

REVIEW

Current level of evidence on causal association between hepatitis C virus and type 2 diabetes: A review



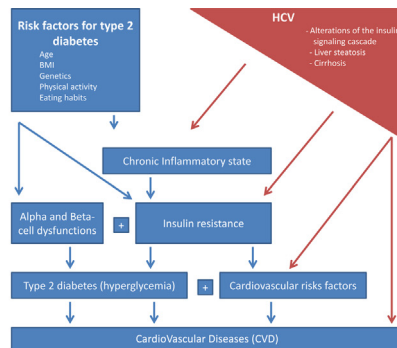
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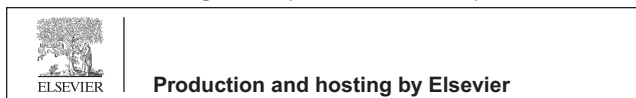
GRAPHICAL ABSTRACT



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ABSTRACT

The association between hepatitis C virus (HCV) infection and type 2 diabetes (T2D) has been known for over 20 years. Cross-sectional and longitudinal studies have shown a higher prevalence and incidence, respectively, of T2D in patients with chronic HCV infection. HCV induces glucose metabolism alterations mostly interfering with the insulin signaling chain in hepatocytes, although extrahepatic mechanisms seem to contribute. Both IR and T2D accelerate the histological and clinical progression of chronic hepatitis C as well as the risk of extra-hepatic complications such as nephropathy, acute coronary events and ischemic stroke. Before the availability of direct-acting antivirals (DAAs), the therapeutic choice was limited to interferon (IFN)-based therapy, which reduced the incidence of the extra-hepatic manifestations but was burdened with several contraindications and poor tolerability. A better understanding of HCV-associated glucose metabolism derangements and their reversibility is expected with the use of DAAs.

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Giacomo Gastaldi is a consultant in the diabetology, endocrinology, hypertension and nutrition division at the Department of Specialty Medicine of the University Hospital of Geneva, Switzerland. He is clinical lead for the use of technology in diabetes, lecturer for undergraduate medical and pharmaceutical students and an active teacher at the HES-SO in Geneva for the bachelor in nutrition. He is a committee member of the Swiss Society for Endocrinology and Diabetology. After qualifying with a degree in Medical Sciences at

Geneva University in 2001, Dr Gastaldi undertook his clinical training in internal medicine and a certificate in psychosomatic and psychosocial medicine. He obtained his MD at the Geneva Faculty of Medicine in 2009 for his work on the molecular factors that control thermogenesis and their role on insulin resistance after bariatric surgery. Shortly afterward he joined the Department of Endocrinology and Diabetology at the University Hospital of Lapeyronie in Montpellier, France, for a two year fellowship. He gained scientific experience on the metabolic consequences of dysfunctional eating patterns in mice and humans as well as skills in diabetes technology. Since 2011 he is board-certified in endocrinology and diabetology. He is now pursuing his scientific work on the influence of induced thermogenesis on glycemic control and metabolism with a specific target on human insulin resistance.



Dr. Nicolas Goossens is currently a fellow in the Division of Gastroenterology and Hepatology at the Geneva University Hospital under Professor Jean-Louis Frossard. Dr Goossens earned his medical degree in 2005 from Geneva University. After training in Geneva and at the Liver Unit at the King's College Hospital in London, UK, he received his FMH specialty title in Gastroenterology in 2013 and his subspecialty title in Hepatology in 2014. From 2014 to 2016 he did a research

fellowship in the Liver Division of the Mount Sinai School of Medicine under Professors Scott Friedman and Yujin Hoshida. Dr Goossens earned his MSc in Clinical Evidence-Based Healthcare from Oxford University. His research interests have focused on the genomic aspects, prediction and prognosis of liver disease, in particular NAFLD/NASH and hepatocellular carcinoma. Dr Goossens has authored or co-authored more than 20 peer-reviewed manuscripts and reviews in the field of hepatology and gastrointestinal disease.



Dr. Sophie Clément is working at the Division of Clinical Pathology of the University Hospitals of Geneva, Switzerland. In 2005, she joined the Viro-pathology Unit, headed by Professor Francesco Negro, in the capacity of senior scientist in charge of supervising the different research projects of the laboratory. Dr Clément has obtained her PhD degree in Human Sciences from the University Claude Bernard in Lyon, France, in 1995. After a 2-year post-doctoral training at Northwestern

University of Chicago, she joined the laboratory directed by Professor Giulio Gabbiani at the Faculty of Medicine, University of Geneva, mainly focusing her interest on myofibroblast differentiation and fibrosis. Since she joined the laboratory of Professor Negro, she is involved in projects focusing on the metabolic disorders associated with HCV infection, and more specifically on the mechanisms leading to insulin resistance and steatosis. She has published 25 peer-reviewed journal articles in the hepatology and hepatitis field as either first author or co-author.



