Author’s response to reviews

Title: CARDIOVASCULAR RISK REDUCTION OVER TIME IN PATIENTS WITH DIABETES OR PRE-DIABETES UNDERGOING BARIATRIC SURGERY: DATA FROM A SINGLE-CENTER RETROSPECTIVE OBSERVATIONAL STUDY

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Author’s response to reviews:

All the changes done are highlighted in the text in yellow.

Reviewer reports:

Ilaria Cavallari (Reviewer 1): Rubio-Almanza et al. aimed to investigate the cardiovascular risk profile of 105 diabetic and pre-diabetic patients up to 60 months after bariatric surgery. The authors concluded that there was a significant reduction of cardiovascular risk across the entire population at 12 months that persisted until 60 months of follow-up.

The main comment is about the evaluation of cardiovascular risk that was performed using the Framingham risk score. Given the fact that diabetes is included in the score, I assume that the cardiovascular risk reduction is driven by the resolution of diabetes. Is this the case? Please, explain in detail how you manage diabetes in the evaluation of CVD risk.

Answer:

To calculate the predicted 10-year risk of cardiovascular disease we used the Framingham Risk Score (8) in patients with type 2 diabetes and prediabetes. The formula requires age, sex, total and high-density lipoprotein cholesterol, smoking, systolic blood pressure, treatment for hypertension and diabetes status. Cardiovascular risk reduction is driven by the resolution of diabetes but also by the resolution or improvement of other cardiovascular risk factors (dyslipidemia and hypertension). The presence of diabetes is an added risk factor in the global calculation of cardiovascular risk.

I have few additional comments:

1) I suggest to change the title of the article as follows: "Cardiovascular risk reduction over time in patients with diabetes or pre-diabetes undergoing bariatric surgery: data from a single-center retrospective observational study".

Answer:

I agree with the reviewer. We are going to change the title of the article as the reviewer advised.

2) In the discussion, could you please mention the results of the CAMELLIA TIMI trial just published in the NEJM? It is important to underline that there are also other options for the treatment of obesity that have shown to be safe. CAMELLIA was the first trial in this setting and there was no signal for cardiovascular harm with lorcaserin.

Answer:

Yes. We have added the results of CAMELLIA as you advised:

Discussion section (page 9, second paragraph):

“Other non-surgical treatment available such as Lorcaserine facilitated weight loss in overweight or obese patients without a high rate of major cardiovascular events. Additionally, this drug has shown to decrease the risk of incidence of diabetes and microvascular complications and to induce remission of hyperglycaemia [19, 20]”.

3) Please, add the following reference regarding the role of body circumferences for the cardiovascular risk stratification in overweight-obese subjects: Maddaloni E. et al. Am J Cardiol 2016.

Answer:

Ok. We added the reference you recommended:

Background section (page 3, first paragraph):

“Anthropometric measurements are useful for assessment of metabolic risk in overweight-obese subjects but not as markers of advanced atherosclerosis [6]”.

4) What about outcomes after surgery? Please, report these data (mortality, in-hospital and long-term complications).

Answer:

We have added these data:

Results section (Final evaluation 5 years after surgery, page 8, paragraph six):

“The mortality rate after surgery was 0% in our cohort of patients. Gastrointestinal bleeding was present in 3% of cases and there were 3 cases of Dumping syndrome”.

5) Do you think that these results could apply also to other types of bariatric surgery? Please, comment.

Answer:

We have added this comment in the article:

Discussion section (page 10, paragraph six):

“Similar outcomes in resolution of type 2 diabetes and obesity comorbidities were reported with other surgical procedures such as VSG [28]”.

6) Please, avoid the use of the word "diabetic" as recommended by ADA.

Answer:

Yes. We have changed the word in all the text as you advised.

7) I don't understand Figure 1. Please, clarify adding a couple of sentences in the legend to guide the reader. On the X-axis, is that the baseline glucose level? Specify what we have in the y-axis.

Answer:

Figure 1:
On the X-axis, the logarithm of the fasting plasma glucose levels is represented for baseline (red) and for month 12 (blue). The Y-axis represents the CVD risk in scale 0-1.

Figure 2:

On the X-axis, the two groups of patients are represented for baseline (red) and for month 12 (blue). The Y-axis represents the CVD risk in scale 0-1.

8) Add p values in figures 2 and 3.

Answer:

P < 0.001.

9) Please, soften the conclusion regarding BMI above 35 as a criterion for metabolic surgery in pre-diabetes. Much more data are needed especially in light of new available promising drugs for the treatment of obesity.

Answer:

We have changed the conclusion as follows:

Conclusions section (page 10):

“Our results support the beneficial effects of metabolic surgery decreasing cardiovascular risk in type 2 diabetes as well as pre-diabetes, and improving glycemic control and obesity comorbidities in both groups. A greater benefit among subjects with diabetes as compared to those with pre-diabetes was observed in our study. More studies are necessary to consider pre-diabetes as a criterion for metabolic surgery in patients with BMI ≥ 35 kg/m2”.

