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SYSTEMATIC REVIEWS

Diabetes mellitus, insulin resistance and hepatitis C virus infection: A contemporary review

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Abstract

AIM

To summarise the literature data on hepatitis C virus (HCV)-infected patients concerning the prevalence of glucose abnormalities and associated risk.

METHODS

We conducted a PubMed search and selected all studies found with the key words "HCV" or "hepatitis C virus" and "diabetes" or "insulin resistance". We included only comparative studies written in English or in French, published from January 2000 to April 2015. We collected the literature data on HCV-infected patients concerning the prevalence of glucose abnormalities [diabetes mellitus (DM) and insulin resistance (IR)] and associated risk [*i.e.*, severe liver fibrosis, response to antivirals, and the occurrence of hepatocellular carcinoma (HCC)].

RESULTS

HCV infection is significantly associated with DM/IR compared with healthy volunteers and patients with hepatitis B virus infection. Glucose abnormalities were associated with advanced liver fibrosis, lack of sustained virologic response to interferon alfa-based treatment and with a higher risk of HCC development. As new antiviral therapies may offer a cure for HCV infection, such data should be taken into account, from a therapeutic and preventive point of view, for liver and non-liver consequences of HCV disease. The efficacy of antidiabetic treatment in improving the response to

antiviral treatment and in decreasing the risk of HCC has been reported by some studies but not by others. Thus, the effects of glucose abnormalities correction in reducing liver events need further studies.

CONCLUSION

Glucose abnormalities are strongly associated with HCV infection and show a negative impact on the main liver related outcomes.

Key words: Hepatitis C virus; Diabetes mellitus; Insulin resistance; Liver fibrosis; Treatment

Core tip: Hepatitis C virus (HCV) infection is associated with increased rates of glucose abnormalities, including diabetes mellitus and insulin resistance. The presence of glucose abnormalities in HCV infected patients, including diabetes mellitus and insulin resistance, is associated with negative liver-related outcomes (*i.e.*, severe liver fibrosis, decreased response to antivirals, and increased occurrence of hepatocellular carcinoma).

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major health problem. The World Health Organization (WHO) estimates that at least 150-170 million people, approximately 3% of the world's population, are chronically infected. These patients are known to be at risk of liver related complications, *i.e.*, cirrhosis and hepatocellular carcinoma (HCC), with an estimated liver-related mortality of 350000 people/year. The total risks of morbidity and mortality are underestimated, because they do not take into account extrahepatic consequences of HCV infection. Numerous extrahepatic manifestations have been reported, suggesting that HCV is more a systemic disease than just a liver disorder. In large prospective cohort studies, up to two-thirds of patients with HCV infection experienced extra-hepatic manifestations[1]. The majority of available data concern HCV-related autoimmune and/or lymphoproliferative disorders, from benign mixed cryoglobulinemia to frank lymphomas, which is consistent with HCV lymphotropism[2]. More recently, other HCV-associated disorders have been reported including cardiovascular, renal, central nervous system and metabolic diseases[3]. Among the latter, some studies assessed the risk of diabetes mellitus (DM) or insulin resistance (IR) while others evaluated the impact of DM/IR on the main liver-related HCV infection outcomes (*i.e.,* liver fibrosis, cirrhosis, HCC). However, the results appear to be conflicting, with great heterogeneity between studies.

In the present study, based on a literature data review, we aimed to analyse: (1) the risk of glucose abnormalities (GA) in HCV-infected patients; and (2) the impact of GA on the main liver-related HCV outcomes, *i.e.,* liver fibrosis, response to interferon alfa-based treatment, and HCC.

MATERIALS AND METHODS

We conducted a PubMed search and selected all studies found with the key words "HCV" or "hepatitis C virus" and "diabetes" or "insulin resistance". We included only comparative studies written in English or in French, published from January 2000 to April 2015. We selected surveys that had evaluated the risk of Type 2 DM or IR in HCV-infected patients compared with healthy controls or with patients with hepatitis B virus (HBV) infection. The definition of DM was usually based on a fasting plasma glucose > 1.26 g/L, or a history of diabetes mellitus, or use of oral antidiabetic agents or insulin. The definition of IR was based on the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) according to the formula: HOMA-IR = fasting glucose (mmol/L) × fasting insulin (mIU/L)/22.5. We also included studies that assessed the association between the presence of glucose abnormalities (DM or IR) and the main HCV infection outcomes (*i.e.,* liver fibrosis, cirrhosis, response to antiviral treatment, HCC). Conversely, studies that evaluated the impact of antiviral treatment on glucose abnormalities were included. We excluded studies with patients infected with the HBV or human immunodeficiency virus, and those for whom the entire manuscript was not available.

RESULTS

Is HCV infection associated with an increased prevalence of glucose abnormalities?

We included two types of studies: (1) those that assessed the HCV prevalence in diabetic patients compared with non-diabetics; and (2) studies that assessed the prevalence of DM and/or IR in HCV-infected patients compared with controls (healthy volunteers or HBV carriers) (Table 1).

Six studies evaluated HCV prevalence rates in diabetic patients compared with non-diabetic healthy volunteers. The number of participants ranged from 180 to 13000. Four out of the six studies showed a significant increased prevalence of HCV infection markers [HCV antibodies (n = 3), HCV RNA (n = 1)] in DM patients, with an odds ratio (OR) between 2.87 and 3.03[4-7]. Of note, only one study used multivariate

