

Original Article

Meta-analysis: impact of sustained virological response on insulin resistance during hepatitis C therapy

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Abstract: Aim: Previous studies have shown that sustained virological response to standard chronic hepatitis C therapy appears to be associated with insulin resistance, however, the discrete relationship remains controversial. This meta-analysis was designed to evaluate whether the achievement of sustained virological response interfered with insulin resistance in chronic hepatitis C patients undergoing treatment with pegylated interferon plus ribavirin. Methods: A systematic search for relevant studies of EMBASE and MEDLINE databases as well as bibliographies of retrieved articles published up to June, 2015 was carried out. Summary estimates were obtained using fixed-effects or random-effects models according to the heterogeneity analysis and subgroup analyses, publication bias tests were analyzed by STATA 12.0. Results: Five studies involving 576 chronic hepatitis C patients were identified. There existed a significant association between sustained virological response rate and improved insulin resistance (SMD: -0.32, 95% CI: -0.51~-0.14). This significant association of sustained virological response and improved insulin resistance was also verified in the analysis for cut-off values of HOMA-IR <3 (SMD: -0.35, 95% CI: -0.55~-0.15, P=0.008), non diabetic patients (SMD: -0.30, 95% CI: -0.49~-0.11, P=0.009) as well as 24 weeks of follow-up (SMD: -0.43, 95% CI: -0.71~-0.15, P=0.003). Conclusion: The results of this meta-analysis suggests a highly related relationship between the achievement of sustained virological response and the reduced Homeostasis Model Assessment of insulin resistance in patients with hepatitis C treated with pegylated interferon and ribavirin.

Keywords: Hepatitis C virus, sustained virological response, insulin resistance, meta-analysis

Introduction

Chronic hepatitis C virus (HCV) infection is believed to be one of the major causes of liver cirrhosis, fibrosis and hepatocellular carcinoma (HCC) as well as various extrahepatic complications such as sialadenitis and mixed cryoglobulinemia [1-3].

Recently, there appears some robust evidence indicating that HCV itself is increasingly recognized as a diabetogenic factor which contributes to the incidence of insulin resistance (IR) and type 2 diabetes mellitus (T2DM) [4, 5]. It is estimated that the occurrence of insulin resistance in chronic hepatitis C patients ranges from 24% to 50%, which is higher than other hepatic disorders [6].

The essential standard combination therapy of HCV is based on pegylated interferon (Peg-IFN)

plus ribavirin (RBV), and its therapeutic effectiveness is reflected by the achievement of sustained virological response (SVR) [7-10]. Interestingly, some studies have demonstrated that IR is able to predict a poor response to the combination therapy of HCV, which accelerates progression of hepatic fibrosis and cirrhosis as well as hepatocellular carcinoma. And SVR is shown to be associated with a reduction in Homeostasis Model Assessment of insulin resistance (HOMA-IR) in chronic hepatitis C (CHC) patients, independent of host metabolic factors [11, 12]. However, other studies implied a different point of view that insulin resistance amelioration is due to the IFN- α -based therapy regardless of the achievement of SVR [13].

To explore the complicated relationship of IR and SVR during antiviral therapy, we performed the meta-analysis to examine the impact of the achievement of SVR on insulin resistance dur-

ing antiviral therapy of Peg-IFN plus ribavirin by evaluating HOMA-IR values in CHC patients.

Materials and methods

Search strategy

We systematically and independently identified studies on human and in English by searching EMBASE and MEDLINE from their inception to June, 2015 so as to evaluate the impact of SVR on IR measured by HOMA-IR in chronic hepatitis C patients. The search terms used in the analysis were “hepatitis C virus or chronic hepatitis C” and “diabetes mellitus, diabetes, hyperglycemia or insulin resistance” and “sustained virological response or SVR”. Moreover, the relevant studies from the retrieved articles were also involved in the analysis.

Criteria for study selection

Inclusion criteria: The studies being eligible for the meta-analysis must meet the following criteria: 1. Including chronic hepatitis C patients treated with Peg-IFN plus ribavirin. 2. Providing information on IR either at baseline and end of follow-up, or IR change from baseline assessed by the HOMA-IR index during antiviral therapy. 3. Providing full-length articles in English.

