Can we cure type 2 diabetes?

The question of whether or not type 2 diabetes remission is achievable has recently been debated in professional and lay media.

Here, Mark Greener investigates the evidence base to date and its potential to inform future clinical practice for the benefit of people with type 2 diabetes.

Introduction

Just a few years ago, most health care professionals believed that type 2 diabetes slowly, inexorably, worsened for the rest of the patient’s life. In 2014, for example, American researchers wrote that: ‘It is widely believed that [type 2 diabetes] is a chronic progressive condition, which at best can be controlled, but never cured, and that once treatment with glucose-lowering medication is initiated, it is required indefinitely and is intensified over time’.1

Indeed, a study that followed 122,781 type 2 diabetes patients for seven years reported that 1.47% of patients showed partial remission (not requiring ongoing drug therapy and at least one year with HbA1c 5.7–6.4% [39–46mmol/mol]). Moreover, 0.14% showed complete remission (not needing ongoing drug therapy and at least one year with HbA1c <5.7% [<39mmol/mol]). Just 0.007% showed complete remission for at least five years. ‘In community settings, remission of [type 2 diabetes] does occur without bariatric surgery, but it is very rare,’ the authors concluded.1

The Counterpoint study overturned this pessimistic view by showing that decreasing food intake could reverse type 2 diabetes, and clarifying the underlying mechanism.2 This set the scene for the Diabetes Remission Clinical Trial (DiRECT), which demonstrated that a weight management programme delivered by existing primary care staff – nurses or practice dietitians – achieved remission in almost half of type 2 diabetes patients.3

‘The findings were all the more striking as the “intervention” was merely 8 hours of structured teaching for the primary care staff,’ says Roy Taylor, Professor of Medicine and Metabolism at Newcastle University and Honorary Consultant Physician, Newcastle upon Tyne Hospitals, who led DiRECT.

Meanwhile, evidence supporting bariatric surgery – before Counterpoint, the only proven way to put type 2 diabetes into remission – is increasing even in people who are well below the current threshold for the procedure. Yet, bariatric surgery seems, in general, to be underused.

DiRECT evidence

Patients in DiRECT’s intervention group replaced all their meals with a formula providing 825–853kcal/day for three months, which could be extended up to five months. During the next two to eight weeks, they reintroduced food following a structured programme. Patients then made monthly visits to maintain their weight loss. Patients discontinued oral antidiabetic drugs and antihypertensives, which were reintroduced according to national guidelines.3

DiRECT enrolled 306 people with BMIs of 27–45kg/m² and aged 20–65 years with type 2 diabetes from 49 general practices in Scotland and North-East England. Twenty-one percent of participants withdrew prematurely, usually for reasons unconnected with the study. Mean body weight fell by 10.0kg in the intervention group compared with 4.2kg in the controls. So, the programme increased the likelihood of remission almost 20-fold (odds ratio 19.7). Across both groups, no one who gained weight and 7% of those who maintained a loss of 0–5kg entered remission. This proportion increased to 34% with 5–10kg loss, 57% with 10–15kg loss and 86% of people who lost at least 15kg. Quality of life improved significantly in the intervention group.3

I was pleased by the findings and many of my colleagues were surprised,’ Professor Taylor says. ‘We’d believed that people with type 2 diabetes showed a gradual worsening that meant half of them needed insulin within 10 years of diagnosis because their beta-cell mass decreases steadily. But these assumptions were based on people who had a steady or worsening BMI. There were no studies following people who lost weight.’

The study also suggests that BMI is something of a blunt instrument to assess an individual’s risk of type 2 diabetes. Professor Taylor notes that some people live with a high BMI without developing type 2 diabetes. On the other hand, an analysis of five cardiovascular studies from the USA found that, on average, 12% of adults had healthy BMIs (18.5–24.99kg/m²) when they develop diabetes.4 Rather than BMI per se, the extent to which adipose tissue deposits in the liver and pancreas probably determines vulnerability to type 2 diabetes.