Table 1 Glucose abnormalities and hepatitis C virus infection

Ref.	Year	Country	Study design	Patients	Patients number	Controls	Controls number	Testing for HCV Ab or RNA	Endpoint	Statistical methods	Association	Statistics
HCV infection markers in patients with type 2 diabetes mellitus												
Sangiorgio *et al*[4]	2000	Italy	Retrospective	DM	1514	HV	1300	Ab	HCV	Univariate	Yes	$P < 0.0001$
Chen *et al*[5]	2006	Taiwan	Cross sectional	DM	820	HV	905	Ab	HCV	Univariate adjusted	Yes	OR = 2.87 [1.51, 5.46]; $P < 0.001$
Huang *et al*[6]	2007	Taiwan	Cross sectional	DM	1237	HV	8595	RNA	HCV	Univariate	Yes	6.9% *vs* 4.5%; $P < 0.001$
Jadoon *et al*[7]	2010	Pakistan	ND	DM	3000	HV	10000	Ab	HCV	Univariate	Yes	OR = 3.03 [2.64, 3.48]; $P = 0.001$
Balogun *et al*[53]	2006	Nigeria	case-control	DM	90	HV[2]	90	Ab	HCV	Univariate	No	NS
Costa *et al*[54]	2008	Brazil	Case-control	DM	206	HV	206	RNA	HCV	Multivariate	No	NS
Glucose abnormalities in HCV infected patients *vs* different control groups												
Vs healthy volunteers												
Knobler *et al*[17]	2000	Israel	Case-control	HCV	45	HV[2]	88	RNA	DM	Univariate	Yes	33% *vs* 5.6%; $P < 0.001$
Mehta *et al*[8]	2000	United States	Cross sectional	HCV	230	HV	9611	Ab	DM	Multivariate	Yes	OR = 3.77 [1.8, 7.87]
Marzouk *et al*[18]	2007	Egypt	Cross sectional	HCV	190	HV	575	RNA	DM	Multivariate	Yes	HR = 3.05 [1.19, 7.81]
Shaheen *et al*[19]	2007	United States	ND	HCV	239	HV	10144	ND	IR	Univariate adjusted	Yes	OR = 1.68; $P = 0.02$
Huang *et al*[6]	2007	Taiwan	Cross sectional	HCV	478	HV[2]	7927	RNA	DM	Multivariate	Yes	OR = 1.53 [1.18, 1.98]; $P < 0.001$
Huang *et al*[21]	2008	Taiwan	ND	HCV	683	HV[2]	515	RNA	DM/IGT[1]	Univariate	Yes	OR = 3.51 [2.7, 4.56]; $P < 0.001$
Park *et al*[20]	2008	South Korea	Prospective	HCV[1]	62	HV[2]	172	RNA	IR	Univariate	Yes	22.5% *vs* 5.2%; $P < 0.001$
Mohamed *et al*[22]	2009	Egypt	Cross sectional	HCV[1]	38	HV[2]	12	RNA	IR	Univariate	Yes	HOMA-IR = 3.98 (normal ALT) and 2.69 (a normal ALT) *vs* 1.92; $P < 0.001$
Duseja *et al*[23]	2009	India	ND	HCV[1]	85	HV[2]	25	RNA	IR	Univariate	Yes	62% *vs* 16%; $P = 0.0002$
Lonardo *et al*[24]	2009	Italy	ND	HCV[1]	97	HV	182	RNA	IR	Univariate	Yes	$P < 0.001$
Huang *et al*[25]	2009	Taiwan	ND	HCV[1]	93	HV	144	Ab	IR	Univariate	Yes	HOMA-IR 2.2 *vs* 1.6; $P = 0.02$
Mostafa *et al*[26]	2010	Egypt	ND	HCV	329	HV	173/795	RNA	DM	Univariate adjusted	Yes	OR = 1.35 [1.06, 1.73]; $P = 0.02$
Miyajima *et al*[27]	2013	Japan	Cross sectional	HCV	40	HV	1780/88	RNA	IR	Univariate	Yes	HOMA-IR 3.0 *vs* 1.3; $P < 0.001$
Younossi *et al*[28]	2013	United States	Retrospective	HCV	177	HV	19568	RNA	DM and IR	Multivariate	Yes	OR for DM 2.3 [1.18, 4.54] OR for IR 2.06 [1.19, 3.57]
Pothineni *et al*[29]	2014	United States	Retrospective	HCV	1434	HV[2]	14799	RNA	DM	Univariate	Yes	11.2% *vs* 5.1%; $P < 0.01$
Dai *et al*[30]	2013	Taiwan	Retrospective	HCV	160	HV[2]	480	RNA	DM	Multivariate	Yes	OR = 1.208 [1.009, 2.799]; $P = 0.004$
Mehta *et al*[10]	2003	United States	Case-control	HCV	12	HV[2]	1072	RNA	DM	Univariate	No	NS
Stepanova *et al*[11]	2012	United States	Nationwide survey	HCV	791	HV	38715	RNA	DM and IR	Multivariate	No	NS
Montenegro *et al*[9]	2013	Italy	Prospective	HCV	616	HV	1856	Ab	DM	Univariate adjusted	No	NS
Ruhl *et al*[55]	2014	United States	Cross sectional	HCV	277	HV	14571	RNA	DM	Univariate adjusted	No	NS
Vs hepatitis B virus infection												
Knobler *et al*[17]	2000	Israel	Case-control	HCV	45	HBV	90	RNA	DM	Univariate	Yes	33% *vs* 12%; $P = 0.004$
Ryu *et al*[31]	2001	South Korea	Prospective	HCV, F4	68	HBV	157	Ab	DM	Univariate	Yes	24% *vs* 10.4%; $P = 0.001$
Wang *et al*[32]	2007	Taiwan	Longitudinal	HCV	926	HBV	544	Ab	DM	Multivariate	Yes	HR = 1.7
Huang *et al*[6]	2007	Taiwan	Cross sectional	HCV	478	HBV	1363	RNA	DM	Univariate	Yes	18% *vs* 11.4%; $P < 0.001$
Moucari *et al*[33]	2008	France	Retrospective	HCV	500	HBV[2]	100	RNA	HOMA-IR	Univariate	Yes	35% *vs* 5%; $P < 0.001$
White *et al*[12]	2008	United States	Meta-analysis	HCV	34 studies	HBV/HV	-	Ab/RNA	DM	Meta-analysis	Yes	Adjusted OR for HV 1.68 and for HBV 1.80
Rouabhia *et al*[34]	2010	Algeria	Prospective cross sectional	HCV[1]	290	HBV	126	RNA	DM	Multivariate	Yes	OR = 4.73 [1.7, 13.2]; $P = 0.0029$