Exclusion criteria: 1. Studies without comparison of the HOMA-IR index between SVR and non sustained virological response (NSVR) groups. 2. Studies on patients co-infected with other hepatic disease such as hepatitis B virus infection, autoimmune hepatitis and alcoholic liver disorders. 3. Studies on patients treated with additional antivirals or diabetic drugs. 4. Reviews, case reports or studies presented as other measurement indicators, such as insulin levels, steady-state plasma glucose (SSPG) concentration instead of HOMA-IR index. When several publications were carried out against the same study group, just the latest recent and complete one was involved in the meta-analysis. Literature search was performed by two investigators with regard to the inclusion and exclusion criteria after reading titles and abstracts, independently.

Data abstraction and quality assessment

Data abstraction was performed independently by investigators using standardized data collection forms. Any differences were resolved by

consensus. The following data were extracted from the selected studies: study name, country, sample size (numbers of subjects achieved SVR and NSVR), cut-off values for diagnosis of insulin resistance, period of follow up, statistical results (standardized mean difference (SMD) with their corresponding 95% confidence interval (CI) for evaluating impact of SVR on IR). The quality of the six enrolled studies in our meta-analysis was assessed by the nine-star Newcastle-Ottawa Scale (NOS) [14]. Studies that received a rating of 7 stars or more were considered as “high quality”.

Endpoints

The main endpoint was the change of mean \pm standard deviation (SD) in HOMA-IR index between SVR and NSVR groups treated with Peg-IFN plus ribavirin.

Statistical methods

In the meta-analysis, heterogeneity of studies was examined using the Cochran Q and I^2 statistics. In the case of heterogeneity, random-effects model was adopted to calculate summary estimate when the P value for heterogeneity was <0.10 (I^2 was $>50\%$), while fix-effects model was used when P value >0.10 (I^2 was $<50\%$) [15]. Subgroup analyses were performed according to cut-off values of HOMA-IR, baseline of CHC patients and period of follow up after therapy. To evaluate the probability of publication bias, Begg's test was used. Change of HOMA-IR index from baseline between responders and non responders to therapy of Peg-IFN plus ribavirin was presented as mean difference \pm standard deviation. A significant level of 0.05 for two-sided tests was considered as α risk. Comparison of percentages between different groups was performed using SMD with 95% CI. All analyses were carried out by STATA statistical software, Version 12.0.

Results

Literature review

As listed in **Figure 1**, we searched EMBASE and Medline for 708 potentially relevant records and 282 records were excluded for duplications and 402 references were excluded for no information on SVR and HOMA-IR after reading titles and abstracts. 24 studies were retained for more detailed analysis. A total of five arti-

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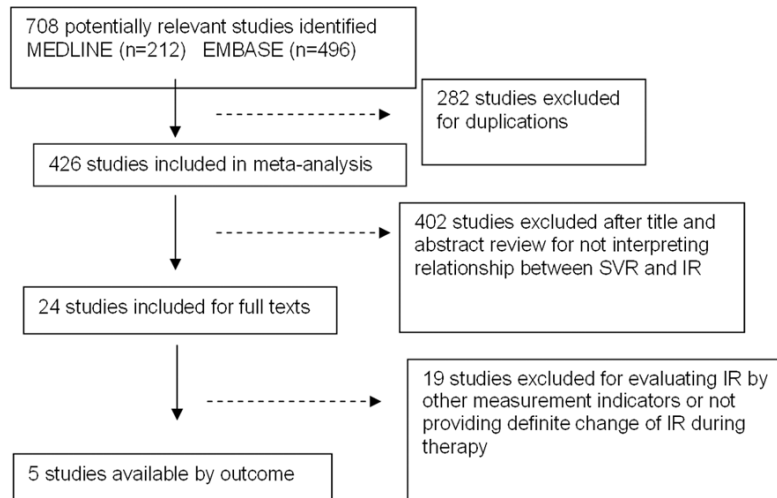


Figure 1. Flow chart of studies screened and included in the meta-analysis.

cles that met the inclusion criteria were finally analyzed. Several studies were excluded for different insulin resistance evaluating methods. The study by Danielle Brandman *et al.* [16] was excluded for measuring IR by steady-state plasma glucose (SSPG) concentration without information on HOMA. Another study by Thompson *et al.* [17] was excluded for just providing the number of patients in HOMA-IR reduction, though it suggested that viral clearance might be a result of improved insulin resistance in genotype 1 chronic hepatitis C infection.

