Author’s response to reviews

Title: GASTRIC BYPASS SURGERY REVEALS INDEPENDENCY OF OBESITY AND DIABETES MELITUS TYPE 2

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RESPONSE TO REVIEWERS

Figures and tables

The tables and the figure have been generated in python a Linux platform. However, the technical quality of the tables and the figure appears to be of modest quality. The manuscript has been written in Word 2000 and the tables are extracted from Excel 2000 using Microsoft Window 7. The figure appears fully colored in the png-format. The reason for the difficulty in reading some of the tables are misalignments, which have been corrected.

Response to reviewer 1

The ethnicity has been stated in the Materials and Methods with the phrase “..all of Caucasian ethnicity..”

Ref comment: The majority of the information in Tables 3-6 is not discussed in the Results or Discussion sections and should be removed or relegated to Supplemental Data.
We agree that some of tables do not need to appear in the text but could be moved to Additional files, as the essential information is commented in the text:

Table 3 has been relegated to the Additional files, and appropriate changes have been made in the text. The most important information is commented in the Result section (e.g. p9, line 30 about “normalization” of the diabetic state). The details forms a background for the discussion of the conclusion about the remission of the diabetic state, but is not further commented, as this to a large degree be a repetition of the remarks in Result (and the content in Table S3).

Tables 4, 5 and 6 have been relegated to Additional files, and appropriate changes are done in the text.

The comment in Table 1 “Biochemical NDM post-surgery, but with treatment” has been changed to “see text” as this subpopulation has been commented in the text.

Ref comments The structural equation modeling…

The classification performed here is very simplistic as only the normalized BMI is used as an outcome in the structural equation modelling (SEM) and no co-variants are included. Other variables could have been used as outcome, but as the primary purpose of RYGB is to reduce weight normalized BMI was used, although this is not always a very accurate measure. More realistic SEM including co-variants is in progress pending analysis in progress of biochemical compounds thought to be directly causal in the physiological processes e.g. sphingolipids like ceramides and sphingsine-1-phosphate.

As explained in the text the Kullback-Leibler divergence is used as a measure of the distance between any two subjects and do not provide the classification of the populations of sub-populations into clusters. This is done in the following k-means step, which have a long history as an efficient but maybe not an optimal classification method. To clarify this the paragraph is started with the sentence “The classification in two steps: 1)” describing the Kullback-Leibler divergence,
Followed by “2)” describing the actual k-mean classification.

We are quite aware that these procedures may not be familiar to the general reads in the field; however, these and other more complex methods have to be implemented if we should have any hope of substantial progress in understanding any physiological process. Dichotomizing into e.g. diabetics/non-diabetics may often be insufficient and inefficient.

Ref comment Most troubling, there appears to be given little, if any, attention to the duration of diabetes prior to surgery, which has consistently been shown to be a strong predictor of diabetes remission and future glycemic control (Schauer et al NEJM 2014: 370:2002-2013, Sjostrom et al JAMA 2014 311:2297-2304) and the issue of “responders and “non-responders”

It has been indicated in several studies that the duration of diabetes is an indicator of remission of diabetes after surgery (e.g. the papers mentioned by the reviewer). We fully agree, that duration and thereby insulin secretory capacity of thee patients is essential for obtaining remission of diabetes.

However, the exact duration of diabetes is difficult establish as it may have been present before noticed by the patient or the doctor. In the study of Sjobgren et al the diabetic status was self-reported or based on medication, but it is the baseline values of glucose that marks the duration in this 15-year long prospective study. In the vast majority of patients banding was performed and the long-term outcome of this procedure is much more sensitive to lifestyle changes if any (e.g. the Schauer paper). You may adopt the point of view that a diabetic has been disposed to diabetes since birth, but first recognized later in life. Several studies have indicated that many patients have had type 2 diabetes for 5-10 years before diagnosis, which also explained that about 20 % of the patients have late diabetes complications from the kidney, eyes and nerves at time of diagnosis. Therefore, it is not straightforward to estimate and explain the duration of the diabetes influence on outcome as in fact the natural life of preclinical diabetes is unknown. A case could be that the subjects differ genetically, that is the cause of diabetes differs between subjects dependent on where in the vast genetic network influential deviations occur. This may result in different duration times, but basically the issue is not resolved. You may argue that the dynamics of the physiological processes are altered, but basically (and at least genetically) the patient is still a diabetic prone (which is actually shown in this study). In fact, all studies report, that relapse of diabetes is observed after bariatric surgery, probably explained by weigh regain in some patients, but also because that with age body composition, insulin sensitivity and insulin secretory capacity change resulting in reduced glucose tolerance.
Figure 1 shows trajectories for non-diabetics and simply illustrates the heterogeneity of the physiological processes (similar for diabetics) – stating that dichotomizing processes and conditions is prone to loss of information and hence power in any analysis. The primary outcome variable in this study was BMI, not the diabetic state. Even using BMI as the sole variable the population could be classified into several sub-populations. Implementing diabetic states and other variables in a sophisticated SEM/latent profile model would increase the accuracy of the classification, but also the number of classes to the limit were each patient is his/her own class or subpopulation.

Ref comment It is important to note that remission rates not only depend, in part, on the definition of remission" should be appended to also include "and the duration of diabetes prior to surgery."

The latter sentence has been added in the text.

Minor points

Ref comments Grammar and readability

INR is now defined in the list of abbreviations

The phrase “the relative entropy of individual trajectories” has been changed to “the distance between individual trajectories”.

Ref comment Definition of diabetes

Diabetes is defined by HbA1c levels above 48 mmol/mol or medication with anti-diabetic drugs. This is clearly stated in the text.

Ref comment Table as poorly assembled

See above

Ref comment “information theoretic approaches”

The phrase “information theoretic approaches” stands as it is (it is and should be a substantive, not a verb)
Therefore has been changed to therefore.

Ref comment "but probably many of the pharmacologically treated patients may in fact have manifest diabetes but not hyperglycaemia." Speculative statement not appropriate for Results section.

The entire sentence has been deleted.

Response to reviewer 2

Rev comment “..rethink abbreviations..”

We have tried to use abbreviations that at least to some extent hints to the content referred to. This is often a difficult issue, but we hope that with the list of abbreviations at hand the text will be readable.

Ref comments “..poor formatting and short figure legends.”

Tables 3-6 have been relegated to Additional files, as the essential points are commente