Petta *et al*[56]	2011	Italy	Retrospective	HCV	170	HBV[2]	170	RNA	HOMA-IR and DM	Univariate	Yes	42.2% *vs* 25.9%, $P = 0.002$ and 8.8% *vs* 3.6%, $P = 0.04$
Imazeki *et al*[57]	2008	Japan	Retrospective	HCV	544	HBV	286	RNA	DM and IR	Multivariate	No	NS
Tanaka *et al*[58]	2008	Japan	Case-control	HCV[1]	30	HBV[2]	30	RNA	IR	Multivariate	No	NS
Mavrogiannaki *et al*[59]	2008	Greece	prospective case control	HCV	108	HBV	81	RNA	glucose intolerance	Univariate adjusted	No	NS
Persico *et al*[60]	2009	Italy	Retrospective	HCV	726	HBV	126	Ab	DM	Univariate adjusted	No	NS

[1]HCV infection not treated; [2]Matched for confounding factors (age and/or gender and/or BMI and/or ALT…). HCV: Hepatitis C virus infection; Ab: Antibody; HV: Healthy volunteers; G1: Genotype 1; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; DM: Diabetes mellitus; FPG: Fasting Plasma glucose; IGT: Impaired glucose tolerance [after oral glucose tolerance test (OGTT)]; CLD: Chronic liver disease; NAFLD: Non-alcoholic fatty liver disease; NS: Not significant; ND: Not determined.

logic regression analysis, while another adjusted the risk for age, gender, body mass index (BMI) and alanine aminotransferase (ALT) levels. One study showed an increased HCV antibody prevalence rate in DM patients with abnormal ALT levels.

Thirty-two studies evaluated DM and/or IR prevalence rates in HCV patients compared with either healthy volunteers ($n = 20$) or HBV patients ($n = 12$). The size of cohorts ranged from 50 to 39506 subjects. All but four studies assessed DM/IR prevalence in HCV-RNA positive patients. In 10 out of 20 studies that compared HCV patients with healthy volunteers, multivariate or univariate analyses with adjustment for age, gender, BMI, socio-economic status and ethnicity were performed. Thirteen studies evaluated DM prevalence ($n = 11$) or occurrence ($n = 2$), while others ($n = 9$) assessed IR in HCV infected patients. Overall, 16 out of 20 studies found a significant association between the presence of glucose abnormalities (DM/IR) and HCV infection, including 7 out of 10 studies with multivariate or adjusted analyses (OR between 1.2 and 3.77). One study reported a higher risk of DM only in patients older than 40 years[8]. Four studies reported "negative" results. Three out these four studies showed a higher risk of DM only in specific populations (*i.e.*, HCV patients with increased ALT levels[9], HCV patients older than 55 years with a BMI > 25 kg/m^2[10], and a cohort studied between 1988 and 1994, but not in the more recent cohort)[11].

When compared with HBV infected patients, 7 out of 11 studies found a significant association of HCV with DM. In one meta-analysis[12], a positive HCV viremia was associated with an increased risk of DM compared with controls (adjusted OR = 1.68) and with HBV patients (adjusted OR = 1.80).

Are diabetes mellitus or insulin resistance associated with liver fibrosis severity in HCV infected patients?

Thirty studies investigated whether DM/IR was associated with liver fibrosis severity in HCV patients (Table 2). Studies were performed in Asia (Taiwan $n = 3$, Japan $n = 3$, other $n = 1$), Europe ($n = 13$), the United States and Australia ($n = 5$), Saudi Arabia ($n = 1$), Turkey ($n = 1$) and Egypt ($n = 3$). The mean size of the cohorts was 451 patients (min-max range 10 to 3068). The authors searched for an association between liver fibrosis severity and DM ($n = 9$), IR ($n = 19$) or impaired fasting plasma glucose ($n = 2$). All but two studies performed multivariate analyses. Twenty-six out of thirty studies reported a significant association of glucose abnormalities with liver fibrosis severity (OR from 1.28 to 13.72). Three of the four "negative" studies were done on small cohorts. There were some differences related to HCV genotypes, but no systematic relationship was found.

Do diabetes mellitus and insulin resistance have an impact on the virological response to HCV treatment?

Twenty-six studies and three meta-analyses investigated whether GA had an impact on the response to interferon alfa-based antiviral treatment (Table 3). The studies originated from Europe ($n = 11$), Asia ($n = 4$), Egypt ($n = 4$), the United States ($n = 5$), Australia ($n = 1$) and Saudi Arabia ($n = 1$). They included a mean of 503 patients (50 to 5944). Nineteen out of twenty-eight studies showed a significant negative effect of GA in response to interferon alfa-based therapy [*i.e.,* lower sustained viral response (SVR) rates], including 15 multivariate analyses and 3 meta-analyses. Of note, studies that did not find an impact of GA on SVR rates had some limitations, including small size of cohorts (60-600 patients), only G1 or G4 patients (3 out of 10 studies), and only Italian patients (4 out of 10). Two of them evaluated patients treated with peginterferon/ribavirin and telaprevir. The three meta-analyses found a significant association between IR and the absence of SVR, regardless of the genotype (OR for G1 = 2.2, G2 = 3, G3 = 4.45 and G4 = 6.7, respectively).

