November 30, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6688-review.doc).

Title: Non-Alcoholic Fatty Liver Disease and Diabetes: From Physiopathological Interplay to Diagnosis and Treatment.

Author: Nathalie C Leite, Cristiane A Villela-Nogueira, Claudia R L Cardoso, Gil F Salles.

Name of Journal: *World Journal of Gastroenterology*

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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 reviewers. All modifications are highlighted in the text.

Reviewer 1:

1-   Page 6: 16,5% , page 9 2.589 please correct these and similar mistakes.

Answer: The mistakes were revised and corrected in the text.

2-   Page 9, please explain "fasting insulin resistance"

Answer: The explanation was added in the text as follows (page 9 line 11): "fasting insulin resistance was assessed by the homeostasis model assessment method (HOMA-IR) and was defined by a HOMA-IR equal or greater than 2".

3-   Page 10, phosphorylation, please correct. Page 12, hipertriglyceridemia, please correct.

Answer: The words were corrected

4-   Page 13, please specify "with a normal ultrasound"

Answer: The phrase was rewritten as follows (page 13 line 24): "However, MR is too expensive to be used routinely, but might be useful in patients under study protocols and in those with a strong suspicious of NAFLD with normal liver echogenicity on US."

5-   Please explain kilopascals (kPa) when used first.

Answer: An explanation of the fibroscan method and the kilopascals unit was added to the text as follows (page 14 line 1): Vibrations of mild amplitude and low frequency are transmitted by the transducer, inducing an elastic shear wave that propagates through the liver. The velocity of wave propagation relates directly to liver stiffness or fibrosis (the stiffer the tissue, the faster the shear wave propagates), which is measured in kilopascals (kPa).

6-   Page 14, "the FIB-4, the BARD score" please explain these abbreviations
Answer: The abbreviations were explained in the text (page 14 line 12).

7-   Page 15, "Citokeratin-18" please correct
Answer: The term was corrected in the text.

8-   Page 18, liraglutide, exenatide; please shortly describe the effects of these drugs.
Answer: The text was modified in order to better understand the effect of the drugs liraglutide and exenatide (page 18 line 28).

9-   Please add blanks in table 1 Table 1, please correct "aspartate aminotransferase"
Answer: The table was corrected as suggested by the reviewer.

10-   A table summarizing current data on treatment would be helpful.
Answer: Two tables summarizing the current data on treatment was added. One comprising non-pharmacological interventions (Table 2) and a second one (Table 3) with the respective studies that evaluated pharmacological intervention.

11-   The paper (Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease the RAED2 randomized trial by Bacchi et al.) has to be cited.

Answer: This is a relevant paper and was inserted in the text as suggested. The references were updated. The new paragraph was written as follows (Page 16, line 18). "In a recent randomized controlled trial, Bacchi et al. compared the effects of aerobic (AER) or resistance (RES) training on hepatic fat content in 31 type 2 diabetic subjects with NAFLD. Hepatic fat content was markedly reduced in both AER and RES training groups. In addition, hepatic steatosis defined as hepatic fat content >5.56% by an in-

opposed-phase magnetic resonance imaging technique was not detected in about one-quarter of the patients in each intervention group."

Reviewer 2:

In this paper, the authors review the association of nonalcoholic fatty liver disease (NAFLD) and diabetes mellitus (DM) with particular emphasis on physiopathological mechanisms, diagnosis, and treatment. NAFLD is rapidly increasing worldwide and DM is one of the most important risk factors of NAFLD. Thus, this review article deals with an important topic, and furthermore, it is generally well written. However, the authors should consider the following points. 1. In page 5, line 27-29, the authors describe that NAFLD prevalence in patients with type 1 DM (T1DM) is due to the increasing prevalence of obesity and insulin resistance. However, I think obesity and insulin resistance are characteristics of type 2 DM. Is this description true? If it is true, references should be cited.

Answer: We agree with the reviewer that the obesity and metabolic syndrome are characteristics of T2 DM, however there is a study showing these characteristics can also occur in T1 DM thus leading to NAFLD. The text was modified and the cited reference included (McGill M, Molyneaux L, Twigg SM, Yue DK. The metabolic syndrome in type 1 diabetes: does it exist and does it matter? J Diabetes Complications. 2008 Jan-Feb;22(1):18-23).

2. In the section "Pathogenetic mechanisms," many factors (such as insulin resistance, reactive oxygen species, inflammatory cytokines, and lipopolysaccharides) are discussed and functions of each factor are difficult to be understood. I recommend the authors to show the functions of each factor schematically as a Figure or a Table to make this manuscript more legible for readers.

Answer: Two figures were added in order to clarify these issues.

3 - References and typesetting were corrected

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

Sincerely yours,

Gil F. Salles.

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