



Gastric Bypass and Sleeve Gastrectomy for Type 2 Diabetes: A Systematic Review and Meta-analysis of Outcomes

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Published online: 17 August 2013
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Abstract Bariatric surgery is effective in the management of type 2 diabetes (T2D) and obesity; however, it is not clear whether Roux-en-Y gastric bypass (GBP) or sleeve gastrectomy (SG) is the most effective procedure. This review compared T2D remission and weight loss in patients with T2D after GBP or SG. All human SG or GBP studies published in English between 1 Jan 2007 and 30 April 2012 reporting on BMI and T2D outcomes were included. Analyses were performed separately for the most frequent distinct time points reported after surgery. A total of 21 prospective (three randomised control trials) and 12 retrospective studies, involving 1375 patients met eligibility criteria. T2D remission defined by hemoglobin A_{1c} of <6.5 % for GBP and SG respectively was 67 and 56 % at 3 months, 76 and 68 % at 12 months, and 81 and 80 % at 36 months. Greater percent excess BMI loss occurred at 12 months (72.5 % after GBP and 66.7 % after SG) compared with 3 months (45.9 % after GBP and 25.9 % after SG). There was no significant difference in either T2D remission or weight loss with GBP compared with SG. Both GBP and SG result in similar early remission

of T2D in 67 and 56 % of patients at 3 months respectively with modest additional T2D remission with time, although weight loss with both procedures increase substantially between 3 and 12 months post-operatively. Further randomised controlled trials comparing SG and GBP in patients with T2D using comparable definitions of diabetes remission with long-term follow-up are needed to evaluate relative benefits.

Keywords Type 2 diabetes · Gastric bypass · Sleeve gastrectomy · Bariatric surgery · Obesity

Introduction

Obesity and type 2 diabetes (T2D) are two increasingly prevalent conditions associated with significant morbidity and mortality. Bariatric surgery is effective in achieving T2D remission and weight loss. T2D remission has been observed to occur soon after bariatric surgery such as Roux-en-Y gastric bypass (GBP) and sleeve gastrectomy (SG) before significant weight loss [1, 2]. It is well known that even a small degree of weight loss can significantly improve insulin resistance and therefore glucose homeostasis, however, other mechanisms underlying the favourable effect of these particular types of bariatric surgery remain unknown.

GBP is the most commonly performed bariatric procedure, where a small stomach pouch is created and anastomosed to the jejunum through a Roux-en-Y alimentary limb [3]. It has been reported to achieve T2D resolution in over 80 % of patients by 2 years [4]. Diabetes resolution in this meta-analysis (which did not include SG) was defined as being off-diabetes medications with normal fasting blood glucose (<5.6 mmol/L) or hemoglobin A_{1c} (HbA_{1c}) of <6 %. Over the past 5 years, SG procedure has become increasingly popular

Electronic supplementary material The online version of this article (doi:10.1007/s11695-013-1030-z) contains supplementary material, which is available to authorized users.

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for achieving weight loss and T2D remission [5]. This is performed by creating a gastric sleeve tube with resection from beyond the incisura on the stomach up to the angle of His [6]. Less-performed procedures are bilio-pancreatic diversion due to side effects but with superior effects on T2D remission [4, 7] and gastric banding that have been shown to be the least effective in T2D remission and sustained weight loss [4]. Currently, there is no consensus as to whether GBP or SG is superior for patients with T2D, in regard to T2D remission and weight loss.

The objective of this review was to determine whether GBP is superior to SG in achieving T2D remission defined by uniform criteria (primary outcome measure) and weight loss as assessed by percent excess weight loss (%EWL) and percent excess BMI loss (%EBMIL; secondary outcome measures).

Methods

Search Strategy and Selection of Articles

A literature search was performed using PubMed and Embase databases to identify all clinical studies that reported on T2D remission and weight loss following GBP or SG listed online between 1 Jan 2007 and 30 April 2012. We constructed search terms as follows: obesity/surgery (MeSH) or key terms: gastric bypass or Roux-en-Y or GBP; or gastric sleeve resection or vertical gastrectomy or SG or greater curvature gastrectomy or gastric reduction; vertical gastroplasty; bariatric. Reference sections of relevant articles were examined.

The following inclusion criteria were used to identify eligible studies: adult patients (aged >18 years) with T2D undergoing either GBP or SG and outcome variables of T2D remission according to specific HbA_{1c} criteria.

Case reports, conference abstracts, review articles, and those concerning revisional surgery were excluded. Studies with greater than 50 % were loss to follow-up, or those not specifying a threshold HbA_{1c} value for defining T2D remission (in addition to cessation of diabetes medications) were also excluded. Studies with the same or overlapping cohort of patients were identified as ‘kinned’, and the largest dataset was chosen from those studies and counted only once.