Table 2 Glucose abnormalities and severe liver fibrosis in hepatitis C virus-infected patients

Ref.	Year	Country	Number of HCV patients	Patient profile	Glucose abnormality	Statistical method	Association with severe fibrosis[1]	Genotypes	Statistics
Konrad *et al*[42]	2000	Germany	10	Non DM	FPG	Multivariate	Yes	All	$P = 0.01$
Sud *et al*[61]	2004	Australia	170	-	HOMA-IR	Multivariate	Yes	All	OR = 1.47 [1.14, 1.89]; $P = 0.003$
Muzzi *et al*[62]	2005	Switzerland	221	Non DM	HOMA-IR	Multivariate	Yes	All (except G3)	OR = 1.57 [1.04, 2.39]
D'souza *et al*[63]	2005	United Kingdom	59	-	HOMA-IR	Multivariate	Yes	All	$P = 0.001$
Taura *et al*[64]	2006	Japan	83	-	HOMA-IR	Multivariate	Yes	All	OR = 7.32 [1.59, 33.73]; $P = 0.01$
Leandro *et al*[65]	2006	Italy	3068	-	DM	Multivariate	Yes	G1	OR = 4.52 [1.07, 19.1]; $P = 0.011$
Bugianesi *et al*[66]	2006	Italy	132	G3 with steatosis	HOMA-IR	Multivariate	Yes	G3	OR = 2.98 [1.13, 7.89]; $P = 0.028$
Kita *et al*[67]	2007	Japan	68	Post tranfusion hepatitis	DM	Multivariate	Yes	All	OR = 8.4 [2.23, 31.54]; $P = 0.002$
Petta *et al*[68]	2008	Italy	201	G1	DM	Multivariate	Yes	G1	OR = 2.69 [1.46, 4.95]; $P < 0.001$
Moucari *et al*[33]	2008	France	500	-	HOMA-IR	Multivariate	Yes	All	OR = 1.8 [1.16, 2.81]; $P = 0.009$
Cua *et al*[69]	2008	Australia	346	G1, G3, untreated	IR	Multivariate	Yes	G3	OR = 3.15 [1.56, 6.35]; $P = 0.001$
Hsu *et al*[70]	2009	Taiwan	528	G1, G2	FPG	Multivariate	Yes	G1	OR = 13.72 [2.15, 87.7]; $P < 0.05$
Moucari *et al*[71]	2009	France	226	G4	HOMA-IR	Multivariate	Yes	G4	OR = 3.86 [1.859, 8.034]; $P < 0.001$
Persico *et al*[60]	2009	Italy	726	-	DM	Multivariate	Yes	All	$P < 0.05$
Hung *et al*[14]	2011	Taiwan	1470	-	DM	Univariate	Yes	All	$P < 0.001$
Patel *et al*[72]	2011	Asia	263	G2, G3	HOMA-IR	Multivariate	Yes	G2 and G3	OR = 8.42 [2.1, 34.3]; $P = 0.003$
Mohamed *et al*[73]	2011	Egypt	50	G4	HOMA-IR	Multivariate	Yes	G4	OR = 3.73; $P = 0.001$
Miyaaki *et al*[74]	2011	Japan	171	-	DM	Multivariate	Yes	All	OR = 8.739 [2.85, 26.85]; $P = 0.0002$
Conjeevaram *et al*[75]	2011	United States	341	G1	HOMA-IR	Multivariate	Yes	G1	OR = 1.28 [1.07, 1.51]; $P = 0.005$
Petta *et al*[56]	2011	Italy	170	G1	HOMA-IR	Multivariate	Yes	G1	OR = 2.64 [1.11, 6.28]; $P = 0.02$
Khattab *et al*[76]	2012	Egypt	107	G4	HOMA-IR	Multivariate	Yes	G4	OR = 1.87 [1.09, 8.29]; $P = 0.04$
Ziada *et al*[77]	2012	Egypt	140	Non DM	HOMA-IR	Multivariate	Yes	All	OR = 1.92 [0.97, 3.4]; $P = 0.049$
Thompson *et al*[13]	2012	United States	1038	Non DM	HOMA-IR	Multivariate	Yes	All	OR = 1.6 [1.1, 2.33]; $P = 0.02$
Alfaleh *et al*[78]	2013	Saudi Arabia	157	-	DM	Multivariate	Yes	All (except G4)	OR = 0.37 [0.148, 0.927]; $P = 0.034$
Dokmeci *et al*[79]	2014	Turkey	104	-	HOMA-IR	Multivariate	Yes	All	OR = 3.36 [1.32, 31.25]; $P = 0.021$
Huang *et al*[80]	2015	Taiwan	1077	-	DM	Multivariate	Yes	All	OR = 1.81 [1.14, 2.65]; $P = 0.002$
Fartoux *et al*[81]	2005	France	141	Non DM	HOMA-IR	Univariate	No	No	NS
Elgouhari *et al*[82]	2008	United States	183	-	DM	Multivariate	No	No	NS
Petta *et al*[83]	2009	Italy	156	Non DM	HOMA-IR	Multivariate	No	No	NS
Rueger *et al*[84]	2014	Switzerland	1461	-	DM	Multivariate	No	No	NS

[1]Severe liver fibrosis: F3 or F4 in Metavir scoring system. HCV: Hepatitis C virus infection; G1: Genotype 1; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; DM: Diabetes mellitus; FPG: Fasting plasma glucose; NS: Not significant.

What is the impact of interferon alfa-based treatment on glucose abnormalities?

Twenty studies assessed the impact of interferon-based antiviral treatment on DM/IR, either as an improvement of GA after treatment or as the occurrence of GA after antiviral treatment (Table 4).