Francesco Negro is Professor at the Departments of Specialty Medicine and of Pathology and Immunology of the University of Geneva, Switzerland. He is also Founder and Chairman of the Swiss Hepatitis C Cohort Study, and Educational Councilor of the European Association for the Study of the Liver. Professor Negro earned his medical degree in 1982 and was board-certified in Gastroenterology in 1986 at the University of Torino, Italy. He undertook post-doctoral training at the Division of Molecular Virology and

Immunology, Georgetown University, USA, and at the Hepatitis Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA, between 1986 and 1989. Professor Negro analyzed hepatitis C virus (HCV) replication at the tissue level using several distinct approaches, establishing anatomic-clinical correlations. His studies led him to associate HCV genotype 3a with a particular form of severe liver steatosis, and to analyze the mechanisms thereof. More recently, Professor Negro's work has focused on the pathogenesis of extrahepatic manifestations associated with HCV, and, particularly, on the mechanisms leading to glucose metabolism alterations, such as insulin resistance and diabetes, and on the epidemiology of HCV. He has participated in several clinical trials in acute and chronic HCV and has authored or co-authored more than 270 peer-reviewed manuscripts in the field of hepatology.

Introduction

Diabetes is one of the most prevalent non-communicable diseases throughout the world, affecting 415 million people in 2015 [1], and one in two patients does not know to suffer from diabetes. The condition is characterized by significant morbidity and mortality with a vast majority of people dying of cardiovascular complications [2].

Hepatitis C virus (HCV) infection is widespread, affecting up to 185 million people worldwide. Most patients are unaware of their infection [3] but at increased risk of liver cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality [4]. People suffering from HCV infection are also at increased risk of extrahepatic manifestations, and may develop T2D and cardiovascular complications such as nephropathy, acute coronary events and ischemic stroke, whose incidence can be reduced by antiviral treatment [5].

The scope of this review is to discuss the current level of evidence in favor of a causal association between HCV and T2D, its clinical impact, and directions for management.

Epidemiology

The epidemic of T2D is still growing particularly in developing countries with the worldwide rise in obesity. One of the epicenter of the epidemic is Asia's large population which tends to develop diabetes at younger age and lower BMI. In Western countries the trend is stable and the aging of the population is the main risk factor for diabetes. Chronic HCV is associated with hepatic and peripheral insulin resistance (IR) and the excess diabetes risk in HCV-infected persons is hotly debated. The epidemiological and clinical interactions between HCV and insulin resistance (IR) are complex and multi-layered and have consequences for the progression of HCV, but also the response to therapy and the development of complications. Below we will detail the different facets of the epidemiological and clinical interactions between HCV and IR.

Epidemiological evidence linking HCV to IR

The prevalence of IR or type 2 diabetes (T2D) in patients infected with HCV has been shown to be high. A study assessing an outpatient clinic of a university hospital estimated that more than 30% of HCV subjects had glucose abnormalities [6]. A twofold higher prevalence has even been reported in a Taiwanese cohort when T2D was diagnosed with the use of a 75 g oral glucose tolerance test (OGTT) [7]. However, there are conflicting results, many studies focusing on the association between HCV and IR had other primary objectives when they were planned and the quality of the evidence is sometimes unsatisfactory, especially in the context of retrospective trials (Table 1).

To address whether HCV infection was associated with IR, a systematic review, combining data from 34 studies and covering more than 300,000 patients, found a pooled adjusted odds ratio (OR) for T2D in HCV-infected persons of approximately 1.7 [8]. This was later confirmed by another systematic review including 35 observational studies with a pooled OR of 1.7 for T2D in HCV subjects compared to uninfected controls and a pooled OR of 1.9 when comparing to hepatitis B virus

(HBV)-infected controls [9]. In the setting of the Third National Health and Nutrition Examination Survey (NHANES-III), out of 9841 subjects evaluated, in which 8.4% had T2D and 2.1% were anti-HCV-positive, the adjusted OR for T2D in subjects older than 40 years was 3.8 compared to those without HCV infection [10]. A large prospective case-cohort analysis of 1084 adults suggested that HCV increases the risk of diabetes especially in HCV patients who are *a priori* already at high risk of developing diabetes, i.e. because affected by severe obesity or older than 65: these persons, during FU, were 11 times more likely to develop diabetes than HCV-negative individuals [11]. A recent community-based prospective study from Taiwan showed an increased risk of developing diabetes for HCV-seropositive vs. HCV-seronegative individuals (hazard ratio 1.53, 95% confidence interval [CI] 1.29–1.81), and this is independently of age and BMI [12]. Although the overwhelming majority of evidence pleads in favor of an association between T2D and HCV, some studies have reported diverging conclusions. For instance, Mangia et al. were the first to disprove the association with a prospective study comparing the occurrence of T2D in 247 cirrhotic patients (63.5% HCV positive), 138 patients with chronic hepatitis (73.8% HCV positive) and 494 patients with an acute trauma. The multi-varied analysis found only age and cirrhosis to be associated with T2D but the control groups who were matched for gender and age but not for BMI and T2D diagnosed relied only on fasting plasma glycemia [13]. A recent cross-sectional study from the NHANES database, including 15,128 adult participants of whom 1.7% were anti-HCV positive (but only 1.1% viremic) and 10.5% were diabetic, failed to find an association between HCV and diabetes or IR (assessed by the homeostasis model assessment – HOMA-IR) [14]. The explanation for this discrepancy with the previous literature is unclear, although important limitations of the latter study include a lack of power due to the low number of HCV viremic patients, a significant proportion of sampled patients were not examined and the absence of a confirmatory OGTT.

