



**HAL**  
open science

## **Meta-analysis: Insulin resistance and sustained virological response in hepatitis C**

Mohammed Eslam, Reyes Aparcero, Takumi Kawaguchi, José A. del Campo, Michio Sata, Mahmoud A Khattab, Manuel Romero-Gomez

► **To cite this version:**

Mohammed Eslam, Reyes Aparcero, Takumi Kawaguchi, José A. del Campo, Michio Sata, et al.. Meta-analysis: Insulin resistance and sustained virological response in hepatitis C. *Alimentary Pharmacology and Therapeutics*, 2011, 34 (3), pp.297. 10.1111/j.1365-2036.2011.04716.x . hal-00646005

**HAL Id: hal-00646005**

**<https://hal.science/hal-00646005>**

Submitted on 29 Nov 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Meta-analysis: Insulin resistance and sustained virological response in hepatitis C**

Journal:	<i>Alimentary Pharmacology &amp; Therapeutics</i>
Manuscript ID:	APT-0202-2011.R2
Wiley - Manuscript type:	Meta-analysis
Date Submitted by the Author:	07-May-2011
Complete List of Authors:	Eslam, Mohammed; Hospital Universitario de Valme, Anenida de Bellavista s/n, Sevilla 41014, Spain, Unit for The Clinical Management of Digestive Diseases and CIBERehd Aparcero, Reyes; Hospital Universitario de Valme, Anenida de Bellavista s/n, Sevilla 41014, Spain, The Clinical Management of Digestive Diseases and CIBERehd Kawaguchi, Takumi; Kurume University School of Medicine, Kurume 830-0011, Department of Digestive Disease Information & Research and Department of Medicine Del Campo, José; Hospital Universitario de Valme, Anenida de Bellavista s/n, Sevilla 41014, Spain, Unit for The Clinical Management of Digestive Diseases and CIBERehd Sata, Michio; Kurume University School of Medicine, Kurume 830-0011, Department of Digestive Disease Information & Research and Department of Medicine Khattab, Mahmoud; Minya University, Internal Medicine, GIT and hepatology Romero-Gomez, Manuel; Hospital Universitario de Valme, Anenida de Bellavista s/n, Sevilla 41014, Spain, Unit for The Clinical Management of Digestive Diseases and CIBERehd
Keywords:	Hepatitis C < Hepatology, Viral hepatitis < Hepatology, Liver < Organ-based, Meta-analyses < Topics

1  
2  
3 The Editor: *Alimentary pharmacology & therapeutic*  
4  
5  
6  
7

8 Sevilla, Mayo 6th, 2011  
9

10 **Re: Meta-analysis: Insulin resistance and sustained virological response in**  
11 **hepatitis C.**  
12  
13

14  
15  
16  
17 Dear Editor,  
18

19  
20 Thanks for the acceptance of our manuscript. We have read, with interest, your minor  
21  
22 modifications. In submitting this revised version of the manuscript, we have  
23  
24 introduced the appropriate changes in the text (highlighted).  
25  
26  
27

28  
29 Yours sincerely,  
30  
31  
32

33  
34 Manuel Romero-Gómez, MD, PhD  
35

36 Director  
37

38 Unit for the Clinical Management of Digestive Diseases and ciberehd,  
39

40 Hospital Universitario de Valme,  
41

42 Universidad de Sevilla,  
43

44 41014 Sevilla,  
45  
46

47 Spain  
48  
49

50 Fax: (+34) 955 01 58 99; Tel: (+34) 955 01 57 61  
51

52  
53 E-mail: mromerogomez@us.es  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

**Meta-analysis: Insulin resistance and sustained virological response in hepatitis C.**

Mohammed Eslam<sup>1</sup>, Reyes Aparcero<sup>1</sup>, Takumi Kawaguchi<sup>2</sup>, José A. Del Campo<sup>1</sup>,  
Michio Sata<sup>2</sup>, Mahmoud Abo-Elneen Khattab<sup>3</sup>, Manuel Romero-Gomez<sup>1</sup>

From:

<sup>1</sup> Unit for The Clinical Management of Digestive Diseases and CIBERehd, Hospital  
Universitario de Valme, Anenida de Bellavista s/n, Sevilla 41014, Spain

<sup>2</sup> Department of Digestive Disease Information & Research and Department of  
Medicine, Kurume University School of Medicine, Kurume 830-0011, Japan

<sup>3</sup> Department of Internal Medicine, Minia University, Minia, Egypt

**Conflict of Interest: None**

**Author contribution:** All authors contributed equally to this article

**Financial support:** None

**Potential competing interests:** None

**Correspondence to:**

**Manuel Romero-Gómez, MD**, Unit for The Medical & Surgical Management of  
Digestive Diseases and CIBERehd, Hospital Universitario de Valme, Avenida de  
Bellavista s/n, Sevilla 41014, Spain. [mromerogomez@us.es](mailto:mromerogomez@us.es)

Telephone: (+34) 955-015761 Fax: (+34) 955-015899

1  
2  
3 **Licence for Publication:** The Corresponding Author has the right to grant on behalf of  
4 all authors and does grant on behalf of all authors, an exclusive licence (or non  
5 exclusive for government employees) on a worldwide basis to the Scholar one  
6 Publishing Group and its Licensees to permit this article (if accepted) to be published in  
7 Alimentary pharmacology& therapeutic editions and any other Scholar one products to  
8 exploit all subsidiary rights, as set out in our licence.  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

### Abstract

**Background&aim:** Higher baseline homeostasis model assessment of insulin resistance (HOMA-IR) score predicted poorer sustained virological response (SVR) rate to peginterferon/ribavirin therapy in treatment-naïve chronic hepatitis C (CHC) patients. We conducted a meta-analysis to evaluate the impact of HOMA-IR on SVR in hepatitis C.

