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Metabolic surgery versus conventional therapy in type 2 diabetes

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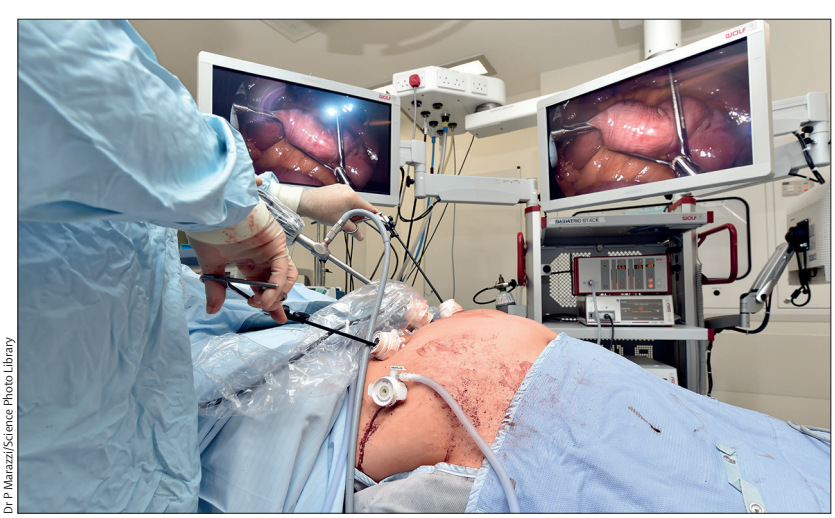
In *The Lancet*, Geltrude Mingrone and colleagues report their trial in which they randomly assigned patients to metabolic surgery or medical therapy for type 2 diabetes.[1] 60 white European patients (32 [53%] women) were evaluated 10 years after Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD), or conventional medical therapy. The primary endpoint was type 2 diabetes remission, defined as glycated haemoglobin (HbA_{1c}) less than 6·5% plus fasting glucose less than 5·55 mmol/L without medication. The retention rate was very good, with a 10-year follow-up rate of 95·0%. 10-year type 2 diabetes remission rates were 50·0% for the BPD, 25·0% for RYGB, and 5·5% for the medical therapy group. Surgery had a greater effect on mean HbA_{1c} at 10 years (–1·2% [95% CI –1·5 to –0·9] for BPD *vs* medical therapy and –0·9% [–1·2 to –0·6] for RYGB *vs* medical therapy), diabetes-related complications, cardiovascular risk, weight loss, medication use, plasma lipids, and quality of life compared with the medical therapy group. No unexpected risks associated with surgery were identified. Previous randomised controlled trial data had shorter follow-up periods (1, 3, and 5 years[2,3]). It is reassuring that we now have 10-year data showing greater efficacy of metabolic surgery than conventional medical therapy. Taken together, addressing an important knowledge gap is changing the attitudes of both patients and diabetologists. Moreover, during the past 12 years, 12 other randomised controlled trials have shown consistent findings,[4] thus providing confidence in the robustness of the data. New generations of diabetologists are now more open to the use of metabolic surgery for patients with suboptimal responses to medical treatments. These methods contrast with older approaches that included endless intensification of insulin therapies and attributing the blame for poor response to inadequate patient compliance.



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The trial by Mingrone and colleagues has several strengths besides the long-term follow-up.[1] Patients included had advanced type 2 diabetes, with half of them taking insulin at baseline. Moreover, detailed information was provided about intensity of lifestyle modification and pharmacotherapy throughout the trial for the medical therapy group. Only two patients from the medical therapy group crossed over to the

surgery group. This finding is relevant and reassuring considering the open-label nature of the study, which could have easily been a source of bias. Despite the intensive efforts of the team looking after the medical therapy group, deterioration of glycaemic control was observed after 5 years in the absence of substantial weight gain. Another strength of the study is the strict definition of type 2 diabetes remission. This definition was in contrast to looser descriptions used in lifestyle modification trials for type 2 diabetes,[5] thus making comparisons between studies potentially misleading. The robust definition in this trial and head-to-head comparisons can now help clinicians and patients make informed decisions about their care, especially given that these operations are life-changing.

Contrasting with a previous meta-analysis published in the early 2000s,[6] the type 2 diabetes remission rates were substantially lower, even after more invasive operations such as BPD. Despite the focus of many in the field on the concept of remission, the reported relapse of type 2 diabetes should be seen in the context of the severity of type 2 diabetes at baseline. Clinicians will be pleased that all patients had meaningful glycaemic improvements after surgery. We also learnt that patients who do not go into remission after 2 years are very unlikely to ever do so. This factor might help us to intensify modern and potent glucose-lowering therapies like SGLT2 inhibitors and GLP-1 receptor agonists earlier after metabolic surgery.[7] The combination of metabolic surgery and glucose-lowering agents could have a positive effect not only on glycaemic outcomes but also on the prevention of the macrovascular and microvascular complications of type 2 diabetes.[8] This hypothesis is relevant to this patient subgroup of non-responders to surgery who remain at higher cardiovascular risk.[9] The dichotomous definition of glycaemic remission should not discourage clinicians from being proactive with pharmacotherapy when surgery on its own is not enough.

The key limitations of the study are highlighted in a balanced discussion. The main limitations are the open-label design and the lack of power to make definitive conclusions about the effects of surgery on type 2 diabetes complications, despite the encouraging findings for cardiovascular risk, retinopathy, neuropathy, and nephropathy. Another limitation was that type 2 diabetes remission was defined as euglycaemia without pharmacotherapy. Thus, it was probably impossible for patients in the medical group to ever go into remission considering how advanced their disease was. Finally, the BPD procedure remains infrequently performed, but is still considered the best operation for glycaemic control. Its strong effect on glucose regulation generates mechanistic hypotheses. The 10-year data from STAMPEDE[3] are now eagerly awaited to see how the sleeve gastrectomy performed over 10 years, but we hope also to gain more insight into the rates of hypoglycaemia and long-term surgical and nutritional complications for all surgical procedures.

The results of this trial will make a noticeable difference in the field and convince even the most sceptical of clinicians about the role of metabolic surgery as part of optimal care for their patients with difficult-to-control type 2 diabetes.

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