

Format for ANSWERING REVIEWERS



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9902-Edited.doc).

Title: Role of adipokines and peroxisome proliferator-activated receptors in nonalcoholic fatty liver disease

Author: Vettickattuparambil George Giby, Thekkuttuparambil Ananthanarayanan Ajith

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 9902

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

1 Format has been updated; **Yes**

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

Yes. Please find the revised MS, the modified areas are given in red font.

(1) Reviewer 1: The paper is interesting and well written. I would suggest to further consider the role of iron overload in the pathogenesis of NAFLD, and the possible interplay with cytokines

Authors' reply: Role of iron overload in the pathogenesis of NAFLD has been included in the revised MS. Please find the page 16 2nd para of the revised MS. Further, language also modified through out the MS.

(2) Reviewer 2: The authors discussed about the roles of adipokines and PPARs in NAFLD pathogenesis and future possibility of PPAR agonist usage against NAFLD development. The reviewer thinks this work is well written overall and convincing. Latest works (within 3 years) are reviewed quite frequently. However, the reviewer also feels this work lacks discussion about the role of these molecules on reactive oxidative stress (ROS), the mainstream pathway of liver inflammation in NAFLD. The authors are advised to discuss about interactions between these molecules and ROS in hepatic steatosis.

Authors' reply: Role of ROS in the pathogenesis of NAFLD has been included in the revised MS. Please find the page 17 page of the revised MS. Further, language also modified through out the MS.

(3) Reviewer 3: A interesting review but it was written without rules for literature.

Authors' reply: MS has been modified effectively with respect to the rules for literature. Language also modified through out the MS.

4) Reviewer 4: This manuscript is about the endocrine and pro-inflammatory role of the adipose tissue in NAFLD, reviewing the adipokines and cytokines involved in this process. I have some minor considerations, the first is the use of inadequate terms such as "accrual" instead of storage or accumulation, or "prognosticator" instead of predictor. The other, in the introduction, the paragraph: "Histologically, NAFLD is characterized" induces to understand that all the histological features have to be present to the diagnose of NAFLD, taking into account that this acronym included the

spectrum of lesions, from simple steatosis to NASH and NASH-cirrhosis. Reference 12 is incomplete. In addition, I have to comment that the strength of this review rests on the role of PPARs in the lipids metabolism and NAFLD, however, the weaknesses are based in the role of adipokines and cytokines in NAFLD, which is less updated mainly in the relationship between adipokines and genetic alterations such as polymorphisms in PNPLA3

Authors' reply: inadequate terms such as "accrual" replaced with 'accumulation', and "prognosticator" replaced with 'predictor'. Histological findings of NAFLD has been replaced as 'NAFLD has a wide histological spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis. In simple NAFLD presence of macro vesicular fat droplets in hepatocytes, foci of lobular inflammation, mild portal inflammation, and lipogranulomas may be seen where as increased portal inflammation has been proposed in untreated NAFLD patients ^[3]. Approximately 25% of the cases, histological signs of fibrosis and necroinflammatory injury that define NASH are present. ^[4]. Patients with NASH are at higher risk of developing fibrosis, cirrhosis and hepatocellular carcinoma ^[4].

Relationship between adipokines and genetic alterations such as polymorphisms in PNPLA3 has incorporated in page 11/1st para. Language also modified in the entire MS.

Further, queries such as WL1, WL2, WL3, WL4, WL5, WL6, WL7 and WL8 were properly answered. All the figures are provided as separate file ie. 'Fig1-5.ppt'

3 References and typesetting were corrected : Corrected as per the direction, incorporated PMID and DOI

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

Sincerely yours,

Dr. Ajith T.A., PhD [Member of EB of WJH, no ID: 02445091]

Professor Biochemistry,

Department of Biochemistry,

Amala Institute of Medical Sciences

Amala Nagar, Thrissur-680 555

Email: taajith@rediffmail.com