Study characteristics

All the enrolled studies [18-22] are full-length published articles. Baseline characteristics of the subjects participating in the studies were summarized and listed in **Table 1**. All patients were treated with Peg-IFN plus ribavirin depending on different viral genotype. The article by Huang JF [20] *et al* presented impact of SVR on IR for two groups, genotype 1/4 as well as 2/3. IR was designated as the cut-off value of HOMA-IR >2 except for two studies. One designated it as HOMA-IR >2.5 [20] and the other as HOMA-IR >3 [22]. As for the confounders by action of IFN-based therapy in short time, the end of post-treatment follow-up period in the included studies is 24 weeks, except one which is 24 months [19].

Meta-analysis of the studies that evaluating the impact of SVR on insulin resistance

To analyze the effect of SVR on IR during antiviral therapy, the random-effects model was car-

ried out on the enrolled 576 chronic hepatitis C patients from the six studies by the use of DerSimonian's and Laird's method. By comparing the change of HOMA-IR between responders and non responders, the result showed that insulin resistance was significantly ameliorated with HCV eradication during the therapy with Peg-IFN plus ribavirin in those CHC patients in **Figure 2** (SMD: -0.32; 95% CI: -0.51 ~ -0.14).

To exclude the effect of different IR definition, the

meta-analysis was only performed in those studies with HOMA-IR index cut-off <3. As shown in **Figure 3A**, the result was shown as SMD: -0.35, 95% CI: -0.55~-0.15, P=0.008, which is consistent with the result above.

Considering the different baseline characteristics of enrolled subjects, we carried out meta-analysis just in non diabetic patients with chronic HCV from the five studies. The result demonstrated that IR was remarkably improved by the achievement of SVR associated with Peg-IFN plus ribavirin therapy in non diabetic patients (**Figure 3B** SMD: -0.30, 95% CI: -0.49~-0.11, P=0.009). Nevertheless, Kim *et al.* demonstrated that clearance of HCV improved insulin resistance with no significance in patients with higher HOMA-IR >3 or lower HOMA-IR <3.

It was previously pointed out that weight loss during Peg-IFN plus ribavirin treatment might improve insulin sensitivity, especially during short period of follow up. To examine the potential bias on IR, the effect of SVR on IR during antiviral therapy was also studied by tracking 24 weeks period of follow-up in the meta-analysis. As shown in **Figure 3C** (SMD: -0.43, 95% CI: -0.71~-0.15, P=0.003), the result still corresponded with those data above.

Publication bias

Funnel plot of Begg's test were analyzed for possible publication bias. The result revealed that no significant publication bias was observed in the meta-analysis (**Figure 4**, Begg's test $z=-0.19$, P=0.851).

Impact of SVR on IR

Table 1. Characteristics of studies evaluated for the impact of SVR on IR measured by HOMA index in the meta-analysis

Author	Year	HOMA-cut off	Gt	n SVR	n NSVR	Base condition	Change SVR	Change NSVR	Follow-up
Mahmoud A Khattab	2012	2	4	61	46	non-diabetic	-0.83±0.52	-0.28±0.72	24 weeks
Alessio Aghemo	2012	2	1/4, 2/3	78	94	non-diabetic	0.07±0.98	0.29±1.14	24 moths Significant 1/4
Jee-Fu Huang	2011	2.5	G-1	59	26	non-diabetic	0.56±1.63	0.93±2.99	24 weeks
Jee-Fu Huang	2011	2.5	G-non-1	104	8	non-diabetic	0.59±1.41	-0.02±0.69	24 weeks
Yasunori Kawaguchi	2009	2	1/2	48	24	non-diabetic	-0.19±1.01	0±1.23	24 weeks
HongJoo Kim	2009	3	1/2	22	6	NA	-2.66±4.12	0.14±1.26	24 weeks

HOMA, Homeostasis Model of Assessment; SVR, sustained virological response; NSVR, non-sustained virological response; NA, non-available; NOS, Newcastle-Ottawa Scale.