Virological response on IR

The effect of sustained virological response (SVR) on various clinical outcomes provides another line of evidence linking HCV infection with IR [15]. SVR is associated with a reduction in HCC incidence, liver-related mortality and overall mortality [16]. A number of clinical trials concurred to demonstrate that SVR was associated also with improved IR. For instance, a longitudinal analysis of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial found that SVR was associated with an improvement in IR as measured by HOMA2-IR [17] and another study based on the Milan Safety Tolerability study cohort found a reduction of *de novo* IR development in SVR patients compared to non-SVR patients although the mean baseline and post-treatment HOMA values were similar in SVR patients [18]. Although there was no significant difference in glucose abnormalities incidence in SVR subjects enrolled in another trial of 202 patients treated for HCV in Italy [19], a recent study from Taiwan showed a reduction of diabetic complications, including renal and cardiovascular complications, after antiviral treatment [20]. Although most of these studies were performed in patients undergoing interferon (IFN)-based ther-

Table 1 Epidemiological evidences on causal association between HCV infection and Type 2 Diabetes.

Author	Date	Country	Type of study	Methods	Diagnostic test for diabetes	N patients with HCV (characteristics)	N group of comparison (characteristics)	Results	Result	Conclusions	Bias
Allison et al. [77]	1994	Taiwan	P	Case-cohort analysis from 1991 to 2001	FPG	21,559	1917 with T2D	1.53 (95% CI: 1.29–1.81)	Positive	There is an increased risk of T2D in patients with HCV	Diagnostic of T2D is registry based
Fraser et al. [78]	1996	Israel	R	Cross-sectional study	FPG	128	40 HBV+		Positive	HCV infection and age were significant and independent predictors for developing diabetes	The HCV+ group had a higher mean age and cirrhosis was more frequent in the HCV+ group
Grimbert et al. [79]	1996	France	R	Cross-sectional study (age gender and cirrhosis-matched)	FPG	152	152 hospitalized with HBV, alcohol induced liver disease	T2D in 24% of patients with HCV and 9% in the control group	Positive	T2D is more prevalent in patients with chronic hepatitis C than in patients with other liver diseases. T2D occurs in the absence of family history and obesity in the HCV group.	Inclusion bias (hospitalized patients)
Mangia et al. [13]	1998	USA	P	Prospective cross-sectional study (age and gender-matched)	FPG	147/385 non-cirrhotic hospitalized patients	(1) 138 chronic hepatitis (HCV/HBV/alcohol abuse) (2) 494 patients hospitalized for acute osteoarticular trauma		Negative	The prevalence of T2D was not different among patients with HCV, HBV infection, or alcohol abuse. At multivariate analysis cirrhosis and age were the only two factors independently associated with T2D	BMI is significantly higher in the control group, the absence of a confirmatory OGTT
el-Zayadi et al. [80]	1998	Egypt	R	Cross-sectional study	FPG	591/150 with T2D	223 HCV–/25 with T2D		Positive	Chronic hepatitis C patients in Egypt is three times more likely to develop T2D than HCV seronegative patients	Inclusion bias
Caronia et al. [81]	1999	Italy	R/P	Cross-sectional study and prospective OGTT in patients with chronic HCV or HBV confirmed by biopsy	FPG, OGTT	1151(retrospective); 197 (prospective)	181 HBV+ (retrospective) 38 HBV+ (prospective)	R: 2.78 (95% CI:1.6–4.79); P: T2D in 24.4% of HCV+ patients and 7.9% in patients with HBV related cirrhosis	Positive	The study confirms an association between HCV and T2D.	Inclusion bias (BMI and hereditary for T2D not considered). T2D is associated with the occurrence of cirrhosis
