Reviewer#1

Udomsinprasert and Colleagues conducted a Minireview on adiponectin in chronic liver diseases and fibrosis. Overall the mansucriptist written well, and the topic is of interest. Is there any data on adiponectin in acute liver failure? More in-depth discussion of environmental factors contributing to chronic liver diseases and fibrosis, such as alcohol (specific substances within alcohol), viral hepatitis, toxins (which?) and interaction with adiponectin would be of interest. More details on genes coding for adiponectin would be welcome, are there any functionally relevant polymorphisms known?

Response

-Thank you very much for your suggestion. We address those comments in

page 6, line 10-11.

"Human adiponectin is encoded by the *Adipo Q* gene, which spans 17 kb on chromosome locus 3q27."

-And page 15, line 14-22.

"Regardless of the role of environmental and genetic factors, adiponectin appears to be strongly associated with the hepatic phenotype, which is a major cause of morbidityin NAFLD. It has also been discovered that gene polymorphism of adiponectin rs266729 was associated with risk of NAFLD, and the patients carrying the GG genotype of rs266729 exhibited significantly lower adiponectin levels than those patients carrying the GC or CC genotypes[65]. It is tempting to speculate that genetic variation of adiponecin and lifestyles choices causing visceral fat deposition/obesity may lead to reduced circulating adiponetin levels in patients with NAFLD and NASH."

The statement: "It is noteworthy that a physiological level of circulating adiponectin is important for defense against metabolic disorders and may be related to other chronic diseases" (p. 6, line 23) should be backup up by further references Discussion: As there only data availabe from small clincial studies, statements in the conclusions should be tempered down. It also seems to be of interest to include in the discussion, that the development of anti-fibrotic therapies in fibrosis/cirrhosis has been largely not successfull yet. p. 11, line 16: "Chief endpoints" : consider alternative terminology

Response

-We include further references in page 7, line 1-4.

"It is noteworthy that a physiological level of circulating adiponectin is important for defense against metabolic disorders and may be related to other chronic diseases including chronic obstructive pulmonary disease[18], chronic kidney disease[19], and knee osteoarthritis[20]."

-We address those comments in page 17, line 10-11 and 18-28.

"To date, the development of anti-fibrotic therepies in fibrosis and/or cirrhosis has been largely unsuccessful."

"The possible effect of adiponectin against liver fibrosis is supported by clinical studies that link hyperadiponectinemia to the severity of liver fibrosis in many liver diseases, including BA, HCV, HBV, and liver cirrhosis; whereas reduced adiponectin levels have been reported to be a key factor in the development of metabolic disorders contributing to NAFLD and NASH.Based on these observations, adiponectin could be a plausible noninvasive biochemical marker identifying the severity of liver fibrosis in patients with CLDs. However, additional investigations are warranted to better understand the precise role of adiponectin in the pathogenesis of liver fibrosis, which will help to develop adiponectin as circulating indicator for distinct CLD patients who are at risk of developing liver fibrosis."

-And page 11, line 18-19.

"The reversal and prevention of these conditions have come to be critical endpoints in clinical trials with novel anti-fibrotic therapies."

Reviewer#2

Reviewers Comments This is a review article summarizing current knowledge regarding role of adeponectin in development of hepatic fibrosis and it's potential as a non-invasive marker for liver fibrosis. overall the manuscript is well written and free of errors. There are minor issues that need to be addressed including description of method for literature search and basis for inclusion or exclusion.

Response

-Thank you very much for your kind suggestion. We address that comments in page 5, line 28-31 and page 6, line 1-6.

"The articles published between 2000-2018 were searched manually from the PubMed and Scopus using the following keywords or combination of keywords: "Adiponectin", "Adiponectin levels", "Liver disease", and "Liver fibrosis". Potentially relevant titles and abstracts were screened, and then full papers were reviewed for inclusion. Human clinical studies of any design providing circulating adiponectin levels associated with the severity of liver fibrosis in patients with various CLDs were eligible for this review. Articles not written in English-language, letters to the editor, case reports/series, and editorials were excluded from this review. There were no restrictions on gender, ethnicity, number of participants, or year of publication."

Major Revision Comment: The authors should describe their method for literature review. The authors describe this as an exciting new field however the most recent study included in this table is from 2015. There is one study each from 2012 and 2013 and remaining studies are from 2011 and older. Please include more recent studies if available.

Response

-We address that comments in page 5, line 28-31 and page 6, line 1-6.

-Moreover, we state that point in page 12, line 11-13 and 29-31.

"This study supports a recent report in which adiponectin levels were significantly elevated in patients with cirrhosis compared to controls and also associated with the severity of hepatic dysfunction in those patients[47]."

"A more recent study by Carvalho*et al*[50] found that patients with HCV infection had significantly greater adiponectinlevels than healthy controls."

-And page 14, line 12-18

"Most recently, Lucero *et al*[57] investigated systemic adiponectin levels in 36 patients with NAFLD related to metabolic syndrome and 24 metabolic syndrome patients without NAFLD. They reported that adiponectin levels were significantly elevated in NAFLD patients with metabolic syndrome when compared to those patients without metabolic syndrome. Besides, circulating adiponectin levels were correlated with metabolic parameters and the degree of liver fibrosis in NAFLD patients."

