& Rayaz A Malik^{1,3}

There is a worldwide increase in obesity and Type 2 diabetes mellitus (T2DM). •

The effect of bariatric surgery on obesity

• Obesity is associated with increased mortality and morbidity.

Shazli Azmi^{*,1}, Uazman Alam¹, Basil Ammori², Handrean Soran¹

For reprint orders, please contact: reprints@futuremedicine.com

and its complications

- Bariatric Surgery is a cost-effective treatment for obesity and Type 2 diabetes, which in the long-term is associated with an improvement in mortality.
- NICE guidelines recommend that all patients with a BMI of 35 or over who have recent-onset T2DM be assessed for • bariatric surgery.
- The outcome on weight of the different surgical procedures affects the remission rates of T2DM. •
- Microvascular outcomes show promising results postbariatric surgery, however, these need to be further evaluated particular on neuropathy.

Diabetes Manag. (2015) 5(5), 393-402

Careful patient selection is important to achieve the best outcomes post bariatric surgery.

Obesity has become a worldwide epidemic that is accompanied by a rise in Type 2 diabetes mellitus. Management of obesity is paramount to prevent the associated mortality and morbidity. Several randomized control trials show that bariatric surgery is an effective method for the treatment of obesity and remission of Type 2 diabetes in the short term. Long-term observational studies have further validated the improvements in weight and Type 2 diabetes as well as cardiovascular events and overall mortality. There is an improvement in microvascular outcomes, in particular retinopathy and nephropathy show promising results but further studies are needed to evaluate hard-end points for neuropathy. Bariatric surgery is cost effective with the cost of surgery being offset by future cost benefits.

There is a worldwide rapid increase in obesity prevalence such that it may be described as an epidemic. Obesity has more than doubled since 1980 such that in 2014 more than 1.9 billion adults were overweight and over 600 million were obese [1]. In 2013, 42 million children under the age of 5 years were overweight or obese [1]. The adverse consequences of this are emphasized when one considers that BMI is a powerful predictor of Type 2 diabetes mellitus (T2DM), cardiovascular (CV) morbidity and mortality [2,3]. There are currently 382 million people in the world with diabetes and this is estimated to reach 592 million by 2035 [4]. Indeed despite the emphasis on malnutrition in the developing world, overweight and obesity are linked to more deaths than being underweight.

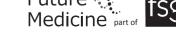
¹Centre for Endocrinology & Diabetes, Institute of Human Development, 46 Grafton Street, Core Technology Facility, Manchester, M13 9NT, UK

KEYWORDS macrovascular

- complications
- microvascular
- complications nephropathy
- neuropathy
 obesity
- overweight
 retinopathy
- Type 2 diabetes mellitus







²Salford Roval NHS Foundation Trust & The University of Manchester, Stott Lane, Salford M6 8HD, UK

³Weill Cornell Medical College, Qatar, Education City, PO Box 24144, Doha, Qatar

^{*}Author for correspondence: Tel.: +07816 916400; shazli.azmi@manchester.ac.uk

Overweight or obesity is the single most important predictor of T2DM [5]. The relative risk of diabetes increased approximately 40-fold as BMI increased from less than 23 kg/m² to more than 35 kg/m² [5]. NICE guidelines recommend that all patients with a BMI of 35 or over who have recent onset T2DM be assessed for bariatric surgery [6]. Of course the BMI may be lower in poorly controlled patients, those with comorbidities or those of Asian origin [6].

Definition

Obesity and overweight are defined as abnormal or excessive fat accumulation that may impair health [1]. The WHO definition of overweight is a BMI > 25 and for obesity it is >30 kg/m². The National Institute of Health defines morbid obesity as a BMI of 40 kg/m² or more or a BMI of 35 kg/m² or more in the presence of obesity-related comorbidities [7].

Medical complications

There is a strong relationship between obesity and T2DM, hence the rise in obesity corresponds to a rise in T2DM [8]. The Nurses Health Study reported an age-adjusted relative risk of 40 for diabetes in women with a BMI >31 kg/m² compared with women with a BMI <22 kg/m² [5]. Obesity is associated with cardiovascular risk factors with a BMI at age 18 and in midlife being positively associated with the occurrence of hypertension. The Swedish Obesity Study (SOS) found the baseline prevalence of hypertension in obese subjects to be 44-51% [9], and similarly the LABS-2 study reported that 68% of obese subjects had hypertension [10] and 63% had dyslipidemia. A meta-analysis reported that weight loss of 1 kg was associated with a decrease in serum total cholesterol of 0.05 mmol/l, LDL cholesterol of 0.02 mmol/l and an increase in HDL of 0.009 mmol/l [11].

Further risks associated with obesity include heart failure, atrial fibrillation and cerebrovascular disease [8]. Other medical complications include gastro-oesophageal reflux, cholelithiasis, nonalcoholic fatty liver disease [8] and obstructive sleep apnea [12].

Types of surgery

Bariatric procedures can be divided into malabsorptive or restrictive. Malabsorptive interventions include Roux-en-Y gastric bypass (RYGB), which involves the creation of a gastric pouch and an intestinal bypass, which is undertaken laproscopically (Figure 1A). Biliopancreatic diversion (BPD) involves a partial gastrectomy followed by reconstruction of the small intestine to divert the bile and pancreatic juices to meet the food closer to the middle or distal small intestine. Restrictive procedures include laparoscopic adjustable gastric banding (LAGB), which involves placing a constricting ring just below the junction of the stomach and esophagus and an inflatable balloon in the lining can be adjusted to regulate food intake (Figure 1C). More recently vertical sleeve gastrectomy (SG) has been introduced which involves a 70% vertical gastric resection creating a narrow canal but without intestinal bypass (Figure 1B).