Knobler et al. [82]	2000	Israel	C-C	Case-control study (age, sex, BMI and origin-matched)	FPG	45 consecutive eligible patients without cirrhosis	90 controls with no liver disease	33% T2D in HCV group and 5.6% T2D in the control group	Positive	Patients with chronic HCV infection have an increased prevalence of type 2 diabetes independently of cirrhosis.	Size of control group
Zein et al. [83]	2000	USA	R	Cross-sectional study (patients with cirrhosis who underwent liver transplantation were compared to a general population)	FPG	73 HCV+ 78 cholestatic disease 53 alcoholic disease	General population	Before transplantation T2D in 16/64 (25%) with HCV alone T2D in 1/78 (1.3%)with cholestatic liver disease T2D in 10/ 53 (19%) with alcoholic liver disease	Positive	The risk of diabetes is increased in patients with liver cirrhosis due to hepatitis C or alcoholic liver disease	Inclusion bias
Mehta et al. [10]	2000	USA	P	Cohort study	FPG, HbA1c, MH	9841	General population in the USA	2.48 (95% CI 1.23–5.01)	Positive	Persistent HCV infection is associated with the subsequent development of T2D	No difference in the prevalence of T2D in persons with HCV antibody but not RNA.
Ryu et al. [84]	2001	Korea	P	Cross-sectional study (age, sex, BMI, cirrhosis, alcohol consumption-matched)	FPG	404	627 T2D	24% T2D in HCV group and 10.4% T2D in HBV group	Positive	Patients with chronic HCV infection have an increased prevalence of type 2 diabetes in Korean patients. Age and alcohol consumption are another risk factor for T2D in such patients.	The absence of a confirmatory oral glucose tolerance test
Mehta et al. [85]	2003	USA	P	Case-cohort analysis	FPG, MH	1048 adults free of T2D	548 developed T2D over 9 years of follow-up	11.58 (95% CI 1.39–96.6)	Positive	Pre-existing HCV infection may increase the risk for T2D in persons with recognized diabetes risk factors.	The absence of a confirmatory oral glucose tolerance test
Arao et al. [86]	2003	Japan	R	Cross-sectional study/case control study to determine the seroprevalence of HCV infection in a cohort of 459 diabetics	FPG, MH	707	159 HBV+	20.9% T2D in HCV group 11.9% T2D in HBV group Case-control: 10.5% HCV+ and 1.1% HBV+ in T2D cohort	In favor	Male sex and cirrhosis were the major independent variable associated with T2D	Male sex and cirrhosis were the major independent variable associated with T2D
Antonelli et al. [87]	2005	Italy	C-C	Case-control study (population-based age-matched control group)	FPG, MH	564 non cirrhotic	302 individuals screened for thyroid disorders (exclusion criteria: history of alcohol abuse, drug addiction, or positivity for markers of viral hepatitis)	The RR for type 2 diabetes in NC-HCV+ patients was 1.81 (95% CI 1.15–2.89) versus control subject and 2.71 (1.08–7.07) versus NC-HBV+ patients	Positive	There is an association of T2D with HCV-related hepatitis. HCV+ T2D patients have a different clinical phenotype (lower BMI, no hereditary factors)	
Papatheodoridis et al. [88]	2006	Greece	R	Cross-sectional study (controlled for HCV genotype, ethnicity, severity of liver disease and fibrosis)	FPG, MH	260	174 HBV+	14% T2D in HCV group; 13% T2D in HBV group	Negative	T2D is strongly associated with more severe liver fibrosis.	Severity of liver disease

Table 1 (continued)