**Methods:** Relevant studies were identified by searching Medline and EMBASE. We identified 17 publications that addressed the influence of insulin resistance (IR) on SVR. The random effect model of Der Simonian and Laird method were used for heterogeneous studies using the Meta-Disc software 1.4, Madrid, Spain.

**Results:** Normal insulin sensitivity was associated with a higher rate of SVR (odds ratio (OR) 2.86 (95% CI: 1.97 to 4.16) in comparison with insulin resistance (IR). Moreover, in separate analysis by genotype selecting studies that used HOMA-IR>2 as cut-off defining IR, SVR was higher in patients with HOMAIR<2 in all genotypes: HCV-1, (O.R.:2.16(95%CI:1.51-3.08), HCV-2&3 (O.R.:3.06(95%CI:1.06-8.82) and HCV-4 (O.R.:6.65(95%CI:2.51-17.61). Studies reporting no association between HOMA and SVR included easy-to-cure cohorts, analyzed variables strongly related with IR like body mass index, steatosis, hyper  $\gamma$ GT, age and fibrosis, and reported differences in handling and interpretation of HOMA-IR.

**Conclusion:** Elevated HOMA-IR was associated with a lower cure rate of patients with hepatitis C treated with Peg-IFN- $\alpha$ /ribavirin irrespective of genotype, and the more difficult-to-treat cohort the better the HOMA-IR prediction. HOMA-IR is as a surrogate marker of IR susceptible to some biases derived from both handling and interpretation.

[Word count = 240]

**Key words:**

*Hepatitis C virus, Insulin resistance, HOMA-IR, sustained virological response*

**Introduction**

Worldwide approximately 200 million people are chronically infected with hepatitis C virus [1]. Chronic HCV infection is characterized by a high rate of fibrosis progression, leading to cirrhosis and ultimately to hepatocellular carcinoma[2,3]. Combination therapy with pegylated interferon alpha and ribavirin (Peg- FN/RBV) represents the current standard of care in chronic HCV [4,5]. Despite the improvements in sustained virologic response (SVR) seen using combination of Peg- FN plus weight-based RBV, SVR rates in genotypes 1 and 4 populations have remained unsatisfactory with reported SVR rates of 28.9% to 54% [6,7]. Even more unsatisfactory SVR rates on the order of 10% to 20% have been seen in difficult-to-treat populations such as African Americans, Hispanics, or insulin-resistant patients [6-8]. Studying the factors influencing SVR in patients with HCV treated with Peg- FN/RBV has been assiduously pursued over the past two decades. Now; there is a great interest by the importance of host factors such as fibrosis progression, genetic factors and metabolic disorders and these have been invoked to explain the reported differences in SVR [9]. Insulin resistance (IR) is the main feature of metabolic syndrome and is characterised by hyperinsulinaemia in patients with normal fasting glucose. It has been associated with increased risk of developing diabetes mellitus (T2DM), cardiovascular disease and non-alcoholic fatty liver disease [10]. Accumulating large body of literature, including molecular, pathological, epidemiological, randomised controlled trials and observational studies, has highlighted the interaction between HCV and glucose metabolism (IR/T2DM) [11,12,13,14,15,16]. Although, earlier works referred to that a higher baseline homeostasis

1  
2  
3 model assessment of insulin resistance (HOMA-IR) score predicted a poorer SVR rate  
4 to Peg-IFN- $\alpha$ /ribavirin in treatment-naïve chronic hepatitis C patients [<sup>8,17,18,19,20</sup>]; this  
5 data was not universally confirmed by all studies [<sup>21</sup>]. In the view of the suboptimal  
6 response to the current standard in therapy; these postulated correlation between IR and  
7 SVR has gain a great importance, as one of the modifiable risk factor. Therefore, we  
8 performed a systematic review and meta-analysis to review the literature systematically  
9 to evaluate, quantify, and summarize the association between HOMA and SVR.

## 19 **Methods**

### 22 **Study Selection Criteria**

23  
24 Inclusion and exclusion criteria were defined prior to commencement of the literature  
25 search. Studies were included if they met the following criteria: they included  
26 treatment-naïve HCV patients aged older than 18 years regardless HCV genotype or the  
27 ethnic group; they provided information on SVR rates; and they were reported in  
28 English as full papers. Studies were excluded if they met the following criteria: they did  
29 not provide information on SVR; they did not allow correlation between the HOMA-IR  
30 and SVR; they included patients who were treated with nonpegylated interferons; they  
31 included patients with additional antivirals to Peg- FN/RBV (eg, amantadine); they  
32 included patients who were not treatment-naïve; they included human  
33 immunodeficiency virus (HIV) coinfecting patients; they included liver transplant  
34 recipients; letters/case reports, studies enrolling fewer than 10 subjects, or articles not  
35 reporting outcomes of interest or primary data (editorials, reviews).

### 52 **Literature Search, Study Selection, and Data Extraction**

53  
54 We searched MEDLINE and EMBASE for studies published in English through  
55 December 2010 using a combination of the following terms: "Hepatitis C"[Mesh] OR  
56 "Hepacivirus"[Mesh] OR "Hepatitis C, Chronic"[Mesh]) AND "Insulin  
57  
58  
59  
60

1  
2  
3 resistance"[Mesh] OR "Homeostasis Model of Assessment"[Mesh] AND "Sustained  
4 virological Response"[Mesh]. Manual search of cited bibliographies was also  
5 performed. Only fully published articles were considered. Two researchers  
6 independently performed the literature search and data abstraction with regard to the  
7 inclusion and exclusion criteria by reading titles and abstracts. When reading titles and  
8 abstracts did not allow identification of eligible studies, articles were read in full.  
9 Relevant reviews and letters to the editor were excluded from the analysis, but read in  
10 full in order to identify potential relevant original studies. Disagreements between the 2  
11 observers were resolved by discussion. Data from selected studies were extracted in a  
12 data sheet by MRG author and checked by a second author (ME). Disagreements could  
13 be resolved by discussion. The following data were extracted: year of publication,  
14 number of patients, cutoff of HOMA-IR to define IR, method of measurement of  
15 insulin, percentage of patients with normal insulin sensitivity and percentage of patients  
16 with advanced fibrosis.