Bariatric surgery effect on Type 2 diabetes

The effect of bariatric surgery has been assessed in randomized control studies (RCTs) to determine the effect on weight loss, Type 2 diabetes, as well as other comorbidities. Schauer et al. conducted a randomized, nonblinded, single-center trial of 150 patients comparing the effect of intensive medical therapy versus bariatric surgery on glycemic control in the STAMPEDE [14]. The average starting HbA1c was 9.2 ± 1.5% and the primary end point was the proportion of patients with an HbA1c of 6.0% or less after 12 months of treatment. Twelve percent of patients in the medical therapy group reached the primary end point compared with 42% in the gastric bypass group (p < 0.002) and 37% in the sleeve-gastrectomy group (p = 0.003). It was noted that weight loss was greater in the bariatric surgery groups compared with those on medical therapy and those on medical therapy needed significantly more oral therapies to control blood pressure, lipids and glycemia compared with the bariatric surgery group. All the patients in the gastric bypass group achieved the target HbA1c without any medications, whereas 28% of patients in the SG group required one or more glucose-lowering medications. Ikramuddin et al. showed remission rates of 49% in a cohort undergoing RYGB and 19% in the control group at 12 months. The remission rates were less than in the STAMPEDE trial, but the end point used by Ikramuddin was more comprehensive with a composite goal of HbA1c less than 7.0%, lowdensity lipoprotein cholesterol less than 100 mg/dl and systolic blood pressure less than 130 mm Hg [15]. More recently Courcoulas et al. noted significantly greater partial and complete

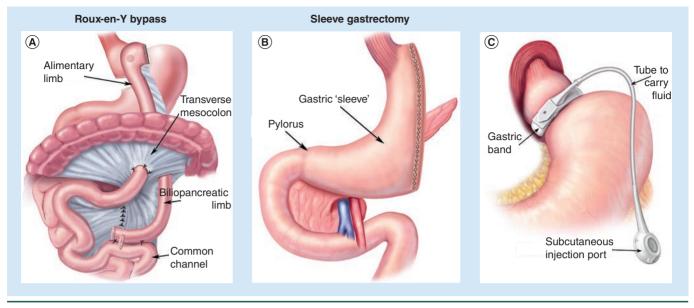


Figure 1. Types of bariatric surgery. Depicting **(A)** a gastric bypass, **(B)** a gastric sleeve and **(C)** a gastric band. Adapted with permission from [13] © Cine-Med Publishing, Inc. (2010).

remission of diabetes in RYBG and LABG subjects at 12 months [16,17]. Halperin et al. found that 58% of RYGB patients achieved the primary outcome of fasting plasma glucose levels less than 126 mg/dl and HbA1c less than 6.5% [17]. This high rate may be attributed to the HbA1c and fasting plasma glucose criteria that were used to define the primary outcome indeed this is only equivalent to the definition of partial remission by the American Diabetes Association [18]. Because these RCTs used different primary outcome measures the rates of patients achieving these outcomes varied considerably across studies. The American Diabetes Association defines partial remission as a HbA1c < 6.5% and a fasting glucose of 100-125 mg/dl with complete remission based on a HbA1c in the normal range and a fasting glucose <100 mg/dl, on no medication for at least a year [18]. Two longer RCTs have found that the bariatric surgery groups had significantly higher rates of Type 2 diabetes remission in 2 years (Table 1) [19,20]. A systematic review of 621 studies that included 135,326 patients has shown that 78.1% of diabetic patients had complete remission (off diabetes medications with a normal fasting glucose (<100 mg/dl) or HbA1c (<6%) [21]. Of course an acknowledged limitation of the RCTs is the difficulty in avoiding bias as patients are recruited from surgical outpatients where there may be a bias toward the surgical treatment. In fact some of the studies have compared bariatric surgery to intensive lifestyle intervention; however, the intensity of the latter may be questionable, as some studies have only employed usual care in the control groups.

Although there are a large number of RCTs to date, the duration of follow-up does not extend beyond 2 years with relatively small numbers of subjects being included. A recent meta-analysis has shown that there are short-term weight loss benefits and better intermediate glucose outcomes in patients undergoing bariatric surgery; however, there is insufficient evidence on longterm outcomes and complications of surgery [22]. To appreciate the longer term outcomes of bariatric surgery we must look to non-RCT's with only a few large studies assessing outcomes of bariatric surgery. The Swedish Obesity Study (SOS) is one of the largest prospective controlled intervention studies to date which involved 4047 obese subjects and commenced in 1987 [23]. A total of 2010 subjects underwent a bariatric intervention; vertical band gastroplasty (68%), gastric banding (19%) and RYGB (13%). The remaining 2037 made up a usual care control cohort. The primary outcome of this study was mortality with secondary outcomes looking at remission from Type 2 diabetes, weight loss, cardiovascular outcomes and cancer. The maximal weight loss that was achieved in the surgical groups occurred at 1-2 years; gastric bypass 32%, vertical band gastroplasty 25% and banding 20%. This then stabilized by 10 years with maximal weight loss from baseline being