Assessment of Methodological Quality

Quality assessment used in this study was adapted from Taylor et al. [8], based on the four principal categories: selection bias, attrition bias, detection bias,

and performance bias. Studies were scored from 0 to 6 as follows:

Category		Point
Selection bias	Consecutive or representative sample (for non-randomised studies) or by concealed allocation (randomised studies)	One
Performance bias	Groups treated equally without co-intervention	One
Detection bias	Randomised/prospective or before/after study	One
	Blinded or independent assessment	One
	Validated/objective outcomes	One
Attrition bias	Follow-up at >80 %	One

Data Extraction

The following data were extracted by author (SY): publication year, country, sample size, mean age, gender composition, baseline HbA_{1c}, and duration of T2D history; BMI, prevalence of T2D, %EBMIL, and %EWL at baseline and follow-up. All discrepancies were resolved by consensus. We did not contact authors for unreported data.

Definitions

T2D remission was defined as cessation of glucose lowering medications and grouped according to specific HbA_{1c} thresholds. If not reported, calculations of %EBMIL and %EWL were made based on reported BMI and weight loss with ideal BMI of 22 kg/m² for Asian and Indian populations and 25 kg/m² for Caucasian populations. Both T2D remission and weight loss data were analysed in groups with the same follow-up time points that were most commonly reported across the majority of studies.

Statistical Analysis

Comprehensive meta-analysis v.2 (Biostat, Englewood, NJ) was used for calculation of effect sizes, tests of heterogeneity, meta-analysis, and forest plots using random-effects models. The *I*² index was used to assess proportion of effect size variability because of non-chance factors. All studies were assessed by funnel plots and tested for asymmetry that may reflect selective publication bias or poor methodological quality. Using ‘trim and fill’, pooled effect estimates were recalculated for each analysis. If required, standard deviations (SD) were estimated based on Hozo et al. [9] Data are reported as mean±SD, unless stated otherwise. A *p* value of <0.05 was considered statistically significant.

Results

Study Characteristics

Initial search identified 2,655 studies, and data from 33 studies were analysed (Fig. 1 Prisma chart).

Three randomised controlled trials (RCT), 30 non-randomised studies (18 prospective and 12 retrospective) were included (Supplementary Table 1). Five studies had both GBP and SG as treatment arms, two of which were RCTs comparing GBP and SG. The remaining studies reported outcome either on GBP or SG as single arm studies or comparative studies with other interventions. Included studies varied in the definition used for T2D remission (with HbA_{1c} of <6, 6.5 or 7 % and fasting glucose, <100 or 125 mg/dL) without glucose lowering therapy.

Quality of Studies

Majority of included studies were of high quality on our assessment tool (score 5 or 6) (Supplementary Table 1).

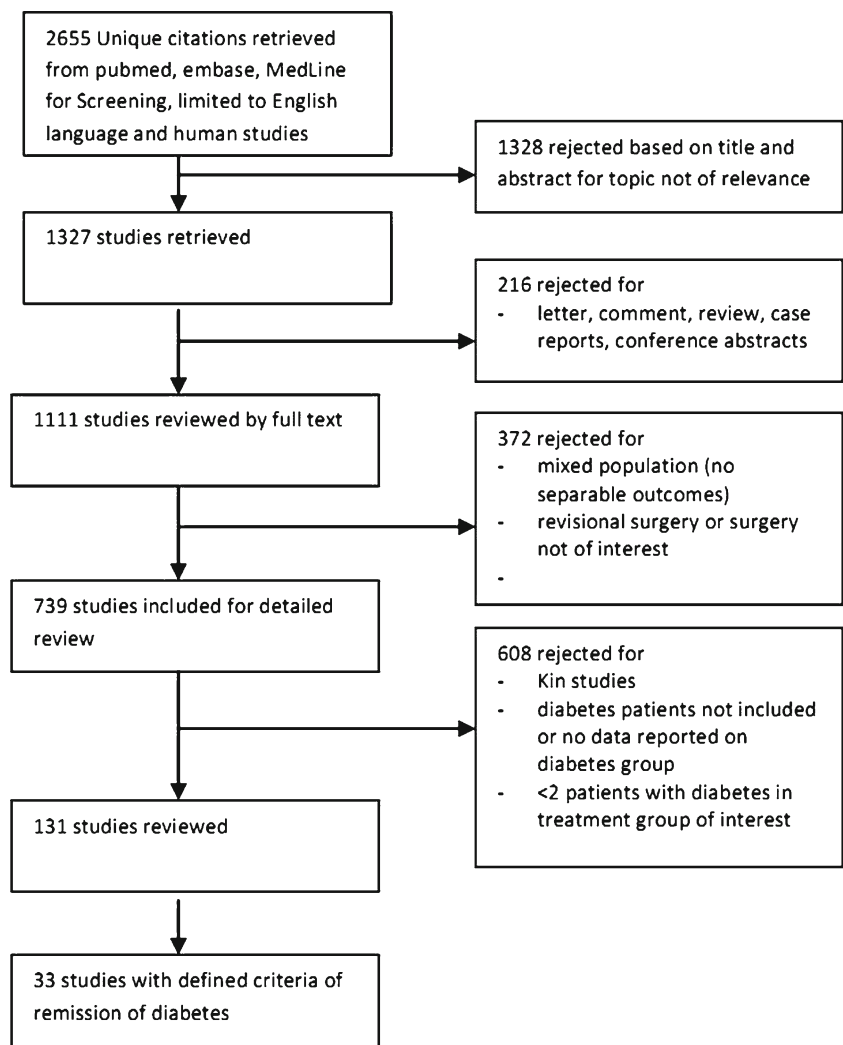
The longest follow-up reported was at 36 months, and most frequently reported were 3 and 12 months.

