December 23, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6876-Topic Highlight, revised).

Title: Hepatitis C virus and metabolic disorder interactions towards liver damage and atherosclerosis

Authors: Vespasiani-Gentilucci Umberto, Gallo Paolo, De Vincentis Antonio, Galati Giovanni, Picardi Antonio

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6876

Dear Editor,
we are very glad that both the reviewers appreciated our work and scored it with a high priority for publication. The manuscript has been further improved according to the suggestions of reviewers and, in particular, to the issues raised by reviewer 01350278:

(1) *Reviewer's comment*: *The current review focused on the HCV on various metabolic pathway and mechanism, however, it is better to include the comparison with other hepatitis, e.g HAV and HBV. Please discuss why HCV is particularly susceptible to metabolic disorders, cardiovascular risk, and so and so. The comparison should be elaborated by providing clinical, epidemiological and laboratory data. Why HCV is specific or unique for the metabolic disorders?*
Answer to the comment: It was not aim of the present work to evaluate all viral hepatitides with respect to their relationship with metabolic disorders and the cardiovascular risk but to specifically analyze HCV, as expressed in the title. However, we agree with the reviewer that the comparison with hepatitis B (not hepatitis A since it is an acute infection) could help to highlight the specificity of HCV in this context. Therefore, two sentences concerning HBV association with glucose metabolism alterations and steatosis have been added in the relative paragraphs.

(2) *Reviewer's comment*: *Authors described several studies as example to explain HCV predisposes to diabetes mellitus (DM). However the argument was not fully described. For example, HCV infection increases the incidence of DM after liver transplantation, but how about the risk of DM after liver transplantation due to other indications? And also, prevalence of HCV infection among DM is higher than in general population, but the HCV infection in DM patients could be secondary to the impaired immunity rather than the primary cause.*
Answer to the comment: Again, it was not the item of the present work to compare HCV with other liver diseases. Actually, we already reported that HCV patients present an increased incidence of post-transplant DM with respect to patients transplanted due to other indications (reference 5). Moreover, the lack of association between HBV infection and DM doesn't support the hypothesis that a certain DM-induced immunodepression could favour HCV infection.

(3) *Reviewer's comment*: *the insulin resistance in impaired in early stage of HCV infection, but not the compensation and decompensation stages. Please explain in details also.*
Answer to the comment: We didn't understand very well was the issue of the reviewer. However, we didn't find any work specifically comparing diabetes prevalence between

patients with compensated and decompensated HCV-related liver disease.

(4) *Reviewer's comment: the calculation of hepatocarcinoma (HCC) risk amongst HCV patients, not in general population nor the DM or obese population only, should be provided. The figures of 37-folds and 100-folds by the co-existence of HCV, DM and or obesity will not be informative.*
Answer to the comment: We agree with the reviewer. The risk of HCC specifically conferred by HCV infection has been added in the relative paragraph.

(5) *Reviewer's comment: authors described the potential roles of oxidative stress, lipid peroxidation and proinflammatory cytokines, but only some inflammatory molecules have been discussed, but not the oxidative stress and lipid peroxidation pathway. Please supplement as well.*
Answer to the comment: We agree with the reviewer. The role of oxidative stress and lipid peroxidation has been now discussed in the relative paragraph.

(6) *Reviewer's comment: Figure 2 was included in conclusions. It is better to be explained in details with a new paragraph before the conclusion.*
Answer to the comment: We agree with the reviewer. A pertinent paragraph summarizing the main points treated in the paper and referring to Figure 2 has been now added before the conclusions.

(7) *Reviewer's comment: table 1: it is better to have country, setting in separate columns. percentage of HCV+, instead of the total participants, in the studies should be provided. also the main results were too long and the outcomes are repetitive, better to be replaced by either positive or negative association, plus the odd ratio, etc.*
Answer to the comment: The table has been revised according to all the suggestions provided by the reviewer.

(8) *Reviewer's comment: others: what is "necroinflammatory"? whether cardiovascular disease is a non-liver-related disorder, please clarify. "dysmetabolism" should be avoided. abstract: "revised" should be "reviewed". core tip: please revise the last sentence.*
Answer to the comment: a) The term "necroinflammatory" has been deleted. b) At the end of the first paragraph (page 4, 8th line from the bottom) it was already specified that cardiovascular disease is among non liver-related disorders. c) The "term" dysmetabolism has been always substituted mainly by "metabolic disorders" or "altered metabolism". d) The last sentence of the core tip has been revised in order to avoid term repetition.

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

Sincerely yours,

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