

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 May 2015 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.



Rethinking the referral pathway

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This journal, and even this column, has talked a lot about the SOS (Swedish Obese Subjects) study, not surprisingly so given its age and gravitas. It was the first long-term, prospective, controlled trial to provide information on the effects of bariatric surgery on obesity and its related comorbidities, and it was one of the first studies in history to demonstrate that deliberate weight loss in obesity is linked with reduction in mortality (Sjöström, 2008). Since then, this finding has generally only been repeated by bariatric surgery studies. The SOS study has its detractors – a bariatric surgery trial is impossible to randomise and double blind; the surgical procedures utilised in the SOS study are over 20 years old and relatively primitive, even obsolete, and more recent updates from the group have had only a small handful of participants left, allowing very little statistical power.

In comparison, for instance, the latest instalment of the Look AHEAD study of weight loss in over 5000 obese people with diabetes, précised on the opposite page, continues to produce remarkable findings. The latest conclusion is that weight loss by lifestyle alone induces significant increases in adiponectin, which improves insulin sensitivity, alongside anti-apoptotic and anti-inflammatory effects. Adiponectin is produced almost entirely by adipose tissue, but as the adipocyte mass expands, less is produced. Unlike the SOS study, there was no observed reduction in cardiovascular events or mortality after the intervention (Look AHEAD Research Group, 2013).

This instalment of the SOS study, summarised alongside, is important and looks again at the data when the trial was at its height to extract more subtle messages. It attempts to predict the patients who will benefit the most from surgery,

and, therefore, who primary care should invest valuable resources in for best outcomes. The complicated trial design divided the original cohort into quartiles of baseline weight and further quintiles of degree of post-operative weight loss. Incidence and remission of diabetes at 2 years was assessed. The main conclusion is that starting BMI is irrelevant to remission of diabetes, i.e. it doesn't matter how big a person is pre-operatively, it is the degree of weight loss from any starting point that is relevant to diabetes remission. This should prompt a rethink of referral pathways; patients' size shouldn't be the main criterion, rather the severity of their comorbidities and their degree of motivation to succeed. This concept fits neatly with the Edmonton Obesity Staging System, which prioritises treatment by degree of medical, psychological or functional comorbidities, rather than size (Sharma, 2009). It also resonates with guidance published by NICE (2014), who have been serially lowering the thresholds for referral for surgery, potentially to as low as a BMI of 30 kg/m², so that young, moderately obese individuals with diabetes can potentially access life-changing treatment early, when it is most effective.

Of the SOS study, 27% of participants at any baseline BMI and who failed to lose any weight after surgery witnessed their diabetes enter remission. This possibly reflects the specific anti-diabetes effect of gastric bypass, which does not rely on mere weight loss for its effect. For participants who lost significant amounts of weight, a 97.1% remission rate occurred, suggesting that we need to select suitable patients carefully and perhaps open the conversation around bariatric surgery more widely to appropriate patients who may not tip the scales at 200 kg. ■

References on the opposite page.

Diabetologia

Degree of obesity at baseline: The effect on diabetes incidence and remission

Readability ////
 Applicability to practice //
 Originality //

1. Taking data produced from the SOS (Swedish Obese Subjects) study, the authors analysed the rates of T2D incidence and remission in relation to weight change (measured by BMI change). In total, 3485 people, some of who had received bariatric surgery, were included in the analyses.
2. Data collection was carried out 2 years after surgery and individuals were grouped into four baseline BMI categories (<35, 35–40, 40–45 or ≥45 kg/m²) and five weight-change categories (major, medium, minor, no change or weight gain).
3. T2D incidence was 7.1% in those with no weight change compared with incidence rates of 1.5% ($P<0.001$), 0.0% ($P<0.001$) and 0.5% ($P=0.009$) in the groups achieving minor, medium and major weight change respectively.
4. T2D remission rates were higher in the groups with minor, medium and major weight loss compared to the group with no weight change ($P<0.001$ for all comparisons against the group with no weight change).
5. The authors showed that the effect of weight change on diabetes prevention and remission is independent of the initial BMI.
6. A limitation noted by the authors was that those who had undergone bariatric surgery and those who had not were combined in the analyses, and as such those who had experienced the most significant weight changes tended to be from the surgery group. With this in mind, it can not be determined whether the above findings were due to the surgery or the weight change itself.