Author	Date	Country	Type of study	Methods	Diagnostic test for diabetes	N patients with HCV (characteristics)	N group of comparison (characteristics)	Results	Result	Conclusions	Bias
Lecube et al. [6]	2006	Spain	C-C	Case-control study	HOMA, OGTT	28	14 HCV-		In favor	Insulin resistance mediated by proinflammatory cytokines, but not a deficit in insulin secretion is the primary pathogenic mechanism involved in the development of diabetes associated with HCV infection	Size of the 2 groups
Simo et al. [89]	2006	Spain	P	Longitudinal (cumulative incidence of glucose abnormalities in HCV treated patients)	FPG, IGT	234/610 screened but excluded due to the presence of T2D or diabetogenic factors	96 SVR; 138 no SVR	0.48 (95% CI:0.24-0.98)	Positive	The incidence of glucose abnormalities are independently related to HCV SVR, baseline triglycerides and γ -GT	
White et al. [8]	2008		M	Meta-analysis (prospective and retrospective studies)		34 studies		R: 1.68 (95% CI 1.15-2.20) and P: 1.67 (95% CI 1.28-2.06)	Positive	Excess T2D risk with HCV infection in comparison to non-infected controls is consistent in both prospective and retrospective studies	Heterogeneity of the studies
Huang et al. [7]	2008	Taiwan	P	Prospective OGTT	FPG, OGTT	683	515 controls age and sex matched	27.7% Normoglycemia, 34.6% IGT and 37.8% T2D in 683 patients with HCV;	Positive	There is a 3.5-fold increase in glucose abnormalities in HCV + patients in comparison with controls when OGTT is used as a screening test	HbA1c was not measured
Jadoon et al. [90]	2010	Pakistan	R	Cross-sectional study	FPG	3000 T2D (13.7% HCV +)	10,000 blood donors (4.9% HCV +)	3.03 (95% CI: 2.64-3.48)	Positive	There is a higher prevalence of HCV infection in patients with T2D	Inclusion bias
Elhawary et al. [91]	2011	Egypt	C-C	Case-control study	FPG	289	289 healthy controls	13.84% T2D in HCV group and 4.15% T2D in healthy controls	Positive	The diabetic patients in the HCV group were older, more likely to have a history of alcohol drinking than the non diabetic HCV cases	Inclusion bias
Soverini et al. [92]	2011	Italy	R	Cross-sectional design (consecutive patients in three Italian centers)	FPG	859 with T2D	(14 HBV + /51 HCV +)		Negative	The prevalence of HBV and HCV is non-negligible in patients with T2DM and such cases may long remain undiagnosed	
Naing et al. [9]	2012		M	Meta-analysis		35 studies		7.39 (95% CI: 3.82-9.38)	Positive	Among HCV-infected patients male patients with age over 40 years had an increased frequency of type 2 diabetes	Heterogeneity of the studies
Memon et al. [93]	2013	Pakistan	P	Case series (period of 4 months in 2009)	FPG	361/120 with T2D (31.5%)		2.01 (95% CI:1.15, 3.43)	Positive	Advancing age, increased weight, and HCV genotype 3 are independent predictors of type 2 diabetes in HCV seropositive patients, and there is a statistically significant association of cirrhosis observed with type 2 diabetes mellitus	The absence of a confirmatory oral glucose tolerance test. Cirrhosis can be a confounding factor
Ruhl et al. [14]	2014	USA	P	Prospective cohort	FPG, HbA1c	15,128 with diabetes status and HCV antibody or HCV-RNA	General population in the USA		Negative	In the U.S. population, HCV was not associated with diabetes or with IR among persons with normal glucose	Low number of HCV viremic patients, a significant proportion of sampled patients were not examined and the absence of a confirmatory oral glucose tolerance test
Lin et al. [12]	2016	Taiwan	P	Case-cohort analysis from 1991 to 2010	FPG	21,559	1917 with T2D	10.9% T2D in the anti-HCV seronegative group and 16.7% T2D in the anti-HCV seropositive group	Positive	Chronic HCV infection was associated with an increased risk for diabetes after adjustment for other risk predictors	Insurance registry database

The types of studies were classified in 4 categories: prospective (P), Retrospective (R), Case-control (C-C) and Meta-analysis (M). The diagnostic tests for T2D are fasting plasma glucose (FPG), Oral glucose tolerance test with 75 g (OGTT), Glycated Hemoglobin (HbA1c), and medical or drug history (MH). N is the number of patients with HCV screened and included and the number of patients included in the control group. All the positive results are statistically significant ($P < 0.05$). Abbreviations: no sustained viral response (no SVR) and sustained viral response (SV), Type 2 Diabetes (T2D), Hepatitis C virus (HCV), Hepatitis B virus (HBV).

apy, recent preliminary reports suggests that direct-acting antiviral (DAA) agents are associated with similar improvement of IR after 12 weeks of treatment [21] and the persistency of a lower fasting glucose levels at 24 weeks from the end of DAA [22].

Therefore, epidemiological evidence linking HCV to IR, is rather compelling, although the association seems strongest in at-risk individuals with additional risk factors such as older age and higher BMI.

T2D and HCV a two-way association [23]

Interestingly, a recent systematic review has also shown a significant association between the presence of T2D and the risk of HCV infection [24]. The review showed that patients with T2D were at an increased risk of acquiring HCV infection compared to non-T2D subjects (pooled OR = 3.50). Although the mechanism underlying this finding could not be identified in this study, the increased risk is likely to be due to the repeated, invasive medical procedures that T2D patients usually undergo, exposing them to blood borne infections if universal precautions are not strictly followed.

