Impact of bariatric surgery on cardiovascular and renal complications of diabetes: a focus on clinical outcomes and putative mechanisms

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Abstract

Introduction—Cardiovascular and renal diseases account for a substantial proportion of the morbidity and mortality associated with obesity and type 2 diabetes mellitus. Bariatric surgery addresses multiple aspects of the pathophysiology of cardiorenal syndrome in obesity and is associated with improved long-term cardiovascular and renal outcomes.

Areas covered—All major case-control, cohort, and randomised controlled trial studies of bariatric surgery in adults with type 2 diabetes mellitus were screened and data on anthropometric measures, metabolic parameters, and pre-specified cardiovascular and renal outcomes collated. Bariatric surgery results in greater weight loss and better metabolic control than best medical therapy. Bariatric surgery reduces all-cause mortality and risk of cardiovascular disease, albuminuria and progressive chronic kidney disease. Patients with poorer glycaemic control and established microvascular disease preoperatively may stand to benefit the most from the surgical approach, particularly in the context of reasonable pancreatic reserve. Preclinical and clinical studies offer insights into the mechanisms potentially underpinning cardiovascular and renal protection after bariatric surgery. Reduced sympathetic drive, remission of glomerular hypertension, enhanced natriuresis, gut microbiota shifts, reduced systemic and renal inflammation, improved lipoprotein profiles and reductions in chronic cardiac remodelling may all be implicated.

Expert commentary—Higher level evidence regarding the impact of bariatric surgery on end-organ complications of diabetes, including cardiovascular and renal disease, is required. Ongoing

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RCTs of bariatric surgery selectively recruiting patients with class 1 obesity and established microvascular complications of diabetes will help to better characterise which subgroups of patients benefit most from this effective therapy.

Keywords

Bariatric surgery; Metabolic surgery; Obesity; Type 2 diabetes mellitus; Cardiovascular disease; Hypertension; Diabetic kidney disease; Diabetic nephropathy; Albuminuria; Chronic kidney disease

1 Introduction

Obesity is a disease characterised by excess hunger and/or reduced satiety after a meal. Cardiovascular and renal diseases account for a significant proportion of the morbidity and excess mortality associated with obesity. Obesity and type 2 diabetes mellitus constitute inter-related pandemics that independently increase the risk of both cardiovascular and renal diseases [1, 2]. Overweight and obesity are more prevalent in individuals subsequently diagnosed with type 2 diabetes mellitus [3]. Data from NHANES demonstrate that elevated body mass index (BMI) is strongly associated with the development of common risk factors for both cardiovascular and renal diseases such as hypertension, type 2 diabetes mellitus, dyslipidaemia, endothelial dysfunction, albuminuria, and systemic inflammation [4]. Excess visceral adipose tissue is in particular strongly associated with a network of inter-related atherogenic and diabetogenic abnormalities including increases in insulin resistance/hyperinsulinaemia and pathogenic alterations in plasma lipid profiles. [5].

The INTERHEART and INTERSTROKE studies have highlighted that visceral adiposity, type 2 diabetes mellitus, hypertension, and dyslipidaemia constitute independent and modifiable risk factors for coronary artery disease and cerebrovascular disease [6, 7]. Furthermore, United States Renal Data System (USRDS) data consistently highlight diabetes mellitus and hypertension as the leading causes of end-stage renal disease [8].

Bariatric surgery is gaining momentum as a treatment of cardiovascular and renal diseases in the context of obesity given its propensity to simultaneously reprogramme multiple pathophysiological processes which characterise obesity-associated cardiorenal syndrome [13]. The focus has shifted from purely weight loss-related outcomes to the consideration of end-organ status such as cardiovascular and renal outcomes [14]. In this narrative review, we will highlight the evidence for bariatric or 'metabolic' surgery in terms of anthropometric measures, metabolic parameters, and cardiovascular and renal disease outcomes.

2 Aims

We aimed to screen all major case-control, cohort, and randomised controlled trial (RCT) studies of bariatric surgery in adults with type 2 diabetes mellitus. Although individuals with established microvascular complications of diabetes may benefit from metabolic surgery, they have been under-represented in studies of bariatric surgery in this population to date. We therefore aimed to highlight the prevalence of microvascular and macrovascular disease at the time of recruitment to studies of bariatric surgery in type 2 diabetes mellitus. Using

the PICO (population, intervention, comparison, outcomes) framework, our approach is summarised as:

- Population: Individuals ≥ 18 years with obesity (BMI ≥ 30kg/m^2) and type 2 diabetes mellitus.

- Intervention: Bariatric surgery (adjustable gastric banding, vertical sleeve gastrectomy, Roux-en-Y gastric bypass surgery, or biliopancreatic diversion with or without concomitant duodenal switch).

- Control group: Lifestyle intervention and/or best medical therapy.

- Outcomes:

  ○ Primary reported outcomes of studies, including anthropometric measures and metabolic parameters.

  ○ Pre-specified secondary cardiovascular and renal outcomes (absolute values of systolic and diastolic blood pressure (mmHg), antihypertensive medication usage, major adverse cardiovascular events including myocardial infarction, stroke, heart failure, and cardiovascular death, albuminuria, glomerular filtration rate, and end-stage renal disease).

3 Cardiovascular and Renal Disease Outcomes in Studies of Bariatric Surgery

3.1 Randomised Controlled Trials

RCTs of bariatric surgery in obese patients with T2DM to date have mainly focused on anthropometrics and glycaemia as outcomes of interest, with inconsistent reporting of the impact of bariatric surgery on microvascular outcomes of diabetes. Some RCTs have excluded patients with longer diabetes duration or at high-risk for microvascular disease, based on the suggestion that early intervention with bariatric surgery in T2DM may achieve complete diabetes remission with minimal residual burden of diabetes complications. T2DM patients with established microvascular complications are under-represented in RCTs of bariatric surgery. Average glycated haemoglobin values were higher at baseline in STAMPEDE and Mingrone et al's RCT compared with CROSSROADS [15, 16, 17]. Interestingly, the degree of postoperative metabolic improvement was less pronounced in CROSSROADS compared with STAMPEDE and Mingrone et al.'s RCT [15], suggesting that individuals with longer diabetes duration and established microvascular complications may derive the most benefit from bariatric surgery [18].

