# Management & prevention of type 2 diabetes

## Weight loss and diabetes remission

**Jason Gill**
*Reader in Exercise and Metabolism, Institute of Cardiovascular and Medical Sciences, University of Glasgow*

Weight loss is a cornerstone of the effective management of obese people with type 2 diabetes, but it is difficult to achieve with conventional management. In this issue of *Diabetes Digest*, two studies extend our knowledge of the effects of bariatric surgery and very-low-energy diets (VLEDs) on potential diabetes remission.

While there is accumulating evidence from randomised controlled trials that bariatric surgery is more effective than conventional medical and lifestyle-based therapies in improving glycaemic control in obese people with type 2 diabetes (e.g. Schauer et al, 2014; Ikramuddin et al, 2015), follow-up in these studies has been limited to 2–3 years, so long-term outcomes and adverse events are not known. In the study summarised alongside, Mingrone and colleagues extend this evidence base, reporting 5-year follow-up data of a randomised controlled trial in which 60 people aged 30–60 years, with BMI ≥35 kg/m$^2$, $HbA_{1c}$ ≥53 mmol/mol (7.0%) and type 2 diabetes of at least 5 years' duration were randomised to medical treatment, Roux-en-Y gastric bypass or biliopancreatic diversion.

In the 53 people who completed the 5-year follow-up, 50% of the surgery recipients but none of the medically treated participants had maintained diabetes remission. However, among the 34 people who had achieved diabetes remission at 2 years, hyperglycaemia relapse was recorded at least once over the study course in 44%. As expected, the surgery groups had maintained substantially greater weight loss than the medical treatment group (around 40 kg vs 10 kg) at 5 years, but the incidence of adverse metabolic events was higher in the former. Thus, these data indicate that diabetes remission can be durable in a substantial proportion of people following surgery, but that continued long-term monitoring of glycaemia and metabolic complications is essential in all patients post-surgery.

Lim et al (2011) had previously demonstrated that, by restricting dietary energy intake to around 600 kcal/day, diabetes could be reversed – at least for 8 weeks – in people with a diabetes duration of less than 4 years, suggesting that dietary as well as surgical approaches could, in principle, lead to diabetes remission. However, it was not known whether this extended to people with longer-duration disease. In Steven and Taylor's recent study (summarised in Roger Gadsby's section on page 14), 15 people with short-duration diabetes (<4 years) and 14 with long-duration diabetes (>8 years) completed an 8-week VLED intervention (approximately 700 kcal/day). Overall, 87% of the short-duration group and 50% of the long-duration group achieved non-diabetic fasting glucose concentrations by the end of the intervention.

These data imply that aggressive dietary intervention can reduce blood glucose concentrations to non-diabetic levels, at least in the short-term, in a substantial proportion of people with long-standing diabetes. Whether this approach will be a viable diabetes treatment strategy in practice will depend on whether weight loss and improved glycaemia can be maintained over the longer term. The ongoing DiRECT study (Diabetes Remission Clinical Trial; available at: www.directclinicaltrial.org.uk), in which people with diabetes undergo a VLED with 2 years of follow-up, should help provide some answers. ■

Ikramuddin S, Billington CJ, Lee WJ et al (2015) Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomised, controlled trial. *Lancet Diabetes Endocrinol* **3**: 413–22

Lim EL, Hollingsworth KG, Aribisala BS et al (2011) Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* **54**: 2506–14

Schauer PR, Bhatt DL, Kirwan JP et al (2014) Bariatric surgery versus intensive medical therapy for diabetes – 3-year outcomes. *N Engl J Med* **370**: 2002–13

## Lancet

### Bariatric surgery vs medical treatment for T2D: 5-year follow-up

| | |
|---|---|
| Readability | ✓✓✓✓✓ |
| Applicability to practice | ✓✓✓✓ |
| WOW! Factor | ✓✓✓✓ |

**1** These authors report the 5-year outcomes of an open-label, randomised controlled trial comparing bariatric surgery and medical therapy in people with T2D.

**2** A total of 60 people with T2D of ≥5 years' duration and BMI ≥35 kg/m$^2$ were randomised in a 1:1:1 ratio to Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD) or medical therapy. Of these, 53 completed the 5-year follow-up.

**3** At 5 years, no-one in the medical group had achieved the primary endpoint of diabetes remission, defined as a fasting glucose level of ≤5.6 mmol/L and an $HbA_{1c}$ of ≤47·5 mmol/mol (6.5%).

**4** However, 50% of the surgery groups (seven of 19 [37%] in the RYGB group and 12 of 19 [63%] in the BPD group) had durable remission at this timepoint.

**5** Among the 34 surgery recipients who had achieved remission at 2 years, hyperglycaemia relapsed in 15 (44%) over the subsequent follow-up. Nonetheless, these people were able to maintain a mean $HbA_{1c}$ of 49.7 mmol/mol (6.7%) at 5 years with just diet and either metformin or no medication.

**6** Overall, 31 surgery recipients (82%) were able to maintain an $HbA_{1c}$ <53.0 mmol/mol (7.0%) despite little or no use of glucose-lowering drugs. Those who did not achieve diabetes remission by year 2 did not improve their glycaemic control by year 5.

