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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 13545
Title: Dysregulation of iron and copper homeostasis in nonalcoholic fatty liver
Reviewer code: 02861277
Science editor: Yue-Li Tian
Date sent for review: 2014-08-27 14:38
Date reviewed: 2014-11-10 23:12

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair	[ ] Grade D: Rejected	BPG Search:	[ ] Rejection
[ ] Grade E: Poor		[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Aigner E. et colleagues well described the physio-pathological factors involved in the iron overload in NAFLD. Moreover, they reported the molecular mechanisms that could explain the liver injury worsening shown in patients affected from iron overload in NAFLD. In addition, the authors described the clinical implications of iron overload and copper deficiency as well as the therapeutic option in NAFLD/NASH patients. Main observations As well underlined from the authors there is a strict connection between iron overload, oxidative stress (..and lipid-peroxidation) and liver injury in NAFLD/NASH. They remembered as NAFLD is both a metabolic and an inflammatory disease. On the base of these considerations, I guess that they should include the role of the adaptive immune responses related to the oxidative stress in NAFLD progression (among the other pathological mechanisms). As the authors reported, the iron, at least in part, is stored in the macrophages and given their pivotal role in NAFLD/NASH. I believe that they should include comments about the activation pattern of these myeloid cells in NASH. Pag 5: The authors reported: "macrophage-derived Kupffer cells". What means? Please clarify. To my knowledge monocytes-derived macrophages and Kupffer cells have a different ontogeny.

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ESPS PEER REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[Y] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

This is a very interesting review article, in my opinion, it summarizes clearly the most important aspects concerning to iron and copper as factors which are involved in the pathophysiology of NAFLD and NASH. The figures are very understandable and presented in a didactic way. However, this paragraph: "From a practical point of view, these studies suggest that iron depletion therapy via phlebotomy may represent a safe add-on therapy for NAFLD patients with elevated ferritin. We have adopted the practice to perform biweekly phlebotomies in these subjects until serum ferritin concentrations are between 50 and 100 ng/L. In contrast to patients with hemochromatosis, biweekly phlebotomies are generally performed in NAFLD patients.[26, 148] As NAFLD patients have impaired iron mobilisation from storage sites they may develop anemia in response to phlebotomy treatment", seems to be structured as a conclusion, in my opinion thisis not entirely correct, then I suggest it must be restructured