Improvement of GA after antiviral treatment was analysed in fifteen surveys that included 13 to 1038 HCV treated patients. Most of these studies performed univariate analyses. A significant decreased prevalence of GA was noted in 12 out of 15 studies. Eleven of these 12 studies reported a significant change of IR

Table 3 Impact of glucose abnormalities on virological response after interferon alpha based treatment

Ref.	Year	Country	Patients number	Patient profile	Association	Statistical method	Impact on virological response	Genotypes	Statistics
D'souza *et al*[63]	2005	United Kingdom	59		HOMA-IR	Multivariate	Yes	All	OR of SVR: 0.44 [0.22, 0.88]; $P = 0.02$
Tarantino *et al*[85]	2005	Italy	80		GMI	Univariate	Yes	All	40% *vs* 7.5%; $P = 0.0009$
Romero-Gomez *et al*[86]	2005	Spain	159		HOMA-IR	Multivariate	Yes	All	OR of SVR 0.55 [0.33, 0.93]; $P = 0.012$
Jian Wu *et al*[87]	2006	China	98		HOMA-IR	Multivariate	Yes	All	OR of SVR: 0.17; $P = 0.015$
Backus *et al*[88]	2007	United States	5944	G1, G2, G3	DM	Multivariates	Yes	All and G1	OR = 0.76 [0.64, 0.71]; $P = 0.002$
Conjeevaram *et al*[89]	2007	United States	401	G1	HOMA-IR	Multivariates	Yes	G1	OR = 0.87 [0.77, 0.99]; $P = 0.028$
Elgouhari *et al*[82]	2008	United States	183		DM	Multivariate	Yes	All	OR of SVR 0.22 [0.07, 0.55]; $P = 0.003$
Poustchi *et al*[90]	2008	Australia	82	G2, G3 non DM	HOMA-IR	Multivariate	Yes	G2, G3	OR of SVR 0.16 [0.03, 0.77]; $P = 0.02$
Romero-Gomez *et al*[91]	2008	Spain	1059		FPG	Multivariate	Yes	All	OR of SVR 0.56 [0.34, 0.93]; $P < 0.02$
Moucari *et al*[71]	2009	France	226	G4	HOMA-IR	Multivariate	Yes	-	OR of SVR: 0.19 [0.07, 0.51]; $P = 0.001$
Dai *et al*[92]	2009	Taiwan	330	G1, G2	HOMA-IR	Multivariate	Yes	G1, G2	OR of SVR 0.872 [0.79, 097]; $P = 0.01$
Hung *et al*[115]	2010	Taiwan	1470		DM	Multivariate	Yes	All	OR of SVR 0.69 [0.5, 0.96]; $P = 0.029$
Khattab *et al*[93]	2010	Egypt	131	Non DM, G4	HOMA-IR	Multivariate	Yes	G4	OR of SVR 0.07 [0.01, 0.43]; $P = 0.004$
Deltenre *et al*[94]	2011	France	2732	G1-6	IR	Meta-analysis	Yes	All	-
Eslam *et al*[95]	2011		2129	G1-6	IR	Meta-analysis	Yes	All	OR of SVR 0.35 [0.24, 0.51]; $P = 0.0004$
Del Campo *et al*[96]	2012	Spain	240	Non DM	HOMA-IR	Multivariate	Yes	G1, G4	OR of SVR 0.44 [0.17, 0.97]; $P = 0.04$
Ziada *et al*[77]	2012	Egypt	140	Non DM	HOMA-IR	Multivariate	Yes	All	OR of SVR 0.41 [0.18, 0.9]; $P = 0.003$
Laurito *et al*[97]	2013	Brazil	2238	G1-6	IR	Meta-analysis	Yes	All	OR of SVR 0.41 [0.3, 0.56]; $P = 0.022$
Abd El-Wahab *et al*[98]	2014	Egypt	392	Non DM	HOMA-IR	Multivariate	Yes	All	OR of virological response: 0.19 [0.1, 0.38]; $P = 0.0001$
Grasso *et al*[99]	2009	Italy	90	Non DM, G1	HOMA-IR	Multivariate	No	G1	NS
Fattovich *et al*[100]	2010	Italy	412		HOMA-IR	Multivariate	No	No	NS
Khattab *et al*[76]	2012	Egypt	107	G4	HOMA-IR	Multivariate	No	G4	NS
Brandman *et al*[101]	2012	United States	23	Non DM	IGT, FGP, SSGP	Univariate	No	No	NS
Aghemo *et al*[102]	2012	Italy	339		HOMA-IR	Univariate	No	No	NS
Fattovich *et al*[100]	2012	Italy	124	Non DM	HOMA-IR	Multivariate	No	No	NS
Serfaty *et al*[103]	2012	France	161[1]	G4	HOMA-IR	Multivariate	No	G4	NS
Alfaleh *et al*[78]	2013	Saudi Arabia	157		DM	Multivariate	No	No	NS
Younossi *et al*[104]	2013	United States	578[1]	G1	HOMA-IR	Univariate adjusted	No	G1	NS
Jung *et al*[105]	2014	Soutk Korea	60		HOMA-IR	Univariate	No	No	NS

[1]Treated with peginterferon/ribavirin telaprevir. HCV: Hepatitis virus infection; G1: Genotype 1; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; IGT: Impaired glucose tolerance; DM: Diabetes mellitus; FPG: Fasting plasma glucose; SSGP: Steady-state plasma glucose; GMI: Glucose metabolism impairment; NS: Not significant; ND: Not determined.

only in patients who achieved a SVR. One survey found a significant change of IR after antiviral treatment only in genotype 1 patients[13].

Five studies evaluated the risk of GA occurrence according to antiviral treatment response. They included 202 to 2842 HCV treated patients, and all performed multivariate analyses. Four out of five studies showed a significant association between GA occurrence and the absence of SVR.

Do glucose abnormalities increase the risk of HCC in HCV infected patients?