### 36 **End Point**

37  
38 The main endpoint was the SVR rate, defined as the percentage of patients with  
39 undetectable HCVRNA (<50 IU/ mL) 24 weeks after treatment completion of therapy.  
40  
41

### 43 **Statistical analysis**

44  
45 Statistical analysis was performed by using the Meta-Disc software 1.4 (Zamora J, et  
46 al., BMC Medical Research Methodology 2006, 6:31.) has been used, considering: i) a  
47 summary of data from individual studies, ii) an investigation of the studies homogeneity  
48 graphical and statistically, iii) calculation of clustered indexes and iv) exploration of  
49 heterogeneity. Our assumption of heterogeneity was tested for each planned analysis  
50 using the Cochran-Q heterogeneity test. Random effects model by Der Simonian and  
51 Laird method was considered when heterogeneity was found. Only 2-sided tests with a  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 significance level of 0.05 were used. Confidence intervals (CIs) of individual studies  
4  
5 were determined or approximated from the available data.  
6  
7

## 8 **Results**

9  
10 Seventeen eligible studies fulfilled the inclusion and exclusion criteria are enrolled in  
11  
12 the analysis (<sup>8,17-21,22,23,24,25,26,27,33,38,43</sup>), three studies without SVR rate according to  
13  
14 baseline HOMA-IR were further excluded (**Figure 1**). The characteristics of these  
15  
16 studies are shown in **Table 1**. Five studies were from Italy, 3 from Japan, 2 from  
17  
18 Taiwan, 1 from Spain, United Kingdom, USA, France, India and Egypt. The used cutoff  
19  
20 values for diagnosis of IR ranged from HOMA>2 in 10 studies to HOMA > 2.5 in 1  
21  
22 study, HOMA>2.7 in 1 study, HOMA>3 in 1 study and HOMA>3.5 in 1 study and was  
23  
24 not available data in three studies. Nine studies found a statistically a significant  
25  
26 association between HOMA-IR and SVR, and the other 5 studies did not find a  
27  
28 significant association between HOMA-IR and SVR (**Figure 2 and Table 1**). Three of  
29  
30 enrolled studies did not show SVR rate according to HOMA-IR. Thus, pooled data  
31  
32 included 2129 patients in 14 studies. The meta-analysis including all 14 studies  
33  
34 demonstrated that insulin resistance was associated with a remarkably lower likelihood  
35  
36 of SVR, using random effects model by Der Simonian and Laird method, odds ratio was  
37  
38 2.86 (95% CI: 1.97 to 4.16) regardless of genotype (**Figure 2**). The test of heterogeneity  
39  
40 (Cochran-Q=36.92; df=13; p=0.0004) inconsistency  $I^2 = 64.8\%$  and Tau-squared =  
41  
42 0.287. Sub-analysis including patients segregated by genotype 1, 2/3 or 4 demonstrated  
43  
44 a negative and significant impact of increased HOMA-IR on SVR; three studies mixed  
45  
46 genotypes were included and were separately analyzed (17, 21, 39) (**Table 2, Figure 3,**  
47  
48 **4, 5**). Even with limiting the analysis to include only studies using cut-off HOMA > 2  
49  
50 for defining IR, the impact on SVR was maintained. Patients with HOMA-IR >2 had  
51  
52 significantly lower rates of SVR compared with patients with HOMA-IR < 2, and this  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 difference was largely independent of HCV genotype: HCV-1 (O.R.:2.16;95%CI:1.51-  
4 3.08), HCV-2&3 (O.R.:3.06;95%CI:1.06-8.82) and HCV-4 (O.R.:6.65;95%CI:2.51-  
5 17.61). The difference in SVR rate in patients with IR compared to those with insulin  
6 sensitivity ranged from 3% to 41% in genotype 1, 5% to 57% in genotype 2/3 and 38%  
7 to 48% in genotype 4. The risk estimate for not achieving SVR from 10 studies using  
8 HOMA-IR > 2 as cutoff value for diagnosis of IR was 3.1 fold. Similarly, the pooled  
9 estimates from 11 studies enrolled patients infected with HCV genotype 1 indicate a  
10 statistically significant 2.16-fold decrease in the incidence of SVR among patients with  
11 IR. Some studies that found no association were characterized by including cohorts of  
12 patients with a mean HOMA-IR <3 and without advanced fibrosis. In these studies;  
13 multivariate analysis demonstrated independent variables associated with SVR strongly  
14 related to metabolic abnormalities showing a tight co-linearity with HOMA-IR like  
15 body mass index, steatosis, elevated  $\gamma$ -glutamyl-transpeptidase (GGT), age and fibrosis.  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33