Clinical consequences of IR/T2D in HCV

Hepatic fibrosis and cirrhosis

Not only is there a strong epidemiological association between HCV and IR and/or diabetes but IR is strongly associated with worse outcomes and increased fibrosis progression in HCV subjects. Type 2 diabetes and IR were independent predictors of liver-related mortality in a NHANES-III study including 264 chronic HCV subjects [25,26]. IR was shown to be an independent factor associated with fibrosis progression in HCV subjects ($P = 0.03$) and was associated with the stage of fibrosis ($P < 0.001$) [27]. IR is also associated with outcomes in cirrhotic HCV subjects as shown by a study conducted on 348 cirrhotic HCV patients that identified baseline diabetes as independently associated with survival and complications of cirrhosis, including bacterial infections and HCC ($P = 0.016$) [28]. This finding was confirmed in a Taiwanese study including 6251 HCV subjects where incident diabetes was a risk factor for cirrhosis and decompensated cirrhosis despite adjusting for a wide range of other factors [29]. Interestingly, DNA polymorphisms in the patatin-like phospholipase domain-containing 3 (*PNPLA3*) gene were the strongest predictor for advanced fibrosis in diabetic subjects although the association was much weaker in non-diabetic subjects, suggesting again a potentiation of constitutional risk factors by IR and diabetes [30]. In addition to liver-related outcomes, a systematic review of 22 observational studies confirmed that HCV was associated with increased cardiovascular diseases, especially in subgroups of patients with diabetes and arterial hypertension [31].

Hepatocellular carcinoma (HCC)

In addition to fibrosis progression and cirrhosis decompensation, diabetes is also associated with an increased risk of HCC development. An association between T2D and HCC across all aetiologies of liver disease had already been shown in previous systematic reviews by pooling case-control or cohort studies (pooled risk ratio, 2.5; 95% confidence interval, 1.9–3.2) [32]. A more recent systematic review assessing the

risk of HCC specifically in HCV subjects found that T2D was associated with an increased risk of HCC in this population of patients [33]. Interestingly, steatosis, strongly associated with HCV, the metabolic syndrome and IR, was also associated with the development of HCC. The association of IR and HCC in HCV subjects was confirmed in a retrospective study from Japan including 4302 HCV positive patients with a mean follow-up of 8.1 years that identified T2D as an independent risk factor for the development of HCC, whereas the risk for HCC was reduced when mean Hemoglobin A1c level was below 7.0%, suggesting that improved control of diabetes may reduce HCC risk in these patients [34]. Thus, T2D and HCV appear to act synergistically as risk factors for HCC.

Zheng et al. have also reported a worse graft outcome in HCV-positive recipients with liver grafts from donors with diabetes. The reason of such association is still debated but could be related to pre-existing graft steatosis and fibrosis induced by IR and the occurrence of post-transplantation fibrosis secondary to the HCV-recurrence [35].

SVR has been shown to significantly reduce the incidence of HCC in subjects treated with IFN-based regimens [36]. However, it has been recently shown that HCC risk somehow persists after IFN-based SVR (annual risk of 0.33% in a Veterans' population): here, diabetes was significantly associated with post-SVR HCC, along with presence of cirrhosis, age and HCV genotype 3 [37]. In addition, recent data in 399 SVR subjects followed-up for a median of 7.8 years have shown that diabetes and cirrhosis are risk factors for HCC development despite SVR [38] and another study has shown that even in patients with early fibrosis stages (F0-F2) a pre-treatment diabetes (or even impaired glucose tolerance) is associated with HCC development after SVR (HR 3.8, 95% CI 1.4–10.1), suggesting that antiviral therapy should be initiated early, i.e. before glucose metabolic alterations occur [39].

The effect of IR on efficacy of antiviral therapy

In the era of interferon (IFN)-based therapy, IR seemed associated with lower SVR rates, regardless of viral genotype [40,41]. Two separate systematic reviews recently addressed this question and found similar results. For instance, when pooling 14 studies involving more than 2700 subjects, HCV subjects with IR had a reduction in SVR rates of 20% compared to HCV subjects without IR and baseline HOMA-IR was strongly associated with response to IFN-based therapy [42]. Nevertheless, attempts to improve IR during IFN-based therapy using antidiabetic drugs have not demonstrated a clear improvement in SVR in the context of pioglitazone therapy [43] or metformin therapy [44]. Interestingly, statin therapy was associated with improved SVR among diabetic subjects receiving IFN-based therapy whereas insulin-dependent diabetic subjects achieved lower SVR rates underlining again the association between IR severity and outcomes in HCV [45].

Although long-term data are lacking, in contrast to the effect on IFN- α based therapy, baseline IR does not seem to affect the outcomes of DAA-based therapy. HOMA-IR scores had no effect on virological response to telaprevir-based regimens [26,46], danoprevir monotherapy [47] or the sofosbuvir/simeprevir combination [48]. These findings suggest that the prognostic relevance of IR and diabetes in HCV therapy outcome is much reduced compared to IFN-based regimens.

Factors involved in the occurrence of insulin resistance (IR)

T2D is the result of IR and pancreatic dysfunction. The latter is not limited to pancreatic beta cells dysfunction but includes also alpha cell dysregulation. The earliest defect is IR [49]. The factor the most associated with IR is visceral fat, even though the metabolic changes related to overweight and fat disposal remain unexplained. Abbasi et al. have shown that only a quarter of the variance of IR is explained by BMI [50]. Lean individuals may be as insulin resistant as obese patients with T2D and in such cases the only clue for the clinician is fasting hyperinsulinemia [51]. The common risk factors for T2D are age, family history, BMI, sedentarity, smoking habits and the occurrence of cirrhosis.