Diabetes remission was defined as HbA1$_c$ ≤ 6% without use of hypoglycaemic medications in STAMPEDE [19], whereas diabetes remission in Mingrone et al.'s RCT required a fasting plasma glucose ≤ 5.6 mmol/L and HbA1$_c$ ≤ 6.5% without use of hypoglycaemic medications for one year [20]. Neither study demonstrated complete remission of diabetes at 5-year follow-up [19, 20]. Thus, the role of bariatric surgery in T2DM is increasingly viewed as that of an adjunctive therapy for those patients not meeting treatment targets despite best

medical therapy with the aim of achieving disease control rather than complete disease remission [14]. In this regard, knowledge of the impact of bariatric surgery on end-organ effects of diabetes (including cardiovascular and renal disease) is important to help stratify which patients will benefit most from this therapy. Tables 1 and 2 present renal and cardiovascular outcomes in RCTs of bariatric surgery to date.

Two RCTs have reported data on albuminuria (defined as urine albumin: creatinine ratio 3mg/mmol) at 5-year follow-up after bariatric surgery [19, 20] (Table 1). 34%, 24%, and 20% individuals had albuminuria at baseline in the RYGB, VSG, and IMT arms of STAMPEDE, respectively [17]. Albuminuria was present in 19% and 11% of the RYGB and VSG arms at 5-year follow-up, respectively, compared with persistence of albuminuria in 22% of the IMT arm [19]. In Mingrone et al.'s cohort, 16%, 11%, and 27% had albuminuria at baseline in the RYGB, BPD, and IMT arms, respectively [16]. Albuminuria was present in 0% of the RYGB and BPD arms at 5-year follow-up compared with persistence of albuminuria in 27% of the IMT arm [20]. These results suggest that durable and sustained reductions in albuminuria are achieved in approximately 50% of patients at 5-year follow-up after bariatric surgery, compared with persistence or progression of albuminuria in those treated with best medical therapy alone.

Baseline serum creatinine and/or estimated glomerular filtration rate (eGFR) data are presented in two RCTs of bariatric surgery in T2DM [17, 21], while the STAMPEDE RCT also presents eGFR data at 5-year follow-up [19]. Mean baseline serum creatinine values in the Diabetes Surgery Study were 0.8 ± 0.2 mg/dL in the RYGB + IMT and IMT alone arms, respectively [21]. Median baseline serum creatinine values in STAMPEDE were: 0.7 [0.6,0.8] mg/dL (eGFR 110 [98, 119] mL/min/BSA) in the RYGB + IMT arm, 0.7 [0.6,0.8] mg/dL (eGFR 109 [97, 114] mL/min/BSA) in the VSG + IMT arm, and 0.7 [0.6,0.8] mg/dL (eGFR 106 [97, 112] mL/min/BSA) in the IMT arm [17]. Median percentage reductions in eGFR at 5-year follow up in STAMPEDE were -8 [-16, 0] % in the RYGB + IMT arm, -6 [-16, -1] % in the VSG + IMT arm, and -1 [-11, 3] % in the IMT alone arm [19]. This change in eGFR may be due to the reduction in muscle mass post-bariatric surgery [22]. However, in combination with a reduction in albuminuria, the reduction in eGFR at 5-year follow-up in the surgical arms of STAMPEDE may represent a remission of glomerular hyperfiltration after RYGB and VSG, compared with persistence of albuminuria and glomerular hyperfiltration in those treated medically [23].

Despite a potential beneficial impact on diabetic kidney disease, some concern exists that bariatric surgery, particularly RYGB and BPD, may be associated with adverse renal consequences such as hyperoxaluria and consequent nephrolithiasis [24, 25]. A composite outcome of 'nephropathy' (defined as one or more of doubling of the serum creatinine level or reduction in eGFR >20%, acute increase in serum creatinine >290 micromol/L, need for renal replacement therapy, or development of macroalbuminuria (urine albumin: creatinine ratio 30 mg/mmol)) was not significantly different between the subgroups in STAMPEDE, developing in 22% of the RYGB arm, 18% of the VSG arm, and 14% of the IMT arm at 5-year follow-up [19]. Nephrolithiasis also did not significantly differ between the subgroups in STAMPEDE at 5-year follow-up (12%, 10%, and 14% in the RYGB, VSG, and IMT arms, respectively) [19]. In the Diabetes Surgery Study, 2% in each of the RYGB and IMT

arms developed nephrolithiasis by 24-month follow-up [26]. Similarly, 5%, 11%, and 0% in the RYGB, BPD, and IMT arms, respectively, of Mingrone et al.'s cohort developed nephrolithiasis at 5-year follow-up [20]. 'Nephropathy' (defined as proteinuria > 0.5g/24 hours) was also not significantly different between subgroups at 5-year follow-up in Mingrone et al.'s cohort (5%, 0%, and 7% in the RYGB, BPD, and IMT arms, respectively) [20].

RCTs of bariatric surgery in T2DM have demonstrated a dramatic reduction in the need for antihypertensive drug therapy to achieve comparable blood pressure control compared to those treated medically (Table 2). For example, in STAMPEDE, mean absolute changes in systolic and diastolic blood pressure at 5-year follow up were -3±23 mmHg and -6±13 mmHg in the RYGB + IMT arm, -8±20 and -8±15 in the VSG + IMT arm, and -4±20 and -4±11 in the IMT alone arm, with no significant between-group differences observed [19]. However, antihypertensive medication usage had decreased from 78% at baseline to 33% at 12 months in the RYGB + IMT arm (p<0.001), 67% to 27% in the VSG + IMT arm (p<0.001), and was similar at baseline (76%) and 12 months (77%) in the IMT arm [17].

Major adverse cardiovascular event rates in RCTs of bariatric surgery in T2DM have been low, likely reflecting the relatively young age, short duration of diabetes, and low prevalence of established microvascular disease amongst recruited individuals. No significant differences in the occurrence of such events between surgically and medically treated patients has been demonstrated to date. Two fatal acute coronary syndromes have occurred during 5-year follow-up (both in the medically treated arms): 1 each in STAMPEDE and Mingrone et al.'s cohort [19, 20]. A single participant in the medical arm of the Diabetes Surgery Study developed heart failure by 24-month follow-up [26], while 1 individual in the VSG + IMT arm of STAMPEDE developed a non-fatal stroke by 5-year follow-up [19].