### 34 Discussion

35  
36 This meta-analysis of published studies indicates that IR assessed by HOMA-IR  
37 is associated with an approximately three fold increase in risk of failure to achieve SVR  
38 to Peginterferon+ribavirin in treatment naive patients with hepatitis C regardless of viral  
39 genotype. The discrepancy between the results of the cohorts in this review may be  
40 referred to fact that the interaction between IR and SVR are very complex depends on  
41 numerous factors that need to be considered when interpreting the data: a) measurement  
42 and interpretation of HOMA-IR; b) colinearity between HOMA-IR and variables  
43 associated with metabolic derangements; and c) the characteristics of the cohort under  
44 study. HOMA-IR which was developed by Matthews et al [28] as an indirect surrogate  
45 marker of IR hampered by many concerns, which may influence the extracted data.  
46 These factors includes; methods of measurement of insulin, handling of blood samples,  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 the conversion factor between SI units and mU/ml, the formula to calculate HOMA-IR  
4  
5 and the threshold to define IR. For example: a) Insulin assays are not standardized and  
6  
7 are not comparable between studies. Insulin inter-assay variations can be large, and  
8  
9 values have varied considerably between different laboratories [<sup>29,30</sup>] b) careful handling  
10  
11 of the blood samples is essential because hemolysis results in the degradation of insulin,  
12  
13 while freezing the samples results in the degradation of C-peptide and glucose, with  
14  
15 false-negative results being one of the consequences. c) Insulin should be reported in  
16  
17 International Units (SI), but the conversion factor from microUnits/mL to SI units is not  
18  
19 uniform among manufacturers; values ranging between 6 and 7.15 with no real  
20  
21 scientific justification [<sup>31</sup>]. d) HOMA-IR could be calculated using the formula from  
22  
23 Matthews et al. or using the HOMA-2 calculator (available at  
24  
25 <http://www.dtu.ox.ac.uk/homacalculator/>). However, results from both methods are  
26  
27 quite different and could bias the final analysis in comparative studies. e) Since insulin  
28  
29 secretion is pulsatile, the use of a single fasting blood sample to diagnose IR in CHC,  
30  
31 although convenient, potentially underestimates the prevalence and degree of this  
32  
33 disturbance. The mean value from three samples taken at 5-min intervals to compute  
34  
35 HOMA is, theoretically, better than a single sample determination [<sup>22</sup>]. However, in  
36  
37 practice a single sample is often taken and, if population estimators are found, this is an  
38  
39 acceptable compromise that yields a similar result for large datasets. No evidence is  
40  
41 available in setting of CHC patients. f) Ultimately; till now; there is no international  
42  
43 consensus regarding the threshold that defines IR by using HOMA-IR. Recently, Lam et  
44  
45 al. showed that HOMA-IR >4 was the optimal value defining IR in hepatitis C setting  
46  
47 when compared with steady-state plasma glucose [<sup>32</sup>]. However, these data need to be  
48  
49 further confirmed in different populations, using euglycaemic hyperinsulinaemic clamp  
50  
51 as gold-standard, and taking ethnicity and obesity into account when evaluating changes  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 in HOMA-IR over time [26]. Second; HOMA-IR shows a strong colinearity, with  
4  
5 several variables implicated in metabolic disturbances such as obesity, hepatocyte  
6  
7 steatosis, elevated GGT, fibrosis and older age. All these variables provide information,  
8  
9 at least in part, on the metabolic abnormalities occurring in the individual, the final  
10  
11 outcome of the multivariate analysis depending on the interactions between them.  
12  
13 Interestingly in our review to the negative studies that failed to find an association  
14  
15 between IR and SVR; the mean baseline HOMA-IR was <3 in all studies, and the  
16  
17 prevalence of advanced fibrosis or cirrhosis was also lower or even these studies had  
18  
19 excluded cirrhosis or had been under-powered. This observation supporting the idea that  
20  
21 the more difficult-to-treat cohort the better the HOMA-IR prediction. In one of the  
22  
23 negative studies, when HOMA-IR was excluded from the multivariate model, one of  
24  
25 these variables emerged as independently associated with SVR. This highlights this type  
26  
27 of statistical bias is very difficult to resolve when strongly related variables were  
28  
29 included in the analysis. Indeed, Dai et al [17] demonstrated that the association of  
30  
31 HOMAIR with SVR was stronger in cohorts including very difficult- to-treat patients.  
32  
33 Ultimately; when more sophisticated methods to measure IR (such as whole-body  
34  
35 insulin sensitivity) were used, a stronger association was reported between IR and SVR  
36  
37 [33]. Thirdly; several viral and host factors have an impact on response to treatment  
38  
39 [34,35], these factors may influence the final outcome and explain the difference of  
40  
41 results of these cohorts. Further study is needed to clarify the interaction of genotype,  
42  
43 the degree of IR, gender, and genetics (such as the IL28 $\beta$  mutation) and viral kinetics.  
44  
45 This Meta-analysis has undoubtedly some limitations, since there is heterogeneity in the  
46  
47 enrolled studies including characteristics cohort, methods for insulin measurement and  
48  
49 HOMA-IR interpretation may have influenced on the concluded results.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 In conclusion, this meta-analysis provides evidence that impaired HOMA-IR was  
4 associated with a lower cure rate of patients with hepatitis C treated with Peg- FN/RBV.  
5  
6  
7  
8 The differences are greater in cohorts of patients who are difficult to cure (higher insulin  
9 resistance, higher prevalence of advanced fibrosis). The inherent limitations in the  
10 determination and calculation of HOMA-IR may explain, at least in part, the variability  
11 detected in the results. Better handling and interpretation of HOMA are mandatory until  
12 the development of new tools for assessment of insulin resistance.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

**Table 1: studies included in meta-analysis addressing the impact of HOMA on sustained virological response**

Table 1: studies included in meta-analysis addressing the impact of HOMA on sustained virological response