Number of patients	Type of surgery	Length of study (months)	Main outcome	Results	Ref.
150	RYGB, SG	12	HbA1c <6% (with or without medication)	12% of patients achieved the primary outcome in the control group, compared with 42% in the RYGB group (p < 0.002) and 37% in the SG group (p = 0.003)	[14]
60	LAGB	24	HbA1c <6.2% and fasting plasma glucose <126 mg/dl (7.0 mmol/l) with no medication	Primary outcomes was achieved in 22(73%) in the SG group compared with 4(13%) in the control group	[20]
60	RYGB, BPD	24	Fasting glucose level of <100 mg/dl (5.6 mmol/l) and a glycated hemoglobin level of <6.5% in the absence of pharmacologic therapy	Primary outcome was achieved in no patients in the control arm compared with 75% in the RYGB group (p < 0.001) and 95% in the BPD arm (p < 0.001)	[19]
120	RYGB	12	Composite goal of HbA1c less than 7.0%, low-density lipoprotein cholesterol less than 100 mg/dl and systolic blood pressure less than 130 mm Hg	Primary outcome was achieved in 28 (49%) in the RYGB group compared with 11 (19%) in the control group (odds ratio: 4.8; 95% Cl: 1.9–11.7)	[15]
69	RYGB, LAGB	12	Partial remission HbA1c <6.5%, fasting glucose 5.6–6.9 mmol/l for at least one year with no medication. Complete remission HbA1c in normal range, fasting glucose <5.6 mmol/l for at least 1 year with no medication	Partial and complete remission of T2DM occurred in 50 and 17%, respectively, in the RYGB group and 27 and 23%, respectively, in the LAGB group ($p < 0.001$ and $p = 0.047$ between groups for partial and complete remission), with no remission in the control group	[16]
38	RYGB	12	Fasting plasma glucose levels less than 126 mg/dl and HbA1c less than 6.5%	Primary outcome was achieved in 58% of RYGB patients compared with 16% in the control group ($p = 0.03$)	[17]

reduced to 25, 16 and 14% respectively, indicating that weight gain had occurred, particularly in the gastric banding group. Overall at 20 years the weight loss in the surgery group was 18%, which was significantly greater than -1% in the control group. A major drawback of this study is that the majority of patients underwent vertical band gastroplasty, which is now obsolete.

Patients who underwent bariatric surgery showed a reduction in mortality after a mean follow-up of 10.9 years with 129 deaths in the control group versus 101 in the surgery group (hazard ratio 0.76, p = 0.04 compare to controls) [24]. When adjusted for sex, age and other risk factors the hazard ratio was 0.71 (p = 0.01). The most common causes of death were myocardial infarction and cancer. The SOS also found that bariatric surgery was associated with a decrease in cardiovascular deaths and a lower incidence of cardiovascular events when compared with usual care [25], and it was also associated with reduced cancer incidence in women but not men [26]. In the first 6 years post surgery those subjects undergoing bariatric surgery required more inpatient and nonprimary care outpatient appointments compared with controls with inpatient stays being 1.7 and 1.2 days, respectively [27]. Subsequently, from 7 to 20 years both groups had on average stay of 1.8 hospital days. The drug costs in this time period were lower in the surgery than control patients.

There was a major improvement in obesityrelated comorbidities and in particular the subjects with T2DM had a 72% remission at 2 years (OR for remission 8.4; ; p < 0.001) with a reduction in this number to 36% at 10 years (OR 3.5; < 0.001). In a subgroup analysis of the SOS, of the 505 subjects at baseline who had Type 2 DM; 345 underwent bariatric surgery and 262 standard care [28]. After a mean follow-up of 13.5 years there was a significant reduction in the incidence of myocardial infarction but no effect on stroke incidence in the bariatric group. Furthermore, the reduction in the incidence of MI was greater in those with higher serum total cholesterol and triglycerides at baseline.

Interestingly in the cohort without T2DM, bariatric surgery reduced the incidence for the development of T2DM with 6.8 cases/1000 developing T2DM in the surgery group compared with 25.4/1000 in the usual care group [29]. It is important to note that in the participants in the 'usual care' group there was a range of intervention from advanced lifestyle modification to 46% receiving no professional guidance. The lack of standardized treatment measures in the control group may account for the high incidence of T2DM, as appropriate lifestyle intervention is paramount in this group. With no intervention it is inevitable that a proportion of the group will go on to develop T2DM. It is important to note that the criteria used to define impaired fasting glycemia was >90 mg/dl, which is not in accordance with the definition of prediabetes. Indeed Caballero et al. have shown an improvement in glycemia in subjects with prediabetes and patients with T2DM undergoing laparoscopic gastric bypass [30]. However, current guidelines do not recommend bariatric surgery to prevent T2DM. A long-term observational study from Utah compared mortality outcomes from 7295 obese subjects undergoing RYGB compared with 7295 matched controls [31]. After a mean duration of 7.1 years they reported a 40% reduction in all-cause mortality and a 92% reduction in mortality related to diabetes, 56% for deaths from cardiovascular disease and 60% in cancer related deaths. The same group in Utah have reported a prospective study of 418 subjects who underwent gastric bypass compared with two control groups; one that had patients seeking to have bariatric surgery but did not have this done (n = 417), and the other that comprised randomly selected obese subjects not seeking any weight loss treatment (n = 321) [32]. In the gastric bypass group there was a significant reduction in weight, diabetes remission, incidence of diabetes and cardiovascular outcomes over 6 years.

The LABS is a multicenter observational study over 3 years [10]. Of 2458 participants undergoing bariatric procedures; 1738 had RYGB, 610 LAGB and 110 other procedures. The majority of weight loss occurred at 1 year and after 3 years those with RYGB had lost 31.5% and LAGB had lost 15.9% of their baseline weight. Of the 774 participants with T2DM at baseline, 216 RYGB participants (67.5%) and 28 LAGB participants (28.6%) had partial remission of diabetes at 3 years with the incidence of diabetes being 0.9% after RYGB and 3.2% after LAGB. In the RYGB participants, dyslipidemia resolved in 61.9% and hypertension resolved in 38.2%, while in the LAGB participants dyslipidemia resolved in 27.1% and hypertension resolved in 17.4%.

The hypertension remission rates in the RYGB group were 38.2% in LABS-2, which was similar to the SOS remission rates of all surgery participants of 34 and 19% at 2 and 10 years follow-up, respectively. The Utah Obesity Study reported hypertension remission of 53 and 42% at 2 and 6 years' follow-up. LABS-2 reported remission of dyslipidemia in 61.9% for RYGB with remission of hyperlipidemia in 59.7% and hypertriglyceridemia in 85.8% at 3 years. The Utah Obesity study has shown similar rates of remission of hyperlipidemia of 57 and 53% at 2 and 10 years, respectively.