Sixteen studies assessed the association between HCC and DM/IR in HCV infected patients (Table 5). These studies included from 120 to 5186 HCV patients, both treated and non-treated. Most of them (10/16)

Table 4 Glucose abnormalities after interferon alpha based treatment

Ref.	Year	Country	Number of HCV patients	Patient profile	Glucose metabolism parameter	Statistical method	Significant association or difference	Genotypes	Statistics
Improvement of glucose abnormalities after HCV treatment									
Konrad *et al*[42]	2000	United States	13		FPG and FI	Univariate	Yes	All	$P < 0.05$ and $P < 0.01$
Romero-Gomez *et al*[86]	2005	Spain	50		HOMA-IR	Univariate	Yes	All	In SVR; $P < 0.05$
Kawaguchi *et al*[106]	2007	Japan	89		HOMA-IR	Univariate	Yes	All	In SVR; $P < 0.01$
Chehadeh *et al*[107]	2009	Kuwait	181	G4	FPG	Univariate	Yes	G4	In SVR; $P < 0.001$
Kim *et al*[108]	2009	Korea	28	G1, G2	HOMA-IR	Multivariate	Yes	G1, G2	In SVR, OR of decreased IR 50 [3.74, 668.35]; $P = 0.003$
Conjeevaram *et al*[75]	2011	United States	341	G1	HOMA-IR	Univariate	Yes	G1	In SVR; $P < 0.001$
Khattab *et al*[76]	2012	Egypt	107	G4, non cirrhotic	HOMA-IR	Univariate	Yes	G4	In SVR ; $P = 0.001$
Thompson *et al*[13]	2012	United States	1038		HOMA-IR	Multivariate[1]	Yes	All	In G1 SVR; $P = 0.007$
Serfaty *et al*[103]	2012	France	161	G1, non cirrhotic	HOMA-IR	Univariate	Yes	G1	In SVR ; $P < 0.05$
Ziada *et al*[77]	2012	Egypt	140	Non DM, non cirrhotic	HOMA-IR	Univariate	Yes	All	$P = 0.009$
Chan *et al*[109]	2013	Australia	86	Non DM	HOMA-IR	Univariate	Yes	All	In SVR; $P = 0.04$
Jung *et al*[105]	2014	South Korea	60		HOMA-IR	Univariate	Yes	All	In SVR; $P = 0.036$
Mello *et al*[110]	2006	Brazil	30	G1, G3	HOMA-IR	Univariate	No	All	NS
Kawaguchi *et al*[111]	2009	Japan	72	Non DM, non cirrhotic	HOMA-IR, SI and ISI	Univariate[1]	No	No	HOMA-IR: NS In SVR, SI $P = 0.002$ and ISI $P = 0.009$
Brandman *et al*[101]	2012	United States	23	Non cirrhotic	SSGP	Univariate	No	No	NS
Occurrence of glucose abnormalities after HCV treatment									
Simó *et al*[112]	2006	Spain	234	Non DM	DM or IGT	Multivariate[1]	Yes	All	In SVR, OR = 0.48 [0.24, 0.48]; $P = 0.04$
Romero-Gomez *et al*[91]	2008	Spain	1059		DM or IGT	Multivariate[1]	Yes	All	In SVR, OR = 0.44 [0.2, 0.97]; $P = 0.04$
Arase *et al*[113]	2009	Japan	2842		DM	Multivariate[1]	Yes	All	In SVR, HR = 0.36 [0.24; 0.56]
Aghemo *et al*[102]	2012	Italy	339	Non DM	HOMA-IR	Multivariate[1]	Yes	All	In SVR, OR = 0.36 [0.18, 0.72]; $P = 0.004$
Giordanino *et al*[114]	2008	Italy	202	Non DM	DM or IGT	Multivariate[1]	No	No	NS

[1]Association with SVR. HCV: Hepatitis C virus infection; G1: Genotype 1; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; DM: Diabetes mellitus; FPG: Fasting plasma glucose; FI: Fasting insulin; IGT: Impaired glucose tolerance; ISI: Insulin sensitivity index; SI: Serum insulin; SSGP: Steady-state plasma glucose; NS: Not significant.

included Asian patients, and all but one performed multivariate analyses.

Five studies looked for the presence of DM/IR in HCV infected patients with HCC compared with HCV patients without HCC. Four out of five studies found a significant association between DM/IR and HCC (as compared with non-HCC) (OR from 2.0 to 11.6).

Nine out of eleven other studies found a significant association between the presence of DM/IR and the development of HCC in the follow-up of HCV infected patients (HR from 1.10 to 6.9). One study found a higher risk of HCC in diabetic patients only with SVR and without cirrhosis[14], while 2 others reported an increased risk of HCC only in diabetic patients with advanced fibrosis[15,16].

DISCUSSION

Many studies have evaluated the association between HCV chronic infection, insulin-resistance and diabetes mellitus. The abnormalities of carbohydrate metabolism, including hyperinsulinemia and IR, known to be *per se* related to chronic hepatic diseases, were the rationale for speculation on this relationship. Insulin-resistance is an often undetected condition, commonly coexisting with obesity and metabolic syndrome, and possibly progressing to type 2 diabetes. HCV-related type 2 diabetes mellitus may arise from a complex interaction between IR, steatosis and inflammatory processes. Epidemiologic studies supporting the association between type 2 diabetes and HCV infection were

Table 5 Glucose abnormalities and hepatocellular carcinoma in hepatitis C virus-infected patients

