

Milestone 14



Role of bariatric surgery in T2D

A landmark study published in 1995 introduced the world to the idea that bariatric surgery could ‘cure’ type 2 diabetes (T2D). In 91% of patients with obesity and either non-insulin-dependent diabetes (now known more commonly as T2D) or impaired glucose tolerance, a gastric bypass operation normalized levels of glucose, insulin and HbA_{1c} for decades. This breakthrough study was important given that then, as now, alternative approaches to T2D therapy (including diet, exercise, insulin and oral agents) had proved inadequate in maintaining long-term euglycaemia.

In the study by Pories et al., 608 patients with a BMI ≥ 35 kg/m² with complications of obesity or a BMI ≥ 40 kg/m² without complications underwent a gastric bypass. The operation was found to produce significant and durable weight loss. However, more striking was the control of T2D that surgery afforded. Of the 608 patients at baseline, 330 had either non-insulin-dependent diabetes or impaired glucose tolerance. Of 298 of these patients with adequate follow-up, 271 (91%) maintained normal values of fasting blood glucose and HbA_{1c} for the 14 years of follow-up. Ten patients did not return to euglycaemia because of technical failures of the surgery (staple line

“alternative approaches to T2D therapy ... had proved inadequate”

breakdowns). Interestingly, patients whose surgery was intact but who did not return to euglycaemia (17 patients) were generally older (48.0 versus 40.7 years) and had diabetes of longer duration (4.6 versus 1.6 years).

Although the study by Pories et al. is now considered pivotal in the discovery of an operation as a means of treatment for T2D, it took several years for randomized studies to confirm the efficacy of bariatric surgery in the long-term control of T2D. The *New England Journal of Medicine* published two such studies in 2012. Schauer et al. compared intensive medical therapy alone versus medical therapy plus Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy in 150 patients with uncontrolled T2D. After 12 months, bariatric surgery achieved glycaemic control in significantly more patients than medical therapy alone. Meanwhile, Mingrone et al. randomly assigned 60 patients to receive medical therapy or to undergo either gastric bypass or biliopancreatic diversion. At 2 years, remission of T2D occurred in no

patients in the medical therapy group, 75% of patients in the gastric bypass group and 95% in the biliopancreatic diversion group. In 2021, the 10-year follow-up data showed that 25% and 50% of patients remained in remission in the gastric bypass group and biliopancreatic diversion group, respectively. These studies have paved the way for further acceptance of bariatric surgery as a treatment for T2D.

But how and why does bariatric surgery work to treat T2D? Back in 1995, Pories et al. described the normalization of glucose metabolism as occurring “with surprising speed, even before there was significant weight loss” and before a reduction in the mass of adipocytes. Instead, they speculated that reduction of caloric intake had an important role. They also tentatively suggested that changes in incretin stimulation might also contribute (such as increases in the levels of glucagon-like peptide 1; GLP1 (Milestone 9)).

Since then, various studies have further investigated the mechanisms of action of bariatric surgery for remission of T2D. In 2006, patients who had undergone RYGB were found to have increased postprandial levels of insulin and GLP1, possibly contributing to improvements in glycaemic control. This finding was further confirmed in 2010. A study in 2013 demonstrated that the Roux limb in RYGB-treated rats undergoes reprogramming of intestinal glucose metabolism, contributing to glycaemic control. In 2014, vertical sleeve gastrectomy (an alternative bariatric surgical procedure that also results in remission of T2D) was found to exert its positive effects on glycaemic control via increased levels of circulating bile acids and changes to gut microbial communities.

More information is clearly needed on the mechanisms behind the positive effects of bariatric surgery on T2D remission. In turn, this knowledge might help in the development of further agents to treat T2D. Meanwhile, bariatric surgery for T2D (now known as metabolic surgery) continues to gain further acceptance as an effective treatment option for this increasingly common disease.

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Nature Reviews

Milestone study

Pories, W. J. et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann. Surg.* **222**, 339–352 (1995)

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