-Also, we include more recent studies in Table 1 and page 12, line 1-6.

"Several studies have been focused on investigating the possible associations between adiponectin concentration and the stage of liver fibrosis in various CLDs, including,

liver cirrhosis, biliary atresia (BA), hepatitis C viral infection (HCV), hepatitis B viral infection (HBV), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH), as summarized in Table 1."

-We also add morereferences page 20, line 9-19 and page 24, line 16-20 and line 30-31.

18. "**Bianco A,**Mazzarella G, Turchiarelli V, Nigro E, Corbi G, Scudiero O, Sofia M, Daniele A. Adiponectin: an attractive marker for metabolic disorders in Chronic Obstructive Pulmonary Disease (COPD). *Nutrients* 2013; **5:** 4115-25. [PMID: 24128974 DOI: 10.3390/nu5104115]
19. **Lim CC,**Teo BW, Tai ES, Lim SC, Chan CM, Sethi S, Wong TY, Sabanayagam C. Elevated serum leptin, adiponectin and leptin to adiponectin ratio is associated with chronic kidney disease in Asian adults. *PLoS One* 2015; **10:** e0122009. [PMID: 25793395 DOI: 10.1371/journal.pone.0122009]
20. **Honsawek S,**Chayanupatkul M. Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. *Arch Med Res* 2010; **41:** 593-598. [PMID: 21199727 DOI: 10.1016/j.arcmed.2010.11.007]"
47. **"da Silva TE,** Costa-Silva M, Correa CG, Denardin G, Alencar MLA, Coelho MSPH, Muraro-Wildner L, Luiza-Bazzo M, González-Chica DA, Dantas-Correa EB, Narciso-Schiavon JL, Schiavon LL. Clinical Significance of Serum Adiponectin and Resistin Levels in Liver Cirrhosis. *Ann Hepatol* 2018; **17:** 286-299. [PMID: 29469045 DOI: 10.5604/01.3001.0010.8659]
50. **Carvalho RF,** Atta AM, de Oliveira IS, Santos TPS, Santos JPA, Schinoni MI, de Sousa-Atta MLB. Adiponectin levels and insulin resistance among patients with chronic hepatitis C. *Acta Trop* 2018; **178:** 258-263. [PMID: 29217381 DOI: 10.1016/j.actatropica.2017.12.004]**"**

-And page 26, line 1-2 and line 24-27.

57. **"Lucero D,**Miksztowicz V, Gualano G, Longo C, Landeira G, Álvarez E, Zago V, Brites F, Berg G, Fassio E, Schreier L. Nonalcoholic fatty liver disease associated with metabolic syndrome: Influence of liver fibrosis stages on characteristics of

very low-density lipoproteins. *ClinChimActa* 2017; **473:** 1-8. [PMID: 28802640 DOI: 10.1016/j.cca.2017.08.006]

62. **Sun LJ,** Yu JW, Shi YG, Zhang XY, Shu MN, Chen MY. Hepatitis C virus core protein induces dysfunction of liver sinusoidal endothelial cell by down-regulation of silent information regulator 1. *J Med Virol* 2018; **90:** 926-935. [PMID: 29350417 DOI: 10.1002/jmv.25034]"

-And page 27, line 8-11.

65. "**Hsieh CJ,** Wang PW, Hu TH. Association of adiponectin gene polymorphism with nonalcoholic fatty liver disease in Taiwanese patients with type 2 diabetes. *PLoS One* 2015; **10:** e0127521. [PMID: 26042596 DOI: 10.1371/journal.pone.0127521]"

Minor revisions 1. Page 6 last line The adipoR1 binds globular adiponectin with a high-affinity receptor and full-length adiponectin with a low-affinity receptor, whereas adipoR2 has an intermediate affinity for both isoforms. Comment: Please clarify. Does the author mean to say that adipoR1 binds globular adiponectin with high affinity and full length adiponectin with low affinity or are they suggesting that there are two isoforms of the adipoR1 (high affinity vs low affinity)

Response

-We clarify that point in page 7, line 20-22.

"The adipoR1 has a greater affinity for globular adiponectin, whereas adipoR2 has an intermediate affinity for both isoforms."

2. Page 9 last paragraph SMAD4 Comment: Kindly use complete form followed by abbreviation in brackets, given that this is the first instance of this acronym in the manuscript

Response

-We state that point in page 10, line 15-19.

"An experimental study further demonstrated that adiponectin diminished the effect of TGF-β1-induced expression of connective tissue growth factor (CTGF, also known as fibrogenic gene) on HSCs *via* suppression of the nuclear translocation of mothers against decapentaplegic homolog 2 (SMAD2)[43]."