All obese people do not develop Type 2 diabetes and in fact 10% of T2DM participants are thin [33,34]. Postbariatric surgery weight loss takes time and therefore does not explain the remission of T2DM, which occurs immediately after surgery. This suggests an alternative mechanism and an important role for gut hormones has been suggested in the remission of Type 2 diabetes. The gut hypothesis suggests that various gut peptides such as ghrelin, GLP-1, neuropeptide YY or a decreased secretion of antiincretin hormones [35,36] may improve insulin sensitivity and first-phase insulin secretion. There may also be gut adaptation and a rise in the level of gut hormones promoting satiety [37]. These differences may explain why different bariatric procedures have varying outcomes on the remission of T2DM. One study compared four procedures in 81 patients with T2DM -LAGB, intervention type Mason (MA), gastric bypass (RYGB) and SG [38], and showed that while weight loss was similar amongst all types of bypass surgery the remission rates of T2DM differed, with RYGB resulting in the best remission rates. This has also been demonstrated in animal models by Rubio et al. who found that bypass of the duodenum and upper jejunum in lean diabetic rats could render them euglycemic with no change in weight [39].

Effects on microvascular complications

One of the largest retrospective population based surveys of 2580 participants undergoing bariatric surgery and 13,371 obese control subjects without operative intervention has reported that surgery is associated with a significant decrease in microvascular events (adjusted HR 0.22 95% CI: 10.09–0.49) and a 65% reduction in major macro- and micro-vascular events [40]. However, the microvascular outcomes assessed were blindness in at least one eye, laser or retinal surgery, nontraumatic amputation or creation of a fistula for dialysis. These represent the end stage microvascular complications and while they are highly clinically relevant, they are no doubt underestimating the progression or improvement in microvascular complications. A further retrospective review of obese participants with T2DM who underwent bariatric surgery identified that in 67 subjects with complete retinal images preoperatively and 12-18 months postoperatively there was an improvement in 5 (7.5%), deterioration in 1 (1.5%) and no change in 61 (91%). Furthermore, 28 subjects who had preoperative retinopathy showed that 5 (17.8%) had an improvement, 1 (3.6%) deteriorated and there was no change in 22 (78.6%) subjects [41]. The subset of patients undergoing RYGB with preoperative albuminuria (n = 32) demonstrated a 3.5-fold decrease in postoperative albumin creatinine ratio. Banks et al. in a case-control study of 45 participants showed that retinopathy progression was paradoxically reduced in the control group (p = 0.03) but not in the group undergoing RYGB [42]. However, given that there was a significant trend in favor of surgery in a rapid improvement in glycemic control, this may well reflect an element of the worsening in retinopathy associated with a rapid improvement in glycemic control. A recent systematic review and meta-analysis highlighted four nonrandomized case series. Of 148 participants, those with preexisting diabetic retinopathy showed no change in 57.4 \pm 18.5%, progression in 23.5 \pm 18.7% and an improvement in 19.2 ± 12.9% [43]. In those subjects who did not have preoperative DR, $92.5 \pm 7.4\%$ remained disease free at followup and $7.5 \pm 7.4\%$ developed DR. These data are supported by a further smaller study looking at retinopathy [44].

The Swedish Obesity Study found that the cumulative incidence of microvascular complications was 41.8 per 1000 person years in the control group (OR: 6.3; 95% CI: 12.2–15.9) compared with 20.6 per 1000 person years in the bariatric surgery group (95% CI: 17–24.9) [45]. The end points that were used were any micro or macrovascular complication requiring hospital or specialist outpatient treatment or that were associated with death during follow-up identified through the Swedish Cause of Death Register and the Swedish National Patient Register.

The SOS found that albuminuria developed in 246 control subjects and in only 126 of the bariatric group (HR: 0.37; 95% CI: 0.30-0.047) [46]. Brethauer et al. conducted a retrospective review of subjects undergoing bariatric surgery (RYGB n = 162, LAGB n = 32, VSG n = 23) and reported that diabetic nephropathy regressed in 53% of participants and remained stable in the rest (47%) [47]. Heneghan et al. reported in 52 participants over a longer follow-up period of 5 years and showed that 37.6% of participants had nephropathy at baseline which resolved in 58.3% of these subjects [48] and the incidence of microalbuminuria was 25%. A further study of 4 years duration in a small group of 25 patients showed that serum creatinine decreased by 16.2 ± 19.6 mmol and eGFR improved by 10.6 ± 15.5 [49]. Hou et al. studied changes in eGFR in 61 patients [50] who were divided into four groups; hyperfiltration $(n = 61) eGFR 146.4 \pm 17.1 ml/min/1.73 m^2$, normal eGFR (n = 127) 105.7 ± 17.1, CKD stage 2, n = 39 (76.8 \pm 16.7) and CKD stage 3, n = 6 (49.5 ± 6.6) . There was a reduction in eGFR in the hyperfiltration group and an increase in all other groups, consistent with improvement. The data show that overall there are improvements in nephropathy however again these are small studies.