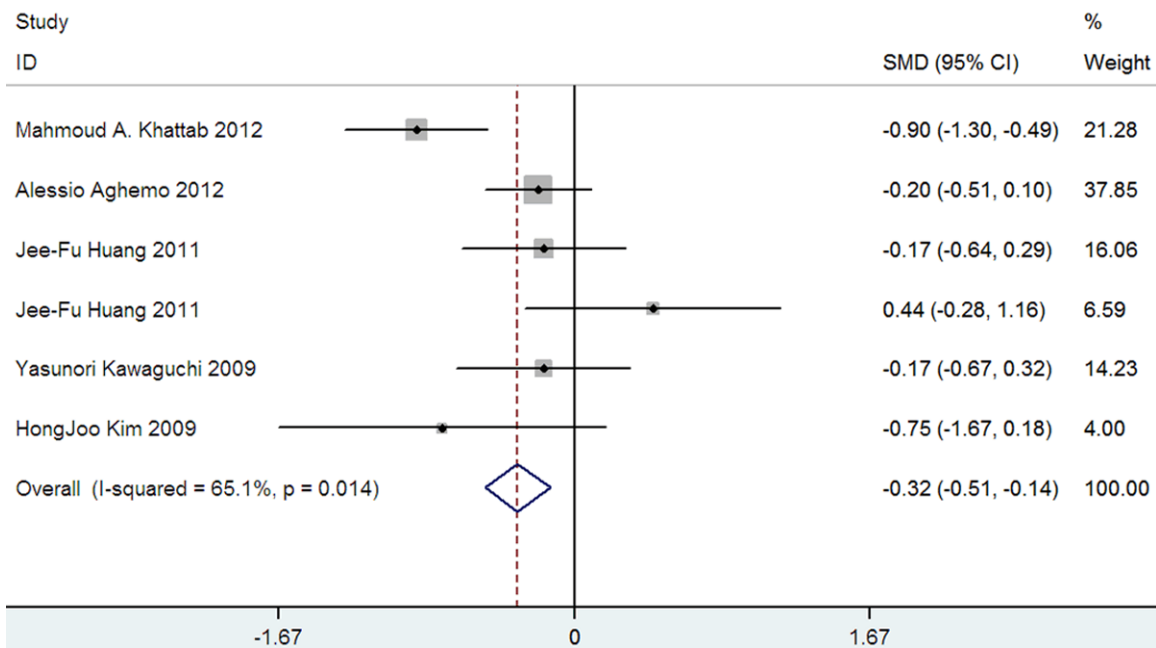


Figure 2. Standardized mean difference and 95% CI for the impact of SVR on IR in chronic hepatitis C patients with antiviral therapy of peg-interferon plus ribavirin, according to the change from baseline of HOMA-IR included in each study.