3.2 Observational Studies

RCTs of bariatric surgery in T2DM have recruited relatively small numbers of subjects (maximum n=150 [17]) with maximum 5-year follow-up reported to date [19, 20]. In contrast, there have been several large, retrospective and prospective observational studies evaluating bariatric surgeries in T2DM which provide important insights into their impact on cardiovascular and renal disease outcomes. Principle studies of interest include the Swedish Obese Subjects (SOS) cohort, the Longitudinal Assessment of Bariatric Surgery (LABS) study, and Adams' et al.'s 'Utah' cohort.

The SOS cohort is a prospective, matched, controlled, non-randomised intervention study comparing bariatric surgery to usual care in a cohort of 4,047 obese adults enrolled between 1987 and 2001 [27]. 2,037 individuals received usual care while 2,010 received bariatric surgery (376 (18%) underwent adjustable or nonadjustable gastric banding (GB), 1,369 (68%) underwent vertical banded gastroplasty (VBG), and 265 (13%) underwent gastric bypass). Over mean follow-up of 11±4 years, mortality was lower in subjects who underwent bariatric surgery (hazard ratio of 0.71 (p=0.01 after adjustment for age, sex, and baseline risk factors)) [28]. Eliasson et al. assessed mortality risk after RYGB in obese adults with diabetes by comparing 6,132 cases who underwent RYGB (identified from the SOS registry and other Swedish databases) with 6,132 matched controls identified from the

Swedish diabetes registry who did not undergo bariatric surgery [29]. Over median follow-up of 4 years, significant reductions in overall mortality (hazard ratio 0.42, p<0.0001), myocardial infarction (hazard ratio 0.51, p=0.021), and cardiovascular death (hazard ratio 0.41, p=0.026) were observed in the RYGB group [29]. Data on impact of bariatric surgery on prespecified secondary cardiovascular and renal outcomes from the SOS cohort have also been published.

Gastric bypass was associated with significant reductions in blood pressure and antihypertensive medication usage in the SOS cohort at 10-year follow-up, while vertical banded gastroplasty and gastric banding were not [30]. Reductions in systolic blood pressure of -5 mmHg and diastolic blood pressure of -6 mmHg were observed in the gastric bypass group at 10 years compared with baseline [30]. Furthermore, 35% of patients in the gastric bypass group were taking antihypertensives at 10 years, compared with 45% in the VBG/GB group (p<0.01) and 53% in the medically managed group (p<0.001) [30]. Bariatric surgery also reduced the number of fatal cardiovascular deaths (adjusted hazard ratio of 0.47, p=0.002) and total cardiovascular events (adjusted hazard ratio of 0.67, p<0.001) after median follow-up of 15 years in the SOS cohort [31]. Baseline BMI did not predict reduction in cardiovascular events after bariatric surgery (p=0.58). However, higher baseline plasma insulin values predicted lower incidence of CVD after bariatric surgery: subjects with a baseline plasma insulin value above compared with at or below the median had NNTs of 21 and 173, respectively, to prevent incident cardiovascular disease after bariatric surgery [31]. After median 10 years of follow-up of 3,108 SOS participants without albuminuria at baseline, 246 patients in the control group and 126 patients in the bariatric surgery group, respectively, had developed albuminuria (adjusted hazard ratio of 0.37, p<0.001) [32]. All 3 types of bariatric surgery employed in the SOS cohort were associated with a reduced incidence of albuminuria during follow-up compared with usual care [32]. No differences between the bariatric surgical groups in terms of albuminuria reduction were noted, although low event rates in the cohort limited statistical power [32]. In addition to reduction in the incidence of albuminuria, bariatric surgery has also been demonstrated to reduce the incidence of all diabetic microvascular and macrovascular complications in those with T2DM at baseline (n=603) [33]. Over a median follow-up period of 18 (IQR 14-20) years and 18 (IQR 15-21) years for the usual care and surgery groups, respectively, bariatric surgery reduced the incidence of microvascular (adjusted hazard ratio of 0.43, p<0.001) and macrovascular (adjusted hazard ratio of 0.74, p=0.01) complications of diabetes. Thus, reductions in albuminuria and other microvascular complications of diabetes appear to be greater than 50% at almost 20 years of prospective follow-up after bariatric surgery.

The LABS-2 cohort is a prospective observational study coordinated across 11 hospitals in 6 centres in the USA that recruited 2,458 individuals to their first bariatric surgical procedure during 2006 to 2009 [34]. There is no control group. 1,738 (71%) individuals underwent RYGB, 610 (25%) underwent LAGB, and 110 (5%) had other bariatric surgical procedures including sleeve gastrectomy, banded gastric bypass, and biliopancreatic diversion with duodenal switch performed. 1,931 (79%) participants were female; 773 (33%) and 199 (9%) had diabetes and abnormal kidney function at baseline, respectively [34]. 7-year follow-up outcomes for those that underwent RYGB and LAGB have been reported. RYGB resulted in sustained reductions in the prevalence of diabetes, high LDL-C, high triglycerides, low

HDL-C, and hypertension at 7 years (p<0.001 for all), while LAGB reduced the prevalence of high triglycerides and low HDL-C at 7 years (p<0.01 for both) but not the prevalence of diabetes or hypertension [35].

