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Column: Topic Highlights

Title: Cholesterol metabolism in the setting of cholestatic liver disease and liver transplantation: From molecular mechanisms to clinical implications

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Reviewer code: 00188499, 02462176 and 02981076

First decision: 2016-05-17 12:16

Dear Ze-Mao Gong,
Science Editor, Editorial Office

Comments to the Editor and Referees are provided below in a point by point fashion:

Response to the Editor

First of all, we thank you very much for the review of our manuscript and the opportunity to revise our manuscript "Cholesterol metabolism in the setting of cholestatic liver disease and liver transplantation: From molecular mechanisms to clinical implications", Manuscript NO.: 26262 according to the reviewers' comments. After re-reading the manuscript with the reviewers' comments in mind, we next detail our responses to each reviewiers's concerns. Please find the comments to the referees below in a point by point fashion.

Again, we appreciate the opportunity to revise our work for consideration for publication in World Journal of Hepatology.

Point-by-point responses, Reviewer's code: 00188499

Thank you for the expert criticism. The corrected text is highlighted with red bold font in the ms.

1. Page 4 line 12 it is not clear description of "to reduce reduced ezetimibe effect" I can't see that in the text?

Response: We have clarified this sentence.

2. Page 4 line 16 …"and low cholesterol levels".. seems not correct?

Response: We have clarified to: 'Low preoperative and peroperative' serum cholesterol levels seem to predict mortality in liver cirrhosis and after liver transplantation.'

3. Page 6 lines 5-8 is not easy to read? What is the (OMIM #607330)? It should be described more clearly of the "cholesterol". Is it the cause or result of the congenital anomalies.

Response: This part is rewritten. The codes describe the genetic disorder. However, the codes have been removed.

4. Page 8 lines 11-12 the description can't be clearly seen in the Figure 1. Such as the "oxidizes the precursor squalene to lanosterol" "inhibited by statins"… where should be the "squalene to lanosterol" and "statin" role:

Response: The order of the enzymes is corrected.

5. Page 9 1line and Figure 2 SREBP-2 in on the ER not in the Golgi? The flow from ER to Golgi should be clearer for readers' reading.

Response: The para is rewritten.

6. Page 9 lines 11-15 "cholesterol esters" is not found in the Figure 1? VLDL to IDL to LDL is not clear in the Figure 1. "the enzymes lipoprotein lipase" not clear in Figure 1.

Response: The figure is meant to give an overview of pathways, and not to show all components involved in an exhaustive/detailed fashion. As mentioned in the text, free cholesterol is first esterified and then… stored in the liver as cholesterol esters. Figure 1 shows "liver storage".

7. Page 13 lines 19-20 is not clear in Figure 4; …." to serum total"?

Response: We have changed the sentence.

8. Page 14 line 18 "associated with reduced post-LT survival" needs revision. Is this for graft or patient survival? Is this contrast to the description in page 11 lines 5-6 "serum cholesterol and lipoprotein measurements do not mirror changes in cholesterol metabolism"?

Response 1: Corrected as "associated with reduced post-LT graft outcome"

Response 2: "Is this contrast to the description in page 11 lines 5-6 "serum cholesterol and lipoprotein measurements do not mirror changes in cholesterol metabolism"?

No, there is no discrepancy. The sentences mean different issues. On page 11 we discuss about the rationale why assessing cholesterol synthesis and absorption with serum non-cholesterol sterols in general.

9. Page 15 line 16, line 25 Some references are needed, such as in page 15 line 16, line 25?

Response: References #60 and #61 added

10. Page 16 line 10 it needs the more detail description of the apo B-100 in diabetes and insulin resistance. How many risks of what? Insulin sensitive and insulin resistance?

Response: The para has been rewritten.

11. "The abbreviation word should have a full description when appeared at first time even in text or figures such as ABCG5/G8 etc."
Response: Corrected

12. "If the middle rectangle, in Figure 3, can be expressed as a liver exterior will be better for reading."
Response: The figure 3 has been changed accordingly.

Point-by-point responses, Reviewer's code: 02462176
Thank you for the expert criticism. The corrected text is highlighted with red bold font in the ms.

