

Date: 21st Jan 2021

To
The Editor-in-Chief
World Journal of Diabetes

Subject: Submission of the revised manuscript titled “Beyond Diabetes Remission-A Step Further: Post Bariatric Surgery Hypoglycemia” Manuscript NO.: 71881, Letter to the Editor

Dear Editor,

We would like to submit this revised manuscript entitled “Beyond Diabetes Remission-A Step Further: Post Bariatric Surgery Hypoglycemia” to your esteemed journal after incorporating the minor revisions as suggested by some reviewers. This letter to editor highlights the importance of recognising post bariatric hypoglycemia as a complication of bariatric surgery, which if appropriately diagnosed can be effectively managed especially in those who have had a remission in pre-bariatric surgery diabetes.

This manuscript has not been published and is not under consideration for publication in any other journal and has been prepared as per the Instructions to the author mentioned on the website. All authors have contributed to the manuscript and approved for submission to this journal. Please find below the reply to the reviewer comments, all changes have been highlighted in the manuscript in red ink.

Reviewer comments

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors have written an appropriate minireview on postbariatric hypoglycemia. This letter to editor will benefit the readers in understanding this important complication of bariatric surgery.

Response: We thank the reviewer for the positive comments and recommending the acceptance of this manuscript.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript entitled “Beyond Diabetes Remission a step further: Post bariatric surgery hypoglycemia” in response to a recently published article on “Progress in treatment of type 2 diabetes by bariatric surgery” addresses an interesting topic on the underlying mechanisms that lead to postbariatric hypoglycemia (PBH) as an increasingly recognized complication of bariatric surgery and the novel emerging therapeutic targets that target these

mechanisms. The title fully reflects the main subject of the manuscript. The abstract summarizes and reflects the conclusions described in the manuscript. The key words reflect the focus of the manuscript. The manuscript adequately describes the background, present status and significance of the findings. The Core Tip is relevant, and sufficient information about the previous findings is presented for readers. The conclusions are clear. The discussion is appropriate. The authors made a systematic contribution to the research literature in the area of investigation. The manuscript may be accepted for publication in its current form.

Response: We thank the reviewer for the positive and detailed review of this paper and recommending the acceptance of this manuscript.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript entitled "Beyond Diabetes Remission a step further: Post bariatric surgery hypoglycemia" is a Letter to the Editor which briefly describes the prevalence, signs and symptoms, pathophysiology, diagnosis and management of Post bariatric surgery hypoglycemia. Overall the data appears to be well summarised and would be very useful to improve the awareness of practicing physicians regarding Post bariatric surgery hypoglycemia. However, discussion regarding pharmacotherapy of Post bariatric surgery hypoglycemia needs more elaboration. The authors may also consider elaborating regarding the drugs in the pipeline including pre clinical studies.

Response: We thank the reviewer for the positive comments. We agree with the reviewer, we have now included the following information regarding the available and upcoming drugs used in the management of post bariatric hypoglycemia.

"Various pharmacological agents have been used with some success for patients who fail MNT, by blunting the inappropriately elevated insulin secretion and ensuing hypoglycemia. These include the alpha-glucosidase inhibitor acarbose, calcium channel antagonists like nifedipine or verapamil, the beta-cell adenosine triphosphate-sensitive potassium channel agonist diazoxide (inhibits insulin secretion by hyperpolarisation) and somatostatin analogues like octreotide. [20]. Refractory patients may require a gastrostomy tube placement or a restrictive procedure, with some undergoing partial or total reversal of the bypass [9,20]. Over the years, GLP-1 has become an increasingly attractive target. A recent phase 2 randomised placebo-controlled crossover study (PREVENT) employing the GLP-1 receptor antagonist avexitide [exendin (9-39)] for 28 days showed a significant decrease in the occurrence of hypoglycemia in response to a mixed meal challenge test requiring rescue as well as on continuous glucose monitoring, with an improved glycemic profile [21]."

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: It is a simple but interesting and concise letter to editor.

Response: We thank the reviewer for the positive comments and recommending the acceptance of this manuscript.

Reviewer #5:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This letter provides a good supplement to the original paper, and gives us a better understanding of the occurrence of hypoglycemia after bariatric surgery, including the incidences, mechanisms and treatment of post bariatric hypoglycaemia. Minor issues: 1. The authors mentioned that post bariatric hypoglycaemia (PBH) is an infrequent but potentially debilitating complication, with incidences of 0.47-0.2% and a two- to sevenfold increased relative risk reported from registries. 0.47-0.2%? According to many relative literatures, the actual incidence and prevalence is far more higher than expected [1]. Please further review the prevalence of PBH in detail. For example: 1. Tzovaras G, Papamargaritis D, Sioka E, et al. Symptoms suggestive of dumping syndrome after provocation in patients after laparoscopic sleeve gastrectomy. *Obes Surg*, 2012, 22 : 23-28. 2. As far as the management of PBH is concerned, the authors stated that the frequent intake of smaller meals comprising carbohydrates with a high glycaemic index helps prevent hypoglycaemia [18]. According to common sense or guidelines, it should actually be low glycemic index foods that reduce reactive hypoglycaemia. This should be corrected.

Response: We thank the reviewer for the positive comments. We have now clarified the actual incidence and prevalence of Post Bariatric Hypoglycemia and included the prevalence described in the study suggested by the reviewer as reference 7. The revised information is presented as below

“Postbariatric hypoglycaemia (PBH) is an infrequent but potentially debilitating complication, with a multicenter registry-based study in Spain having reported 22 patients developing hypoglycemia following 4,645 interventions, amounting to an incidence rate of 0.47%. [3] In another study using registry data, 5,040 Swedish patients that underwent Roux-en-Y gastric bypass (RYGB) were matched with 10 non-surgical controls each, with no preoperative difference in the frequency of hypoglycemia or potentially related diagnoses such as confusion, seizures or syncope. Following gastric bypass, 0.2% of the post-gastric bypass cohort were admitted for hypoglycemia versus 0.04% of the general population. Although the overall incidence is variable, these patients were at a two- to sevenfold increased risk of hypoglycemia and related diagnoses when compared to their controls. The authors also found that there was no significant increase in the risk of postbariatric hypoglycemia or related diagnoses among patients undergoing restrictive procedures, namely vertical banded gastroplasty (4,366) and gastric banding (2,917) when matched with controls. Patients without diabetes especially are at an increased risk of hypoglycemia following bariatric surgery versus those managed medically [5]. Greater frequencies of hypoglycemia (32.6% and 22.6%) are observed in gastric bypass (GBP) and sleeve gastrectomy patients subjected to a two-hour oral glucose tolerance test (OGTT) [6], with much lower rates (2.3%) [6] reported in those undergoing gastric banding [5-6]. In another study by Tzovaras et al, 29% experienced definite dumping syndrome while another 16% had symptoms suggestive of the same. [7]”

We thank you for providing an opportunity to revise this manuscript and look forward to your reply.

Thanking you,

Best Wishes,

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