We have changed the conclusion of the abstract as follows:

Abstract section (page 2):

“Given that patients with type 2 diabetes benefit the most, more studies are necessary to consider the state of pre-diabetes as a criterion for metabolic surgery in patients with BMI ≥ 35 kg/m2”.

Mario Luca Morieri (Reviewer 2): Dear Editor and Authors,

I've read with interest this paper aiming to compare the CVD risk reduction between obese patients with type 2 diabetes and prediabetes, before and after bariatric surgery. To reach their
The authors did a retrospective longitudinal study of 105 subjects, with a follow-up of up to 5 years.

The paper has the following strengths:

- Adequate number of patients with a long follow-up
- Prediabetes status has been evaluated with an oral glucose tolerance test
- It covers an interesting topic, it is overall well written, except for the results that need editing

And limits:

- While the background, discussion, and methods are well written, the results section require more attention and different paragraphs are not understandable to this reviewer
- Additional analyses (see below) are required to test some of the main hypothesis of the paper
- Some conclusions are slightly exaggerated and should be modified

These are the specific comments:

Major comments:

1) Please reconsider this conclusion "the state of prediabetes should become a criterion to be considered in metabolic surgery in patients with BMI ≥ 35 in the future" that is far beyond the degree of evidence suggested by this retrospective study. Furthermore, the study is focused on the effect of bariatric surgery in subjects with diabetes Vs those with prediabetes, while to draw similar conclusions the design of the study should have compared subjects with prediabetes that underwent medical treatment+bariatric surgery Vs medical treatment alone. Please correct throughout the manuscript.

It should also be noted that in their current presentation (although additional analyses have been suggested, see below) the data reported by the authors show a greater benefit among subjects with diabetes as compared to those with pre-diabetes, and this should be adequately highlighted in discussion and in the abstract.

Answer:

We have changed a part of the discussion:
Discussion section (page 9, paragraph 3):

“Despite this evidence, patients with type 2 diabetes benefit the most from surgery and much more studies are needed to consider pre-diabetes itself a comorbidity of sufficient weight to be included as a criterion for surgery in patients with BMI >35”.

We have changed the conclusion as follows:

Conclusions section (page 10):

“Our results support the beneficial effects of metabolic surgery decreasing cardiovascular risk in type 2 diabetes as well as pre-diabetes, and improving glycemic control and obesity comorbidities in both groups. A greater benefit among subjects with diabetes as compared to those with pre-diabetes was observed in our study. More studies are necessary to consider pre-diabetes as a criterion for metabolic surgery in patients with BMI ≥ 35 kg/m²”.

We have changed the conclusion of the abstract as follows:

Abstract section (page 2):

“Given that patients with type 2 diabetes benefit the most, more studies are necessary to consider the state of pre-diabetes as a criterion for metabolic surgery in patients with BMI ≥ 35 kg/m²”.

2) Methods: To this reviewer is unclear why Authors tested "The association of glycemic status with CVD risk was assessed using a beta regression model including the interaction between fasting blood glucose levels and time in order to study the different trends over time between patients with high and low glucose levels".

But they did not formally test the association between diabetes/prediabetes status and CVD risk reductions (testing the null hypothesis that are similar). Indeed, since the main goal of the paper is to compare diabetes Vs pre-diabetes, authors should formally test (eg. with regression model) if the CVD risk reduction from baseline to 12-months is different in the two groups. For example, such models, might be as simple as a linear regression (or beta regression if preferred) testing the association of diabetes/prediabetes status with CVD risk at 12 months (dependent variable), adjusted for CVD risk at baseline (and other covariates if needed).

We agree with the reviewer that the explanation of our results regarding associations between diabetes/prediabetes and CVD risk was not clearly written. We have modified all this paragraph to improve the understanding of our results:

Results section (Association between CVD risk and fasting glucose levels, page 7, paragraph one):
“Higher glucose levels at baseline were clearly associated with a higher CVD risk (OR= 4.35 [2.73, 6.99], p < 0.001) and the effect. The difference between baseline and month 12 was also statistically significant (OR = 0.31 [0.26, 0.36], p < 0.001). Nevertheless, after the intervention all patients reached similar levels of CVD risk regardless of their previous status. Therefore, patients with higher fasting glucose levels are the ones that benefit the most from the intervention regarding CVD risk (OR = 0.44 [0.27, 0.71], p < 0.001)”

3) Also related to the point 2: in the results, the following sentence (page 7) is unclear to this reviewer. "patients with type 2 diabetes experienced a clear benefit after the intervention compared to prediabetes (Figure 2), with a large reduction in CVD risk at 12 months compared to the baseline risk (OR =3.22 [2.33, 4.46], p< 0.001). Although the great benefit appeared in diabetic patients, a significant decrease in CVD risk was observed in prediabetic patients 12 months after surgery, compared to their baseline risk (OR= 0.49 [0.40, 0.59], p < 0.001).” The reported Odds Ratio are confusing. To what is referred the OR of 3.22 ? it is the association of prediabetes compare to diabetes with CVD risk reduction? Which is the unit of the dependent variable, single % point of CVD risk? Or CVD below-above the cut-off of 20%. Please clarify both the text in the results and methods.

