

Format for ANSWERING REVIEWERS

August 16, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 12140-review.doc).

Title: Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver

Author: : Sanja Stojšavljević, Marija Gomerčić Palčić, Lucija Virović Jukić, Lea Smirčić Duvnjak, Marko Duvnjak

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12140

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

(1) To first reviewer: As the first reviewer requested we made major rearrangement to the manuscript. We shortened the information in the text and incorporated all the studies in tables (key cytokines and adipocytokines in each separate table) as the first reviewer requested. Some of the proposed review articles were included in the text and cited accordingly (Lonardo A, Lombardini S, Ricchi M, Scaglioni F, Loria P. Review article: hepatic steatosis and insulin resistance. *Aliment Pharmacol Ther* 2005; 22 (2 Suppl): 64-70 [PMID: 16225477]). In the IL-6 part of the manuscript panel of cytokines was discussed (Grigorescu M, Crisan D, Radu C, Grigorescu MD, Sparchez Z, Serban A. A novel pathophysiological-based panel of biomarkers for the diagnosis of nonalcoholic steatohepatitis. *J Physiol Pharmacol* 2012; 63: 347-353 [PMID: 23070083]). We didn't refer to other panels since that is beyond the topic of this review.

(2) To second reviewer: Since gut microbiota has emerged as an important metabolic organ and thus studies in the pathogenesis of obesity, IR, NAFLD and MS, as the second reviewer proposed we added in the introduction a paragraph concerning microbiota and cited the references of addressed studies accordingly (references from 4-15). We also added some of the proposed review articles (references under number 3, 23, 30).

(3) To third reviewer: Since the third reviewer made the mark that the manuscript was too long, we shortened it by making rearrangement and placing most of the detailed information on studies conducted in tables. We also excluded the statistical analysis as was proposed.

3 References and typesetting were corrected

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

Format for ANSWERING REVIEWERS

October 20, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12140-review.doc).

Title: Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease

Author: Sanja Stojšavljević, Marija Gomerčić Palčić, Lucija Virović Jukić, Lea Smirčić Duvnjak, Marko Duvnjak

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12140

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

(1) To first reviewer: Thank you for your acceptance of our manuscript.

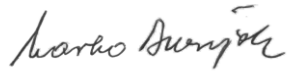
(2) To second reviewer: Thank you for your comments and notes. According to your suggestion we rewrote the core tip by highlighting the conclusions in this review, however detailed conclusions regarding the reviewed chemokines were reserved for the main manuscript, since core tip has a maximum of 100 words. Regarding the comment on understanding the link between adipokines, genetics and NAFLD/NASH we have to emphasize that the title of the manuscript refers to adipokines and cytokines in NAFLD. In this context, an extensive discussion on PNPLA3 would require an extensive discussion on other genetic variants and major polymorphisms what could be a review article on its self regarding the complexity and extent of the topic. We therefore are humble and sorry to comment that we don't find appropriate for this to be incorporated in this manuscript but are concordant that this is an important topic which deserves a review on its self. We revised the tables and simplified the sentences as you suggested.

(3) To third reviewer: Thank you for your comments and notes. According to your concern on the multiple hit theory we revised that part of the manuscript. Multistep theory is indeed a different point of view on the course from simple steatosis to liver cirrhosis. Because of the complexity of that path, we are of the oppinion that it should be better regarded as a multiple step process. According to your suggestion we rewrote the sentence regarding the classification of NAFLD and the presence of fibrosis. Regarding your third comment, we rewrote the part that contains the "third hit". We propose that the "third hit" leads to the progression of the cirrhosis and subsequent development of HCC in addition to the long lasting necroinflammation. We are concordant that a schematic representation would enhance readers understanding, but the time to revise the manuscript according to your comments was too short for such a demanding task. We apologize for that. We also corrected all the minor concerns.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Marko Duvnjak', with a stylized flourish at the end.

Marko Duvnjak

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