Response document

Title of review: Iron and liver fibrosis: mechanistic and clinical aspects

We deeply thank the reviewers for their encouraging comments and greatly value their suggestions to further enhance this review.

- This document details all modifications suggested by the reviewers and editor.
- All alterations indicated here have been highlighted yellow in the manuscript.

Comments from Reviewer 1

Scientific Quality:	Grade B (Very good)
Language Quality:	Grade A (Priority publishing)
Conclusion:	Minor revision

This is a well written review on iron and liver disease. It outlines clearly current knowledge on the underlying basic mechanisms of action of iron in the development of fibrosis in a range of chronic liver diseases.

Minor comments to be addressed. Table 2 and p12 There are inconsistencies in the data in Table 2, p12 and Ref 7. In Table 2 “Iron level/accumulation” in “Normal” Total iron in body range is listed as 3-4 g not 3-5 g as given in cited Ref 7. In Table 2 “Hereditary Haemochromatosis” ….can reach up to 25-30 g. This is the hepatic iron level as stated in Ref 7 and p12 not total iron. I suggest that both total body and hepatic iron levels for Normal and Hereditary Haemochromatosis subjects are included in Table 2.

Response: We thank the reviewer for pointing this out and we have now made the corrections to Table 2 page 44.

In the “Normal” cell, we have now distinctly mentioned total body iron and liver iron. In the “Hemochromatosis” cell we have clarified that it is liver iron. We prefer not to mention (generalise) total body iron levels in hemochromatosis as it can hugely vary between patients depending on the type of genetic mutation, stage, and factors such as age, sex and alcohol consumption. Also, for diagnostic purposes, rather than total body iron, serum ferritin levels and transferrin saturation are key parameters, which we have

included in the table. These do not always reflect the iron levels within tissues, which we believe acts as a confounding factor in asserting a reference value of total body iron levels that would include all hemochromatosis patients (1–3). Other important diagnostic measure for hemochromatosis is the MRI scan that measures liver iron (4,5). Hence, we have stated liver iron content in hemochromatosis patients in the "Hemochromatosis" cell.

2. p13 para 1. Correct LP-repair-mechanism to LPC-repair-mechanism.

Response: We have now corrected this-page 13

3. p22 Add LPC to Abbreviations.

Response: We have now added this in Abbreviations-page 23

4. References are not formatted correctly. Check instructions to authors for details.

Response: We have now formatted the references as required by the journal, after confirming this with the Science Editor of the journal.

Comments from reviewer 2

Scientific Quality:	Grade A (Excellent)
Language Quality:	Grade A (Priority publishing)
Conclusion:	Accept (High priority)

This review presents very interesting opinion on the relationship between iron and hepatic manifestation that are clearly of broad interest and deserve publication. Thus, the paper is an important contribution and I recommend that it be accepted for publication.

Response: We deeply thank the reviewer for these comments.

Below alterations have been made based on the suggestions from the editor.

1. The following have been submitted as a part of revision:
    - Figures in power-point
    - Audio core tip
2. Manuscript is in 12-pt Book Antiqua with 1.5 line spacing
3. Page 1: UK changed to United Kingdom
4. Page 1: Format of Author Contributions is altered as suggested
5. Page 1: Correspondence is now changed to corresponding author
6. Page 2: ABSTRACT changed to Abstract
7. Page 22: SUMMARY changed to CONCLUSION
8. Subtitles formatted as suggested (2nd level-made bold and italics) throughout the text
9. Page 24: All references have been changed to match the required style and both, PMID numbers and DOIs have been added following the citation where possible.
10. Page 42: Abbreviations in figure titles have now been explained in full
11. Page 42: Figure legends- all abbreviations in the legends have now been explained in full.
12. Pages 43-45: All abbreviations in the table titles (tables 1 and 2) have now been explained in full.
13. Pages 43-45: All abbreviations in tables 1 and 2 have now been explained in full in their corresponding key to table.

References

1. Lee MH, Means RT. Extremely elevated serum ferritin levels in a university hospital: associated diseases and clinical significance. Am J Med. 1995 Jun;98(6):566–71.
2. Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. Gastroenterology. 2010 Aug;139(2):393–408, 408.e1-2.
3. Loréal O, Deugnier Y, Moirand R, Lauvin L, Guyader D, Jouanolle H, et al. Liver fibrosis in genetic hemochromatosis. Respective roles of iron and non-iron-related factors in 127 homozygous patients. J Hepatol. 1992 Sep;16(1–2):122–7.
4. Queiroz-Andrade M, Blasbalg R, Ortega CD, Rodstein MAM, Baroni RH, Rocha MS, et al. MR imaging findings of iron overload. Radiogr Rev Publ Radiol Soc N Am Inc. 2009 Oct;29(6):1575–89.
5. Legros L, Bardou-Jacquet E, Latournerie M, Guillygomarc'h A, Turlin B, Le Lan C, et al. Non-invasive assessment of liver fibrosis in C282Y homozygous HFE hemochromatosis. Liver Int Off J Int Assoc Study Liver. 2015 Jun;35(6):1731–8.