Kidney disease was a prespecified outcome of the LABS-2 study. Serial serum creatinine and cystatin C along with urine ACR values were collected. Renal functional trends 7 years post-bariatric surgery in LABS-2 have been published [36]. 2,144 individuals in the LABS-2 cohort had baseline data available for CKD risk stratification; 1,696 (80%) were female and 691 (32%) had diabetes. 824 individuals had data available for CKD risk stratification at year 7 [36]. Risk of chronic kidney disease (CKD) was assigned using KDIGO criteria at baseline, annually for 5 years, and in a subset of patients for 7 years. Four KDIGO CKD risk categories are recognised based on eGFR and urine ACR values [37]:

1. Low risk: eGFR   60 mL/min/BSA and urine ACR <3 mg/mmol;

2. Moderate risk: eGFR 45-59 mL/min/BSA and urine ACR <3 mg/mmol or eGFR   60 mL/min/BSA and urine ACR 3-30 mg/mmol;

3. High risk: eGFR 30-44 mL/min/BSA and urine ACR <3 mg/mmol, eGFR 45-59 mL/min/BSA and urine ACR 3-30 mg/mmol, or eGFR   60 mL/min/BSA and urine ACR   30 mg/mmol;

4. Very high risk: eGFR <30 mL/min/BSA and urine ACR <3 mg/mmol, eGFR <45 mL/min/BSA and urine ACR 3-30 mg/mmol, or eGFR <60 mL/min/BSA and urine ACR   30 mg/mmol.

1,788 (83%), 254 (12%), 73 (3%), and 29 (1%) individuals were at low, moderate, high, and very high CKD risk, respectively [36]. CKD risk worsened in those with low baseline CKD risk in a relatively small proportion (4-9%) of patients between baseline and years 1-7. In the moderate baseline CKD risk group, 53% improved and 5-8% worsened their CKD risk category by year 7. In the high baseline CKD risk group, 56% improved and 3-10% worsened their CKD risk category by year 7. 23% of the very high baseline CKD risk group improved their CKD risk by year 7. Five patients developed end-stage renal disease during 7-year follow-up. Overall, CKD risk categories improved for a substantial proportion of patients over 7 years after bariatric surgery, particularly in those with baseline moderate and high CKD risk [36].

Adams et al. examined mortality after RYGB amongst 9,949 individuals who had surgery at a single centre in Utah, USA between 1984-2002 [38]. The surgical group were compared with 9,628 randomly selected individuals with a BMI   35 kg/m^2 who did not undergo bariatric surgery. 86% of individuals in the RYGB arm were female and mean BMI was 45±8 kg/m^2. Over mean follow-up of 7 years, overall mortality (HR 0.63, p<0.001), death from cardiovascular disease (HR 0.50, p<0.001), and death from diabetes (HR 0.10, p=0.003) were lower in the RYGB group [38]. Reduction in death from cardiovascular disease was primarily driven by a reduction in coronary artery disease-related deaths (HR 0.36, p<0.001), and not mortality from heart failure or stroke [38]. Rate of diabetes-related deaths was low (n=26 for the whole cohort) [38]. Information on renal outcomes was not provided.

4 Improved Cardiovascular and Renal Disease Outcomes after Bariatric Surgery: Putative Mechanisms

Bariatric surgery is effective at achieving sustained weight loss, with approximate sustained reductions in weight of 25% reported after RYGB [28, 39], the most commonly performed bariatric surgical procedure worldwide. A phenotype of severe insulin resistance characterises T2DM patients with progressive diabetic kidney disease and other advanced microvascular complications [40, 41]. The reduction in adipose tissue mass and systemic inflammation that accompanies bariatric surgery improves peripheral insulin resistance, to the point where pre-morbid diabetes may undergo partial or complete remission postoperatively [42]. Blood pressure and dyslipidaemia are also more effectively controlled and with fewer medications after bariatric surgery compared with medically treated patients. Thus, common risk factors for both cardiovascular disease and chronic kidney disease improve after bariatric surgery. Additionally, independent of the degree of postoperative weight loss achieved, bariatric surgery can modulate multiple signalling pathways to further ameliorate the dysmetabolic milieu of obesity and to directly exert renoprotective and cardioprotective benefits [43].

4.1 Alterations in adipocytokine signalling

Obesity-associated hypertension is characterised by a relatively higher degree of sympathetic nervous system activation than hypertension in lean individuals [44]. Leptin is an adipocyte-derived hormone which acts on the hypothalamus to decrease food intake and increase energy expenditure. Numerous studies have demonstrated reductions in plasma leptin after bariatric surgery which is proportional to the degree of weight loss achieved [45], a finding which is congruent with the concept that leptin is secreted in proportion to adipose tissue mass. Postoperative reductions in leptin secretion minimise tachycardia and hypertension caused by sympathetic nervous system activation, and at least partially account for reductions in blood pressure after bariatric surgery.

Obesity-associated hypoadiponectinaemia impairs insulin signalling and secretion to increase risk for T2DM [46]. Adiponectin levels were measured in a subgroup of 1,570 participants in the SOS study, and increased by 1,807-1,958 ng/mL per 10 kg weight loss at 2-year follow-up [47]. At 12- and 24-month follow-up of participants in the VSG and RYGB arms of STAMPEDE, plasma adiponectin levels were significantly higher in those who achieved remission of T2DM compared with those who did not [48]. Plasma adiponectin levels are negatively correlated with albuminuria in obese individuals [49]. Murine models have demonstrated that adiponectin deficiency impairs podocyte function to result in albuminuria and accelerated renal functional decline [50, 51], while administration of adiponectin to cultured podocytes upregulates AMPK activity and downregulates NADPH oxidase activity to minimise podocyte oxidative stress and albuminuria [50]. Thus, restoration of adiponectin release from adipose tissue after bariatric surgery may confer metabolic benefits as well as direct renoprotective effects through enhanced podocyte differentiation.

4.2 Remission of glomerular hypertension

Glomerular haemodynamics are altered in patients with obesity and diabetes due to activation of the renin-angiotensin-aldosterone system (RAAS) [52]. Angiotensin II-mediated efferent arteriolar vasoconstriction via AT_1 receptors coupled with afferent arteriolar vasodilatation due to reduced tubuloglomerular feedback elevates intra-glomerular blood pressures in patients with diabetic kidney disease [53]. High intra-abdominal pressures in obese individuals increase renal venous pressure, which exacerbates glomerular hypertension [54]. Glomerular capillary wall stress promotes reorganisation of the podocyte cytoskeleton to result in foot process effacement, which in turn compromises the glomerular filtration barrier and serves as a nidus for the development of albuminuria [55].

