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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

ESPS manuscript NO: 26293

Title: Understanding the true nature of bilirubin: cytotoxic or protective?

Reviewer's code: 03642003

Reviewer's country: China

Science editor: Jing Yu

Date sent for review: 2016-04-07 12:39

Date reviewed: 2016-05-20 10:24

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

1.The title should be limited in CAD according to the manuscript. It is more appropriate as a mini review if published. 2. The manuscript give more epidemiology description and ignore the comparisons within studies. Most importantly, the specific mechanism of protective or cytotoxic is only slightly mentioned, and this part should be extended. 3. The figure is unsharp.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

ESPS manuscript NO: 26293

Title: Understanding the true nature of bilirubin: cytotoxic or protective?

Reviewer's code: 03498793

Reviewer's country: Denmark

Science editor: Jing Yu

Date sent for review: 2016-04-07 12:39

Date reviewed: 2016-05-14 06:42

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input checked="" type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
		BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The authors have drafted a review to describe the bilirubin metabolism and possible impact on cardiovascular disease (CVD) risks. They systematically report on prior studies confirming or denying the hypothesis that high levels of bilirubin reduce the risks of cvd. General Comments: The review may benefit by addressing the central questions more directly, such as: "How likely is bilirubin to be directly associated with cardiovascular risks?" "The protection from cardiovascular disease is most likely multifactorial. What are the main contributors beyond bilirubin?" As of yet, these things are commented upon throughout the manuscript, but trying to answer the main questions more directly would improve the paper. Did authors perform any systematic literature search? Please describe. Introduction, page 4 It is important to notice that the study by Vitek et al. showed that 1/50 patients with GS had IHD at baseline, and it is unclear how authors came to the conclusion that the prevalence was different in the two groups. The same study showed, that during three-year follow-up there was no difference in incident IHD in analyses adjusted for baseline factors. Using this as the main reference in support of lower risks of CVD with elevated bilirubin is questionable. Furthermore, the fact that no difference is observed when adjusting for baseline risk



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factors is interesting and in agreement with previous studies such as DOI: 10.1016/j.numecd.2013.12.009. Bilirubin metabolism, page 5 The introduction of Crigler-Najjar and Dublin-Johnsson syndrome is interesting. The authors should consider relating this syndrome to cardiovascular risks specifically, if known, also including why the type 1 syndrome is lethal. Cardiovascular, hepatic, hematological causes or other? Prospective properties of bilirubin, page 5/6. The authors state that: "which in turn retards the peroxidation of lipids, hence, restricting the progression of atherosclerosis [10]." Reference 10 was an in vitro study which concluded that bilirubin may help reduce the risk of atherogenesis. The authors infer causal effects in vivo based on this study. Prospective properties of bilirubin, page 5/6. "Bilirubin protects" infer causality. Please rephrase. Evidence supporting the protective effect of bilirubin on CAD, general Please consider reporting on trends and conclusions rather than the specific numbers for each study. Focusing on the study conclusions and limitations would be more informative. Genetic Polymorphisms of UGT1A1*28, page 13 The authors need to comment on potential genetic penetrance, because if the gene always leads to higher bilirubin levels, then the gene might very well be an intermediate variable which could explain why the gene is not associated with outcomes in multivariate analyses. Expert commentary, general This section brings forward some possible confounders that puts into question the causal effects of bilirubin on lower risks of CVD. The authors should consider introducing this general concept, followed by a restructured discussion on the confounders mentioned in this section. Expert commentary, page 16. "Thus, a conclusion can be safely inferred that if at all bilirubin is protective in CAD, it might be possible that it is not just the bilirubin excretion but the production of bilirubin, which indirectly is by induction of heme oxygenase and is also accompanied by the production of carbon monoxide." This is confusing as the, by the authors, implied causal effects of bilirubin must be directly related to bilirubin to be causal. Implying that bilirubin may exert causal effects through other mechanisms (heme oxygenase, CO, etc.) is self-contradictory. Expert commentary, page 16. "And it is being reflected that bilirubin has protective effect on CAD whereas, actually it does not." Please rephrase. Expert comment, page 17. First paragraph. The hypothesis put forward is not

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

ESPS manuscript NO: 26293

Title: Understanding the true nature of bilirubin: cytotoxic or protective?

Reviewer's code: 02636210

Reviewer's country: Turkey

Science editor: Jing Yu

Date sent for review: 2016-04-07 12:39

Date reviewed: 2016-05-22 13:20

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
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		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Journal: World Journal of Gastroenterology Manuscript number: 20160402111951 Manuscript title: Understanding the true nature of bilirubin: cytotoxic or protective? I thank to authors and congratulate them regarding their nice and brief paper that reviewing the positive and negative results of several studies with bilirubin. Comments *Please include a short paragraph regarding the management options (if present) for equilibration of bilirubin levels in human body – any study with drugs or life style changes that has impact on bilirubin levels? *Any animal study showing a direct evidence that bilirubin have had anti-oxidant effect and decrease atherosclerosis? Please include