IFN- $\alpha$  therapy. Other studies suggest that IFN- $\alpha$  therapy can stimulate pancreatic autoimmunity and, in certain cases, lead to the development of T1DM<sup>[150,175,177,180,181,190-223]</sup>.

The relationship with T1DM does not account for all of the effects of IFN- $\alpha$  therapy on diabetes. Indeed, from a completely different perspective, antiviral therapy with IFN should also be considered in HCV-positive patients because of its potential role in limiting the progression of this metabolic disturbance (see later discussion).

## OUTCOME IN DIABETIC HCV-POSITIVE PATIENTS

CHC is an insidiously progressive form of liver disease that leads to cirrhosis<sup>[224-226]</sup> and HCC<sup>[227-231]</sup>. Diabetic HCV-positive patients have increased risk compared with non-diabetic subjects, and DM itself seems to have a selective impact on HCC development<sup>[232-251]</sup>.

The main characteristic of diabetic patients is IR, which plays a crucial role in fibrosis progression and has a negative impact on treatment responses to antiviral therapy in patients with CHC<sup>[52,252,253]</sup>. Reduced insulin sensitivity is at the basis of compensatory hyperinsulinemia and elevated levels of insulin-like growth factor 1 (IGF-1), which stimulates cell proliferation and inhibits apoptosis. Additionally, this phenomenon has strong mitogenic effects on a wide variety of cancer cell lines<sup>[254-256]</sup>. At the same time, insulin activates the IGF-1 receptor, which has a growth-promoting effect that includes modulating cell cycle progression. Excess insulin may also indirectly affect the development of cancer by downregulating the level of IGF-binding protein 1, which increases the level and bioavailability of total circulating IGF-1. Additional factors, such as obesity and physical inactivity, also cause hyperinsulinemia and are thus also ultimately associated with accelerated cancer progression<sup>[255-258]</sup>.

Genotype differences in terms of liver disturbance progression have been described as well. Genotype 3a is more strongly correlated with steatosis than other

genotypes<sup>[259,260]</sup>, and the HCV genotype 3 may have a cytopathic effect<sup>[261]</sup>. Steatosis in genotype 1 infection is instead thought to be an expression of metabolic syndrome caused by the activation of proinflammatory mechanisms as well as underlying obesity and IR<sup>[262]</sup>. The degree of steatosis in this genotype is independent of the HCV viral load, and antiviral therapy does not improve steatosis in these patients. Similar data have been obtained for genotype 4 infection, whereas few data are available for genotype 2<sup>[263]</sup>.

The presence of HCV infection in patients with DM may also increase the proportion of DM-related chronic nephrologic complications<sup>[86,264]</sup>.

## PREVENTION AND TREATMENT

CHC is a complex disease with systemic effects that require a multidisciplinary treatment approach<sup>[265]</sup>.

The potential relationship between HCV infection and the development of DM increases the need for the implementation of prevention measures. Prevention must be directed toward lifestyle changes that can reduce the risk of HCV infection and/or diabetes development<sup>[266]</sup>; regular diabetes screening for anti-HCV-positive people; and the analysis of other risk factors that can accelerate the progression of both CHC and DM, such as obesity, dyslipidaemia, and alcohol consumption. In these high-risk patients, comprehensive treatment, including lifestyle modifications, must be recommended. Animal models also provide clues regarding the prevention and clinical management of diabetes in the setting of HCV infection<sup>[108]</sup>. Indeed, identifying patients who are at risk of developing diabetes, and have CHC, reduces liver disturbance progression<sup>[267,268]</sup>, the incidence of HCC and transplant-related morbidity and mortality. Additionally, this identification improves the response to antiviral therapy<sup>[269-271]</sup>, even reducing the side effects of the treatment<sup>[270]</sup> by encouraging the pretreatment of IR and DM<sup>[265]</sup>.

Moreover, clinical trials on HCV-positive patients have reported improvement in glucose metabolism after antiviral treatment<sup>[187]</sup>. As discussed earlier, many factors may surely affect the antiviral response that modulates the IFN signalling pathway. Among these factors, the HCV genotype, genetic host factors, and comorbidities have been taken into account. In particular, recent studies have reported obesity<sup>[272]</sup> and hypercholesterolaemia<sup>[273]</sup> as potential factors that interfere with a sustained viral response. These observations suggest additional therapeutic options for HCV infection, including dietary changes, anti-diabetic drugs, and statins. Concerning anti-diabetic drugs, it is not currently clear whether the best approach is to use a peroxisome proliferator-activated receptor agonist or a biguanide, such as metformin<sup>[274-276]</sup>. Concerning statins, these drugs are capable of inhibiting HCV replication *in vitro*<sup>[277-279]</sup> but not *in vivo*<sup>[280]</sup>.

Further studies are needed to improve prevention policies and to foster adequate and cost-effective pro-

grammes for the surveillance and treatment of diabetic CHC patients. The final goal must be to cure two diseases, diabetes and CHC, with one multifaceted treatment.

## CONCLUSION

Many epidemiological studies have shown an association between T2DM and CHC. The processes through which HCV is associated with DM seem to involve direct viral effects, IR, proinflammatory cytokines, chemokines, suppressors of cytokine signalling, and other immune-mediated mechanisms. Other factors, such as metabolic syndrome and a family history of diabetes, also seem to be important risk factors for the development of diabetes. Few data on the association of CHC and T1DM have been reported, and reports on the potential association between T1DM and acute HCV infection are even rarer. A small number of studies have indicated that IFN- $\alpha$  therapy can stimulate pancreatic autoimmunity and, in certain cases, lead to the development of T1DM. Diabetes and CHC have important interactions. Diabetic CHC patients have an increased risk of developing cirrhosis and HCC compared with non-diabetic CHC subjects. Additionally, clinical trials on HCV-positive patients have reported improvement in glucose metabolism after antiviral treatment. Further studies are needed to improve prevention policies and to foster adequate and cost-effective programmes for the surveillance and treatment of diabetic CHC patients.

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