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

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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).

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. | Study design | Year | Country | Patients controls | Controls number | Testing for HCV Endpoint | Statistical methods | Association | OR or HR | 95% CI | p | p correction |
|------|--------------|------|---------|------------------|-----------------|--------------------------|---------------------|-------------|----------|--------|-----|-------------|
| [4]  | Case-control | 2000 | Italy   | DM               | 654             | HCV                      | Univariate         | Yes         | OR = 2.87 [1.51, 5.46] | p < 0.001 | NS   | 27% to 55% |
| [5]  | Retrospective | 2006 | Taiwan  | DM               | 1000            | HCV                      | Univariate         | Yes         | OR = 3.771 [1.8, 7.9]    | p = 0.02  | NS   | 62% to 76% |
| [6]  | Cross-sectional | 2010 | Pakistan | DM               | 1000            | HCV                      | Multivariate       | Yes         | OR = 3.05 [1.5, 6.4]      | p = 0.01  | NS   | 35% to 52% |
| [7]  | Case-control | 2008 | Brazil  | DM               | 206             | HCV                      | Multivariate       | Yes         | OR = 1.35 [1.06, 1.73]    | p = <0.001 | NS   | 11% to 12% |
| [8]  | Cross-sectional | 2009 | India   | DM               | 1072            | HCV                      | Multivariate       | Yes         | OR = 1.68 [1.19, 2.35]    | p = 0.02  | NS   | 23% to 35% |
| [9]  | Cross-sectional | 2010 | Egypt   | DM               | 1000            | HCV                      | Multivariate       | No          | OR = 1.80 [1.09, 2.92]    | p = 0.04  | NS   | 25% to 37% |
| [10] | Cross-sectional | 2013 | United States | DM               | 1000            | HCV                      | Multivariate       | No          | OR = 1.208 [1.09, 2.92]   | p = 0.04  | NS   | 25% to 37% |

### Desbois AC et al. Diabetes, insulin resistance and HCV

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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 the cohorts ranged from 50 to 39,506 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, DM was found more frequently in the HCV group (25.9% vs 3.6%, p = 0.04). In another study, DM was found more frequently in HCV patients (8.8%) compared with HBV patients (2.8%). A recent study found a higher risk of DM only in patients older than 40 years of age.

When compared with HBV infected patients, 7 out of 11 studies found a significant association of HCV with DM. In one meta-analysis, a positive HCV viremia was associated with a higher risk of DM (OR = 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.