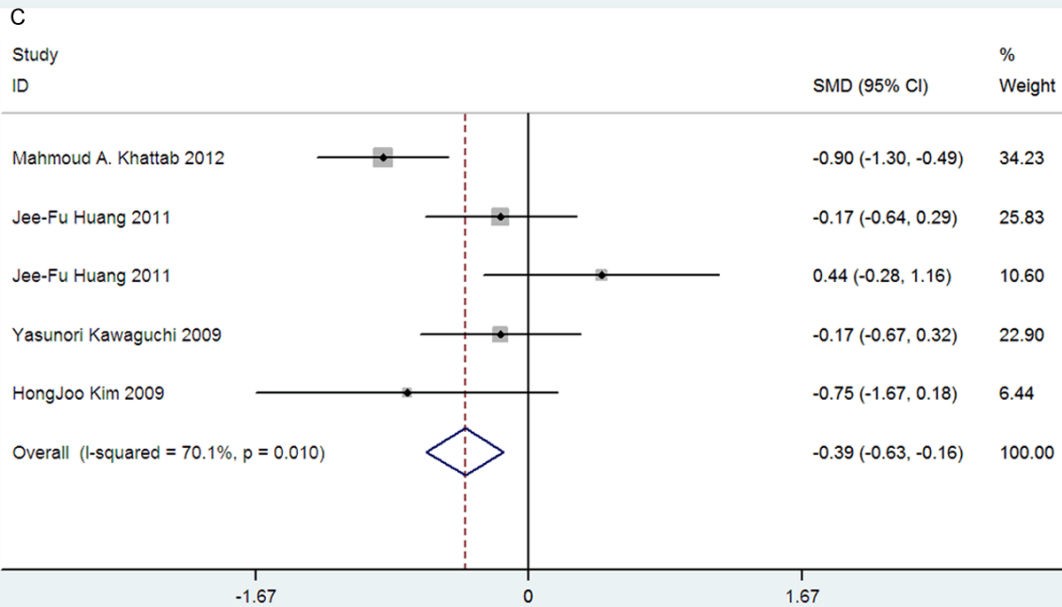
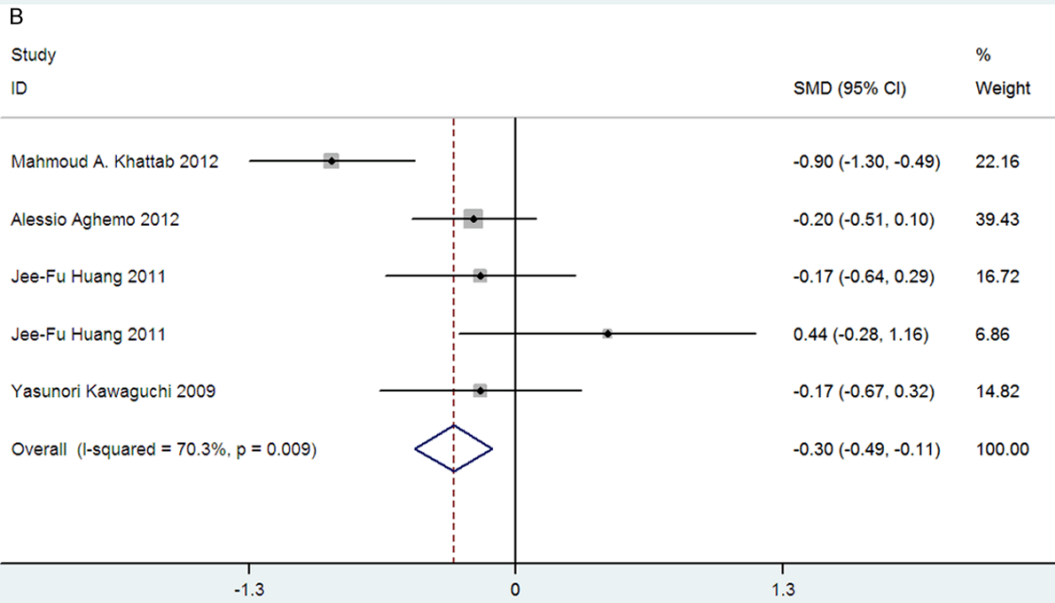
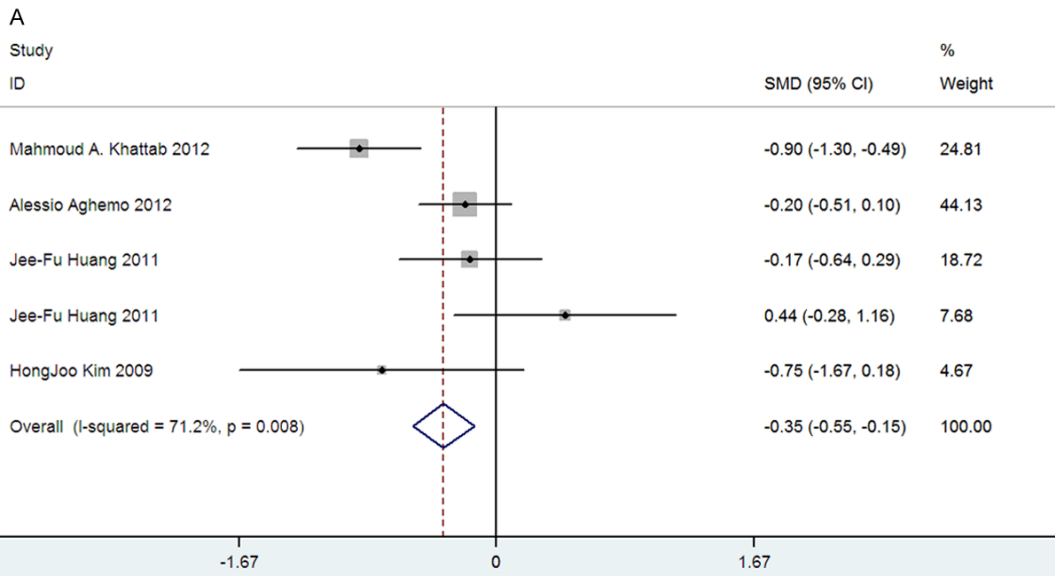
Discussion