Obesity, visceral fat and ectopic lipids in skeletal muscles are associated with peripheral and hepatic IR. The mechanisms are mediated through circulating free fatty acids and include generation of lipid metabolites (diacylglycerol), pro-inflammatory cytokines (tumor necrosis factor alpha [TNF α], interleukin (IL)-1beta, IL-6, monocyte-chemoattractant-protein-1 [MCP-1]) and the production of reactive oxygen species [52]. The consequences of the altered adipose tissue metabolism are that in turn it affects skeletal muscle glucose homeostasis and induces both peripheral IR [53,54] and hepatic IR.

More recently, dysfunctions in the amino acid metabolism have also been associated with impaired insulin sensitivity and increased risk for future diabetes. Wang et al. have

found that in a fasting routine examination a panel of amino acids predicted the future development of diabetes in otherwise healthy, normoglycemic individuals and that in obese individuals three amino acids predict future diabetes with a 5-fold higher risk [55]. Other studies have shown in normoglycemic women that an increase in serum branched-chain amino acid concentrations is linked to IR, independently of obesity. The postulated mechanisms could be a downregulation of genes involved in mitochondrial energy metabolism and an increased expression of adipose tissue inflammatory genes [56] even though the branched-chain amino acids have also a direct action on stimulating insulin secretion and potentially participation in early pancreatic beta cell exhaustion.

In individual at high risk of diabetes (impaired fasting or impaired glucose tolerance) lifestyle intervention can reduce the risk of developing diabetes as shown in the Da Qing study or in the Finnish Diabetes Prevention Study [57,58]. All the interventions were characterized by modest weight loss, improved glycemic control and a reduction in the need for antidiabetic treatment. The supposed mechanism is a reduction of IR associated with preserved insulin secretory capacity due to limited beta cell dysfunction. The improvements observed in glycemia are therefore most likely to occur early in the natural history of diabetes.

Because HCV infection occurs frequently in normoglycemic individuals with unknown degrees of IR and distinct risk factor for T2D, the individual risk is difficult to establish. More-

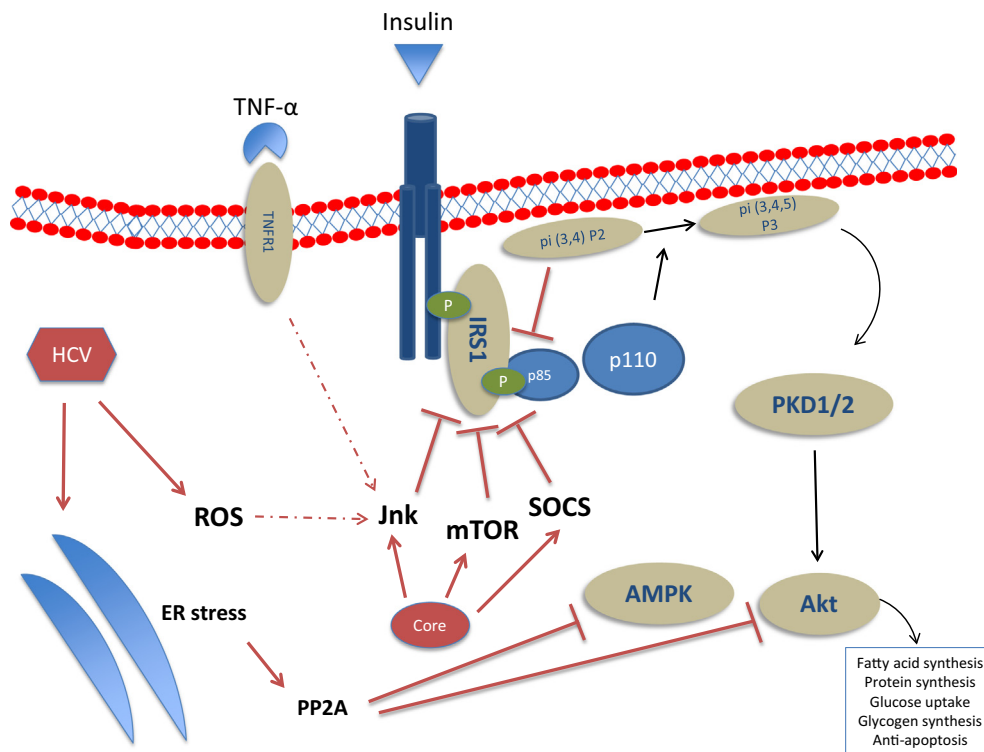


Fig. 1 Schematic representation of the HCV interactions (both direct and indirect) on the hepatocyte insulin signaling pathway. HCV core can directly activate inhibitors of insulin signaling: the mammalian target of rapamycin (mTOR), the suppressor of cytokine signaling (SOCS)-3, and the c-Jun N-terminal kinase (JNK). HCV increases endoplasmic reticulum (ER) stress which can lead to the activation of the protein phosphatase 2A (PP2A), an inhibitor of Akt and AMP-activated kinase (AMPK) which are key regulators of gluconeogenesis. Other abbreviations: PKD1/2: protein kinase D1/2; p85/p110: subunits p85 and p110 of phosphatidylinositol 3-kinase.