There are fewer studies assessing neuropathy. Schauer et al. described the presence of diabetic neuropathy in 47 patients preoperatively (25%), and symptomatic improvement was reported in 50% of patients after surgery: 33% much improved, 17% improved, 39% no change, 7% worse and 4% unknown [51]. It is unclear as to how neuropathy was defined in these subjects and the reported improvement was through a questionnaire which assessed improvement of chronic diabetes-related complications. To date we lack studies that assess objective markers of neuropathy. Muller-Stich et al. have reported in a small group of 12 patients with preoperative peripheral neuropathy that symptomatic neuropathy reversed in 67% of patients [52]. There was an improvement in the neuropathy symptom score (NSS) from a median of 8 (range, 0-10) to 0 (range, 0-9) postoperatively (p = 0.004), with eight patients scoring an NSS of 0. Preoperatively the median neuropathy disability score was 6

(range, 2-8), which improved to 4 (range 0-8), postoperatively (p = 0.027). Conversely, individual case reports have identified the development of rare forms of neuropathy such as acute motor axonal neuropathy post bariatric surgery [53]. There is also some focus on nutritional deficiencies that arise post surgery that may lead to neuropathy secondary to vitamin B12 and thiamine deficiency as well as vitamin D deficiency leading to osteomalacia [54-57]. Indeed post bariatric surgery neuropathic pain has an incidence of 33% and can greatly affect quality of life. It is important that any nutritional deficiencies, lipid abnormalities and poor glycemic control or indeed neuropathy related to a rapid improvement in glycemic control, so called 'insulin neuritis' are identified early so the patient can be managed effectively [58].

The studies, although small suggest good evidence for improvement of microvascular complications postbariatric surgery. The benefits on albuminuria and nephropathy are particularly encouraging, as all studies have shown a positive effect even at 4–5 years duration. It is harder to interpret the evidence from retinopathy studies as overall it seems that early retinopathy remains stable and can improve, but it may progress in those with advanced retinopathy and therefore one needs to consider the adverse outcomes related to a rapid improvement in glycemic control.

Mortality & complications of bariatric surgery

In the SOS Sjostrom et al. reported that 0.25% of patients who underwent surgery died postoperatively and of the 343 patients with Type 2 diabetes, 0.58% died postoperatively. Thirteen percent had postoperative complications and in 2.2% of these patients the postsurgical complications were serious enough to warrant re-operation [45]. Chang et al. undertook a meta-analysis that reported relatively low rates of operative mortality [59]. RCTs report perioperative mortality rates of 0.08% (95% CI: 0.01-0.24%), and a postoperative mortality rate of 0.31% (95% CI: 0.01-0.75%). Observational studies have reported higher perioperative and postoperative mortality rates, 0.22% (95% CI: 0.14-0.31%) and 0.35% (95% CI: 0.20-0.52%), respectively, with different rates reported for the various procedures. Adjustable gastric band was found to have the lowest perioperative and postoperative mortality rates (0.07% [95% CI: 0.02-0.12%]

and 0.21% [95% CI: 0.08–0.37%]), then SG (0.29% [95% CI: 0.11–0.63%] and 0.34% [95% CI: 0.14–0.60%]) with the highest rate in those undergoing gastric bypass (0.38% [95% CI: 0.22–0.59%] and 0.72% [95% CI: 0.28–1.30%]). Zigmond *et al.* reported mortality rates of 0.33% at 30 days and 0.91% at 1 year in 60,077 patients who underwent RYGB [60].

The risks associated with bariatric surgery depend on the type of procedure performed. Laparoscopic RYGB complications/risks include bleeding (0.4-4%), anastomotic leak (0-4.4%) which is a serious complication that confers a mortality rate up to 30%, wound infection (2.9%), deep vein thrombosis (0-1.3%), pulmonary embolism (0-1.1%), anastomotic strictures (2-16%), marginal ulcers (0.7-5.1%) and bowel obstruction (3%) [61,62].

There is also a 7% risk of conversion to the open RYGB which itself confers more risks such as greater postoperative pain, higher rates of iatrogenic splenectomy and abdominal wall complications such as incisional hernias. At 1 year postbariatric surgery it has been found that 38-52% of patients have developed cholelithiasis and within 3 years 15-28% of all patients require an urgent cholecystectomy [63,64]. Nutritional deficiencies may occur in the longer term after surgery with iron deficiency occurring in 13 to 52% of patients within 2 to 5 years post surgery emphasizing the need to monitor and replace postsurgery needs in the long term. For LAGB the complications include bleeding (0.1%), iatrogenic bowel perforation (0.5%), wound infection (0.1-8.1%), deep vein thrombosis (0.01–0.15%) and pulmonary embolism (0.1%). There are also band-related complications such as tube or port malfunction requiring re-operation (1.7%), band erosion into the gastric lumen (0.6%) and pouch dilatation or band slippage (5.6%). O'Brien et al. have reported that post LAGB there is a lower rate of early major complications (1.5%), but higher incidence of late complications [65,66].

Cost-effectiveness of bariatric surgery

A review of cost-effectiveness studies identified six studies using three different models to predict the cost-effectiveness of bariatric surgery. These included statistical models, a Markov model and assumption-based models which all showed surgery to be a cost-effective method for the treatment of obesity [67]. Furthermore Henteleff *et al.* found gastric bypass and gastric banding are cost-effective methods of reducing mortality and diabetes-related complications in severely obese adults with diabetes [68]. More recently Borisenko et al. reported a saving of €8408 Euros with surgery, generating an additional 0.8 years of life and 4.1 QALYs per patient, which equates to 32,390 QALYs and savings of 66 million Euros for their cohort in 1 year [69]. Hoeger et al. undertook a cost-effectiveness analysis in obese patients with Type 2 diabetes undergoing bariatric surgery [70], and showed that it reduced mortality and diabetes-related complication but there was no apparent cost saving. In those patients with newly diagnosed Type 2 diabetes they reported that gastric bypass led to 1.72 life years gained, 2.21 QALYs gained and a cost-effectiveness ratio of \$7000/OALY. Gastric banding led to 1.14 life-years gained, 1.57 QALYs gained with a cost-effectiveness ratio of \$11,000/QALY. In those with established Type 2 diabetes, there were even fewer life years gained with gastric bypass leading to 1.09 life-years gained, 1.70 QALYs gained and a cost-effectiveness ratio of \$12,000/QALY. Gastric banding led to 0.94 life-years gained, 1.34 QALYs gained and a cost-effectiveness ratio of \$13,000/QALY. Bleich et al. examined healthcare utilization and costs in 7806 individuals with Type 2 diabetes over 6 years after bariatric surgery [71], and reported no reduction in healthcare costs compared with before surgery. The ratio of hospital costs post surgery compared with presurgery was higher in years 2 to 6 after surgery and increased over time (1 year: OR: 0.58 [95% CI: 0.50-0.67]; 6 years: OR: 3.34 [95% CI: 2.60-4.53]). The adjusted ratio of inpatient days was higher after surgery (1 year: OR: 1.05 [95% CI: 0.94-1.16]; 6 years: OR: 2.77 [95% CI: 1.57-4.90]). However, there were fewer primary care visits after surgery (1 year: OR: 0.80 [95% CI: 0.78–0.82]; 6 years: OR: 0.66 [95% CI: 0.57-0.76]).