Although kinetics and mediators of early reductions in albuminuria post-bariatric surgery remain to be fully elucidated, improved glycaemia and blood pressure l post-RYGB closely tracks reductions in glomerular hyperfiltration-mediated podocyte injury and albuminuria [56]. Elevated urinary albumin excretion independently and continuously predicts a higher risk of cardiovascular disease, even at levels below the threshold for diagnosis of microalbuminuria [57, 58]. Hyperglycaemia-induced alterations in the extracellular matrix increase microvascular permeability, resulting in albuminuria at the level of the glomerulus and increased lipoprotein deposition in peripheral vessels [59]. Albuminuria likely reflects systemic endothelial dysfunction rather than directly contributing to elevated risk of cardiovascular disease [60]. Nevertheless, reductions in albuminuria post-bariatric surgery independently confer a lower risk of fatal cardiovascular disease.

4.3 Natriuresis

In the SOS cohort, 24-hour urine output and sodium excretion were 0.17L and 20mmol higher, respectively, in those who underwent gastric bypass compared with vertical banded gastroplasty or gastric banding at 10-year follow-up [30]. Higher urine volume and sodium excretion independently predicted lower blood pressure in the gastric bypass group. In a prospective, observational study of 5 normotensive female patients undergoing RYGB, median urinary sodium increased by 2.3-fold from 0.9 mEq/kg/24 hours preoperatively to 1.9 mEq/kg/24 hours at 20 months postoperatively [61]. Thus, increased urinary sodium excretion appears to be an important determinant of postoperative blood pressure reductions after RYGB, but not restrictive bariatric surgical procedures.

Natriuresis post-RYGB may be explained by physiological responses of the RAAS and cardiac natriuretic peptide systems, the two principal determinants of renal sodium handling, to postoperative weight loss [62]. For example, reduced RAAS activity may be explained by reduced renin release in response to lower intra-abdominal pressure [63] decreased leptin concentrations and a reduction in sympathetic tone [64], as well as lower angiotensinogen levels occurring as a consequence of less adipose tissue mass [65]. Furthermore, weight loss may promote increased natriuretic peptide release [66] and reduced circulating neprilysin [67], the major peptidase involved in the degradation of natriuretic peptides.

The enhancement of gut-kidney signalling involving glucagon-like peptide-1 (GLP-1) after RYGB or VSG to augment natriuresis is also plausible [68]. The secretion of GLP-1, a 30-

amino acid peptide, from enteroendocrine L-cells in response to nutrient intake is enhanced post-RYGB [69, 70]. GLP-1 enhances glucose-dependent insulin secretion from pancreatic beta-cells and lowers glucagon secretion [71], and is thus centrally implicated in observed improvements in glycaemia post-RYGB. In addition to its anti-diabetic effect post-RYGB, GLP-1 may also lower cardiovascular morbidity through its antihypertensive natriuretic effect. In rodent models, oral sodium loading induces a significant increase in plasma GLP-1 levels within 5 minutes, and infusion of the GLP-1 mimetic Exenatide increases urinary fractional sodium excretion [72]. GLP-1 infusion over 3 hours in healthy and obese men increased urinary sodium excretion by reducing proximal renal tubular sodium reabsorption, an effect that reduced glomerular hyperfiltration [73].

4.4   Gut microbiota shifts

Alterations in the gut microbiome have been noted post-bariatric surgery and are implicated in improved energy homeostasis, incretin release, and weight loss [74]. Furet et al. demonstrated that faecal samples are selectively enriched for Proteobacteria, specifically in the *Escherichia* genus, at 6 months post-RYGB [75]. Colonic short-chain fatty acids, generated through bacterial fermentation of dietary fibre, triggered an incretin response by stimulation of the FFAR2 receptor for short-chain fatty acids on intestinal L-cells in mice [76]. In humans, daily direct colonic delivery of 10 grams of the short-chain fatty acid propionate enhanced GLP-1 and PYY secretion from colonic cells, which was associated with improvements in weight, intra-abdominal adiposity, insulin sensitivity, and intrahepatic steatosis [77]. Thus, gut microbiota shifts post-RYGB may result in improved glycaemia and blood pressure control through enhanced GLP-1 secretion from colonic L-cells. Similar metabolic benefits may be achieved in medically treated patients with T2DM by direct colonic delivery of short-chain fatty acids.

4.5   Reduced systemic and renal inflammation

Obesity is a state of chronic, low-grade inflammation. Endothelial dysfunction, oxidative stress, and inflammation promote the progression of atherosclerosis and diabetic kidney disease. Serum levels of high-sensitivity C-reactive protein and multiple pro-inflammatory cytokines such as IL-1, IL-6, IL-18, and TNF-alpha correlate with progression of both atherosclerotic cardiovascular disease and diabetic kidney disease [78, 79, 80]. There is substantial preclinical and clinical trial activity in the area of anti-inflammatory therapeutics for both atherosclerotic disease and diabetic kidney disease [81, 82, 83]. Bariatric surgery simultaneously targets multiple pathophysiological processes to ameliorate inflammation accompanying obesity, resulting in reductions in pro-inflammatory cytokines and enhanced secretion of anti-inflammatory cytokines [84]. Bariatric surgery reduces renal inflammation, a finding which correlates with improved renal function after bariatric surgery [85]. Comparable reductions in urinary MCP-1/creatinine ratios were observed after RYGB, VSG, and LAGB at 12 months. However, RYGB appeared to reduce urinary CCL-18/creatinine ratios more than VSG and LAGB [85].

4.6   Role of high-density lipoprotein cholesterol

Obesity induces endothelial dysfunction which is an early event in the progression of atherosclerosis, but also contributes to insulin resistance in peripheral tissues. Obesity,

insulin resistance, and endothelial dysfunction share a common defect in reduced nitric (NO) oxide bioavailability [86, 87]. Obesity is characterised by a triad of atherogenic dyslipidaemia, high LDL-C and triglyceride levels combined with low HDL-C levels [88], but also dysfunctional HDL-C which is less effective at preserving endothelial NO bioavailability and thus further exacerbating endothelial dysfunction [89].

