Author's response to reviews

Title: Reversal of Fibrosis in Patients with Nonalcoholic Steatohepatitis After Gastric Bypass Surgery

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Reviewer reports:

Geltrud Mingrone (Reviewer 1): The paper of Parker et al. examines the effect of gastric bypass on liver function and histology.

I have some major comments:

The modality to select the patients with NASH who have been restudied after bariatric surgery is unclear to me. In the result section the Authors state that 26 (25%) patients had NASH without fibrosis or with stage 1 or 2 fibrosis; and 11 (10%) patients had NASH with stage 3 or 4 fibrosis". Therefore, 37 patients had NASH. However, just few lines above it is stated that "A subset of the 45 patients with histologically diagnosed NASH was re-evaluated once patients lost
60% of their preoperative excess weight or weight loss plateaued after surgery". Which is the number of patients with NASH, 37 or 45?

The authors apologize that the selection of patients was unclear to Reviewer 1. Also, the Reviewer is correct in that 37 patients with NASH or NASH with fibrosis were identified for follow-up biopsy. The manuscript has been corrected.

Lines 236-240: Again, why the figures of NASH histological modifications are not referred to the entire sample (i.e. 12/15 instead of 12/13 and so on)?

The entire sample of patients who had both pre and post RYGB biopsies was 15. Importantly, several subsets of patients exists in this albeit small sample where steatosis and NAFLD were present and distinct histologically. These patient subsets represent the lesser denominators, i.e. 12/13.

Table 3 is misleading. In fact, it seems that 11 out of 27 patients with NASH diagnosed at the time of the intraoperative liver biopsy had still steatosis at the follow up and so on. I would suggest to report only the histological features of the patients who had liver biopsy both at the baseline and after surgery.

The authors acknowledge Reviewer 1’s concern that matching pre and post RYGB data only would be ideal. However, the authors believe that since biopsies were collected on all pre RYGB patients, including this data is important to define the cohort studied and illustrates the variability of liver disease present in this population, regardless of whether a post RYGB biopsy was able to be obtained.

Table 4 is unclear, if the Authors want to keep it then they should also report the individual histological features for all the 15 patients examined.

The authors apologize that Table 4 is unclear to Reviewer 1. The intent of its inclusion is to clearly illustrate the histologic criteria used by the hepatopathologist in determining the extent of disease at baseline and after RYGB and subsequent weight loss using the criteria by Kleiner et al.

In Table 6 the Odds Ratio was significant only for AST, ALT, ALK, however the multivariable model included AST, ALT, ALK, bilirubin, albumin, PT and ICG. I don't believe it is a correct procedure and a statistician should give his/her opinion.

The analysis was prepared by our statistical co-author, Jing You. The general approach these days is to avoid data-driven models which tend to over-fit models, and instead include all likely factors in the analysis. In this case, a multivariable logistic regression model to predict liver function and determine a correlation with what was observed histologically should include AST, ALT and ALK because they are surrogates of traditional liver function/damage, along with synthetic function surrogates (bilirubin, albumin, and PT) and non-metabolized clearance of ICG.
I would like also to recommend to discuss the important results reported in the papers of

And of

The authors are grateful for the recommended above references and have included comments pertinent to them in the Discussion section of the manuscript.

Minor comments:

Line 165 Wilcoxon instead of Wilcoxin.

The authors have made the correction.

Homero Rivas, MD, MBA (Reviewer 2): Excellent manuscript. It would be very interesting to actually have liver biopsies after the bypass, however based on the lack of clinical need, this would put patient at risk. On the other hand, any of these patients who may have need a reoperation, it would have been of great value to repeat biopsy for pathology re-staging of liver disease.

The authors thank Reviewer 2 for their comments. We also agree that any opportunity for restaging of liver disease would be helpful, especially if reoperation proves necessary.