Author	year	HOMA Cut-off	SVR association	Insulin method	mean HOMA-IR (SD)	% patients with IS	Genotype	n	SVR in IS	non-SVR in IS	SVR in IR	non-SVR in IR	Delta %SVR IS - IR	O.R. (95%CI)
Akuta et al	2009	3.5	NO	NA	2.6 (2.6)	0,28	1	123	11	9	26	26	0,05	0.82(0.29-2.33)
Bortoletto et al	2010	3	YES	EIA	1.9 (1.1)	0,61	1	36	8	14	2	12	0,22	0.29(0.051-1.49)
Camma et al (*)	2006	NA	NO	NA	2.65 (2.01)		1	291	NA	NA	NA	NA		NA
Chu et al.	2008	2	YES	EIA	2.93 (0.14)	0,31	1	133	38	3	50	42	0,38	0.14(0.005-0.54)
Conjeevaram et al	2007	2	YES	NA	3.5 (5.0)	0,33	1	399	65	68	96	170	0,13	0.87(0.77-0.99)
Dai et al.	2009	2.5	YES	RIA	2.24 (2.46)	0,71	1	150	75	31	22	22	0,21	0.87(0.75-0.97)
Fattovich et al	2010	2	NO	ECLIA	2.7 (2.5)	0,44	1	181	37	43	44	57	0,03	0.9(0.5-1.64)
Grasso et al	2009	2	NO	EIA	2.6 (2.1)	0,77	1	90	34	35	8	13	0,11	0.63(0.23-1.72)
Miyaaki et al	2009	2	NO	NA	1.9 (0.87)	0,51	1	39	11	9	6	13	0,23	0.37(0.1-1.38)
Mizuta et al	2010	2	YES	NA	1.92 (1.92)	0,51	1	51	17	9	6	19	0,41	0.17(0.049-0.57)
Petta et al.	2009	2.7	NO	EIA	2.73 (1.69)	0,65	1	83	32	22	14	15	0,11	0.64(0.17-3.03)
Romero-Gomez et al.	2005	2	YES	ECLIA	3.01 (2.67)	0,38	1	113	26	17	23	47	0,28	0.55(0.33-0.93)
Walsh et al (*)	2006	NA	NO	NA	2.02 (0.19)		1	66	NA	NA	NA	NA		NA
Bortoletto et al	2010	3	YES	EIA	1.9 (1.1)	0,67	2&3	21	14	0	3	4	0,57	NC
Dai et al.	2009	2.5	NO	RIA	2.24 (2.46)	0,71	2&3	180	117	11	44	8	0,07	0.87(0.75-0.97)
Fattovich et al	2010	2	NO	ECLIA	2.7 (2.5)	0,57	2&3	209	93	26	66	24	0,05	0.8(0.42-1.54)
Poustchi et al.	2008	2	YES	RIA	3.34 (3.34)	0,41	2&3	82	32	2	31	17	0,30	0.15(0.03-0.77)
Walsh et al (*)	2006	NA	NO	NA	2.02 (0.19)		2&3	79	NA	NA	NA	NA		NA
Khatab et al.	2010	2	YES	ECLIA	2.82 (1.19)	0,40	4	131	47	6	32	46	0,48	0.07(0.01-0.43)
Moucari et al	2009	2	YES	ECLIA	3.7 (4.0)	0,49	4	108	39	20	14	35	0,38	0.19(0.07-0.51)
(*) Not included in meta-analysis due to lack of data								2565						
HOMA: Homeostasis Model of Assessment														
SVR: Sustained virological response														
SD: Standard deviation														
O.R.: Odds ratio														
IS: Insulin sensitivity (HOMA under cut-off)														
IR: Insulin resistance (HOMA above cut-off)														
NA: Non-available														
ECLIA: Electrochemiluminescence Immunoassay														
EIA: Enzyme Immunoassay														
RIA: Radio Immuno Assay														
NC: Calculation not allowed														

**Table 2: Random effect Model for pooled data according to genotypes.**

Genotype	Studies number	Pooled data O.R.(95%CI)	Heterogeneity (Cochran-Q)	Inconsistency
All	14	0.35 (0.24- 0.51)	36.92 p=0.0004	I <sup>2</sup> =64.8%
Genotype 1	11	0.46 (0.32 – 0.66)	18.05 p=0.05	I <sup>2</sup> =44.6%
Genotype 2&3	4	0.33 (0.11-0.94)	8.78 p=0.03	I <sup>2</sup> =65.8%
Genotype 4	2	0.15 (0.05 - 0.40)	2.35 p=0.12	I <sup>2</sup> =57.4%
HOMA cut- off 2	10	0.33 (0.20 - 0.53)	35.9 P=0.0001	I <sup>2</sup> =72.1%

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Figure 1. Chart flow of studies screened and included in meta-analysis**