In a rodent model of diet-induced obesity, RYGB was associated with higher plasma GLP-1 levels, improved nitric oxide bioavailability, and enhanced endothelium-dependent vasorelaxation compared with sham-operated rats [90]. Additionally, RYGB resulted in improved HDL-C functionality, characterised by increased endothelial NO synthase activation and HDL-C-mediated efflux of cholesterol from blood vessel walls. The protective effects of RYGB were prevented after administration of the GLP-1 receptor antagonist Exendin (9-39) and mimicked in control rats treated with Liraglutide, demonstrating the central role of GLP-1 in improved endothelial function after RYGB.

4.7 Cardiac repair

Obesity may result in maladaptive left ventricular modelling progressing to non-ischaemic dilated cardiomyopathy and the clinical syndrome of heart failure [91]. Weight loss after bariatric surgery may minimise and reverse obesity-associated left ventricular remodelling. In a recent systematic review of studies evaluating cardiac structure and function before and after bariatric surgery using echocardiography or cardiac MRI, bariatric surgery was associated with improvements in cardiac structure (decreased left ventricular mass index, decreased left ventricular end-diastolic volume, and left atrial diameter) as well as cardiac function (increased left ventricular ejection fraction and increased E/A ratio) [92]. Similar improvements in right ventricular structure and function have also been reported after bariatric surgery [93]. Improvements in cardiac imaging characteristics after bariatric surgery translate into clinically meaningful outcomes such as a reduction in the incidence of heart failure. Follow-up of 1,724 patients who underwent RYGB over a median of 5.8 years demonstrated an adjusted hazard ratio of 0.38 (95% CI, 0.22-0.64, p=0.0003) for the development of heart failure compared with medically managed controls [94].

5   Expert commentary

Over the past 10 years, several RCTs with modest numbers of participants have demonstrated the efficacy of bariatric surgery in treating the metabolic dysfunction which accompanies obesity and T2DM [15, 16, 17, 21, 95], the results of which which have been durable at up to 5 years of follow-up [19, 20]. Obese individuals with T2DM randomised to bariatric surgery have experienced greater weight loss and better glycaemic and blood pressure control using less hypoglycaemic and antihypertensive medications compared with their counterparts treated with best medical therapy. Observational studies demonstrate that bariatric surgery reduces the risk of cardiovascular disease, progressive chronic kidney disease, and mortality in the setting of obesity [28, 31, 36, 38].

The question remains which obese patients with T2DM stand to benefit most from bariatric surgery. RCTs of bariatric surgery in T2DM have mainly focused on glycaemic control and diabetes remission to date, rather than end-organ complications related to microvascular and

macrovascular complications of diabetes. The magnitude of metabolic improvement after bariatric surgery in CROSSROADS was lower compared with other RCTs, possibly reflecting a lower average glycated haemoglobin level at baseline in the surgical arm of this study [15]. Higher glycated haemoglobin levels for longer durations preoperatively predicts a higher risk of microvascular disease [96], and the greater metabolic improvements after bariatric surgery in STAMPEDE and Mingrone et al.'s RCT compared with CROSSROADS suggest that those with established microvascular disease may benefit the most from bariatric surgery [15, 19, 20].

Durable reductions in albuminuria at 5-year follow-up in STAMPEDE correlate with findings from the SOS cohort, where there were reductions in the incidence of microvascular complications of greater than 50% approaching 20 years post-operatively [19, 33]. The Diabetes Control and Complications Trial (DCCT) confirmed the glucose hypothesis, whereby intensive glycaemic control (median HbA_{1c} 7%) compared with conventional therapy (HbA_{1c} 9%) in patients with type 1 diabetes mellitus reduced the onset of microvascular disease by 35-76% at mean 6.5 years of follow-up [97]. Intensive glycaemic control plays an important role in the reducing the burden of microvascular disease in patients with T2DM also, although the microvascular benefit appears to be less pronounced and potential risks and benefits must be carefully considered [98]. Bariatric surgery dramatically improves glycaemic control in T2DM and holds promise in reducing the burden of microvascular disease more effectively and with a more favourable side-effect profile than intensive medical therapy. Thus, patients with diabetic kidney disease appear to be a subgroup of obese T2DM patients who may particularly benefit from bariatric surgery.

BMI has traditionally been a key measure in the selection of patients for bariatric surgery, with bariatric surgery being reserved for those with the highest BMIs. 34% of participants in STAMPEDE had a BMI <35 kg/m^2 [17], while BMI <35 kg/m^2 was an exclusion criterion for Mingrone et al.'s RCT [16]. However, BMI does not predict the presence of microvascular complications of diabetes nor does it predict improvements in metabolic parameters such as glycated haemoglobin after bariatric surgery. Traditional BMI cut-offs to bariatric surgery are being challenged as they may deny suboptimally controlled T2DM patients from an effective therapy. In response to this, the International Diabetes Federation has suggested that bariatric surgery be considered in T2DM with a BMI <35 kg/m^2 who are not meeting targets on medical therapy alone [99], although this has failed to significantly impact clinical practice. This has also been endorsed by the second Diabetes Surgery Summit in 2016 [14].

6 Five-year view

Two RCTs are underway to assess the potential renal benefits of bariatric surgery in obese T2DM patients with lower BMIs and established microvascular disease: Prevention and Treatment of Diabetes Complications with Gastric Surgery or Intensive Medicines (PRODIGIES) and Metabolic Outcomes after Microvascular Surgery (MOMS). PRODIGIES (NCT01974544) involves 3 study arms (RYGB + IMT vs VSG + IMT vs IMT alone), has selectively recruited individuals with class 1 obesity (BMI <35 kg/m^2) and established or at high-risk for microalbuminuria, and will follow patients to 36 months

postoperatively [100]. MOMS (NCT01821508) incorporates 2 study arms (RYGB + IMT vs IMT alone), has also selectively recruited individuals with class 1 obesity (BMI <35 kg/m^2), and will follow patients to 60 months postoperatively [101]. The final 60-month follow-up visit is scheduled for April 2021 in the MOMS study [101]. The RYGB + IMT group in MOMS achieved greater complete remission of albuminuria compared with IMT alone at 12 months post-operatively (unpublished data). Individuals with chronic kidney disease stages 4 and 5 have been excluded from both PRODIGIES and MOMS.