Ref.	Year	Country	Patient number	Patient profile	Association	Statistical method	Association DM and HCC	Statistics
Diabetes mellitus/insulin resistance in HCV-related HCC								
K-Kutala *et al*[15]	2014	France	162	HCC, not treated for HCV	DM and HCC	Multivariate	Yes[3]	HR = 3.13 [1.17, 8.38]; *P* = 0.022[3]
Hung *et al*[115]	2010	Taiwan	188	59 HCC; 129 non-HCC	DM and HCC	Multivariate	Yes	OR = 11.6 [2.500, 53.800]; *P* = 0.002
Hung *et al*[115]	2010	Taiwan	188	59 HCC; 129 non-HCC	HOMA-IR and HCC	Multivariate	Yes	OR = 2.0 [1.35, 3]; *P* = 0.001
Khattab *et al*[116]	2012	Egypt	294	147 HCC; 147 non-HCC	HOMA-IR and HCC	Multivariate	Yes	OR = 2.5 [1.7, 3.69]; *P* = 0.001
Mohamed *et al*[73]	2011	Egypt	100	50 HCC; 50 non-HCC; 20 non HCV	HOMA-IR and HCC	Univariate	No	NS
Diabetes mellitus/insulin resistance and development of HCC in HCV-infected patients								
Chen *et al*[117]	2008	Taiwan	1095	-	DM and HCC	Multivariate	Yes	OR = 3.52 [1.29, 9.24]
Veldt *et al*[16]	2008	Europe	541		DM and HCC	Multivariate	Yes[3]	OR = 3.28 [1.35, 7.97]; *P* = 0.009[3]
Konishi *et al*[118]	2009	Japan	197	Non DM, treated for HCV	DM[1] and HCC	Multivariate	Yes	HR = 4.63 [1.677, 12.766]; *P* = 0.003
Hung *et al*[14]	2010	Taiwan	1470	Treated for HCV	DM and HCC	Multivariate	Yes[2]	HR = 4.32 [1.23, 15.25]; *P* = 0.023[2]
Nkontchou *et al*[119]	2010	France	248	Cirrhotics	HOMA-IR and HCC	Multivariate	Yes	HR = 1.10 [1.01, 1.21]; *P* = 0.026
Takahashi *et al*[120]	2011	Japan	203	Non DM, treated for HCV	DM[1] and HCC	Multivariate	Yes	HR = 6.9 [1.7, 28.4]; *P* < 0.05
Arase *et al*[121]	2013	Japan	4302	Non treated for HCV	DM and HCC	Multivariate	Yes	HR = 1.73 [1.3, 2.3]; *P* < 0.001
Elkrief *et al*[45]	2014	France	348	Cirrhotics	DM	Multivariate	Yes	HR = 1.938 [1.129 , 3.328]; *P* = 0.016
Toyoda *et al*[122]	2015	Japan	522	Patients with SVR	DM and HCC	Multivariate	Yes	HR = 2.08 [1.0170, 4.0133]; *P* = 0.045
Lai *et al*[123]	2006	Taiwan	2141	-	DM and HCC	Multivariate	No	NS
Chen *et al*[124]	2013	Taiwan	5186	-	DM and HCC	Multivariate	No	NS

[1]Association of abnormal post-challenge hyperglycaemia and HCC; [2]Only in SVR patients without cirrhosis; [3]Only in advanced liver fibrosis. HCV: Hepatitis virus infection; HCC: Hepatocellular carcinoma; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; DM: Diabetes mellitus; NS: Not significant.

first published in the early 1990s. More recently, larger epidemiologic studies gave more in-depth analyses of the relationship between HCV chronic infection and glucose abnormalities and were included in the present analysis.

HCV infection is associated with increased rates of glucose abnormalities, including diabetes mellitus and insulin resistance

In the present analysis, most studies found a significant association between HCV infection (whether active HCV RNA positive, or not *i.e.,* HCV Ab positive) and diabetes mellitus or insulin resistance. This tight association was confirmed in both directions by the increased rates of HCV infection markers in DM/IR patients and the high rates of glucose abnormalities in HCV infected patients. The consistency of this association was supported by the confirmation of such results compared with different control groups, such as healthy volunteers or HBV carriers[6,8,12,17-34]. The variability of HOMA-IR cut-offs used (between 1.8 and 2.5 generally) may explain the heterogeneous results reported in the literature. Confounding factors might have also led to significant bias. Indeed, some studies comparing HCV patients with healthy volunteers did not perform multivariate analysis or adjust for confounding factors. However, seven out of ten multivariate analyses found a significant increased risk of DM/IR in HCV patients (OR = 1.2-3.7), after adjusting for confounding variables such as age, gender, BMI, ethnicity and education level.

How are we able to explain the increased risk of DM in HCV infected patients? Some authors have suggested that diabetic patients might have been infected by HCV due to injections or nosocomial transmission. The association of HCV infection with IR and the widespread use of universal precautions nowadays in hospitals to avoid virus transmission probably dis-

qualify this hypothesis. There are a variety of other possible mechanisms of increased risk of DM/IR in HCV patients. As shown in this study, glucose abnormalities in HCV patients are associated with liver fibrosis severity. Severe liver fibrosis and cirrhosis are well-known conditions that are able to induce glucose metabolism impairment. However, studies with other liver diseases, including cirrhosis, still showed an excess of risk in HCV patients compared with HBV patients[6,12,17,31-34]. The ability of HCV, particularly genotype 3 viruses, to induce liver steatosis on its own, which might in turn increase the risk of DM/IR, has also been suggested in previous studies[35,36]. Other underlying mechanisms may involve HCV *per se*. Experimental data suggest the role of inflammation. Increased HOMA-IR has been correlated with soluble Tumor Necrosis Factor Receptor1 (sTNFR1) and sTNFR2 levels[37]. Increased abnormal HOMA-IR was not associated with elevated serum levels of TNFα, IL6 and adiponectin in another study[38]. Other studies have also suggested an impairment of glucose uptake in HCV-infected patients. Glucose uptake and the surface expression of Glucose Transporters (GLUT1 and 2) were suppressed in cells infected by HCV compared with controls[39]. Interferon alfa restored glucose uptake, GLUT2 surface expression, mRNA expression and GLUT2 promoter activities. HCV has also been shown to impair glucose uptake and to promote IR by increasing suppressor of cytokine signalling 3 (SOC3), which inhibits insulin phosphorylation of AKT and phosphoinositide 3-kinase (PI3K)[40]. HCV may be involved in the regulation of phosphorylation of insulin receptor substrate 1 (ISR-1), implicated in the insulin pathway[41]. In HCV core transgenic mice, the viral protein was able to induce increasing TNFα levels in the liver, which in turn promoted the induction of IR. The high levels of TNFα inhibited the ISR-1, causing IR and its possible progression to diabetes. A decreased expression of ISR-1 and ISR-2 mediated by ubiquitination was observed and was inversely proportional to the liver fibrosis stage.

