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Dear Editor,

Please find enclosed the edited manuscript 6852 in Word format (6852 Review.doc)

Title: Insulin Sensitizers for the Treatment of Non-alcoholic Fatty Liver Disease

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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;

Reviewer 00504962

(1). In order to provide readers with a global perspective on the use of insulin-sensitizing medications in NAFLD patients, the recommendations from EASL and AASLD/ACG/AGA guidelines regarding those drugs should be mentioned (Ratziu V et al. J Hepatol 2010 and Chalasani N et al. Hepatology 2012). It would be particularly important to emphasize that those guidelines do not recommend the use of metformin and generally restrict the indication of TZDs, as specific liver-directed therapy, only to patients with biopsy-proven NASH.

The recommendations of AASLD and EASL special meeting were added for both metformin and also TZDs. Page 6, line 10-14 and page 9, line 12-17.

(2). It has been demonstrated that metformin inhibits hepatocyte proliferation and could inhibit liver oncogenesis, which could reduce the risk of developing hepatocellular carcinoma (Chen HP et al. Gut 2012; Bhalla K et al. Cancer Prev Res 2012; Zhang ZJ e tal. J Clin Endocrinol Metab 2012). This should be briefly discussed by authors.

This issue has been discussed with suggested references. Page 6, line 15-23.

(3). For the sake of completeness, the existence of several meta-analyses on the effects of TZDs in patients with NAFLD should be mentioned and their conclusions should be briefly discussed (Musso G et al. Hepatology 2010; Boettcher E et al. Aliment Pharmacol Ther 2012; Mahady SE et al. J Hepatol 2011; Musso G et al. Diabetologia 2012 [already discussed]; Rakoski MO et a. Aliment Pharmacol Ther 2010; and Shyangdan D et al. Health Technol Assess 2011).

It has been added and discussed briefly. Page 8, last paragraph.

(4). The lack of evidence on the efficacy of TZDs in diabetic patients should be further discussed.

A sentence about it has been added together with AASLD recommendation in page 9, line 14-16

(5). Conclusion section. It would be in the best interest of readers to clearly state authors' opinion on which NAFLD patients are the best candidates to be treated with TZDs.

A new sentence stressing best candidates has been added to conclusion section. (Page 10, line 3-4)

(6). It would also be interesting for readers if the relationship between insulin resistance and NAFLD pathophysiology could be better characterized by including a simplified figure.

A simplified figure about the pathogenesis of NAFLD has been added as Figure 1..

Reviewer 00608153

Two points should be addressed in this review.

(1). The major pathogenesis of NAFLD is related to obesity that leads to insulin resistance in liver. Insulin resistance may not be the primary deficiency in NAFLD.

We agree with the reviewer that major pathogenesis of NAFLD is related to obesity and obesity cause to insulin resistance in liver. Insulin resistance may not be the primary deficiency in NAFLD but the key metabolic factors causing steatosis and lipotoxicity. Besides, it has been shown in multiple studies that the presence of steatosis in liver is an important marker of insulin resistance, independent of BMI, percent body fat and visceral fat mass. Because of the significant metabolic alterations in liver occur in the setting of insulin resistance, investigations usually have focused on to understand and block these mechanisms. This never meant it is an independent pathogenetic factor distinct from obesity. A new sentence has added to revised paper stressing the role of obesity in the pathogenesis more clearly. Page 4, Line 5-7.

(2). All the mentioned insulin sensitizer is used as antihyperglycemic agent. Although these agents improve insulin sensitivity, they are not used as insulin sensitizer as only treatment purpose in clinical practice. In several pathological conditions with insulin resistance, such as in subjects with essential hypertension, these agents could not be only used to improve insulin sensitivity.

Since insulin resistance has been a key factor in the pathogenesis of NAFLD, the role of insulin sensitizers have been investigated intensely in recent years. This paper does not defend or directly suggest their usage in the treatment of NAFLD but review their role in the treatment based on the current literature. Throughout the paper including conclusion, it has been stressed that insulin sensitizers do not satisfy expectations for the treatment of NAFLD and they have a limited effect. Treatment of underlying disease causing insulin resistance such as obesity have stressed in conclusion. By the way, insulin sensitizers play an important role in the treatment of some pathological conditions with insulin resistance such as polycystic ovary syndrome.

Reviewer 00504962

The present review provides an overview of insulin sensitizers in the treatment of non-alcoholic fatty liver disease (NAFLD). The topic of review is very important. It would be better to add the pathophysiological mechanism including several factors related insulin sensitizers.

The pathophysiological mechanism related to insulin resistance has been discussed in the background section briefly. A new figure has also been added showing the role of insulin resistance in the pathogenesis. Page 4 line 3-23 and Figure 1

3. References and typesetting were corrected

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

With my best regards.

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