Recent RCTs of bariatric surgery in obese patients with T2DM have cemented its role as an adjunctive therapy in those not meeting treatment targets despite optimal medical therapy. Higher level evidence regarding the impact of bariatric surgery on end-organ complications of diabetes, including cardiovascular and renal disease, is required. Ongoing RCTs of bariatric surgery which are selectively recruiting patients with class 1 obesity and established microvascular complications of diabetes will help to better characterise which subgroups of patients benefit most from this effective therapy. We hypothesise that the PRODIGIES and MOMS RCTs will demonstrate that bariatric surgery substantially improves glycaemic control, stabilises or improves estimated glomerular filtration rate, and reduces albuminuria. Accordingly, we anticipate that type 2 diabetic kidney disease will become an important indication for bariatric surgery in obese adults.

7 Key issues

- Cardiovascular and renal diseases account for a substantial proportion of the morbidity and mortality associated with obesity and type 2 diabetes mellitus (T2DM).

- Obese individuals with T2DM randomised to bariatric surgery have experienced greater weight loss and better glycaemic, blood pressure, and lipid control at up to 5-year follow-up compared with their counterparts treated with best medical therapy. These RCTs include STAMPEDE, the Diabetes Surgery Study, CROSSROADS, and Mingrone et al., and have collectively enrolled a relatively low proportion of individuals with established microvascular complications of T2DM.

- Prospective observational studies with extended follow-up (primarily the Swedish Obese Subjects [SOS] cohort and Longitudinal Assessment of Bariatric Surgery [LABS] cohort) in patients who are not exclusively diabetic have demonstrated that bariatric surgery reduces the risk of cardiovascular disease, albuminuria and progressive chronic kidney disease, and mortality in the setting of obesity.

- Multiple factors confer cardiovascular and renal protection after bariatric surgery, including reduced sympathetic drive, remission of glomerular hypertension, enhanced natriuresis, gut microbiota shifts, reduced systemic and renal inflammation, enhanced high-density lipoprotein functionality, and reductions in adverse cardiac remodelling.

- Higher level evidence regarding the impact of bariatric surgery on end-organ complications of diabetes, including cardiovascular and renal disease, is required. Ongoing RCTs of bariatric surgery which are selectively recruiting patients with class 1 obesity and established microvascular complications of diabetes will help to better characterise which subgroups of patients benefit most from this effective therapy. We anticipate that type 2 diabetic kidney disease will become an important indication for bariatric surgery in obese adults.

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** Of considerable interest

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Table 1

Baseline characteristics, metabolic parameters, and renal outcomes of bariatric surgery RCTs in obese patients with T2DM.

Study	Study arms	Follow-up (months)	n	Age	Gender (% male)	T2DM duration (years)	Body weight (kg)	BMI	HbA1c (%)	Albuminuria [a] (n(%))	SCr	eGFR
Schauer et al. (STAMPEDE) [24, 26, 110]												
	RYGB + IMT	0	50	48.3±8.4	42%	8.2±5.5	106.7±14.8	37.0±3.3	9.3±1.4	17 (34.0)	0.69 [0.59, 0.81]	107.6 [98.3, 117.9]
		12	50	-	-	-	77.3±13.0	26.8 ± 3.2	6.4±0.9	-	-	-
		36	48	-	-	-	80.6±15.5	27.9	6.7±1.3	-	-	-
		60	49	-	-	-	83.4±15.3	28.9	7.3±1.5	9 (19.2)	-	-
	VSG + IMT	0	50	47.9±8.0	22%	8.5±4.8	100.8±16.4	36.2±3.9	9.5±1.7	12 (24.0)	0.68 [0.57, 0.82]	108.7 [96.5, 118.7]
		12	49	-	-	-	75.5±12.9	27.2±3.5	6.6±1.0	-	-	-
		36	49	-	-	-	79.3±15.1	29.2	7.0±1.3	-	-	-
		60	47	-	-	-	81.9±15.0	29.3	7.4±1.6	5 (11.1)	-	-
	IMT	0	50	49.7±7.4	38%	8.9±5.8	106.5±14.7	36.8±3.0	8.9±1.4	10 (20.0)	0.70 [0.60, 0.80]	105.2 [96.7, 111.7]
		12	41	-	-	-	99.0±16.4	34.4±3.7	7.5±1.8	-	-	-
		36	40	-	-	-	100.2±16.6 -	34.8	8.4±2.2	-	-	-
		60	38	-	-	-	99.0±17.0	34.0	8.5±2.2	8 (21.6)	-	-
Ikramuddin et al. (DSS)[28, 33]												
	RYGB + IMT	0	60	49±9	37	8.9±6.1	98.8±14.0	34.9±3.0	9.6±1.0	-	0.81±0.20	-
		12	57	-	-	-	73.0±13.6	25.8±3.5	6.3±0.9	-	-	-
		24	56	-	-	-	-	26.5±5.4	6.5±1.6	-	-	-
	IMT	0	60	49±8	43	9.1±5.6	97.9±17.0	34.3±3.1	9.6±1.2	-	0.79±0.19	-
		12	56	-	-	-	90.1±17.0	31.6±3.7	7.8±1.5	-	-	-
		24	54	-	-	-	-	31.8±6.7	8.4±2.9	-	-	-
Mingrone et al. [23, 27]												
	RYGB + IMT	0	20	43.90±7.57	40	6.03±1.18	129.84±22.58	44.85±5.16	8.56±1.40	3 (16)	-	-
		24	19	-	-	-	84.29±13.35	29.31±2.64	6.35±1.42	-	-	-
		60	19	-	-	-	90.3±12.7	31.3±2.5	6·7±0·5	0 (0)	-	-
	BPD + IMT	0	20	42.75±8.06	50	6.00±1.26	137.85±30.35	45.14±7.78	8.88±1.71	2 (11)	-	-
		24	19	-	-	-	89.53±17.84	29.19±4.90	4.95±0.49	-	-	-
		60	19	-	-	-	92.8±14.0	30.3±4.0	6.4±0.4	0 (0)	-	-
	IMT	0	20	43.45±7.27	50	6.08±1.24	136.40±21.94	45.62±6.24	8.51±1.24	4 (27)	-	-
		24	18	-	-	-	128.06±19.77	43.07±6.44	7.69±0.57	-	-	-
		60	15	-	-	-	127.1±20.5	42.1±5.8	6.9±0.6	4 (27)	-	-