Interferon alfa use might lead to glucose metabolism impairment and is a potential bias. However, increased DM/IR rates have been also reported in HCV patients not taking interferon alfa[20,22-25,34]. Many studies found a decreased rate of glucose abnormalities in HCV patients who showed a SVR after interferon alfa-based therapy, and even in non virological responders in one study[42]. This strongly suggests a direct/indirect role of HCV on glucose metabolism impairment. As eradication of HCV seems to be effective in decreasing the occurrence rate of DM/IR, it will very be interesting to analyse the impact of new direct antiviral agents (DAAs) for preventing DM/IR and eventually cardiovascular disorders. Indeed, in a recent study, IFN-free antiviral regimen resulted in rapid changes in serum lipid profiles and intrahepatic expression of lipid-related genes in G1 patients[43].

Presence of glucose abnormalities in HCV infected patients, including diabetes mellitus and insulin resistance, is associated with negative liver-related outcomes

Severe liver fibrosis, the absence of SVR after interferon alfa-based treatment, and the development of HCC are the main negative outcomes of chronic HCV infection. Interestingly, the presence of DM or IR in HCV patients showed a pejorative impact on each of these end points. Most studies found an independent association of glucose abnormalities with advanced liver fibrosis, absence of SVR after antiviral treatment and HCC occurrence. Only few studies did not confirm such associations. This might be explained by the small size cohort of such studies, the heterogeneity of criteria for DM or HOMA-IR and the very high prevalence of other metabolic risk factors (such as elevated BMI) which may underestimates the impact of DM/IR. Our data is consistent with recent studies that demonstrated that DM increases cumulative incidence of decompensated cirrhosis[44]. In another recent survey, diabetes was independently associated with transplantation-free survival, development of ascites, renal dysfunction, bacterial infections, and HCC during the follow-up[45].

Experimental data suggest that increased insulin levels after hyperglycaemia leads to interferon signalling impairment. Insulin may inhibit the ability of interferon alfa to block HCV replication due to the activation of PI3K by insulin, thus leading to inhibition of STAT-1, which is involved in the interferon alfa pathway[40].

The impact of glucose abnormalities on virological response needs to be further evaluated with new DAA, interferon-free combinations. To date, there is very few data on the impact of GA on virological response to new DAA. Preliminary results suggest that the presence of diabetes does not appear to be predictive of treatment failure in G1 patients[46,47]. Further studies are needed to confirm these data and to evaluate the impact of DM on SVR in patients without poor prognostic factors.

Should glucose abnormalities be corrected to increase SVR rates?

A prospective study, including 155 HCV genotype 1 patients with IR, showed no difference in SVR rates after peginterferon alfa and ribavirin were given, regardless of whether or not patients had received pioglitazone, an antidiabetic drug[48]. Of note, most glycemic control indexes improved significantly in the pioglitazone group except for HbA1c. Another study found higher SVR rates in G4 patients treated with pioglitazone[49]. Pioglitazone may alter NK cell functions and thus impair clearance of infected hepatocytes[48]. A retrospective cohort from Taiwan (19349 diabetic patients, 1.7% HCV positive) showed that patients taking metformin and thiazolidinediones had the lowest risk of HCC (HR 0.49 and 0.56, respectively)

after adjusting for age, gender and comorbidities[50]. Consistently, in a prospective cohort of 100 HCV patients with ongoing cirrhosis, metformin treatment was independently associated with a decrease of HCC occurrence and liver-related death or transplantation[51]. In a two-year prospective follow-up of 85 patients with HCV-related HCC, HCC recurrence-free survival was increased in diabetics taking pioglitazone *vs* non-treated diabetics (44.2% *vs* 36.5%, respectively, $P = 0.37$)[52]. A significant decrease in HCC recurrence was observed in the pioglitazone group for patients with a BMI > 24.

We acknowledge some limitations of this study. Although we tried to include all published studies, we may have missed others in non-English literature or data only presented at meetings. Some studies were done with a limited number of patients. For some studies included in the present analysis, it is possible that there are some remaining bias and residual confounding factors. Despite multivariate analyses, the association between glucose abnormalities improvement and improved outcome may have been influenced by unmeasured confounding factors. Such final confirmation should arise from controlled clinical trials with long-term follow-up.

In conclusion, HCV chronic infection is associated with an increased risk of DM or IR, by a likely direct effect on glucose metabolism. In such patients, DM and IR are associated with a pejorative liver-related prognosis, as shown by increased rates of severe liver fibrosis, HCC occurrence, and decreased SVR rates after interferon-based therapy. This tight relationship between DM/IR and HCV infection needs to be further analysed with new DAAs, interferon-free combinations, with special attention to improvement in glucose abnormalities and long-term follow-up.

COMMENTS

Background

During hepatitis C virus (HCV) infection, extra-hepatic disorders are very frequent and polymorphous. Studies that have evaluated the link between glucose metabolism impairment and HCV reported heterogeneous data.

Research frontiers

Further studies are needed to evaluate the impact of glucose abnormalities in patients treated with interferon-free antiviral therapies. The effects of correction of glucose abnormalities in reducing liver event rates also need to be further studied.

Innovations and breakthroughs

This systematic review allows clarifying the close relationship between glucose abnormalities, HCV infection and poor liver outcomes. HCV infection is associated with increased rates of glucose abnormalities, including diabetes mellitus and insulin resistance. The presence of glucose abnormalities in HCV infected patients, including diabetes mellitus and insulin resistance, is associated with negative liver-related outcomes (*i.e.*, severe liver fibrosis, decreased response to antivirals, and increased occurrence of hepatocellular carcinoma).

Applications

These data strongly encourage clinicians to systematically screen HCV-infected patients for the presence of glucose abnormalities. Considering the impact of glucose abnormalities on liver-related outcomes in HCV infected patients, antiviral treatment should also be considered in HCV-infected patients with metabolic syndrome.

Peer-review

This review talks about the relationship between HCV infection and glucose abnormalities. There are already lots of articles about the topic. This review summarizes those articles published from January 2000 to April 2015 in PubMed and gives us a conclusion about the topic.

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