Reviewer#3

I have read with deep interest the minireview "Adiponectin as a novel biomarker for liver fibrosis" by Udomsinprasert W et al. This is an interesting and comprehensive update about the role of adiponectin in liver fibrosis. The protective role of adiponectin in liver fibrosis has been widely described by several authors and, as updated in this review, different approaches to increase the adiponectin concentrations have been investigated. But on thecontrary, a few studies have reported that increased plasma level of adiponectin correlates with liver fibrosis progression in different chronic liver diseases. In order to improve the manuscript, authors might discuss briefly the postulated hypothesis about these contradictory findings. Why the adiponectin levels are increased in liver fibrosis?, Is there any problem with adiponectin receptors or signaling in patients with chronic liver diseases?

Response

-Thank you very much for your kind advice. We address that point in page 13, line26-31 and page 14, line 1-9.

" Although previous clinical studies have demonstrated a direct link between adiponectin and liver fibrosis in patients with various CLDs, the exact mechanism responsible for an increase in circulating adiponectin in liver fibrosis remains uncertain. The possible explanation for these findings might be attributed to a reduction in its clearance. In CLD patients with liver fibrosis, declined adiponectin clearance could result from reduced uptake of adiponectin by liver sinusoidal endothelial cells (LSECs), which may lead to elevated adiponectin levels in the circulation. It is widely known that dysfunction of LSECs is one of pathologic events in liver fibrogenesis. In the healthy liver, LSECs generally promote HSCs quiescence. During the process of liver fibrosis, LSECs undergo phenotypic changes with the loss of several receptors and LSECs fenestration, leading to the capillarization of liver sinusoids accompanied by the impairment of various substances uptake[3]. It has been shown that adiponectin levels and adipoR2 expression are decreased in the LSECs response to liver injury[62]. These phenomena may help explain why hyperadiponectinemia has been observed in CLDs patients with liver fibrosis. "

-And page 15, line 6-8.

“The reasons for these conflicting findings remain unexplained. These are likely due to differences in populations, disease advancement, or measurements applied, or to incomplete control of confounding variables. ”

Special comments from the editor:

1. Some sentences of the main text need to be re-wrote. Please make a minor revision according to my comments and the CrossCheck report which can be downloaded from the system.

Response

-Thank you very much for your suggestion. We re-wrote some sentences based on the CrossCheck report, as shown in the manuscript. According to the Editor's comments, we address those comments in page 5, line 18-20.

"Initially, titles and abstracts related to the keywords were screened, and further full papers were evaluated for inclusion."

- Page 5, line 24-25.

"No restrictions on sex, ethnicity, number of study subjects, or year of publication were applied."

- Page 5, line 29-31 and Page 6, line 1-2.

"Human adiponectin encoded by the *Adipo Q* gene spanning 17 kb on chromosome locus 3q27 is a multimeric protein hormone and exists in different biologically active isoforms. The encoded protein comprises an N-terminal signal sequence being a collagenous domain and a C-terminal globular domain maintaining biological properties after cleavage."

- Page 6, line 6-8.

"The globular domains of adiponectin form three major complexes including trimers, hexamers, and high-molecular-weight (HMW) multimers, classically existing in the circulation"

- Page 7, line 2-7 and 22-24.

"…adiponectin receptor type 1 (adipoR1) and adiponectin receptor type 2 (adipoR2). These two major receptors have been identified in numerous tissues. In human tissues, both of them are observed in the brain and peripheral tissues. However, adipoR1 is ubiquitously detected, most abundantly in the skeletal muscle. The major expression of adipoR2 is in the liver."

"It is conceivable that adiponectin interacting with its specific receptors influences the activation of an appropriate signaling pathway that becomes altered in liver pathologies."

- Page 8, line 2-5 and 11-13.

"Activation of AMPK inhibits the transcriptional activity of glucose-6-phosphatase (G-6-Pase) and phosphoenolpyruvate carboxykinase (PEPCK), which in turn decreases gluconeogenesis."

"AMPK phosphorylation can limit the activity of sterol regulatory element binding protein-1c (SREBP-1c), which is a transcription factor regulating lipid combustion in the liver."

- Page 9, line 10-11.

"Apart from its primary roles in regulating insulin sensitivity and fatty acid metabolism, adiponectin has been shown to possess anti-inflammatory effects"

- Page 10, line 19-22.

"The activity of suppressor of cytokine signaling-3 (SOCS-3) mediated by the long form of the leptin receptor (Ob-Rb), and inducing the expression and activation of protein tyrosine phosphatase 1B (PTP1B)."

- And page 11, line 10-12 and 29-31.

"…..will be necessary to monitor the development and progression of disease in addition to the response to treatment."

"Besides, serum adiponectin levels were positively associated with surrogate associations between adiponectin levels and surrogate markers of markers of hepatic liver fibrosis, including transient elastography, fasting serum bile acids, and hyaluronate in patients with CLD."

2 About the grant, please offer the grant approval file;

Response

We uploaded the grant approval file in the system.

3 Ref 34 repeat with ref 4; Ref 42 repeat with ref 7; Ref 48 repeat with ref 8; please correct them.

Response

-Thank you very much for your kind advice. We rechecked all references in the mauscript.