

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7232-review.doc).

Title: Hepatitis C virus infection and insulin resistance.

Author: Sandip K. Bose and Ranjit Ray

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 7232

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer no: 00496285

Comments to Authors: This manuscript by Dr. Bose and Dr. Ray reviews the existing literature on insulin resistance in hepatitis C virus infection. General comments: This review is timely and its subject is of great interest when considering the large number of patients with hepatitis C virus infection worldwide and the diabetes epidemic.

In general, the authors should spell out the conditions followed by an abbreviation when first appearing and afterwards the authors should use the abbreviation consistently. **Response:** We have incorporated the changes in red as suggested (Page 1, line 11, Page 2, line 36-37).

Specific comments: Introduction: -I suggest moving "Currently HCV vaccine is not available." Line 2 page 4 to line 15 page 3 after "...currently infected with HCV(6)." because this would be a more logic place to highlight that there's no immunological methods to prevent the high number of infected individuals. **Response:** We have moved the sentence as suggested.

-The aim of the review should be stated in the Introduction. **Response:** We have added the aim of the review in the introduction section (Page 4, line 71-72).

Glucose uptake & insulin resistance: -The paragraph is highly relevant, but could be significantly improved: The authors should focus on T2DM only and not T1DM, which is completely irrelevant to this review. The content of the paragraph should be presented more straightforward and redundancies should be removed. **Response:** We have removed the redundancies and sentence on T1DM as suggested.

-“In type II diabetes mellitus (T2DM), sufficient insulin is produced”: This is simply, by definition, incorrect. **Response:** We have corrected the sentence as “Type II diabetes mellitus (T2DM), occurs when the production of insulin is not sufficient to overcome a difficulty the body has in properly using insulin. This difficulty is called insulin resistance, resulting in increased glucose levels.” (Page 5, line 88-90).

-Last sentence page 4: Why is only one of the major complications to T2DM mentioned? **Response:** We have included other major complications associated with T2DM (Page 5, line 93).

-Be consistent: Signaling or signalling? **Response:** We have changed Signalling to signaling everywhere in the text.

-The liver plays a major role in T2DM (the 2nd most important tissue following skeletal muscle) and this should be acknowledged and mentioned in this paragraph (including references). Otherwise, it is not clear to the reader why this review is so important. **Response:** We have acknowledged the importance of liver in T2DM and have included appropriate reference. (Page 5, line 93-95).

Chronic HCV infection and insulin resistance: -I suggest changing the headline to "Chronic HCV infection & insulin resistance" to continue the use of "&" from the previous paragraph. **Response:** We have changed the headline as suggested. (Page 6, line 115).

Modulation of insulin receptor substrate by HCV: -"...phosphorylation, marking its for degradation via...": I doesn't make sense to me. **Response:** Ser³¹² and Ser¹¹⁰¹ phosphorylation are key inhibitory phosphorylations of the insulin receptor substrate-1 (IRS-1) and phosphorylation at these sites stimulates IRS-1 degradation by the ubiquitin proteasome pathway. The details have been referenced.

Impaired lipid and glucose metabolism by HCV: -"...and more blood sugar...": Please rephrase to "...increased plasma glucose..." **Response:** We have rephrased the sentence as suggested (Page 9, line 182).

-"...leading to insulin resistance (Fig. 1)." Please add "is presented in" before (Fig. 1). **Response:** We have added the phrase as suggested (Page 9, line 184).

Therapeutic approaches and future goals: -To my opinion this paragraph is not ambitious enough when it comes to the treatment of impaired insulin resistance and overt T2DM. E.g. what is the specific treatment goal with regards to glucose homeostasis? How do we evaluate patients with HCV and impaired glucose tolerance? What upper limit for HbA1c is acceptable? When lifestyle interventions fail when is pharmaceutical means needed and what drugs are first and second choice? When it comes to T2DM in HCV infection, is the diabetes treated as usual or is there documentation for using other first line drugs? **Response:** We have added a separate paragraph in the Therapeutic approaches and future goals section, including some of the available information which the reviewer has asked for. (Page 12-13, line 252-267). Also the parameters and treatment strategy may vary in different geographic regions. Further, we do not have expertise on this area, and this information may not be relevant to out theme of the review. However, if the editor wish he/she may add a couple of lines on this area in the review while editing.

Reviewer no: 00433336

Major revisions: 1. Manuscript organization. Recommended to introduce figure 1 as the lead into section "MODULATION OF INSULIN RECEPTOR SUBSTRATE BY HCV" of the manuscript as an overall "road map" to the discussion. **Response:** We have introduced figure 1 as the lead into section "MODULATION OF INSULIN RECEPTOR SUBSTRATE BY HCV" as suggested by the reviewer. (Page 7, line 135-136).

Would recommend organizing the discussion further as follows: 1. mechanisms underlying increased glucose production **Response:** We have added the mechanism underlying increased glucose production in the glucose uptake & insulin resistance section. (Page 4, line 76-82).

and 2. mechanisms underlying insulin resistance. **Response:** We have previously discussed about mechanisms underlying insulin resistance (Page 5, line 98-106). We have also included some other mechanisms which underlies development of insulin resistance (Page 6, line 109-111).

2. Clinical translation: recommend adding a section of the clinical implications of HCV-mediated insulin resistance including discussions of 1. the impact of HCV treatment on insulin resistance and glucose homeostasis and 2. implications for glucose lowering agents, i.e., is there a rationale, based on the earlier discussion in the manuscript, that an insulin sensitizer approach like metformin or TZD, would be preferable to other approaches. **Response:** We have added a section on clinical implications of HCV-mediated insulin resistance and have included the points suggested by the reviewer. (Page 11, line 220-234).

Reviewer no: 00495228

The review by S. Bose and R. Ray provide a good and extensive description of modulation of hepatic metabolic pathways under pathological conditions of hepatitis C virus infection. The paper is well written and contains up to date information on the topic. **Response:** We thank the reviewer for appreciation.

Reviewer no: 00506347

interesting topic. well thought out review. **Response:** We thank the reviewer for appreciation.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Diabetes*

Sincerely yours,

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