In the study above, we have evaluated the impact of sustained virological response on insulin resistance. Our results of meta-analysis demonstrated that SVR was associated with improved insulin resistance in the enrolled 576 chronic hepatitis C patients upon to Peg-IFN plus ribvirin therapy (SMD: -0.32, 95% CI: -0.51~-0.14) (Figure 2). The significant association of SVR and improved IR was also verified in the analysis on cut-off values of HOMA-IR <3 (Figure 3A SMD: -0.35, 95% CI: -0.55~-0.15, P=0.008), non diabetic patients (Figure 3B SMD: -0.30, 95% CI: -0.49~-0.11, P=0.009) as

well as 24 weeks of follow-up (Figure 3C SMD: -0.43, 95% CI: -0.71~-0.15, P=0.003).

Recently, more studies have revealed that HCV appears to interfere with glucose homeostasis resulting in T2DM in some certain patients [23-26]. Although the accurate mechanisms of HCV-mediated IR remains poorly understood, several hypotheses have been raised. Qian *et al.* [27] raised the possibility that HCV impairs insulin secretion through its direct infection of the pancreatic beta cells since HCV RNA was found to be presented within the pancreatic acinar and epithelial cells. HCV infection was also found to impair insulin pathways. Upon

Impact of SVR on IR



Impact of SVR on IR

Figure 3. A. Standardized mean difference and 95% CI for the impact of SVR on IR in chronic hepatitis C patients with antiviral therapy of Peg-IFN plus ribavirin, including studies of HOMA-IR index cut-off <3. B. Standardized mean difference and 95% CI for the impact of SVR on IR in chronic hepatitis C patients with antiviral therapy of Peg-IFN plus ribavirin, including studies of baseline of subjects in each study of no diabetes. C. Standardized mean difference and 95% CI for the impact of SVR on IR in chronic hepatitis C patients with antiviral therapy of Peg-IFN plus ribavirin, including studies of 24 weeks of follow-up.

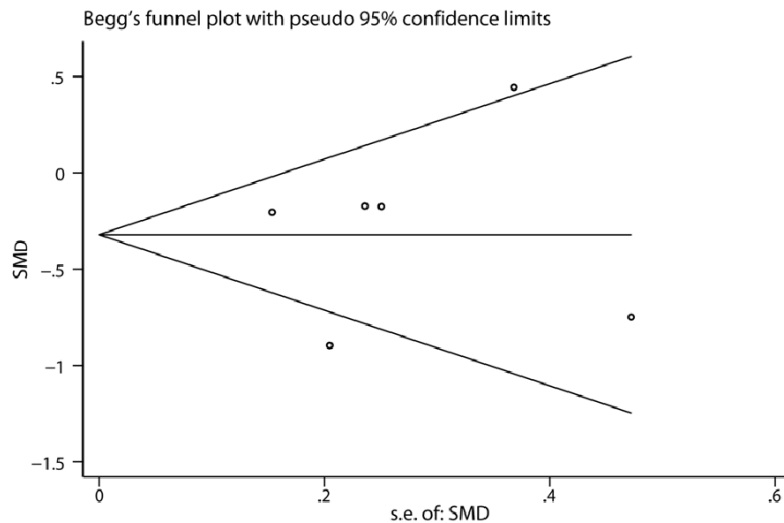


Figure 4. Begg's test was used for estimating publication bias and showed a non-significant publication bias ($P=0.851$).

HCV infection, tumor necrosis factor (TNF)- α system was activated and the levels of interleukin-6 increased, which disturbed tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1). The levels of suppressor of cytokine signaling-3 (SOCS-3) then increased, which promoted proteasomal degradation of IRS-1/2 [28-30]. In addition, HCV was able to inhibit post-receptor insulin signaling through the interaction with P28 γ , to induce the activity of late proteasome and inhibit the transcription of glucose transporter type 4 (GLUT4) [31, 32]. All of which evoked storm of increased oxidative stress, peroxidation and inflammatory responses, participating in the development of insulin resistance [33].

