August 13th, 2020

Dr. Ke-Qin Hu, MD,
Dr. Koo Jeong Kang, MD,
Dr. Nikolaos Pyrsopoulos, MD, PhD, MBA
Editors-in-Chief
World Journal of Hepatology

Dear Drs. Hu, Kang, and Pyrsopoulos:

We are re-submitting (Ms. No. 01221925.R1) for publication our original study titled: **"Metabolic syndrome and liver disease in the era of bariatric surgery: What you need to know!".**

We would like to thank you for the opportunity to submit a revised manuscript. We have carefully reviewed the recommendations and have revised our manuscript accordingly. Detailed replies to the reviewer's comments are provided below.

Reviewer 1:

Comment R1.1: "*1. the division of procedure based on perceived mechanisms of restriction and malabsorbtion is a concept that even the surgical fraternity is trying to say good bye to and most updated published data would seem to suggest multiple downstream effects of bariatric surgery that result in weight loss and metabolic amelioration and not only restriction or malabsorbtion. One such example is " Mechanisms of Diabetes Improvement Following Bariatric/Metabolic Surgery" by Davide E Cumming that was published sometime back in Diabetes*"

Response:

We appreciate the insightful comment by the reviewer. We updated our manuscript to reflect the most current concepts regarding the mechanisms that have been implicated in the weight loss, glucose homeostasis, and metabolic benefits of bariatric procedures. We have modified appropriately the section entitled "Surgical management" and subsequent procedure specific sections with relevant references.

Comment R1.2: "*2. In the RYGB section you have alluded to remission of comorbidities and in mention them you have spoken of hypertension, hyperlipidemia and etc. But like diabetes there is resurgence after sometime and thus may be its worthy to mention that hyperlipidemic patients may still benefit from life long therapy and blood pressure medications should be tailored to need*"

Response:

Thank you for this important comment. We added a relevant statement in the RYGB section to signify the importance of anti-hypertensive and lipid-lowering therapy in patients undergoing RYGB due to the long-term risk of resurgence after the procedure.

Comment R1.3: *"3. Post-operative complications of RYGB - inguinal hernia? please cross check again"*

Response:

We apologize for that oversight. We deleted that complication.

Comment R1.4: *"4. In the SG section - you speak of loss of ghrelin as the main driver for weight loss after SG but studies have shown this not to be the case as well"*

Response:

The aforementioned statement, involving ghrelin as the main determinant of weight loss in the SG section, was removed according to the reviewer's suggestion. In addition, we have modified our manuscript to reflect the most current data regarding the mechanisms involved in the metabolic effects of bariatric surgery.

Comment R1.5: *"5. in the SG section you state " Postoperative, most insulin-dependent patients ....." the sentence gives me an impression that SG is not worth for treating patients with diabesity. In this particular group of patients even the best bypass procedure may not be able to deliver remission and thus for a simple procedure to achieve lower dosing of medications and improving glycemia is a great achievement to me."*

Response:

We appreciate the reviewer's comment. We have accordingly modified the SG section to stress the importance of SG as a simple procedure, which can indeed result in significant post-procedure benefits in populations with metabolic syndrome, diabetes, and/or obesity.

Comment R1.6: *"6. SG in nutritional deficiency - you claim nutritional complications to be only present in RYGB - not really true LSG patients have iron, B12, vitamin D deficiencies too so they are not exclusive to RYGB"*

Response:

Following the reviewer's recommendation, we mentioned the potential risk of postoperative nutrient deficiencies in patients undergoing sleeve gastrectomy and notified the importance of ongoing monitoring and supplementation.

Comment R1.7: *"7. SG in super super obese individuals as similar morbidity as compared to others"*

Response:
We have modified our SG section accordingly and have mentioned that the morbidity is similar to other bariatric surgeries in extremely obese patients.

Comment R1.8: *"8. BPDS - I wouldn't say its restricted to super super obese patients, please refer to ASMBS guidelines for procedures"*

Response:

We modified our statement to make sure that the reader becomes aware of the effectiveness of BPD in extremely obese patients and patients with MS resistant to other treatments/procedures.

Comment R1.9: *"9. BPDS - a major set back is the need for very stringent compliance to supplementation failing which fat soluble vitamin deficiencies are inevitable."*

Response:

We have modified our BPD section according to the reviewer's recommendation to raise awareness about lipid soluble vitamin deficiencies and added relevant literature.

Comment R1.10: *"10. ASMBS recommendation is life long supplementation after all bariatric procedures not only RYGB and BPDS.."*

Response:

We modified our statement to mention the nutritional deficiencies and the need for lifelong supplementation in all bariatric procedures.

Comment R1.11: "*11. I would like to see something written on how bariatric surgery impacts different stages of the NASH - cirrhosis. when to recommend it and when patients are not suitable for it.*"

Response:

We added a section on "The role of bariatric surgery in NAFLD/NASH" and a Table with previously published studies on the histologic improvements of bariatric surgery for NASH.

Thank you for the opportunity to submit a revised version of our manuscript. We hope that we have satisfactorily addressed your concerns.

Sincerely,

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