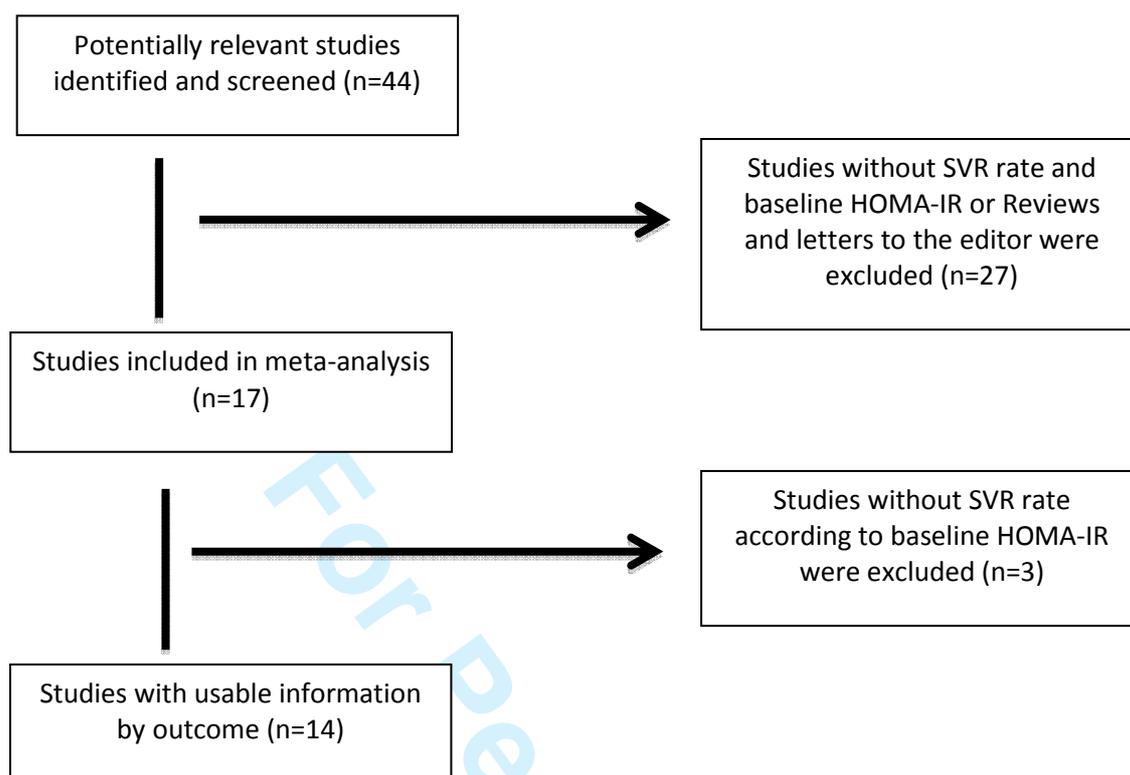


Figure 2. Odd Ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in chronic hepatitis C patients treated with interferon + ribavirin in 14 studies. Black boxes indicate point estimates for OR.

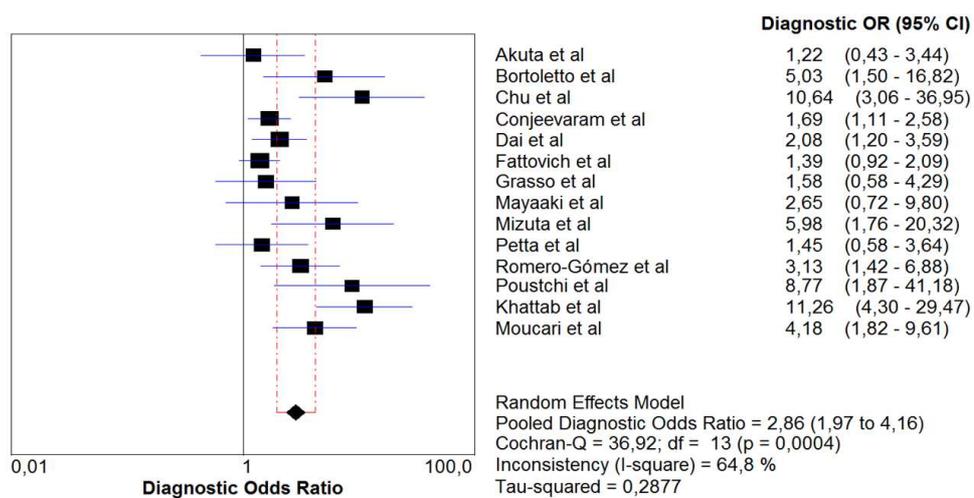


Figure 3. Odd Ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in genotype 1 chronic hepatitis C patients treated with interferon + ribavirin in 11 studies. Black boxes indicate point estimates for OR

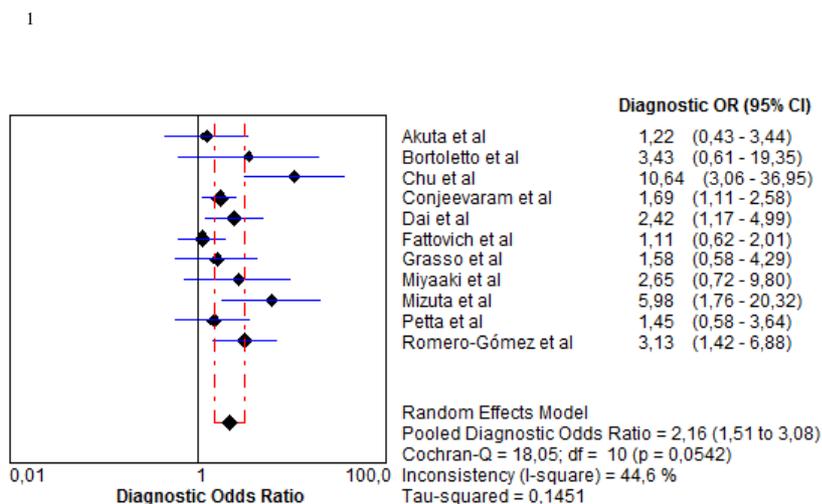


Figure 4. Odd Ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in genotype 2 and 3 chronic hepatitis C patients treated with interferon + ribavirin in 4 studies. Black boxes indicate point estimates for OR

