Type 2 diabetes: multimodal treatment of a complex disease

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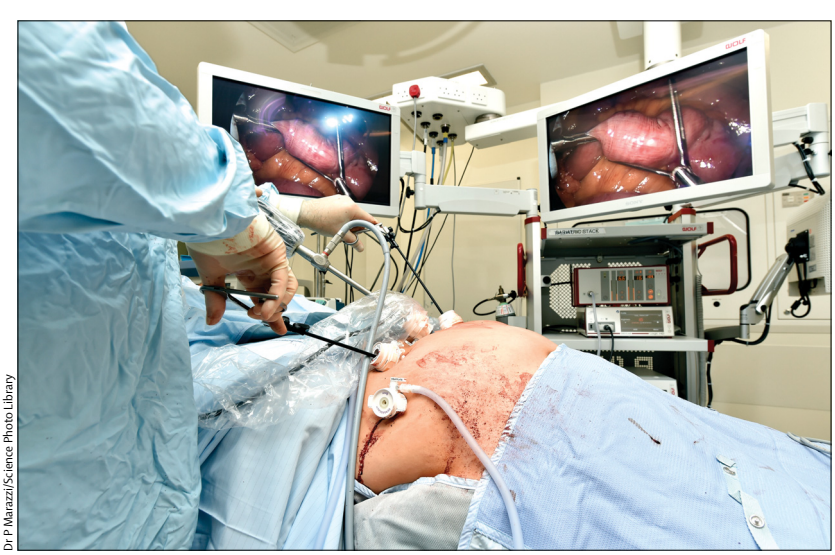
Type 2 diabetes is becoming the plague of the 21st century. With the so-called diabesity epidemic the disease threatens to reduce life expectancy for future generations globally. Surgery for diabetes has been marketed as an effective treatment option for patients with obesity and type 2 diabetes. Different surgical procedures have been used successfully, with some changing the anatomy of the stomach, bypassing parts of the gut, or using devices. These trials have provided an intriguing model to study the role of the gut in maintaining glucose homoeostasis. Indeed, some of the clinical and mechanistic findings have been impressive.

The concept of cessation of antidiabetic drugs and even cure of diabetes has evolved over time into the more realistic term of remission.[1] As is often the case with novel treatments for complex clinical disorders, the widespread enthusiasm for the initial results needs to be confirmed in studies with long follow-up. Particularly for diabetes, the need for studies with robust endpoints such as diabetes-related complications, cardiovascular events, and mortality has been emphasised.[2]

Geltrude Mingrone and colleagues' follow-up study in *The Lancet* provides much needed high-quality data.[3] In the study, which assesses 5 year outcomes from the group's open-label, single-centre, 2 year randomised controlled trial,[4] the investigators compared conventional medical treatment with Roux-en-Y gastric bypass or biliopancreatic diversion surgery in 60 obese patients with type 2 diabetes. Surgery was more effective than medical treatment for controlling diabetes, with 19 (50%) of the 38 surgical patients (seven [37%] of 19 in the gastric bypass group and 12 [63%] of 19 in the biliopancreatic diversion group) maintaining partial diabetes remission at 5 years, compared with none of the 15 medically treated patients, but was no more curative. No patients in either treatment group achieved complete remission at 5 years according to the American Diabetes Association (ADA) definition, and relapse of hyperglycaemia was recorded in 15 (44%) of the 34 surgery patients who achieved 2 year remission.



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These findings, which are consistent with those from other, non-randomised, studies,[5] remind us of the initial outcomes for upper gastrointestinal surgery for some common types of cancer, such as cancer of the oesophagus and stomach. Cancer surgeons proved that multimodal treatment consisting of best surgical treatment combined with the best medical treatment is better than any one treatment on its own and this combination approach has now become the standard of care.[6] This model could be followed for diabetes, with use of best medical care to maintain remission, which is often only possible with surgery. Future randomised controlled trials should focus on different combinations of modalities, the timing of the intervention (eg, early *vs* late surgery or early or late medical treatment after surgery), but all surgical groups should receive intensive medical treatment and close follow-up at some stage because, as Mingrone and colleagues' have now shown, not doing so results in relapse of diabetes.

The present study shows the need to move away from how to achieve remission and focus on how to maintain remission once it has been achieved. However, remission is not the only desired goal. It is remarkable that more than 80% of patients in the surgery group achieved the ADA treatment goal of glycated haemoglobin A_{1c} less than 7·0% (53 mmol/mol), but also had a greater reduction of diabetes-related complications than patients who received medical treatment, something that would be very difficult to achieve without surgery.[7] This finding confirms those from prospective studies[8,9] and could be informative for every physician who is treating patients with diabetes. The importance of good glycaemic control cannot be overemphasised because a short period of good control might be associated with improved survival,

as shown in the UKPDS study;[10] however, this hypothesis has not been tested in patients undergoing surgery.

Surgery for diabetes seems to be safe,[11] effective in terms of glycaemic control, and is now associated with reduced complications of diabetes.[3] The ultimate question is whether diabetes surgery is associated with reduced mortality. Extension of follow-up in the trials already done, and future well-designed and appropriately powered studies, will provide some much needed answers. Data from worldwide registries will complement the available information with real-life data that will reduce the impact of the Hawthorne effect and provide the large number of patients needed for meaningful analysis. Until then, diabetes surgery will need to remain safe and become more available because only a few patients who will benefit are currently offered this potentially life-saving option. The driving force to facilitate the implementation of change in health-care delivery, particularly in the current financial environment, will have to be multidisciplinary. Mingrone and colleagues' study lays the foundation to start the hard work of maintaining diabetes remission once surgery has levelled the playing field.

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Oral corticosteroids for multiple sclerosis relapse

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Corticosteroids are the oldest immunological treatment for multiple sclerosis, but are no longer used as disease-modifying agents because of the serious adverse effects associated with chronic administration and the development of more effective disease-modifying drugs. Nevertheless, high-dose intravenous steroid is the best available treatment to induce accelerated remission from a multiple sclerosis attack, and to limit the residual neurological deficits.[1,2] Clinical reports about the positive effects of corticosteroids on relapses are supported by MRI studies.[3–5] A study in a group of patients with early relapsing-remitting multiple sclerosis[6] reported a significant improvement in the magnetisation-transfer ratio (MTR), a measure of tissue damage, in the recovery phase of the newly enhancing lesions treated with high-dose intravenous methylprednisolone (1 g for 5 days) compared with untreated lesions. The substantial drop in MTR during contrast enhancement, with a variable recovery during the following months, as a consequence of remyelination and tissue reorganisation after acute inflammatory damage, usually reaches a plateau after 6–9 months. The effects of steroids on MTR was sustained for at least 19 months and can be explained by the more rapid closure of the blood–brain barrier,[6] paralleling the effects of intravenous methylprednisolone on the accelerated recovery from a relapse.

Unfortunately, the intravenous administration of steroids, even if limited to 3 days, needs patients to be admitted to hospital or treated at home by appropriate professionals, with consequent personal burden and