Professor Taylor’s group performed detailed studies in 64 people in the intervention group and 26 controls in DiRECT. On average, the liver’s fat content in the intervention group declined from 16.0% at baseline to 3.1% at 12 months: in other words, from very high levels to normal. ‘Losing fat from inside the pancreas and liver seems to be central to putting type 2 diabetes into remission,’ Professor Taylor remarks.

‘Some people with a BMI of 40kg/m² went into remission when they dropped to 36kg/m². But we also had people who went into remission after dropping from 27 to 23kg/m². BMI is relevant as a population measure of risk, but it tells you relatively little about an individual. Nevertheless, it’s useful to track an individual patient’s progress.’

Plasma triglyceride levels and the fat content of the pancreas declined in the 29 people in this part of the study who were in remission. Assuming patients maintained weight loss, the changes in lipid metabolism and intra-organ lipid levels remained
steady over 12 months. Beta-cell function rapidly improved among people in remission, which was sustained for 12 months.\(^5\)

The findings are consistent with the Counterpoint study that followed 11 type 2 diabetes patients (average BMI 33.6kg/m\(^2\)) who consumed a restricted energy (600kcal/day) diet for eight weeks. Fasting plasma glucose normalised after one week of restricted energy intake. During Counterpoint, beta-cell function and hepatic insulin sensitivity also normalised, which was associated with decreased pancreatic and liver fat (triacylglycerol) stores.\(^2\)

**Outstanding issues**

'DiRECT was an amazing piece of work,' says Shaw Somers, President of the British Obesity and Metabolic Surgery Society (BOMSS) and Consultant Surgeon at Streamline Surgical and Portsmouth Hospitals NHS Trust. 'However, most people treated with behavioural interventions regain any lost weight within five years.\(^6\) We don’t currently know whether the weight loss seen in DiRECT will be durable.' Professor Taylor has presented results from a two-year follow up of DiRECT at the Diabetes UK Professional Conference in March. The group has funding from Diabetes UK to follow patients for three years. They have also applied for further funding to allow follow up of the intervention group for a total of five years, which should offer an insight into persistence.

Patients in DiRECT had lived with diabetes for medians of 3.1 and 2.6 years in the intervention and control group respectively. Many health care professionals and patients would, however, like to try weight loss at diagnosis, before starting an oral antidiabetic drug.

'We need definitive studies,' adds Emily Burns, Head of Research Communications at Diabetes UK. 'DiRECT has focused on people living with type 2 diabetes for under six years and we need to understand the link between remission and diabetes duration in more detail. In general, however, we’d expect that intervention as early as possible would maximise the likelihood of remission.'

Indeed, Professor Taylor believes that DiRECT’s results may be especially relevant to people who have just been diagnosed with type 2 diabetes mellitus. 'For many people, the diagnosis is a terrible shock,' he says. 'That’s the best time to take decisive action.'

DiRECT excluded people receiving insulin, while 26% of the intervention group did not receive oral antidiabetic drugs.\(^3\) 'However, their HbA\(_1c\) was clearly in the diabetic range and many of them should have received oral antidiabetic drugs according to the guidelines,' Professor Taylor says. 'We’ve been inundated with emails from patients after we published the findings. From this anecdotal evidence we know that many people on insulin can either improve so much that they do not need insulin or completely reverse diabetes after substantial weight loss.'

'DiRECT is the largest study to date to examine remission, but is still relatively small – so there’s much still to learn,' says Dr Burns. 'DiRECT also enrolled a predominantly white population and future research needs to investigate remission of type 2 diabetes in different patient groups.'

'The results have, in currently unpublished research, been replicated in people from Barbados and the study has attracted interest from Europe, Australia and New Zealand,' Professor Taylor comments. 'The American Diabetes Association also changed its guidelines to state remission as an aim for treatment, which underscores how seriously people are taking our research.'

