

Diabetes Digest

Diabetes Digest summarises recent key papers published in the area of coexistent diabetes and obesity – diabetes. To compile the digest a PubMed search was performed for the 3 months ending June 2012 using a range of search terms relating to type 2 diabetes, obesity and diabetes. Articles have been chosen on the basis of their potential interest to healthcare professionals involved in the care of people with diabetes. The articles were rated according to readability, applicability to practice, and originality.



What is the role of surgical interventions in the management of diabetes in obese individuals?

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In 1921, diabetes was a terminal condition. In 1922, thanks to Frederick Banting and his team's work on insulin, it became treatable. A cure for diabetes is still a pipe dream, but bariatric surgery is arguably getting close to a cure for type 2, specifically.

The STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) study (Schauer et al, 2012; summarised on the facing page) presents new evidence for the management of diabetes in obese individuals by medical versus surgical means. The word "cure" is still forbidden, as the duration of resolution by any means is unknown and referring to a "cure" implies that long-term follow-up and risk management is no longer required, which is not the case. Nevertheless, a primary outcome target of $HbA_{1c} \leq 42$ mmol/mol (6.0%) as aspired to here, represents normoglycaemia. STAMPEDE's results are remarkable and should change practice and be considered by those needing to balance cost and clinical effectiveness in austere times.

Walter Pories, pioneer of modern bariatric surgery research, once called an early paper on gastric bypass (GB) "Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus" (Pories et al, 1995). This was not a very scientific title, and slightly smug as the diabetes-resolving effect was a chance finding and the putative hormonal mechanism of action is still unknown. It is true, however, that the ability of surgery to modify the enteroinsular axis in some way is remarkable, and demonstrated here to an impressive degree. An average post-GB HbA_{1c} of 46 mmol/mol (6.4%) in previously uncontrolled diabetes with baseline HbA_{1c} of 77 mmol/mol (9.2%), is the best long-term treatment that can be offered; 49 mmol/mol (6.6%) with sleeve gastrectomy (SG) is not far behind. SG describes the removal of the greater curvature of the stomach to restrict food intake, possibly lowering ghrelin secretion to reduce hunger. Originally designed to be the first part of a two-part procedure in patients too overweight for immediate GB, it was observed as safe and successful in its own right. A benefit of SG is maintenance of the stomach architecture – the cardiac and pyloric sphincters remain

in control of gastric function. Opinions on the reason for the enhanced and rapid effects of GB on diabetes vary. The "hindgut theory" suggests an increase in the release of incretin hormones including GLP-1 from the L-cells of the intestine as nutrients are delivered more rapidly to the lower small intestine. The "foregut theory" describes the elimination of a putative "anti-incretin" hormone which, if it exists, promotes fat deposition and thus insulin resistance. Pories' study hints at a world in which a patient with an inguinal hernia will be referred by the GP for a curative procedure, and a newly diagnosed person with diabetes will be referred for his or her definitive operation.

Evidence supporting Pories' paper is increasing. The SOS (Swedish Obese Subjects) trial (Sjöström et al, 2004), looking at patients who underwent basic bariatric procedures >20 years ago, has shown that rates of hypertriglyceridaemia, diabetes and hyperuricaemia were lower in the surgically treated group than in controls after up to 10 years. A study by Adams et al (2007) showed that long-term all-cause mortality with surgery was reduced by 40% compared with controls, and that cause-specific mortality also decreased for coronary artery disease, diabetes and cancer. In 2009 a review by Picot et al concluded that bariatric surgery is more effective for weight loss than non-surgical options, is better at improving and resolving comorbidities and is cost-effective. The National Bariatric Surgery Registry (NBSR) analysed data from 8710 operations over a year and showed the effects of obesity surgery in treating a whole range of life-threatening diseases, including type 2 diabetes (NBSR Data Committee, 2010).

Other notable papers provide the context in which STAMPEDE needs to be judged. Adjustable gastric bands have been shown by Dixon and O'Brien (2002) to induce resolution of diabetes in 73% of patients, but only in drug-naïve, newly diagnosed individuals. There is no doubt that weight loss following gastric band insertion can lead to significant improvement in diabetes, but this seems to be dependant on weight loss. The Buchwald et al (2004) meta-analysis confirmed GB as the most effective of

the commonly performed operations, demonstrating resolution of diabetes in 83.7% of patients, but the paper predated routine SG.

Recently, Himpens et al (2010) gave an appraisal of the sleeve, describing excellent initial weight loss, but questionable long-term maintenance. This put the effectiveness of SG under scrutiny. Did the operation provide long-term benefit, and did GB not offer far superior resolution of diabetes? STAMPEDE was published in this context.

The STAMPEDE results are impressive because of the effects of SG on diabetes. Patients who underwent SG had a non-significantly lesser degree of weight loss than those who underwent GB bypass, with good normalisation of glucose. Furthermore, 72% of the SG group were able to stop glucose-lowering therapy, in contrast to the bypass group who were all able to stop all medications. Although STAMPEDE seems to confirm bypass as the gold standard, it suggests an elevation of status of SG. Similarly impressive was the weight loss achieved by medical means in people with poorly controlled diabetes, of whom 12% achieved an $HbA_{1c} \leq 42$ mmol/mol (6%), possibly through the frequent use of newer agents such as GLP-mimetics. Another observed outcome was the enhanced reduction of medication for cardiovascular (CV) risk. However, this is a complex area; studies like SOS demonstrate that, although a person's global CV risk is significantly reduced by bariatric surgery, he or she is still at higher risk than the general population, so drugs should not necessarily be stopped on normalisation of a particular risk factor. The long-term treatment of a permanently post-obese individual needs careful study.