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

- 1 Organization WH. Fact sheet: obesity and overweight (2006). www.who.int/dietphysicalactivity/ publications/facts/obesity/en
- 2 Pischon T, Boeing H, Hoffmann K *et al.* General and abdominal adiposity and risk of death in europe. *N. Engl. J. Med.* 359(20), 2105–2120 (2008)
- 3 Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of US adults. *N. Engl. J. Med.* 341(15), 1097–1105 (1999).
- 4 Diabetes: facts and stats (2014). www.diabetes.org.uk/Documents/About%20 Us/Statistics/Diabetes-key-stats-guidelines-April2014.pdf
 - Hu FB, Manson JE, Stampfer MJ *et al.* Diet, lifestyle, and the risk of Type 2 diabetes mellitus in women. *N. Engl. J. Med.* 345(11), 790–797 (2001).

Conclusion

Bariatric surgery is an effective means of achieving weight loss and improving the management of Type 2 diabetes with an overall low-complication rate. The cost of surgery can be offset by the decreased cost of future complications and indeed improved quality of life. Although studies assessing retinopathy and nephropathy outcomes are encouraging, studies in neuropathy are limited and lack clear end points. Therefore, we advocate larger studies assessing the benefits on the microvascular complications, particularly in neuropathy where small fibers should be assessed by deploying the noninvasive ophthalmic technique of corneal confocal microscopy [72].

Future perspective

Obesity and T2DM are continuing to increase with people developing these at a younger age. The number of bariatric surgical procedures will rise over the next 5–10 years as the population becomes more obese and access to these services becomes more accessible. Whether or not bariatric surgery is the answer to the problem is still debated and bariatric surgery should not be thought of as a cure for obesity-related morbidities. Given the relatively modest improvements in long-term outcomes following lifestyle intervention, bariatric surgery is increasingly becoming more appealing. However, justifying this procedure, especially on the NHS requires more robust studies with clearly defined outcomes.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

- 6 Bai X, Zhi X, Zhang Q et al. Inhibition of protein phosphatase 2a sensitizes pancreatic cancer to chemotherapy by increasing drug perfusion via hif–1alpha-vegf mediated angiogenesis. *Cancer Lett.* 355(2), 281–287 (2014).
- 7 Hubbard VS, Hall WH. Gastrointestinal surgery for severe obesity. *Obes. Surg.* 1(3), 257–265 (1991).
- 8 Malnick SD, Knobler H. The medical complications of obesity. QJM 99(9), 565–579 (2006).

5

The effect of bariatric surgery on obesity & its complications **REVIEW**

- 9 Sjöström CD, Lissner L, Wedel H, Sjöström L. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS intervention study. *Obes. Res.* 7(5), 477–484 (1999).
- One of the largest studies in showing the improvement in metabolic factors following bariatric surgery
- 10 Courcoulas AP, Christian NJ, Belle SH *et al.* Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. *JAMA* 310(22), 2416–2425 (2013).
- 11 Dattilo AM, Kris-Etherton P. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am. J. Clin. Nutr. 56(2), 320–328 (1992).
- 12 Fritscher LG, Mottin CC, Canani S, Chatkin JM. Obesity and obstructive sleep apnea-hypopnea syndrome: the impact of bariatric surgery. *Obes. Surg.* 17(1), 95–99 (2007).
- 13 Jones DB, Schneider BE, Olbers T. Atlas of Metabolic and Weight Loss Surgery. Ciné-Med Publishing Inc., CT, USA (2010).
- 14 Schauer PR, Kashyap SR, Wolski K et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N. Engl. J. Med. 366(17), 1567–1576 (2012).
- •• One of the largest randomized controlled trial (RCT) showing the effects of Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) versus medical therapy.
- 15 Ikramuddin S, Korner J, Lee W-J et al. Roux-en-Y gastric bypass vs intensive medical management for the control of Type 2 diabetes, hypertension, and hyperlipidemia: the diabetes surgery study randomized clinical trial. JAMA 309(21), 2240–2249 (2013).
- Highlights the benefit of adding gastric bypass surgery to lifestyle and medical management to achieve better outcomes.
- 16 Courcoulas AP, Goodpaster BH, Eagleton JK *et al.* Surgical vs medical treatments for Type 2 diabetes mellitus: a randomized clinical trial. *JAMA Surg.* 149(7), 707–715 (2014).
- •• Compares RYGB and LAGB versus medical management and use the ADA criteria for T2DM remission as an end point.
- 17 Halperin F, Ding S-A, Simonson DC *et al.* Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with Type 2 diabetes: feasibility and

1-year results of a randomized clinical trial. *JAMA Surg.* 149(7), 716–726 (2014).