NHS England and NHS Scotland are currently running pilot projects to deliver the DiRECT approach into routine clinical practice. The NHS England study plans to enrol 5000 patients. NHS Scotland is examining interventions aimed at inducing remission soon after or at diagnosis. These and the other DiRECT-inspired initiatives worldwide should provide robust, real-world evidence of the benefits of the approach in a less selected population.

'We’re confident that the findings are generalisable,' Professor Taylor says. 'Weight loss induces remission by working on basic biological processes. Metabolic and phenotypic differences between, for example, ethnic backgrounds are relatively minor. There’s no reason to suppose that the results will not apply to a wider range of patients than we included in DiRECT.'

'These studies are potentially really exciting,' Dr Burns says. 'DiRECT isn’t the end of the story, it’s just the beginning.'

**The implementation barrier**

‘Achieving smooth transfer to routine health service provision is the big challenge,’ Professor Taylor comments. 'We have demonstrated beyond doubt that type 2 diabetes is easily understood and usually reversible. We know it works. We know the mechanism through which it works. Now we need to make it work as part of NHS services.'

Hopefully, the studies to date and the huge interest DiRECT generated in the lay and professional media will facilitate implementation. Moreover, the changes in DiRECT are intentionally straightforward. ‘People did not need to struggle with numerous choices at mealtimes. A structured programme makes this much easier,’ Professor Taylor says.

Patients also focus on one part of their unhealthy lifestyle at a time. Professor Taylor stresses that people should not also start an exercise programme when they begin to lose weight. ‘Considerable evidence suggests that people who exercise can increase compensatory eating, which ironically means they gain weight,’ he says. ‘Of course, increased, tolerable and sustainable physical activity is important to avoid weight regain. So, it’s a two-stage process: get the weight off and then increase activity while eating a moderate calorie diet.’

To aid implementation, Diabetes UK is currently developing an information prescription about type 2 diabetes remission to support health care professionals to counsel patients, which should be published later this year. In 77 people who fed back their experiences of attempting to reverse diabetes to Professor Taylor’s team after the publication
of the Counterpoint study, self-reported weight fell from 96.7kg to 81.9kg, while fasting blood glucose levels declined from 8.3mmol/L to 5.5mmol/L. The team estimated that 61% of patients showed a reversal in their diabetes. The proportion ranged from 80% of those who lost more than 20kg to 53% of those who lost less than 10kg. Sometimes, it seems, offering information is enough to motivate profound behavioural changes.

Making the most of bariatric surgery

Mr Somers argues, however, that the NHS isn’t making the most of another effective approach that can place type 2 diabetes in remission. ‘Bariatric surgery isn’t regarded as a central part of the type 2 diabetes treatment options,’ he says. ‘Yet it offers the prospect of a durable remission even for difficult-to-treat type 2 diabetes patients.’

Bariatric surgery typically results in a sustained weight loss of about 30%, which means, Mr Somers says, between 60% and 90% of type 2 diabetes patients attain remission. During a Roux-en-Y gastric bypass, for example, the surgeon creates a small stomach pouch and bypasses the proximal small bowel. Researchers from Denmark followed 1111 people who underwent Roux-en-Y gastric surgery and 1074 matched controls for about 5.2 and 5.3 years respectively. The authors defined remission as not using glucose-lowering drugs with HbA1c less than 48mmol/mol (less than 6.5%) or metformin monotherapy with HbA1c less than 42mmol/mol (less than 6.0%). During the first six months, 65% of those who underwent surgery entered remission, which rose to 74% at 12 months. Of those in remission during the first year of follow up, 6% relapsed after two years, increasing to 12%, 18% and 27% three, four and five years after the procedure respectively. In those who entered remission by the end of the first year, the risk of microvascular events was 57% lower compared with those who did not show remission. The risk of macrovascular events was 24% lower, although this was not statistically significant.