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

Do diabetes mellitus and insulin resistance have an impact on the virological response to HCV treatment?
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 | Genotypes | Statistics |
|------|------|---------|------------------------|---------------|-------------------|-------------------|---------------------------|-----------|------------|
| Konrad et al \[53\] | 2000 | Germany | 10 | Non DM | FPG | Multivariate | Yes | All | P = 0.01 |
| Sud et al \[53\] | 2004 | Australia | 170 | - | HOMA-IR | Multivariate | Yes | All | OR = 1.47 [1.14, 1.89]; P = 0.003 |
| Muzzi et al \[56\] | 2005 | Switzerland | 221 | Non DM | HOMA-IR | Multivariate | Yes | All (except G3) | OR = 1.57 [1.04, 2.39]; P = 0.001 |
| D’Souza et al \[56\] | 2005 | United Kingdom | 59 | - | HOMA-IR | Multivariate | Yes | All | P = 0.01 |
| Taura et al \[56\] | 2006 | Japan | 83 | - | HOMA-IR | Multivariate | Yes | All | OR = 7.32 [1.59, 33.73]; P = 0.01 |
| Leandro et al \[52\] | 2006 | Italy | 3068 | DM | Multivariate | Yes | G1 | OR = 4.52 [1.07, 19.11]; P = 0.011 |
| Bugianesi et al \[56\] | 2006 | Italy | 132 | G3 with steatosis | HOMA-IR | Multivariate | Yes | G3 | OR = 2.98 [1.13, 7.99]; P = 0.026 |
| Kita et al \[71\] | 2007 | Japan | 68 | Post transfusion hepatitis | DM | Multivariate | Yes | All | OR = 8.4 [2.23, 31.54]; P = 0.002 |
| Petta et al \[56\] | 2008 | Italy | 201 | G1 | DM | Multivariate | Yes | G1 | OR = 2.69 [1.46, 4.95]; P < 0.001 |
| Moucari et al \[56\] | 2008 | France | 500 | - | HOMA-IR | Multivariate | Yes | All | OR = 1.8 [1.16, 2.81]; P = 0.009 |
| Cua et al \[72\] | 2008 | Australia | 346 | G1, G3, untreated | IR | Multivariate | Yes | G3 | OR = 3.15 [1.56, 6.35]; P < 0.001 |
| Hsu et al \[74\] | 2009 | Taiwan | 528 | G1, G2 | FPG | Multivariate | Yes | G1 | OR = 13.72 [2.15, 87.7]; P < 0.05 |
| Moucari et al \[74\] | 2009 | France | 226 | G4 | HOMA-IR | Multivariate | Yes | G4 | OR = 3.86 [1.85, 8.034]; P < 0.001 |
| Persico et al \[77\] | 2009 | Italy | 726 | - | DM | Multivariate | Yes | All | P < 0.05 |
| Hung et al \[79\] | 2011 | Taiwan | 1470 | - | DM | Univariate | Yes | All | P < 0.001 |
| Patel et al \[79\] | 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 \[79\] | 2011 | Egypt | 50 | G4 | HOMA-IR | Multivariate | Yes | G4 | OR = 3.73; P = 0.001 |
| Miyaaki et al \[79\] | 2011 | Japan | 171 | - | DM | Multivariate | Yes | All | OR = 8.739 [2.85, 26.85]; P = 0.0002 |
| Conjeevaram et al \[79\] | 2011 | United States | 341 | G1 | HOMA-IR | Multivariate | Yes | G1 | OR = 1.28 [1.07, 1.51]; P = 0.005 |
| Petta et al \[79\] | 2011 | Italy | 170 | G1 | HOMA-IR | Multivariate | Yes | G1 | OR = 2.64 [1.11, 6.28]; P = 0.02 |
| Khattab et al \[79\] | 2012 | Egypt | 107 | G4 | HOMA-IR | Multivariate | Yes | G4 | OR = 1.87 [1.09, 8.29]; P = 0.04 |
| Ziada et al \[79\] | 2012 | Egypt | 140 | Non DM | HOMA-IR | Multivariate | Yes | All | OR = 1.92 [0.97, 3.4]; P = 0.049 |
| Thompson et al \[79\] | 2012 | United States | 1038 | Non DM | HOMA-IR | Multivariate | Yes | All | OR = 1.6 [1.1, 2.33]; P = 0.02 |
| Alfaleh et al \[79\] | 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 \[79\] | 2015 | Taiwan | 1077 | - | DM | Multivariate | Yes | All | OR = 1.81 [1.14, 2.65]; P = 0.002 |
| Faroux et al \[81\] | 2005 | France | 141 | Non DM | HOMA-IR | Multivariate | No | No | NS |
| Elgouhari et al \[81\] | 2008 | United States | 183 | - | DM | Multivariate | No | No | NS |
| Petta et al \[81\] | 2009 | Italy | 156 | Non DM | HOMA-IR | Multivariate | No | No | NS |
| Rueger et al \[81\] | 2014 | Switzerland | 1461 | - | DM | Multivariate | No | No | NS |

\[56\] 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.
only in patients who achieved a SVR. One survey found a significant change of IR after antiviral treatment only in patients who achieved a SVR.