Answer:

We agree with the reviewer that the explanation of our results regarding associations between diabetes/prediabetes and CVD risk was not clearly written. We have modified all this paragraph to improve the understanding of our results:

Results section (Association between CVD risk and fasting glucose levels page 7, paragraph 3):

“At baseline, patients with type 2 diabetes showed a statistically significant higher CVD risk compared to patients with pre-diabetes (OR 3.23 [2.32, 4.50], p<0.001). Patients with pre-diabetes showed a significant reduction in risk (OR: 0.49 [0.40, 0.60], p<0.001) 12 months after surgery, compared to their baseline risk. Nevertheless, at that time point (month 12), patients with type 2 diabetes showed a larger reduction in CVD risk than those with pre-diabetes (OR 0.40 [0.30, 0.63], p<0.001”).

Which is the unit of the dependent variable?

The Y-axis represents the CVD risk in scale 0-1. (We have added the explanation in figure legends)

The unit of the dependent variable is single % of CVD risk.

We have added this sentence in Methods section, page 4 paragraph 5:

“The FRS was expressed as a percentage (%). A FRS >20% was considered a high CVD risk.”
Minor comments:

The following sentences are unclear to this reviewer, please rephrase them:

- **Introduction:** "Due to prediabetes is an intermediate metabolic state between normoglycemia and type 2 diabetes, to explore if bariatric surgery can reduce cardiovascular disease risk would be interesting"

**Answer:**

Introduction section (page 2, paragraph 3):

“Considering pre-diabetes as a metabolic state between normoglycemia and type 2 diabetes, would be interesting to explore if bariatric surgery can reduce cardiovascular disease risk in this group of patients”.

- **Methods:** "Body fat percentage was measured by bio-electrical bio-impedance (Bodystarâ 1500) once a year and high body fat percentage was considered > 25% in men, respectively, >33% in women"

**Answer:**

Methods section (page 5, paragraph 8):

“Body fat percentage was measured by bio-electrical bio-impedance (Bodystarâ 1500) once a year. Body fat percentage > 25% in men and >33% in women was considered elevated [10].

- **Discussion:** "Our results showed a high type 2 diabetes remission rate (92%) 5 years after surgery but it is specially highlighted no prediabetic patient developed type 2 diabetes."

**Answer:**

Discussion section (page 10, paragraph 6):

“Our results showed a high remission rate in patients with type 2 diabetes (92%) 5 years after surgery with RYGB, and no patient with pre-diabetes developed type 2 diabetes”.

Please define cut-off used to define OSA. Did all patients underwent polysomnography before and after surgery? please clarify.

**Answer:**

All the patients underwent polysomnography before surgery. After surgery, resolution of OSA was considered if CPAP (Continuous Positive Airway Pressure) was removed by the physician pneumologist.
One decimal is more than sufficient for BMI and waist circ measures:

Answer:

Yes. We have changed in the text and tables.

Since you have roughly 100 patients overall, please report the N of patients in the text together with % value (that can be rounded to integer number).

Answer:

We have added the N of patients in the next together with % and we have rounded the % to single decimal digit.

Numbers at the beginning of a sentence should be spelled out.

Answer:

We have changed a sentence as follows:

Results section (page 6, paragraph 5):

“Fifty-seven (54.2%) patients of the cohort had pre-diabetes”.

Table 1 and table 2: please consider to report decimal only when meaningful, to this reviewer most of the values could be rounded to integer or single digit decimal. Furthermore please use numbers of decimal consistently for measures in the same line. This will improve the readability of tables.

Answer:

We have rounded to single digit decimal in Table 1 and Table 2.

Table 1, please consider adding a column with a P-value for differences between the two groups might help the reader.

Answer:

Table 1 is a description of the characteristics of our sample, so hypothesis tests are not adequate, as indicated in STROBE guidelines:


Results: in the following sentence pg 6-7: "Higher glucose levels at baseline were clearly associated with a higher CVD risk (OR= 4.35 [2.73, 6.99], p < 0.001)." It is unclear the unit for the reference, to which unit is the OR referred to? Please specify.

Answer:

Since we are using fasting glucose levels as a continuous variable in the logarithmic scale, the OR refers to an increase of one unit (in the log scale) in these levels. (odds(x+1)/odds(x)).

In the section "Evolution of the different secondary clinical parameters after surgery", since the main goal of the paper is to compare the effect of bariatric surgery among subjects with diabetes Vs prediabetes, it might be very useful to test whether the evolution is different in the two groups. Can authors run an exploratory analysis to test this within models including the "diabetes/prediabetes status" by "time" interaction term in the mixed model?

We had already performed these analyses and stated the results in our text (Results section, evolution of the different secondary clinical parameters after surgery, pages 7) : “There were no statistically significant differences in evolution of BMI, body fat percentage, SBP and DBP between the DMbaseline group and the preDMbaseline group”.