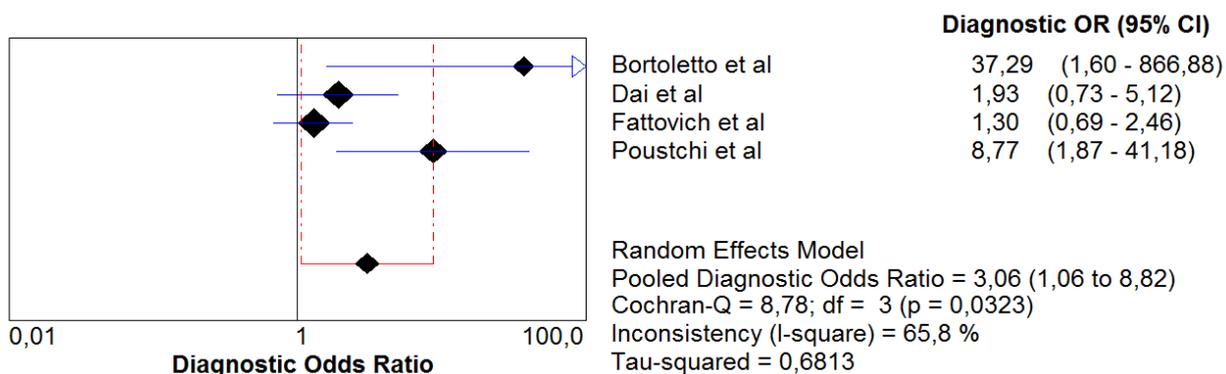


Figure 5. Odd Ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in genotype 4 chronic hepatitis C patients treated with interferon + ribavirin in 2 studies. Black boxes indicate point estimates for OR

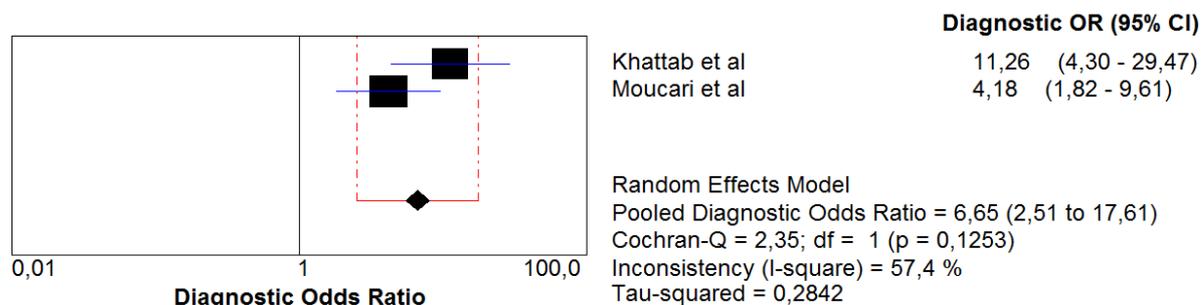
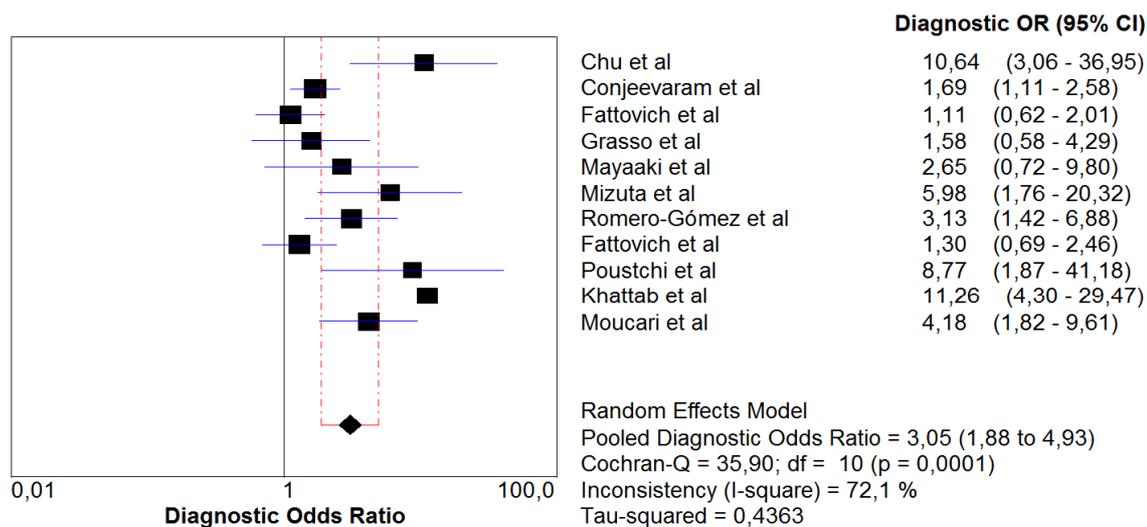


Figure 6. Odd Ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in chronic hepatitis C patients treated with interferon + ribavirin in 10 studies using HOMA-IR > 2 as cut-off defining insulin resistance. Black boxes indicate point estimates for OR



## REFERENCES

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 
- <sup>1</sup> World Health Organisation. Weekly epidemiological record. *Wkly Epidemiol* 363 Rec. 77:41-48 (2002).
- <sup>2</sup> Alter MJ. The epidemiology of acute and chronic hepatitis C. *Clin Liver Dis* 1997;**1**:559–569.
- <sup>3</sup> Seeff LB. The history of the “natural history” of hepatitis C (1968–2009). *Liver Int* 2009;**29**(Suppl. 1):89–99.
- <sup>4</sup> Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335–74.
- <sup>5</sup> APASL Consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. APASL Hepatitis C Working Party, et al. *J Gastroenterol Hepatol* 2007;**22**L615-33.
- <sup>6</sup> Fried MW, Jensen DM, Rodriguez-Torres M, et al. Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: randomized study of higher doses of peginterferon  $\alpha$ -2a and ribavirin. *Hepatology* 2008;**48**:1033–1043.
- <sup>7</sup> Rodriguez-Torres M, Jeffers LJ, Sheikh MY, et al. Peginterferon alfa-2a and ribavirin in Latino and non-Latino whites with hepatitis C. *N Engl J Med* 2009;**15**:257–276.
- <sup>8</sup> Romero-Gomez M, Del mar Vilorio M, Andrade RJ, et al. Insulin resistance impairs sustained virologic response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005;**128**:636–641.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

---

<sup>9</sup> Khattab MA. Targeting host factors: A novel rationale for the management of hepatitis C virus. *World J Gastroenterol* 2009;**15**(27): 3471-3479.