Some studies suggest that the benefits of bariatric surgery are not simply the result of a loss of appetite and the subsequent reduction in weight and adipose tissue, which enhances insulin sensitivity. A fundamental endocrinological change could theoretically drive type 2 diabetes remission following bariatric surgery. ‘We are unsure of exactly how bariatric surgery results in remission of type 2 diabetes,’ Mr Somers says. ‘But the body seems to become more responsive to pancreatic insulin following bariatric surgery, more rapidly than can be explained by weight loss.’

Levels of the gut hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) rise after bariatric surgery. GLP-1 mediates a glucose-dependent increase in insulin secretion. Both GLP-1 and PYY delay gastric emptying, which seems to contribute to satiety. A recent study used animal and human experiments to demonstrate that bariatric surgery delivers nutrient more rapidly to the distal gut. This increases levels of GLP-1, PYY and insulin after glucose ingestion. Blocking GLP-1 receptors reduced insulin secretion. So, increased GLP-1 seems to be largely responsible for the increased insulin levels following bariatric surgery. ‘Once we figure out the mechanisms through which bariatric surgery results in remission of type 2 diabetes, we might be able to develop new non-surgical treatments that work through the same pathways,’ Mr Somers says. He suggests that such insights might, in particular, help the 1 in 8 people who develop type 2 diabetes despite having a normal BMI.

However, some studies suggest that weight loss accounts for the improvements. In one study, 10 type 2 diabetes patients were admitted to hospital for 10 days before and after bariatric surgery, separated by at least six weeks. They received the same diet during each admission. Patients lost, on average, 7.3kg and 4.0kg during the pre- and post-surgery periods respectively. Daily glycaemia was significantly lower in the pre-surgery compared to the post-surgery periods (1293.58 and 1478.80mg/dL a day respectively). The improvements in the fasting and maximum post-stimulation glucose and 6-hour glucose area under the curve were similar during both periods.

Another study compared nine patients who underwent a Roux-en-Y gastric bypass and the same number who received a very low calorie diet. After seven days, mean weight loss was greater after surgery than the very low calorie diet: 5.1% and 3.5% respectively, largely reflecting greater loss of lean and water mass. Fat mass decreased by a mean of 3.0kg in both groups. However, the reduction in liver fat was greater following the bypass than the very low calorie diet: 29.8% and 18.6% respectively.

The early rise in plasma glucose and acute insulin secretion were greater after gastric bypass than following a very low calorie diet, which might reflect the more rapid absorption. While the rise in GLP-1 was sevenfold greater following gastric bypass than after a very low calorie diet, this did not translate into a greater improvement in fasting glucose level or area under the curve for glucose. Clearly, further research needs to resolve these conflicting findings.

A lack of interest

Mr Somers notes that bariatric surgery as soon as possible after type 2 diabetes diagnosis improves the likelihood of remission. ‘Type 2 diabetes is associated with profound endocrinological changes,’ he says. ‘It’s important to perform bariatric surgery before the diabetes leaves the pancreas burnt out, which generally takes about 10 years after diagnosis. In general, if you perform surgery within three to five years of type 2 diabetes diagnosis, there is a high chance of remission and patients will not require any medication.’

According to BOMSS, bariatric surgery costs about £5000 per patient. But the savings in, for example, drugs amount to about £1500 a year. ‘Despite the clinical and economic benefits, NHS England doesn’t seem interested in performing bariatric surgery,’ Mr Somers says. ‘They seem to focus...’
on the immediate costs of surgery rather than the savings that occur later. In type 2 diabetes, bariatric surgery pays for itself in about three years. The direct costs of managing diabetes, according to Diabetes UK, reach some £10 billion a year. ‘It seems reasonable to top-slice some of that money to offer rapid access to bariatric surgery,’ Mr Somers argues.