- 18 Buse JB, Caprio S, Cefalu WT *et al*. How do we define cure of diabetes? *Diabetes Care* 32(11), 2133–2135 (2009).
- 19 Mingrone G, Panunzi S, De Gaetano A *et al.* Bariatric surgery versus conventional medical therapy for Type 2 diabetes. *N. Engl. J. Med.* 366(17), 1577–1585 (2012).
- 20 Dixon JB, O'brien PE, Playfair J *et al.* Adjustable gastric banding and conventional therapy for Type 2 diabetes: a randomized controlled trial. *JAMA* 299(3), 316–323 (2008).
- Buchwald H, Estok R, Fahrbach K *et al.* Weight and Type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am. J. Med.* 122(3), 248–256, e245 (2009).
- 22 Maggard-Gibbons M, Maglione M, Livhits M *et al.* Bariatric surgery for weight loss and glycemic control in nonmorbidly obese adults with diabetes: a systematic review. *JAMA* 309(21), 2250–2261 (2013).
- 23 Sjöström L. Review of the key results from the swedish obese subjects (sos) trial-a prospective controlled intervention study of bariatric surgery. *J. Intern. Med.* 273(3), 219–234 (2013).
- 24 Sjöström L, Narbro K, Sjöström CD *et al.* Effects of bariatric surgery on mortality in swedish obese subjects. *N. Engl. J. Med.* 357(8), 741–752 (2007).
- The largest and longest prospective study to evaluate mortality following bariatric surgery.
- 25 Sjöström L, Peltonen M, Jacobson P *et al.* Bariatric surgery and long-term cardiovascular events. *JAMA* 307(1), 56–65 (2012).
- 26 Sjöström L, Gummesson A, Sjöström CD Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish obese subjects study): a prospective, controlled intervention trial. *Lancet Oncol.* 10(7), 653–662 (2009).
- A unique arm of the Swedish obese subjects (SOS) which investigated cancer incidence in patients treated with bariatric surgery.
- 27 Neovius M, Narbro K, Keating C *et al.* Health care use during 20 years following bariatric surgery. *JAMA* 308(11), 1132–1141 (2012).
- 28 Romeo S, Maglio C, Burza MA *et al.* Cardiovascular events after bariatric surgery in obese subjects with Type 2 diabetes. *Diabetes Care* 35(12), 2613–2617 (2012).
- 29 Carlsson LM, Peltonen M, Ahlin S et al. Bariatric surgery and prevention of Type 2 diabetes in swedish obese subjects. N. Engl. J. Med. 367(8), 695–704 (2012).

- 30 Caballero MaC, Jiménez J, Castro MJ, Solórzano JO, Arango A. Outcomes in weight loss, fasting blood glucose and glycosylated hemoglobin in a sample of 415 obese patients, included in the database of the European accreditation council for excellence centers for bariatric surgery with laparoscopic one anastomosis gastric bypass. *Nutr. Hosp.* 30(5), 1032–1038 (2014).
- 31 Adams TD, Gress RE, Smith SC *et al.* Long-term mortality after gastric bypass surgery. *N. Engl. J. Med.* 357(8), 753–761 (2007).
- 32 Adams TD, Davidson LE, Litwin SE *et al.* Health benefits of gastric bypass surgery after 6 years. *JAMA* 308(11), 1122–1131 (2012).
- 33 Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. *JAMA* 286(10), 1195–1200 (2001).
- 34 American Association for the Study of Obesity et al. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. National Institutes of Health, National Heart, Lung, and Blood Institute, NHLBI Obesity Education Initiative, North American Association for the Study of Obesity (2000).
- 35 Cummings DE, Weigle DS, Frayo RS et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N. Engl. J. Med. 346(21), 1623–1630 (2002).
- An interesting study posing a hypothesis with regards to a mechanism that may contribute to weight loss post bariatric surgery.
- 36 Basso N, Capoccia D, Rizzello M et al. First-phase insulin secretion, insulin sensitivity, ghrelin, glp–1, and pyy changes 72 h after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis. Surg. Endosc. 25(11), 3540–3550 (2011).
- 37 Borg C, Le Roux C, Ghatei M, Bloom S, Patel A, Aylwin S. Progressive rise in gut hormone levels after roux-en-y gastric bypass suggests gut adaptation and explains altered satiety. *Br. J. Surg.* 93(2), 210–215 (2006).
- Pham S, Gancel A, Scotte M *et al.*Comparison of the effectiveness of four bariatric surgery procedures in obese patients with Type 2 diabetes: a retrospective study.
 J. Obes. 2014 (2014).
- 39 Rubino F, Forgione A, Cummings DE et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the

REVIEW Azmi, Alam, Soran, Ammori & Malik

pathophysiology of Type 2 diabetes. *Ann. Surg.* 244(5), 741 (2006).

- 40 Johnson BL, Blackhurst DW, Latham BB et al. Bariatric surgery is associated with a reduction in major macrovascular and microvascular complications in moderately to severely obese patients with Type 2 diabetes mellitus. J. Am. Coll. Surg. 216(4), 545–556 (2013).
- 41 Miras AD, Chuah LL, Lascaratos G et al. Bariatric surgery does not exacerbate and may be beneficial for the microvascular complications of Type 2 diabetes. *Diabetes Care* 35(12), e81–e81 (2012).
- 42 Banks J, Adams ST, Laughlan K et al. Roux-en-Y gastric bypass could slow progression of retinopathy in Type 2 diabetes: a pilot study. Obes. Surg. 1–5 (2014).
- 43 Cheung D, Switzer NJ, Ehmann D, Rudnisky C, Shi X, Karmali S. The impact of bariatric surgery on diabetic retinopathy: a systematic review and meta-analysis. *Obes. Surg.* 25(9), 1604–1609 (2015).
- Varadhan L, Humphreys T, Walker AB, Cheruvu CV, Varughese GI. Bariatric surgery and diabetic retinopathy: a pilot analysis. *Obes. Surg.* 22(3), 515–516 (2012).
- 45 Sjöström L, Peltonen M, Jacobson P *et al.* Association of bariatric surgery with long-term remission of Type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 311(22), 2297–2304 (2014).
- 46 Carlsson L, Romeo S, Jacobson P *et al.* The incidence of albuminuria after bariatric surgery and usual care in Swedish obese subjects (SOS): a prospective controlled intervention trial. *Int. J. Obes.* 39(1), 169–175 (2015).
- 47 Brethauer SA, Aminian A, Romero-Talamás H et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with Type 2 diabetes mellitus. Ann. Surg. 258(4), 628 (2013).
- 48 Heneghan HM, Cetin D, Navaneethan SD, Orzech N, Brethauer SA, Schauer PR. Effects of bariatric surgery on diabetic nephropathy after 5 years of follow-up. *Surg. Obes. Relat. Dis.* 9(1), 7–14 (2013).
- 49 Jose B, Ford S, Super P, Thomas GN, Dasgupta I, Taheri S. The effect of biliopancreatic diversion surgery on renal function – a retrospective study. *Obes. Surg.* 23(5), 634–637 (2013).