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.[24] | 2000 | United States | 13 | DM, non cirrhotic | FPG and F1 | Univariate | Yes | All | P < 0.05 and P < 0.01 |
| Romero-Gomez et al.[11] | 2005 | Spain | 50 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | All | In SVR, P < 0.05 |
| Kawaguchi et al.[25] | 2007 | Japan | 89 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | All | In SVR, P < 0.01 |
| Chehadeh et al.[30] | 2009 | Kuwait | 181 | DM, non cirrhotic | FPG | Univariate | Yes | G4 | In SVR, P < 0.001 |
| Kim et al.[31] | 2009 | Korea | 28 | DM, non cirrhotic | HOMA-IR | Multivariate | Yes | G1, G2 | In SVR, OR of decreased IR 50 [3.74, 668.35]; P = 0.003 |
| Conjeevaram et al.[28] | 2011 | United States | 341 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | G1 | In SVR; P = 0.001 |
| Khattab et al.[29] | 2012 | Egypt | 107 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | G4 | In SVR; P = 0.01 |
| Thompson et al.[32] | 2012 | United States | 1038 | DM, non cirrhotic | HOMA-IR | Multivariate | Yes | All | In G1 SVR; P = 0.007 |
| Serfaty et al.[33] | 2012 | France | 161 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | G1 | In SVR; P < 0.05 |
| Ziada et al.[34] | 2012 | Egypt | 140 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | All | P = 0.009 |
| Chan et al.[35] | 2013 | Australia | 86 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | All | In SVR, P = 0.04 |
| Jung et al.[36] | 2014 | South Korea | 60 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | All | In SVR, P = 0.036 |
| Mello et al.[37] | 2006 | Brazil | 30 | DM, non cirrhotic | HOMA-IR, SI and ISI | Univariate | Yes | G1, G2 | In SVR; P = 0.002 and ISI P = 0.009 |
| Kawaguchi et al.[38] | 2009 | Japan | 72 | DM, non cirrhotic | HOMA-IR | Univariate | Yes | All | In SVR, SI P = 0.002 and ISI P = 0.009 |
| Brandman et al.[39] | 2012 | United States | 23 | Non cirrhotic | SSGP | Univariate | No | No | NS |

Occurrence of glucose abnormalities after HCV treatment

| Ref. | Year | Country | Number of HCV patients | Patient profile | Glucose metabolism parameter | Statistical method | Significant association or difference | Genotypes | Statistics |
|------|------|---------|------------------------|-----------------|------------------------------|-------------------|----------------------------------------|------------|------------|
| Simó et al.[40] | 2006 | Spain | 234 | DM or IGT | FPG and F1 | Multivariate | Yes | All | In SVR, OR = 0.48 [0.24, 0.84]; P = 0.04 |
| Romero-Gomez et al.[41] | 2008 | Spain | 1059 | DM or IGT | DM or IGT | Multivariate | Yes | All | In SVR, OR = 0.44 [0.2, 0.97]; P = 0.04 |
| Arase et al.[42] | 2009 | Japan | 2842 | DM | DM | Multivariate | Yes | All | In SVR, HR = 0.36 [0.24; 0.56] |
| Aghemo et al.[43] | 2012 | Italy | 339 | DM | HOMA-IR | Multivariate | Yes | All | In SVR, OR = 0.36 [0.18, 0.72]; P = 0.004 |
| Giordanino et al.[44] | 2008 | Italy | 202 | DM | DM or IGT | Multivariate | Yes | All | NS |

1Association 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; F1: Fasting insulin; IGT: Impaired glucose tolerance; ISI: Insulin sensitivity index; SI: Serum insulin; SSGP: Steady-state plasma glucose; NS: Not significant.