In summary, the SG is a relatively safe procedure, without long-term results to prove its effectiveness, although the GB is still judged to be superior in terms of weight loss, weight maintenance and resolution of comorbidities. STAMPEDE adds evidence relating to how the SG, an operation in its relative infancy, fits within the firmament of bariatric surgery, and paints a more optimistic picture than other studies. ■

References on right-hand side of following page.

Obesity Surgery

Gastric bypass surgery exerts positive effect on adiponectin levels

Readability ✓✓
 Applicability to practice ✓
 Originality ✓✓✓

1. Adiponectin has a negative correlation with insulin resistance.
2. This study measured omental adiponectin gene expression in 25 patients undergoing gastric bypass surgery.
3. Omental adiponectin increased five-fold after surgery, reaching levels equivalent to age-matched non-obese individuals.

Chen J et al (2012) Omental gene expression of adiponectin correlates with degree of insulin sensitivity before and after gastric bypass surgery. *Obes Surg* 22: 472-7

New England Journal of Medicine

Lifestyle interventions slow decline in mobility in obese people with type 2 diabetes

Readability ✓✓
 Applicability to practice ✓✓✓
 Originality ✓✓

1. The aim of this study, part of the ongoing Look AHEAD (Action for Health in Diabetes) study, was to assess the effect of intensive lifestyle interventions in slowing the loss of mobility in obese people with type 2 diabetes.
2. A total of 5145 overweight or obese adults with type 2 diabetes (aged between 45 and 74 years) were randomised to receive either an intensive lifestyle intervention or a diabetes support and education programme.
3. Markov models and mixed-effects ordinal logistic regression were used to assess disability states and the probability of functional decline, respectively.
4. The authors measured self-reported limitation in mobility with annual assessments for 4 years as the primary outcome.
5. In total, 5016 participants were included in the analysis. After 4 years, the lifestyle intervention group had a reduction in the odds of mobility loss of 48% compared with the support and education group (odds ratio, 0.52 [95% confidence interval, 0.44-0.63; $P < 0.001$]).
6. Weight loss and improved fitness were significant mediators of the observed effect (both $P < 0.001$).
7. At 1 year, those individuals in the lifestyle intervention group had a slightly higher frequency of musculoskeletal adverse effects.
8. Overall, this study demonstrated that the decline in mobility in overweight adults with type 2 diabetes was slowed by weight loss and improved fitness.

Rejeski WJ et al (2012) Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med* 366: 1209-17

Diabetes, Obesity and Metabolism

Who is most at risk of type 2 diabetes and obesity?

Readability ✓✓✓
 Applicability to practice ✓✓✓
 Originality ✓✓

1. This timely review pulls together current data on the burden of obesity and diabetes, describing the physiological changes and how to identify people requiring interventions. The author stressed that obesity should be seen as a metabolic disorder rather than personal weakness, and the need to work closely with the patient.

Garber A (2012) Obesity and type 2 diabetes: which patients are at risk? *Diabetes Obes Metab* 14: 399-408

“Decline in mobility in overweight adults with type 2 diabetes was slowed by weight loss and improved fitness”

New England Journal of Medicine

Effect of bariatric surgery versus intensive medical therapy on glycaemic control

Readability ✓✓✓
 Applicability to practice ✓
 Originality ✓✓

1. Previous studies have shown improvement in patients with type 2 diabetes after bariatric surgery.
2. The aim of this randomised, non-blinded study in the US was to evaluate medical therapy versus medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy in 150 obese patients with type 2 diabetes.
3. The primary endpoint was the proportion of patients with $HbA_{1c} \leq 42$ mmol/mol (6%).
4. In the patients who completed 12 months of follow up, 12% in the medical therapy group achieved the primary endpoint versus 42% in the gastric bypass group and 37% in the sleeve gastrectomy group ($P = 0.008$).
5. In this study, 12 months of medical therapy plus bariatric surgery achieved glycaemic control in more patients than medical therapy alone.

Schauer PR et al (2012) Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 366: 1567-76

Surgery for Obesity and Related Diseases

Duodenal bypass improves insulin resistance more quickly than sleeve gastrectomy

Readability ✓✓
 Applicability to practice ✓
 Originality ✓✓✓

1. This study evaluated metabolic changes in the early stages following two types of bariatric surgery: biliopancreatic diversion of Scopinaro (BPD) and sleeve gastrectomy (SG).
2. The study involved 31 morbidly obese patients without diabetes; 18 underwent BPD and 13 underwent SG. They were examined pre-surgery and at 15, 30, 45 and 90 days post-surgery.
3. Serum glucose, cholesterol, triglycerides, high-density lipoprotein cholesterol and free fatty acids were significantly reduced in the BPD group. In the SG group, the changes in these parameters were not significant.
4. Insulin resistance decreased significantly in the BPD group over the 90 days post-surgery. In the SG group, insulin resistance worsened at 15 days, then decreased.

Garrido-Sanchez L et al (2012) Bypass of the duodenum improves insulin resistance much more rapidly than sleeve gastrectomy. *Surg Obes Relat Dis* 8: 145-50

Adams TD et al (2007) *N Engl J Med* 357: 753-61
 Buchwald H et al (2004) *JAMA* 292: 1724-37
 Dixon JB, O'Brien PE (2002) *Diabetes Care* 25: 358-63
 Himpens J et al (2010) *Ann Surg* 252: 319-24
 NBSR Data Committee (2010) *Dendrite Clinical Systems*. Available at: <http://bit.ly/QTYo6F> (accessed 17.09.12)
 Picot J et al (2009) *Health Technol Assess* 13: 1-190, 215-357
 Pories W et al (1995) *Ann Surg* 222: 339-52
 Sjöström L et al (2004) *N Engl J Med* 351: 2683-93