Despite of the exact mechanisms underlying HCV-induced IR, our findings shed light on its potential clinical significance that the additional benefit of antiviral therapy should be the improvement of IR in HCV patients. In agreement with previous studies [34, 35], the meliorative IR not only reduces the risk of incident glucose abnormalities and related metabolic disorders, but also decreases occurrence of

subsequent cirrhosis and hepatocellular carcinoma in CHC patients.

Based on previous studies, the relationship between SVR and IR is very complex. Kim *et al.* [18] demonstrated that there was significant amelioration of β -cell function in SVR group, compared with non-responders. The study by Kawaguchi *et al.* [36] also demonstrated that the clearance of HCV was associated with ameliorated IR and enhanced β -cell function although it was not related to HOMA-IR index. Considering the different cut-off values of HOMA-IR definition, we only

analyzed the studies of HOMA <3, the impact of SVR on IR was maintained for different genotypic groups (**Figure 3A**). Thompson *et al.* [17] showed that for HCV G-1 infection, SVR was independently followed with reduced IR reduction in a clinical trial cohort study, suggesting that the impact of SVR on IR might be genotype-specific. On the other hand, we also analyzed the studies of non diabetic patients at baseline and the results were shown in **Figure 3B**. Our results were somewhat in contradiction with the HALT-C (Hepatitis C Antiviral Long-Term Treatment against Cirrhosis) study, which recruited patients with more advanced fibrosis by Huang *et al.* [20], showing that the significant decline of HOMA-IR was achieved only in G-1 and -2 patients with high baseline of HOMA-IR in response to standard therapy, which does not matter with SVR achievement. Moreover, as shown in **Figure 3C**, SVR was demonstrated to be correlated with IR during the 24 weeks of follow-up. As the follow-up period in the selected studies is relatively short, it is preferable to re-evaluate the impact of SVR on insulin resistance during longer follow-up period with exact endpoint. Overall, the somewhat discordant

results may imply that the relationship between HOMA-IR with SVR may be affected by various factors such as baseline of patients for obesity, liver steatosis and fibrosis, race, age and cut-off value of IR definition. Since the emergence of IR is multifarious, the interplay of genetics (such as the IL28b SNP) and viral kinetics needs to be further clarified [37-39].

With respect to the complicated connection of HCV and IR, our study is well consistent with previous studies of SVR being associated with a reduction in the follow-up of patients with IR 24 weeks since treatment was completed although the potential bias of weight loss during Peg-IFN plus ribavirin treatment with transiently reduced HOMA values and improved insulin sensitivity [40].

However, the extent of SVR associated with antiviral therapy on insulin resistance improvement is not yet known and needs to be further elucidated. Based on previous studies, it is possible that there exists a kind of balance between SVR and IR. Once the balance is disequibrated, the effect of SVR on insulin resistance improvement may go to an opposite direction. As shown in some discordant studies, IR and subsequent DM were improved after IFN-based therapy with unknown mechanisms. In this sense, the interplay for IFN-based antiviral therapy with alteration of insulin sensitivity needs to be further elucidated.

There exist some limitations in our study. For example, there is heterogeneity in the enrolled studies including characteristics cohort, methods for insulin collection and measurement, and HOMA-IR cut-off values of defining insulin resistance. The occurrence of insulin resistance is strongly affected by several factors, such as obesity, extensive fibrosis, elevated GGT and age. Since HOMA is an indirect and surrogate measurement of IR, the results derived from HOMA-IR index need to be further confirmed by gold-standard method of euglycaemic hyperinsulinaemic clamp [41, 42].

Conclusions

In conclusion, the meta-analysis demonstrated that in patients with chronic hepatitis C, the rates of IR occurrence reduced after successful therapy by Peg-IFN plus ribavirin, and IR improvement closely correlated with SVR,

which not merely acts as a surrogate marker of therapy efficacy but is an actual aim to pursue in some chronic hepatitis C patients.

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Disclosure of conflict of interest

None.

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