over, there is not a proper definition of expected insulin sensitivity or reference values permitting to stratify subjects for hepatic or peripheral insulin sensitivity. A 2-step euglycemic hyperinsulinemic clamp is required to establish IR and the HOMA-IR model suffers from a lack of sensitivity on an individual base.

The fact that IR is increased in chronic HCV is confirmed by two studies which have shown in non-obese, non-diabetic hepatitis C patients the existence of hepatic insulin resistance and a decreased peripheral glucose uptake [59,60]. The extrahepatic propagation of IR in hepatitis C may involve the propagation of inflammatory factors such as TNF- α , IL-8, monocyte chemoattractant protein 1 (MCP-1), IL-18, chemerin and visfatin [61,62]. Nonetheless, HCV has been shown to directly inhibit the insulin signaling cascade in hepatocytes (Fig. 1). When liver tissue fragments taken from 42 non-obese, non-diabetic chronic hepatitis C patients and age- and BMI-matched controls were incubated with insulin, the insulin-stimulated insulin receptor substrate (IRS)-1 tyrosine phosphorylation, phosphoinositide-3-kinase activity and Akt phosphorylation were decreased in HCV infected *vs.* uninfected subjects [63,64]. Experimental models have shown that the HCV core protein is sufficient to induce IR *via* several mechanisms acting downstream of the insulin receptor. In hepatoma cell lines, HCV core protein stimulates the proteasome degradation of -1 and -2 *via* the activation of the suppressor of cytokine signaling-3 [65,66]. HCV may also activate the mTOR [67] or the protein phosphatase 2A (PP2A), an inhibitor of Akt, *via* an increased endoplasmic reticulum (ER) stress [68] or through a direct activation of the mTOR/S6K1 signaling pathway [69] which occurs in a PTEN-dependent manner [70].

Among the indirect mechanisms, increased endoplasmic reticulum (ER) stress has also been reported to lead to the activation of PP2A by a dual mechanism involving induction of PCG1-alpha and dephosphorylation of FoxO1 resulting in Akt inhibition [71]. HCV-induced liver inflammation, leads to an increased release of pro-inflammatory cytokines, such as TNF- α , which may activate stress kinases such as the c-Jun N-terminal kinase (JNK) [64], since a JNK inhibitor was able to revert the effects of the HCV core protein-mediated Ser312 phosphorylation of IRS-1 in an *in vitro* infection assay. Anti-TNF- α abolished IR also in HCV core transgenic mice [72]. These indirect mechanisms may also be implicated in the pathogenesis of the extrahepatic component of HCV-induced IR, as suggested by the two aforementioned studies, where a combination of euglycemic hyperinsulinemic clamp and calorimetry assay performed in HCV patients without stigmata of the metabolic syndrome pointed out a failing glucose uptake oxidation under hyperinsulinemic conditions, suggesting a HCV-associated reduced glucose uptake, mostly occurring in striated muscles [59,60].

Conclusions

Since HCV influences the overall metabolism and favors IR by disturbing hepatic and peripheral glucose uptake there is an increased risk of diabetes in susceptible individuals. Limitations include the fact that most of the HCV infected patients studied were younger and of Caucasian or Asian descent. It is therefore expected that not all the study results show a link

between HCV infection and T2D, due to preservation of the pancreatic response. Nevertheless, the actual knowledge provides sufficient evidence to clinical physicians and public-health researchers for increasing diabetes screening and prevention among HCV infected patients.

The impact of T2D and HCV infection on health expenditures is a major one. Prevention and screening should be considered as a public health priority [73]. Even though such approach is not yet supported by current guidelines, the simplicity of diabetes screening (HbA1c and fasting glycemia) in HCV infected persons invites the clinician to test regularly. On the other hand, systematic HCV screening in every diabetic patient is not realistic and would involve major costs [74–76]. Practically, to increase the standards of medical care for patients with T2D and HCV endocrinologist and gastroenterologist need to further collaborate, promptly refer hyperglycemic patients and test the cost efficacy of the existing algorithms [23].

Further research in this area should focus on one hand on the metabolic pathways linking HCV infection and diabetes: the unravelling of these mechanisms may provide insights into the pathogenesis of T2D in general. On the other hand, remaining challenges in the field consist in the management of chronic hepatitis C patients and its complications, both before and after antiviral-induced eradication.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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