<sup>10</sup> Cannon CP. Mixed dyslipidemia, metabolic syndrome, diabetes mellitus, and cardiovascular disease: clinical implications. *Am J Cardiol* 2008; **102**: 5L-9L.

<sup>11</sup> Shintani Y, Fujie H, Miyoshi H, *et al.* Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology* 2004; **126**: 840-48.

<sup>12</sup> Paziienza V, Clément S, Pugnale P, *et al.* The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. *Hepatology* 2007; **45**:1164-71.

<sup>13</sup> Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. *J Hepatol* 1994; **21**: 1135-9.

<sup>14</sup> White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol* 2008; **49**:831-44.

<sup>15</sup> Kawaguchi T, Ide T, Taniguchi E, *et al.* Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *Am J Gastroenterol* 2007; **102**: 570-6.

<sup>16</sup> Romero-Gómez M, Fernández-Rodríguez CM, Andrade RJ, *et al.* Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. *J Hepatol* 2008; **48**: 721-7.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

---

<sup>17</sup> Dai CY, Huang JF, Hsieh MY, *et al.* Insulin resistance predicts response to peginterferon-alpha/ribavirin combination therapy in chronic hepatitis C patients. *J Hepatol* 2009;**50**:712–718.

<sup>18</sup> Chu CJ, Lee SD, Hung TH, *et al.* Insulin resistance is a major determinant of sustained virologic response in genotype 1 chronic hepatitis C patients receiving peginterferon alpha-2b plus ribavirin. *Aliment Pharmacol Ther* 2009;**29**:46–54.

<sup>19</sup> Khattab M, Eslam M, Sharwae MA, Shatat M, Ali A, Hamdy L. Insulin resistance predicts rapid virologic response to peginterferon/ribavirin combination therapy in hepatitis C genotype 4 patients. *Am J Gastroenterol* 2010; **105**:1970-77.

<sup>20</sup> Poustchi H, Negro F, Hui J, *et al.* Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol* 2008; **48**: 28-34.

<sup>21</sup> Fattovich G, Covolo L, Pasino M, *et al.* The homeostasis model assessment of the insulin resistance score is not predictive of a sustained virological response in chronic hepatitis C patients. *Liver Int.* 2011;**31**(1):66-74.

<sup>22</sup> Moucari R, Ripault MP, Martinot-Peignoux M, *et al.* Insulin resistance and geographical origin: major predictors of liver fibrosis and response to peginterferon and ribavirin in HCV-4. *Gut.* 2009;**58**(12):1662-9.

<sup>23</sup> Cammà C, Bruno S, Di Marco V, *et al.* Insulin resistance is associated with steatosis in nondiabetic patients with genotype 1 chronic hepatitis C. *Hepatology* 2006;**43**:64-71.

<sup>24</sup> Conjeevaram HS, Kleiner DE, Everhart JE, *et al.* Race, insulin resistance and hepatic steatosis in chronic hepatitis C. *Hepatology* 2007;**45**:80-7.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

---

<sup>25</sup> Akuta N, Suzuki F, Hirakawa M, *et al.* Amino acid substitutions in the hepatitis C virus core region of genotype 1b are the important predictor of severe insulin resistance in patients without cirrhosis and diabetes mellitus. *J Med Virol* 2009;**81**:1032-9.

<sup>26</sup> Miyaaki H, Ichikawa T, Nakao K, *et al.* Predictive value of suppressor of cytokine signal 3 (SOCS3) in the outcome of interferon therapy in chronic hepatitis C. *Hepatol Res* 2009;**39**:850-5.

<sup>27</sup> Petta S, Cammà C, Di Marco V, *et al.* Time course of insulin resistance during antiviral therapy in non-diabetic, non-cirrhotic patients with genotype 1 HCV infection. *Antivir Ther.* 2009;**14**(5):631-9.

<sup>28</sup> Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412-9.

<sup>29</sup> Miller WG, Thienpont LM, Van Uytvanghe K, Clark PM, Lindstedt P, Nilsson G. Insulin Standardization Work Group *et al.* Toward standardization of insulin immunoassays. *Clin Chem* 2009; **55**: 1011–8.

<sup>30</sup> Staten MA, Stern MP, Miller WG, Insulin Standardization Work Group *et al.* Insulin assay standardization: leading to measures of insulin sensitivity and secretion for practical clinical care. *Diabetes Care* 2010; **33**: 205–6.

<sup>31</sup> Heinemann L. Insulin assay standardization: leading to measures of insulin sensitivity and secretion for practical clinical care: response to Staten *et al.* *Diabetes Care* 2010; **33**: e83.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

---

<sup>32</sup> Lam KD, Bacchetti P, Abbasi F, *et al.* Comparison of surrogate and direct measurement of insulin resistance in chronic hepatitis C virus infection: Impact of obesity and ethnicity. *Hepatology* 2010;**52**:38-46.

<sup>33</sup> Mizuta T, Kawaguchi Y, Eguchi Y, *et al.* Whole-body insulin sensitivity index is a highly specific predictive marker for virological response to peginterferon plus ribavirin therapy in chronic hepatitis C patients with genotype 1b and high viral load. *Dig Dis Sci* 2010; **55**: 183–9.

<sup>34</sup> Zeuzem S. Heterogeneous virologic response rates to interferon- based therapy in patients with chronic hepatitis C: who respond less well ? *Ann Intern Med* 2004; **140**: 370–81.

<sup>35</sup> Tanaka Y, Nishida N, Sugiyama M, *et al.* Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009;**41**:1105-9.