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

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].
Desbois AC et al. Diabetes, insulin resistance and HCV

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[[13]]  | 2014 | France  | 162            | HCC, not treated for HCV | DM and HCC  | Multivariate       | Yes³                  | HR = 3.13 [1.17, 8.38]; P = 0.022² |
| Hung et al[[29]]      | 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[[29]]      | 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[[30]]   | 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[[31]]   | 2011 | Egypt   | 100            | 50 HCC; 50 non-HCC | HOMA-IR and HCC | Multivariate       | No                    | NS         |
| Diabetes mellitus/insulin resistance and development of HCC in HCV-infected patients |
| Chen et al[[32]]      | 2008 | Taiwan  | 1095           | -               | DM and HCC  | Multivariate       | Yes                   | OR = 3.52 [1.29, 9.24] |
| Veldt et al[[33]]     | 2008 | Europe  | 541            | -               | DM and HCC  | Multivariate       | Yes³                  | OR = 3.28 [1.35, 7.97]; P = 0.009² |
| Konishi et al[[34]]   | 2009 | Japan   | 197            | Non DM, treated for HCV | DM² and HCC  | Multivariate       | Yes                   | HR = 4.63 [1.677, 12.766]; P = 0.003 |
| Hung et al[[35]]      | 2010 | Taiwan  | 1470           | Treated for HCV  | DM and HCC  | Multivariate       | Yes³                  | HR = 4.32 [1.23, 15.25]; P = 0.023² |
| Nkontchou et al[[36]] | 2010 | France  | 248            | Cirrhotics       | HOMA-IR and HCC | Multivariate       | Yes                   | HR = 4.10 [1.01, 1.21]; P = 0.026 |
| Takahashi et al[[37]] | 2011 | Japan   | 203            | Non DM, treated for HCV | DM² and HCC  | Multivariate       | Yes                   | HR = 6.9 [1.7, 28.4]; P < 0.05 |
| Arase et al[[38]]     | 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[[39]]   | 2014 | France  | 348            | Cirrhotics       | DM           | Multivariate       | Yes                   | HR = 1.938 [1.129, 3.328]; P = 0.016 |
| Toyoda et al[[40]]    | 2015 | Japan   | 522            | Patients with SVR | DM and HCC  | Multivariate       | Yes                   | HR = 2.08 [1.0170, 4.0133]; P = 0.045 |
| Lai et al[[41]]       | 2006 | Taiwan  | 2141           | -               | DM and HCC  | Multivariate       | No                    | NS         |
| Chen et al[[42]]      | 2013 | Taiwan  | 5186           | -               | DM and HCC  | Multivariate       | No                    | NS         |

¹Association of abnormal post-challenge hyperglycaemia and HCC; 2 Only in SVR patients without cirrhosis; ³Only 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.\textsuperscript{[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.\textsuperscript{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 Receptor 1 (sTNFR1) and sTNFR2 levels.\textsuperscript{37} Increased abnormal HOMA-IR was not associated with elevated serum levels of TNF\(_\alpha\), IL6 and adiponectin in another study.\textsuperscript{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.\textsuperscript{39} Interferon alpha 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 (SOCS3), which inhibits insulin phosphorylation of AKT and phosphoinositide 3-kinase (PI3K)\textsuperscript{40}. HCV may be involved in the regulation of phosphorylation of insulin receptor substrate 1 (ISR-1), implicated in the insulin pathway.\textsuperscript{41} In HCV core transgenic mice, the viral protein was able to induce increasing TNF\(_\alpha\) levels in the liver, which in turn promoted the induction of IR. The high levels of TNF\(_\alpha\) 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 alpha 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 alpha.\textsuperscript{20,22-25,34} Many studies found a decreased rate of glucose abnormalities in HCV patients who showed a SVR after interferon alpha-based therapy, and even in non virological responders in one study.\textsuperscript{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.\textsuperscript{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 alpha-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 underestimate the impact of DM/IR. Our data is consistent with recent studies that demonstrated that DM increases cumulative incidence of decompensated cirrhosis.\textsuperscript{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.\textsuperscript{45}

Experimental data suggest that increased insulin levels after hyperglycaemia leads to interferon signalling impairment. Insulin may inhibit the ability of interferon alpha 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 alpha pathway.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{49} Pioglitazone may alter NK cell functions and thus impair clearance of infected hepatocytes.\textsuperscript{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\cite{55}. 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\cite{54}. 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, $P = 0.37$)\cite{55}. 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 and improved 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.

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