‘While bariatric surgery has its place, it is no substitute for prevention and for cutting obesity, and costs taxpayers a great deal more,’ a spokesperson for NHS England told Practical Diabetes. ‘There are a number of effective programmes in place already, including the NHS diabetes prevention programme, which helps those at risk from developing type 2 diabetes.’

‘We want bariatric surgery to be an option for people with type 2 diabetes who could benefit,’ Dr Burns remarks. ‘Not everyone who is eligible wants to undergo surgery. But there is robust evidence that bariatric surgery can result in remission of type 2 diabetes and the benefits can persist for up to 15 years. The NHS has strict criteria about who is eligible for bariatric surgery and in some parts of the country, it seems that not everyone is able to access the service.’ Mr Somers comments that there is adequate capacity to meet increased demand across the NHS as a whole. ‘The peak in bariatric surgery was in 2012 and 2013,’ he says. ‘The number of procedures has since fallen. There’s no good medical explanation for this decline; it seems to be a reluctance to fund and a reluctance to refer.’

People with type 2 diabetes may, however, be at increased risk of surgical complications compared with the general population. In the Danish study, 7.5% were readmitted with a surgical complication in the first 30 days after the procedure. The 90-day mortality rate following gastric by-pass surgery was less than 0.5%.8

‘The complication rate is very low,’ Mr Somers says. ‘Bariatric surgery is one of the safest abdominal operations with a lower complication rate than a gall bladder procedure or an appendectomy. In addition, surgeons have performed bariatric procedures for more than 50 years. We know the operations have very few long-term sequelae, while reducing the risk of cancer, cardiovascular disease and other conditions that are associated with obesity.’

‘A major problem with bariatric surgery, which is extremely useful for some patients, is the absence of an authoritative and objective survey of longer-term side effects,’ Professor Taylor says. ‘Post-meal hypoglycaemia are commonest, but the less common social problems, alcoholism, vitamin deficiency and divorce tend to be ignored. Certainly, the appropriate use of surgery is to be encouraged, but only with a balanced prior discussion of overall effects.’ In Professor Taylor’s studies of bariatric surgery, for example, about a third of people reported post-prandial hypoglycaemia following bariatric surgery.

‘Some people use eating as a mechanism to cope with stress,’ Mr Somers says. ‘Bariatric surgery can remove this coping strategy and patients may need emotional and psychiatric support to find an alternative.’ Professor Taylor notes that some people may turn to alcohol as a substitute for comfort eating. He adds that patients may also struggle with the changes in body image. He notes, for example, that a big man who is the focus of attention can easily become pushed aside and ignored. Marital break down, Professor Taylor adds, can result from the post-surgical partner not being the same as the person whom they married or one person becoming more sexually attractive.

Over the last 50 years, advances in bariatric surgery, in particular minimally invasive laparoscopic procedures, dramatically reduced the risk of complications. So, bariatric surgeons are now discussing lowering the threshold for intervention. The NHS currently funds bariatric surgery for people with a BMI of 40kg/m2 or more or a BMI between 35 and 40kg/m2 and an obesity-related comorbidity that might improve with weight loss. Mr Somers notes that, because the benefits are not solely due to weight loss, bariatric surgery can benefit people with type 2 diabetes and BMIs of 26 or 27kg/m2. ‘There’s a strong argument for reducing the threshold to 30kg/m2 in people with comorbidities and to 28.5kg/m2 in people of Asian or Middle Eastern ethnic background,’ he says. ‘Moreover, as bariatric surgery is a bona fide treatment for type 2 diabetes, we should consider offering the procedure as an alternative to escalation of therapy with insulin.’

‘We need to have a range of options to prevent and treat type 2 diabetes,’ Dr Burns concludes. ‘After all, while remission of type 2 diabetes won’t be possible for everyone, the conversation has really changed in the last couple of years. Instead of being a condition for life, remission of type 2 diabetes is now a feasible therapeutic option for some.’

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References