- 50 Hou C-C, Shyu R-S, Lee W-J, Ser K-H, Lee Y-C, Chen S-C. Improved renal function 12 months after bariatric surgery. *Surg. Obes. Relat. Dis.* 9(2), 202–206 (2013).
- 51 Schauer PR, Burguera B, Ikramuddin S et al. Effect of laparoscopic Roux-en-Y gastric bypass on Type 2 diabetes mellitus. Ann. Surg. 238(4), 467 (2003).
- 52 Müller-Stich BP, Fischer L, Kenngott HG et al. Gastric bypass leads to improvement of diabetic neuropathy independent of glucose normalization – results of a prospective cohort study (diasurg 1 study). Ann. Surg. 258(5), 760–766 (2013).
- 53 Landais AF. Rare neurologic complication of bariatric surgery: acute motor axonal neuropathy (aman), a severe motor axonal form of the Guillain Barré syndrome. *Surg. Obes. Relat. Dis.* 10(6), e85–e87 (2014).
- 54 Becker DA, Balcer LJ, Galetta SL. The neurological complications of nutritional deficiency following bariatric surgery. J. Obes. 2012 (2012).
- 55 O'donnell KB, Simmons M. Early-onset copper deficiency following roux-en-y gastric bypass. *Nutr. Clin. Pract.* 26(1), 66–69 (2011).
- 56 Aasheim ET, Hofsø D, Hjelmesæth J, Sandbu R. Peripheral neuropathy and severe malnutrition following duodenal switch. *Obes. Surg.* 18(12), 1640–1643 (2008).
- 57 Panda S, Sharma K. Osteomalacia induced peripheral neuropathy after obesity reduction surgery. Ann. Indian Acad. Neurol. 16(4), 690 (2013).
- 58 Kailasam VK, Decastro C, Macaluso C, Kleiman A. Postbariatric surgery neuropathic pain (PBSNP): Case report, literature review, and treatment options. *Pain Med.* 16(2), 374–382 (2014).
- 59 Chang S-H, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA Surg.* 149(3), 275–287 (2014).
- 60 Zingmond DS, Mcgory ML, Ko CY. Hospitalization before and after gastric bypass surgery. JAMA 294(15), 1918–1924 (2005).
- 61 Podnos YD, Jimenez JC, Wilson SE, Stevens CM, Nguyen NT. Complications after laparoscopic gastric bypass: a review of 3464 cases. Arch. Surg. 138(9), 957–961 (2003).

- 62 Brethauer SA, Chand B, Schauer PR. Risks and benefits of bariatric surgery: current evidence. *Cleve. Clin. J. Med.* 73(11), 993–1007 (2006).
- 63 Sugerman HJ, Brewer WH, Shiffman ML et al. A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypassinduced rapid weight loss. Am. J. Surg. 169(1), 91–97 (1995).
- 64 De Oliveira CIB, Chaim EA, Da Silva BB. Impact of rapid weight reduction on risk of cholelithiasis after bariatric surgery. *Obes. Surg.* 13(4), 625–628 (2003).
- 65 O'brien PE, Dixon gi. Lap-band®: outcomes and results. J. Laparoendosc. Adv. Surg. Tech. A 13(4), 265–270 (2003).
- 66 O'brien PE, Dixon JB, Brown W *et al.* The laparoscopic adjustable gastric band (lap-band®): a prospective study of medium-term effects on weight, health and quality of life. *Obes. Surg.* 12(5), 652–660 (2002).
- 67 Wang BC, Furnback W. Modelling the long-term outcomes of bariatric surgery: a review of cost–effectiveness studies. *Best Pract. Res. Clin. Gastroenterol.* 27(6), 987–995 (2013).
- 68 Henteleff HJ, Birch DW, Hallowell PT. CAGS and ACS evidence based reviews in surgery. 45: cost-effectiveness of bariatric surgery for severely obese adults with diabetes. *Can. J. Surg.* 56(5), 353 (2013).
- 69 Borisenko O, Adam D, Funch-Jensen P et al. Bariatric surgery can lead to net cost savings to health care systems: results from a comprehensive European decision analytic model. Obes. Surg. 1–10 (2015).
- 70 Hoerger TJ, Zhang P, Segel JE, Kahn HS, Barker LE, Couper S. Cost–effectiveness of bariatric surgery for severely obese adults with diabetes. *Diabetes Care* 33(9), 1933–1939 (2010).
- 71 Bleich SN, Chang H-Y, Lau B et al. Impact of bariatric surgery on healthcare utilization and costs among patients with diabetes. *Med. Care* 50(1), 58 (2012).
- 72 Malik RA. Why are there no good treatments for diabetic neuropathy? *Lancet Diabetes Endocrinol.* 2(8), 607–609 (2014).