Sjöholm K, Pajunen P, Jacobson P et al (2015) Incidence and remission of type 2 diabetes in relation to degree of obesity at baseline and 2 year weight change. *Diabetologia* 58: 1448–53

Diabetes Care

Adiponectin levels: Findings from the Look AHEAD study

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

- Adiponectin is an insulin-sensitising hormone with anti-inflammatory and anti-apoptotic properties. It is made mainly in the adipose tissue, and its levels are significantly decreased in T2D and obesity.
- In this analysis of the Look AHEAD study, the effect of an intensive lifestyle intervention (ILI) on adiponectin was investigated. Total and high-molecular weight adiponectin, weight and cardiorespiratory fitness were measured in 1379 people at baseline and 1 year later when the ILI of the Look AHEAD study was at its most intense.
- At 1 year, the ILI caused greater improvements in weight, fitness and adiponectin levels compared to the control arm of the study who followed diabetes support and education ($P < 0.0001$).
- Weight loss and improved fitness were both associated with changes in adiponectins in men and women ($P < 0.001$ for all) after adjusting for baseline characteristics.
- In male participants, compared to increased fitness the weight loss achieved contributed an additional 4–5% to the variance of change in adiponectin.
- In women, the contribution of fitness and weight loss to adiponectin change were similar.
- When weight loss and fitness were both accounted for, weight loss in men and increased fitness in women were still significantly associated with adiponectin change ($P < 0.0001$ for both).
- The improvements caused by the ILI were favourably associated with adiponectin change.

Belcalzar LM, Lang W, Haffner SM et al (2015) Improving adiponectin levels in individuals with diabetes and obesity: insights from Look AHEAD. *Diabetes Care* 13 May [Epub ahead of print]

Ann Intern Med

Evidence in favour of the obesity paradox in T2D

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

- The aim of this study was to determine whether the obesity paradox is present using a large UK cohort of people with T2D who have been followed prospectively since 1995.
- The obesity paradox suggests that once cardiovascular disease occurs, obesity confers a better prognosis and reduced mortality among people with T2D.
- In total, 10 568 people with T2D with a median age of 63 years were followed for a median of 10.6 years. The median baseline BMI was 29 kg/m², and during the follow-up period 3728 people died.
- In the cohort, overweight or obese people (BMI >25 kg/m²) had a higher rate of cardiac events than those of normal weight (BMI 18.5–24.9 kg/m²). However, being overweight was associated with a lower mortality risk, whereas obese people (BMI >30 kg/m²) had a mortality risk similar to that of normal-weight people.
- The authors note that one of the limitations of the study was that it was unknown whether the causes of death were cardiovascular or non-cardiovascular related.
- The authors conclude that individuals with the lowest BMI have the worst prognosis and being overweight is associated with a lower mortality risk, but being obese is not.
- The implication of these findings is that overweight and obese individuals have an increased risk of cardiovascular events, but that there appears to be some sort of survival advantage found in overweight people but not obese people.

Costanzo P, Cleland JG, Pellicori P et al (2015) The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. *Ann Intern Med* 162: 610–8

Diabetes Res Clin Pract

Impact of obesity on kidney function in people with T2D

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

- These authors evaluated the contribution of obesity to the impairment of kidney function, as defined by urinary albumin excretion (UAE) and glomerular filtration rate (GFR), in people with T2D.
- In a cross-sectional, prospective study, 855 people with T2D were compared with 84 volunteers without the condition, all stratified according to obesity levels (measured in BMI stages).
- Participants with T2D had the same age, diabetes duration and HbA_{1c} levels across BMI stages. However, UAE increased from 21 mcg/mg in normal-weight people to 30, 33 and 51 mcg/mg in overweight, obese and morbidly obese people, respectively ($P < 0.001$ for trend).
- After adjustment for age, gender, systolic blood pressure and the presence of T2D, morbid obesity was associated with a risk of microalbuminuria (odds ratio [OR], 1.99; $P < 0.001$) and macroalbuminuria (OR, 2.33; $P = 0.006$).
- In people without T2D, body surface-adjusted GFR was not correlated with obesity stage. In people with T2D, GFR was lower overall and further reduced as obesity levels increased ($P < 0.001$).
- There was a significant interaction between the presence of T2D and obesity stage with unadjusted GFR ($P = 0.02$). For body surface-adjusted GFR, the trend approached significance ($P = 0.07$).
- The authors conclude that obesity interacts with T2D to impair kidney function, and that treatment should be targeted at both conditions in such people.

Belhatem N, Mohammedi K, Rouzet F et al (2015) Impact of morbid obesity on the kidney function of patients with type 2 diabetes. *Diabetes Res Clin Pract* 108: 143–9

“The authors showed that the effect of weight change on diabetes prevention and remission is independent of the initial BMI.”

References of the commentary

- Look AHEAD Research Group (2013) Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 369: 145–54
- NICE (2014) *Obesity: identification, assessment and management of overweight and obesity in children, young people and adults* (CG189). NICE, London
- Sharma A (2009) *Edmonton Obesity Staging System*. Dr Sharma's Obesity Notes, Canada. Available at: <http://bit.ly/1HEaxX4> (accessed 14.07.15)
- Sjöström (2008) Bariatric surgery and reduction in morbidity and mortality: experiences from the SOS study. *Int J Obes (Lond)* 32(Suppl 7): S93–7