

Format for ANSWERING REVIEWERS

July 24, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 4205-review.doc).

Title: Effects of glucagon-like peptide-1 (GLP-1) receptor agonists on renal function

Author: Filippatos TD, Elisaf MS

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 4205

The manuscript has been improved according to the suggestions of reviewers:

REVIEWER 1

General: This is a highly relevant topic being covered for the first in a dedicated review. The perspective is more on clinical implications than on basic physiology and case reports and safety issues are covered in very great detail. Although the method section states that searches have been performed up to June 2013, important papers are missing. Especially, a paper covering the basic renal physiology of GLP-1 in humans (1) and a paper elucidating a GLP-1 - ANP axis in mice (2) are mandatory in a review as this. In general it should be specified if findings are based on rodent or humans studies. The review has a tendency of becoming a long listing of study findings with only few reflexions from the authors.

We thank the reviewer for reminding these important papers which were missed during our search. We added information regarding these papers in the relevant sections (page 10, lines 14-16; page 12, last paragraph; page 16, first paragraph). We now state throughout the text if the studies mentioned are based on rodent or human studies. We also added 2 tables in which we provide information regarding the studies mentioned in the text. Finally, we added some comments regarding the study findings mentioned in the text (page 11, second paragraph; page 15, last paragraph; page 17, last paragraph).

Abstract/Core Tip/Conclusion: More renal research have been performed with exenatide compared to liraglutide, but there is no evidence that exenatide protects the kidney better than liraglutide (the text could be interpreted that way). Further, it should be stated that this possible protection is based almost solely on rodent studies. Exenatide also affects water-sodium balance in humans (3) (also from studies already cited). Liraglutide also affects water-sodium balance in rodents (2).

We agree with the reviewer that no evidence exist showing exenatide to be better than liraglutide in terms of kidney protection, so we removed the phrase "especially exenatide" from the abstract, core tip and conclusion (pages 3 and 17). We now state clearly in the abstract and core tip that the evidence regarding diabetic nephropathy is based on animal studies. We also state in the abstract and the conclusion that both GLP-1 receptor agonists affect electrolyte and water balance (pages 3 and 17). Finally, we added information regarding the paper (3) in the exenatide and renal function section (page 12, last paragraph) and made some comments regarding the effects of GLP-1 receptor agonists in blood pressure levels (page 12, last paragraph).

Sections regarding GLP-1/exenatide/liraglutide actions on renal function: The above mentioned papers (1,2) should be discussed. It should be mentioned that renal receptors in glomeruli and proximal tubules are animal findings which have not been replicated in humans (to my knowledge).

We added specific details of the mentioned papers (page 12, last paragraph; page 16, first paragraph). We agree with the reviewer that according to our knowledge the finding of renal GLP-1 receptors in proximal

cells is based on animal studies, so we now specifically state this information (page 11, *Effects on water and electrolyte balance* section, line 3).

Liraglutide safety: Here are two more case reports of acute kidney injury (4)

1. Skov, J., et al. Glucagon-Like Peptide-1 (GLP-1): Effect on Kidney Hemodynamics and Renin-Angiotensin-Aldosterone System in Healthy Men. *J Clin Endocrinol Metab* 98, E664-671 (2013). 2. Kim, M., et al. *Nature medicine* (2013). 3. Mendis, B., Simpson, E., Macdonald, I. & Mansell, P. Investigation of the haemodynamic effects of exenatide in healthy male subjects. *Br J Clin Pharmacol* 74, 437-444 (2012). 4. Narayana, S.K., Talab, S.K. & Elrishi, M.A. Liraglutide-induced acute kidney injury. *Practical Diabetes* 29, 380-382 (2012).

We now provide information regarding these case reports.

We thank the reviewer for his comments which helped to substantially improve our mini review.

REVIEWER 2

This review is well written, comprehensive and up to date. I only have the following, few, minor comments: 1-it would be helpful to devote a few lines in the Introduction, to the actions(both established and putative)of GLP-1. A figure would also be welcome. I would summarize two tables the studies regarding exenatide and liraglutide (distinguishing between animal and human studies), besides providing detail in the text

We added information regarding GLP-1 actions in the Introduction (page 4, second paragraph). According to the reviewer's suggestion we added two tables regarding exenatide and liraglutide, in which animal and human studies are now clearly distinguished. Also, we now provide this information (animal or human studies) throughout the text.

REVIEWER 3

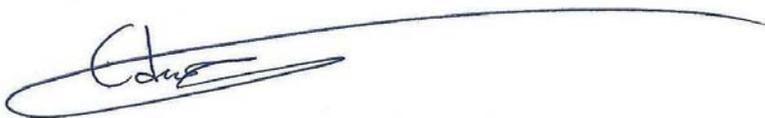
Well done and helpful analysis of a concern of growing import to the management of Type 2 Diabetes. The only addition that I would suggest is to note that there have been numerous examples of drugs evaluated in rodents with induced diabetes that when translated into clinical trials were ineffective. The best example is the sequence of failures of advanced glycoylated endproduct (AGE) inhibitors that proved worthless in clinical trials. Thus, caution should be expressed when citing rodent data as a clinical guide.

We thank the reviewer for his kind comments. We added a comment regarding drugs with positive results in rodents that are ineffective in clinical trials (page 17, last paragraph).

The text was checked by a native English speaker and language has been improved.

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

Sincerely yours,



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