1.I suggest that the authors modify figure 1 such, that it give an overview on the pathways of cholesterol and of cholesterol synthesis. In an additional figure, e.g. Fig. 1B the authors might consider giving an enterocyte and a hepatocyte with the relevant systems involved in uptake and export of cholesterol. I think that such a distinction this might be of help for the non-experts in the field.
Response: Thank you for the suggestion. This can certainly be done in many ways, as also witnessed by numerous different figures of cholesterol metabolism in the literature. We feel the present figure would work best in this particular manuscript.

2. With respect to cholesterol in bile I suggest that the authors also deal with cholesterol transport in cholangiocytes and explain the role of MDR3 in canalicular cholesterol export. **Response**: Albeit MDR3, the phosphatidylcholine translocator across the hepatocyte canalicular membrane, is of great worth and interest, we consider that maybe it is not quite essential to be described in our review and we prefer to leave it out. In addition, the word count limits our possibilities.

3. I suggest that the authors summarize all disease related to cholesterol homeostasis, which are covered here in a table in addition to the mentioning of e.g. OMIM numbers in the text.
Response: Because of criticism related to the OMIM numbers we have deleted them. Regarding the liver diseases related to disturbances in cholesterol homeostasis, we have dealt only with cholestasis. The reduced cholesterol absorption was already mentioned in the chapter "Difficulties in assessment of cholesterol metabolism in cholestasis", para 2, but we have revised this sentence regarding cholesterol homeostasis, and the disruption of choleostasis in cholestasis is added to the Core Tip, page 5.

4. I miss more explanations on the role of reverse cholesterol transport in the context of liver disease. E.g. the authors might include the following overview: Endocr. Pract. 18: 90-97 (2012).
Response 1: We prefer not to enlarge our text, which is already within the word count limits.
Response 2: The suggested references have been added, as # 46 and #47.

Joukhadar R, Chiu K. Severe hypercholesterolemia in patients with graft-vs-hos disease affecting the liver after stem cell transplantation. *Endocr. Pract.* 2012; **18**: 90-97 [PMID: 21940276 DOI: 10.4158/Ep11212.RA]

Chow A, Rifici VA, Schneider SH. Lipoprotein X in a patient with lymphoplastic sclerosing cholangitis: An unusual cause of secundary hypercholesterolemia. *AACE Clinical Case Reports* 2016; **2**: e20-24 [DOI: 10.4158/EP14249.CR]

Point-by-point responses, Reviewer's code: 02981076

Thank you for the expert criticism. The corrected text is highlighted with red bold font in the ms.

This work proposes a professional review on cholesterol metabolism in liver disease from molecular mechanisms to clinical implications. The topic of article is of interest, However, the article was difficult to read because of too many language problems, and several issues below need to be addressed.

1. Please ask someone familiar with English language to help you rewrite this paper, paying particular attention to English grammar, sentence structure and spelling so that the article is clear to readers.
Response: The manuscript has now undergone professional language editing.

2. In the abstract, the aim of this paper was not well-defined.
Response: The aim of the review is added to Abstract.

3. Considering the knowledge level of readers, common sense should not be included. e.g. "Cholesterol is insoluble in water."
Response: Sentence now deleted.

4. There are some wrong expressions in sentences e.g. "The importance of cholesterol to human life and the critical role of the liver in cholesterol metabolism is exemplified by lathosterolosis".
Response: The sentence has been revised.

5. The content and logic is confusing due to the misuse of grammer.
Response: Grammar has been checked.

6. The focuses should be clear and cumuli of relative content should be avoided in this article.
7. The paragraphs with similar content should be combined together. e.g. sections "LIPOPROTEIN X" and "CHOLESTEROL AND LIVER REGENERATION"
Responses to 6 and 7: We do not feel that these sections contain similar content. Lipoprotein X-chapter is about cholestasis-induced changes in cholesterol metabolism and lipoprotein X, whereas "Cholesterol and liver regeneration" is about the significance of cholesterol to liver regeneration in settings where the liver suffers from damage of variable etiologies.