

Diabetes remission off medications is not a suitable endpoint for comparing bariatric/metabolic surgery with pharmacotherapy

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Abbreviations

ILMI	Intensive lifestyle and medical intervention
RYGB	Roux-en-Y gastric bypass
STAMPEDE	Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently

To the Editor: In their publication in *Diabetologia*, Cummings et al [1] describe how they used a randomised trial to compare the best available intensive lifestyle and medical intervention (ILMI) against Roux-en-Y gastric bypass (RYGB), and concluded that surgery achieved greater type 2 diabetes remission in mildly to moderately obese patients. However, mean HbA_{1c} values were not statistically different between groups at the end of study, which was not explicitly stated in the abstract. An OR for diabetes remission (defined as HbA_{1c} <6.0% [<42.1 mmol/mol], off all diabetes medicines) of

almost 20 looks quite impressive, but in our opinion this is not a suitable study endpoint for analysis. Given that the comparison group received intensive lifestyle with optimal medical intervention, and therefore the very point of the intervention was the use of medication, it seems inappropriate that a criterion of the primary endpoint of interest was whether or not the patient was off medication. It is well established that diabetes is a chronic disease and most patients are unable to control their diabetes with intensive lifestyle interventions (the same applies to obesity itself, despite being associated with greater and persistent stigma). Therefore, the discontinuation of several classes of medications for type 2 diabetes would give rise to disease deterioration. As expected with any other chronic disease, the control group could be well controlled, but, of course, on medication. Since a surgical procedure can be considered a chronic treatment for diabetes (because the anatomical changes are permanent), this seems to be an unfair comparison. We believe that a better judgment (which still would favour surgery in the great majority of cases) would be an HbA_{1c} target that was independent of medication use. We acknowledge that the criteria for remission were not developed solely for this article and are being used in most bariatric/metabolic surgery studies, but because of the conclusion of the abstract and the absence of statistically significant differences in HbA_{1c} at the end of the treatment, this comment seems appropriate at this point.

Also of note is the conclusion about individuals with a BMI <35 kg/m². It is stated in the Results section that ‘In exploratory analyses, diabetes remission was not predicted by baseline BMI, age or sex, or by the amount of weight lost during 1 year, and there was no correlation between change in body weight and change in HbA_{1c} at 6 or 12 months among those having RYGB; however, the study was not specifically powered to detect this.’ Furthermore, in the Discussion section the authors state that ‘there is still limited evidence from RCTs

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examining surgical approaches to type 2 diabetes treatment in patients with a BMI <35 kg/m², the standard threshold for bariatric surgery, and our study adds Level-1 data to that evidence base'. We would like to emphasise that no more than five patients with a BMI <35 kg/m² underwent surgery in this study, an obviously undersized sample from which to make inferences about this population separately. In fact, in RCTs performed to date, fewer than 150 diabetic patients with a BMI <35 kg/m² have been studied, making it difficult to assess how their glycaemic control and diabetes respond to various interventions [2–4]. Moreover, in larger studies involving patients with higher baseline BMI, such as the Swedish Obese Subjects (SOS) study, the degree of weight loss was significantly associated with glycaemic improvement; when stratified by weight, there were no differences between restrictive and malabsorptive (i.e. 'metabolic') surgical procedures [5, 6]. Insofar as the present study was not powered to evaluate that question, as the authors correctly state, no conclusions different from what we already know from much bigger datasets can be reached. Although those who defend the similarity of glycaemic improvement between individuals with a BMI >35 kg/m² and those with a BMI <35 kg/m² generally cite the paper on the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study by Schauer et al [4], which demonstrated similar HbA_{1c} reductions in individuals with BMIs above and below 35 kg/m², the data presented in the supplementary appendix of this 3-year study clearly demonstrate that the daily average type 2 diabetes medication use at 36 months in the surgical group was higher in those patients with a BMI <35 kg/m² compared with those with a higher BMI, so in this case, the 'remission rate' was significantly different between groups.

We acknowledge that nearly all bariatric surgery studies demonstrated better glycaemic control than 'usual care' diabetes treatment; we clearly believe that in moderately to morbidly obese diabetic patients, bariatric surgery is cost effective, improves diabetes control, and is likely to reduce cardiovascular risk and mortality. However, we should be cautious of extrapolating these findings to less obese patients, as prior studies indicate that the degree of weight loss is predictive of glycaemic improvement [5], of the cardiovascular risk reduction [7], and many other important endpoints including albuminuria reduction, as well as improvement of sleep apnoea and steatohepatitis, for example.

Moreover, a recent study found that despite frequent nutritional and medical visits at follow-up, at the 2-year follow-up, 80% of patients who underwent bariatric surgery presented with nutrition deficiency and five of 56 patients presented with fractures [2]. In the 3-year follow-up analysis of another study, bone and lean mass were reduced in RYGB patients [3]. The incidence of nephropathy and foot ulcers was

elevated in the surgical groups (especially in the RYGB group) in the 3-year follow-up of the STAMPEDE study [4]. Other studies have reported surgical complications, including anastomotic stricture, bleeding, bowel obstruction, kidney stones and fractures [8].

In this modern era where some cardiovascular safety trials with diabetes drugs have demonstrated that these drugs provide cardiovascular protection [9, 10], we need more data on hard outcomes to better assess their efficacy and safety in very large series before advocating the widespread indication of bariatric surgery in the subpopulation of type 2 diabetic patients with a BMI <35 kg/m², which, in absolute numbers, is the majority of diabetic patients.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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