Study	Study arms	Follow-up (months)	n	Age	Gender (% male)	T2DM duration (years)	Body weight (kg)	BMI	HbA1$_c$ (%)	Albuminuria[a] (n(%))	SCr	eGFR
Cummings et al. (CROSSROADS) [104]												
	RYGB + IMT	0	15	52.0±8.3	20	11.4±4.8	108.8±14.9	38.3±3.7	7.7±1.0	-	-	-
		12	15	-	-	-	-	-	6.4±1.6	-	-	-
	ILMI	0	17	54.6±6.3	41.2	6.8±5.2	112.8±16.5	37.1±3.5	7.3±0.9	-	-	-
		12	17	-	-	-	-	-	6.9±1.3	-	-	-
Dixon et al.[105]												
	LAGB + IMT	0	30	46.6±7.4	50	-	105.6±13.8	37.0±2.7	7.8±1.2	-	-	-
		24	29	-	-	-	84.6±15.8	-	6.00±0.82	-	-	-
	IMT	0	30	47.1±8.7	43	-	105.9±14.2	37.2±2.5	7.6±1.4	-	-	-
		24	26	-	-	-	104.8±15.3	-	7.21±1.39	-	-	-

[a]Albuminuria = urine albumin/creatinine ratio   3mg albumin per mmol of creatinine

Mean±SD are presented for normally distributed continuous variables' median [25th, 75th percentile] are provided for skewed continuous variables

BMI = body mass index; BPD = biliopancreatic diversion; DSS = Diabetes Surgery Study; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HbA1$_c$ = glycated haemoglobin; ILMI = intensive lifestyle and medical intervention; IMT = intensive medical therapy; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; SCr = serum creatinine; T2DM = type 2 diabetes mellitus; VSG = vertical sleeve gastrectomy.

Table 2

Cardiovascular outcomes of bariatric surgery RCTs in obese patients with T2DM.

Study	Study arms	Follow-up (months)	n	Acute coronary syndrome (n(%))	TIA/ stroke (n(%))	Heart failure (n(%))	Cardiovascular death (n(%))	Antihypertensive therapy (n(%))	SBP (mmHg)	DBP (mmHg)
Schauer et al. (STAMPEDE) [24, 26, 110]										
	RYGB + IMT	0	50	-	-	-	-	39 (78)	134.6 ± 18.7	81.8 ± 10.2
		12	50	0	0	0	0	16 (33)	132.3 ± 15.5	78.3 ± 10.0
		36	48	0	0	0	0	-	136.3 ± 22.32	77.60 ± 10.42
		60	49	0	0	0	0	-	131.4±18.77	75.98±11.57
	VSG + IMT	0	50	-	-	-	-	33 (67)	135.8 ± 18.8	82.2 ±11.6
		12	49	0	0	0	0	13 (27)	130.8 ± 14.3	78.6 ± 8.9
		36	49	0	0	0	0	-	131.4 ± 17.21	75.92 ± 12.57
		60	47	0	1 (2)	0	0	-	128.3±11.60	74.11±11.49
	IMT	0	50	-	-	-	-	31 (76)	135.5 ± 17.0	82.6 ± 11.0
		12	41	0	0	0	0	30 (77)	131.4 ± 14.0	78.2 ± 10.6
		36	40	0	0	0	0	-	136.0 ± 16.80	75.60 ± 10.43
		60	38	1 (2)	0	0	1 (2)	-	131.5±14.55	77.62±9.83
Ikramuddin et al. (DSS)[28, 33]										
	RYGB + IMT	0	60	-	-	-	-	41 (68)	127±15	78±12
		12	57	0	0	0	0	23 (38)	115±14	68±9
		24	56	0	0	0	0	25 (42)	120±23	70±15
	IMT	0	60	-	-	-	-	43 (73)	132±14	79±10
		12	56	0	0	0	0	42 (71)	124±12	74±9
		24	54	0	0	1 (2)	0	37 (63)	125±22	75±14
Mingrone et al. [23, 27]										
	RYGB + IMT	0	20	-	-	-	-	-	145.75±20.54	91.50±14.15
		24	19	0	0	0	0	-	132.11±10.45	84.21±4.79
		60	19	0	0	0	0	-	132.5±6.2	84.2±3.5
	BPD + IMT	0	20	-	-	-	-	-	154.50±29.73	95.90±12.87
		24	19	0	0	0	0	-	129.21±8.04	82.37±4.21
		60	19	0	0	0	0	-	129.2±5.8	83.5±3.0
	IMT	0	20	-	-	-	-	-	155.20±34.18	96.00±17.52
		24	18	0	0	0	0	-	134.44±10.97	87.28±9.32

Study	Study arms	Follow-up (months)	n	Acute coronary syndrome (n(%))	TIA/ stroke (n(%))	Heart failure (n(%))	Cardiovascular death (n(%))	Antihypertensive therapy (n(%))	SBP (mmHg)	DBP (mmHg)
		60	15	1 (7)	0	0	1 (7)	-	132.3±4.2	84.0±2.8
Cummings et al. (CROSSROADS) [104]										
	RYGB + IMT	0	15	-	-	-	-	-	129.3±20.6	77.0±10.2
		12	15	0	0	0	0	-	110±10	-
	ILMI	0	17	-	-	-	-	-	120.1±9.6	74.8±7.5
		12	17	0	0	0	0	-	116±10	-
Dixon et al.[105]										
	LAGB + IMT	0	30	-	-	-	-	20 (69)	136.4±15.6	86.6±9.4
		24	29	0	0	0	0	6 (21)	130.4±19.0	85.4±7.0
	IMT	0	30	-	-	-	-	15 (58)	135.3±14.4	84.5±9.8
		24	26	1 (4)	1 (4)	0	0	15 (58)	132.6±17.7	83.1±8.5

BMI = body mass index; BPD = biliopancreatic diversion; DSS = Diabetes Surgery Study; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HbA1$_c$ = glycated haemoglobin; ILMI = intensive lifestyle and medical intervention; IMT = intensive medical therapy; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; SCr = serum creatinine; T2DM = type 2 diabetes mellitus; VSG = vertical sleeve gastrectomy.