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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

ESPS manuscript NO: 20577

Title: Erythropoietin and diabetes mellitus

Reviewer's code: 03351380

Reviewer's country: China

Science editor: Fang-Fang Ji

Date sent for review: 2015-06-11 21:57

Date reviewed: 2015-07-30 18:06

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 checked="" 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

This is a review updated the research progress of EPO, a well-known and multi-effective growth factor, in the field of Diabetes Mellitus. The key statements of the review are, in general, adequately supported by comprehensive and appropriate references. And the article was well organized with brief description. However, a few points still require attention: 1, The first part of the main body "Erythropoietin: Discovery and Biology" seemed to take too much space describing EPO, for EPO has been known well for long. Introducing it with shorter paragraphs is suggested. 2, The last part : "Conclusions and Future Perspectives" needs to be more conclusive and a brief summary, For example Line 347-359 and line 403-412 reads a little repetitive. 3, Line 322 contained a words error with two "provide" together.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

ESPS manuscript NO: 20577

Title: Erythropoietin and diabetes mellitus

Reviewer's code: 02446208

Reviewer's country: United States

Science editor: Fang-Fang Ji

Date sent for review: 2015-06-11 21:57

Date reviewed: 2015-07-23 21:52

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 checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input 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

This is a fairly well written short review article on erythropoietin and its potential use in the treatment of diabetes-related complications. It cites fairly up-to-date literature on EPO and its studies in diabetes settings. The manuscript is closely related to diabetes and is relevant to diabetes treatment. On the other hand, it covers more on erythropoietin than on diabetes, making it little bit imbalanced. As a result, the title of the manuscript is somewhat misleading. It may be more appropriate to be renamed as "Erythropoietin and its potential use in the treatment of Diabetes Mellitus". The manuscript can be accepted for publication after some necessary major and minor revisions. Major concerns 1. It covers in molecular details for EPO and EPO-related signaling pathways and key factors involved. However, more should be described for diabetes if the title is unchanged, particularly those diabetes-related complications that could be potentially addressed by EPO. 2. Although the author claimed that EPO has significant potential in the treatment of diabetes, this reviewer is not fully convinced that this is the case according to the description for the cited studies of EPO in diabetes. Only fewer than 15 papers were cited in the review for potential benefits of EPO in diabetes, but about 10 papers were cited on the side effects of EPO on diabetes. To



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balance the two sides, there is no convincing evidence to show that EPO can really be used for treating diabetes. More problematic, some of the side effects cited seem to be quite serious. These may be exact reasons why there have been no clinical trials for EPO in the treatment of diabetes. Although author suggests that targeting downstream factors such as Akt, mTOR, and AMPK may be more specific and side effects-avoiding for EPO, these targets have been targeted already by other drugs. For example, Metformin has been used to target AMPK. If these downstream factors are targeted, then EPO will NOT be used anymore. Exactly what author is trying to suggest? Combined therapies? Author should be more specific on this point and expand the discussion. 3. A single figure may not be the best way to summarize all the points author is trying to convey. It is recommended that the single figure be separated into different parts. For example, figure 1 will be for EPO and its pathways only; Figure 2 or a Table should be added to summarize all the known beneficial effects of EPO in diabetes as well as all the known side effects. References should be included in the new figure(s) or Table(s). The current figure should be more descriptive. Minor points 1. Why no full address and no phone number provided? 2. Writing and grammatical errors: 2-1. Abstract - line 50, “)” is wrong and should be removed. 2-2. Page 4, line 103, there are two “upon”. One should be removed. 2-3. Page 4, lines 99 - 106, amino acid residues in EPO were written in two forms. They should be consistent. For example, Serine126 and serine 126 were used. One or the other format should be used, but not both. 2-4. Page 4, line 118, “EPO is expressed throughout the body.” What is the function of this sentence? It appears that this sentence has no relations with other contents of this paragraph. It should be either removed or rewritten. 2-5. Page 7, Line 203 “praline rich”. Should that be “proline rich”?

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

ESPS manuscript NO: 20577

Title: Erythropoietin and diabetes mellitus

Reviewer's code: 03287643

Reviewer's country: Greece

Science editor: Fang-Fang Ji

Date sent for review: 2015-06-11 21:57

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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 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 checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
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<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input 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

This is a thorough review of EPO signalling pathways and their potential significance in DM. In my opinion this should be reflected in the title of the manuscript instead of the current title: EPO and diabetes mellitus. Moreover, a couple of points need some clarification: A) The author states that EPO has been proved clinically effective in improving cardiac function, minimize fatigue etc. However, these actions are mediated by the erythropoietic activity of EPO and not by the tissue protective one. In fact, clinical applications of EPO for cyto- and tissue- protection have failed so far and I think this should be reported. Useful citations are the following for example: 1: Vlachopoulos G, Kassimatis TI, Agrafiotis A. Perioperative administration of high-dose recombinant human erythropoietin for delayed graft function prevention in kidney transplantation: a meta-analysis. *Transpl Int.* 2015 Mar;28(3):330-40. doi: 10.1111/tri.12506. Epub 2015 Jan 6. PubMed PMID: 25516244. 2: Endre ZH, Walker RJ, Pickering JW, Shaw GM, Frampton CM, Henderson SJ, Hutchison R, Mehrstens JE, Robinson JM, Schollum JB, Westhuyzen J, Celi LA, McGinley RJ, Campbell IJ, George PM. Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). *Kidney Int.* 2010 Jun;77(11):1020-30. doi: 10.1038/ki.2010.25. Epub 2010 Feb 17.



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PubMed PMID: 20164823. B) The author states that specific targeting of the signalling pathways can minimize undesired side effects of the drug. But how exactly can this happen? Will EPO be used in different dosages? Or maybe a modified form of EPO can achieve that? I think the author should elaborate more on this issue if there are data.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

ESPS manuscript NO: 20577

Title: Erythropoietin and diabetes mellitus

Reviewer's code: 02616718

Reviewer's country: United States

Science editor: Fang-Fang Ji

Date sent for review: 2015-06-11 21:57

Date reviewed: 2015-08-03 08:38

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 checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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<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

The author reviewed the history and recent progress of use of EPO in diabetes treatment in a comprehensive manner. A total of 248 papers were cited. The information provided in review may be helpful to some readers who want to have a general understanding of the field. However, the author did not critically discuss the published results and the review is not very valuable in its current version. I have following comments and recommendations to improve the manuscript: 1. The "signal Transduction pathways for Erythropoietin" section involves many signaling proteins and is very difficult to follow. In addition, the information in this section has significant overlap with published reviews. I recommend a revision of this section with emphasis on relevance of EPO signaling to DM treatment. 2. The information in section "Erythropoietin, Oxidative Stress, and Cell Survival" has been reviewed extensively in many review articles. It may be incorporated in the signaling section. 3. "Novel Avenues for Erythropoietin and Metabolic Disease" is the most important section. I recommend that the author critically analyze the conclusions drawn in the original study and point out the advantages and/or the limitations of the studies. 4. The author stated that the potential adverse effect of EPO may be avoided by targeting more specific pathways in the paragraph at page



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13. However, how the adverse effect to be avoided was not clearly discussed. 5. The "conclusion and future perspectives" section should be more specific and not simply repeat what have been discussed in previously. 6. The figure is confusing and not informative. The figure should depict the relationships of the signaling proteins in the relevant signaling pathways and indicate potential strategies to increase the clinical beneficial outcome and to limit the adverse effects. 7. At page 7, the sentence "EPO phosphorylates Akt at 186 serine473 to activate this kinase" is not correct. EPO is a cytokine and does not phosphorylate Akt.