Mingrone G, Panunzi S, De Gaetano A et al (2015) Bariatric–metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* **386**: 964–73

## Diabetologia

### Sleep-time BP is a prognostic marker of T2D risk

| | |
|---|---|
| Readability | ✓✓✓✓ |
| Applicability to practice | ✓✓✓✓ |
| WOW! Factor | ✓✓✓✓✓ |

1 In this study, the authors used ambulatory blood pressure (BP) monitoring to prospectively evaluate whether the risk of developing T2D was associated with variables such as daytime and night-time BP and nocturnal dipping pattern.

2 A total of 2656 people without T2D underwent 48-hour ambulatory BP monitoring at least once per year and whenever changes were made to their hypertension treatment, if applicable.

3 Over a mean follow-up of 5.9 years, 190 participants developed T2D. New-onset T2D was associated with the following baseline characteristics: fasting plasma glucose, waist circumference, age, chronic kidney disease and taking antihypertensive medication in the morning rather than at bedtime.

4 After adjustment for these confounders, asleep mean systolic BP (SBP) was the most significant predictor of T2D risk, with a hazard ratio of around 1.40 for each 1-SD elevation in sleep-time SBP.

5 Daytime BP and mean 48-hour ambulatory BP had no independent predictive value.

6 Analyses of BP changes over follow-up revealed a 30% reduction in the risk of new-onset T2D per 1-SD decrease in asleep mean SBP, independent of changes in clinic BP, awake BP or 48-hour BP.

7 These prospective findings suggest that a higher sleep-time SBP is associated with T2D risk, and that sleep-time BP dysregulation precedes rather than follows T2D development.

Hermida RC, Ayala DE, Mojón A, Fernández JR (2016) Sleep-time BP: prognostic marker of type 2 diabetes and therapeutic target for prevention. *Diabetologia* **59**: 244–54

## Diabetes Care

### Skipping breakfast leads to increased hyperglycaemia after lunch in T2D

| | |
|---|---|
| Readability | ✓✓✓✓ |
| Applicability to practice | ✓✓✓✓✓ |
| WOW! Factor | ✓✓✓✓ |

1 In this crossover study, the authors explored the postprandial glycaemic response to identical lunch and dinner meals, either with or without breakfast, in 22 people with T2D (mean duration, 8.4 years; age, 57 years; BMI, 28 kg/m$^2$; $HbA_{1c}$, 61 mmol/mol [7.7%]).

2 Compared with the breakfast arm, the area under the curve (AUC) at 0–180 minutes after the lunch meal was 37%, 41% and 15% higher for plasma glucose, free fatty acid and glucagon levels, respectively, in the no-breakfast arm. Conversely, the AUC for insulin and glucagon-like peptide-1 (GLP-1) levels was 17% and 19% higher.

3 Similarly, after dinner, the AUC for glucose, free fatty acid and glucagon levels was 27%, 30%, and 12% higher, respectively, and the AUC for insulin and GLP-1 levels 8% and 17% lower, in the no-breakfast arm.

4 The omission of breakfast also resulted in impaired insulin secretion after lunch and dinner, as demonstrated by a 30-minute delay in insulin peak and reduced plasma levels of insulin and C-peptide.

5 The authors posit that these differences may be due to increased beta-cell responsiveness induced by the first meal of the day, higher GLP-1 levels as a result of the breakfast or circadian clock misalignment due to skipping breakfast.

6 Whatever the mechanisms, these results suggest that breakfast consumption should be encouraged.

Jakubowicz D, Wainstein J, Ahren B et al (2015) Fasting until noon triggers increased postprandial hyperglycemia and impaired insulin response after lunch and dinner in individuals with type 2 diabetes: a randomized clinical trial. *Diabetes Care* **38**: 1820–6

## BMJ

### Liraglutide added to multiple daily insulin injections in people with T2D

| | |
|---|---|
| Readability | ✓✓✓✓✓ |
| Applicability to practice | ✓✓✓✓✓ |
| WOW! Factor | ✓✓✓✓ |

1 In this multicentre, double-blind trial, 122 people with T2D and inadequate glycaemic control despite being on multiple daily injections of insulin were randomised to receive either liraglutide or placebo in conjunction with their ongoing therapy.

2 The participants had a mean age of 63.7 years, a mean diabetes duration of 17 years and a mean $HbA_{1c}$ of 75 mmol/mol (9.0%).

3 Over a follow-up of 24 weeks, $HbA_{1c}$ reduced in both groups but to a greater extent in the liraglutide group (mean reduction, 17 mmol/mol vs 5 mmol/mol [1.5% vs 0.4%]; $P<0.001$ for comparison). The difference between the groups became significant at 6 weeks.

4 More participants in the liraglutide group (43% vs 5%; $P<0.001$) reached the target $HbA_{1c}$ of <53 mmol/mol (7.0%).

5 Body weight also reduced with liraglutide but not placebo (mean reduction, 3.8 kg vs 0.0 kg; $P<0.001$).

6 The rate of hypoglycaemia was similar in the two groups (mean, 1.29 vs 1.24 events per person), and severe hypoglycaemia did not occur in either group.

7 Gastrointestinal symptoms (50% vs 13%) and nausea (33% vs 2%) were more common in the liraglutide group. Two liraglutide recipients discontinued owing to these adverse effects.

8 The study was supported by Novo Nordisk but was initiated, designed, conducted and written by the authors.

Lind M, Hirsch IB, Tuomilehto J et al (2015) Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). *BMJ* **351**: h5364

> *"These prospective findings suggest that a higher sleep-time systolic blood pressure is associated with type 2 diabetes risk, and that sleep-time blood pressure dysregulation precedes rather than follows diabetes development."*