Sensitivity analysis was performed by subgroup analysis of studies according to quality scores. No significant differences were seen. Visual inspection of funnel plots revealed asymmetry in both analyses with five studies showing unbalanced effects for the analyses on GBP and two for studies on SG. By trim and fill methods [10, 11], the influence of these small studies on the pooled effect was insignificant when analysis was repeated by omitting these studies and filling in ‘missing studies’.

Patient Characteristics

Based on studies reporting baseline demographic data, the average duration of T2D was 6.9±4.5 (GBP group) and 7.4±2.8 years (SG group); the proportion of patients treated with insulin was 27.1±30.2 (GBP group) and 23.8±13.3 % (SG group); average baseline BMI was 44.0±5.6 (GBP

Fig. 1 Prisma chart of study selection process



group) and 43.3 ± 6.6 kg/m² (SG group). There were no significant differences between the two groups for these baseline characteristics (Table 1).

Impact on T2D after GBP Versus SG

Little additional T2D remission occurred at 12 and 36 months compared with 3 months after both GBP and SG surgery (Figs. 2 and 3). Meta-analysis of GBP studies at 3 months did not appear to increase according to higher HbA_{1c} criteria used: 66.7 and 60.6 % remission based on HbA_{1c} criteria of <6.5 and <7 %, but at 12 months, this was 56.5, 75.5, and 65.5 % based on HbA_{1c} criteria of <6, <6.5, and <7 %, respectively, and at 36 months, single studies reported 50.0 and 81.3 % based on HbA_{1c} criteria of <6 and 6.5 %, respectively.

Meta-analysis of SG studies reporting T2D remission was 56.3 % at 3 months based on HbA_{1c} criteria of <6.5 %. Small differences in glycemic definitions resulted in large differences in reported T2D remission at 12 months of 44.0, 67.8, and 75.8 % based on HbA_{1c} of <6, <6.5, and <7 %, respectively. A single study reported 80.0 % T2D remission at 36 months based on HbA_{1c} of <6.5 % (Table 2).

Meta-analysis of the two RCTs did not demonstrate statistically significant difference in T2D remission between GBP and SG (OR of 5.0 (0.7, 38.1)) [12, 13]. However one RCT [12] of 60 Taiwanese patients (mean pre-operative BMI, 30.3 kg/m²) reported greater T2D remission after GBP than SG (93 versus 47 %) based on HbA_{1c} of <6.5 % at 12 months, while the other RCT [13] conducted in 99 patients in the USA (mean pre-operative BMI, 36.6 kg/m²) reported no significant difference in T2D remission (42 versus 27 %) based on HbA_{1c} of <6 % at 12 months. Duration of T2D and proportion on insulin therapy was not stated in the Taiwanese study but was 8.4 years and 44 % in the US study [13].

Impact on Weight Loss After GBP Versus SG

Included studies involving patients with T2D reporting %EWL, demonstrated a greater %EWL with longer follow-up time after both GBP and SG. GBP showed a %EWL of 31.2 and 68.9 % for follow-up at 3 months

and at 12 months, respectively, and a similar result after SG at 36.3 and 67.1 % (Table 2). Similarly, a greater %EBMIL was seen amongst studies reporting %EBMIL at a longer duration of follow-up after GBP and SG (Table 2; Fig. 4). Mean %EBMIL after GBP was 46.0 and 72.5 % at 3 and 12 months follow-up, respectively. Mean %EBMIL after SG at 3 and 12 months was 25.9 and 66.7 %. There was no significant difference in %EBMIL or %EWL between GBP and SG at these follow-up time points of 3 and 12 months (Fig. 5). Weight change data were not reported by included studies with 36 months of follow-up [14, 15].

Meta-analysis of the two RCTs [12, 13] showed similar %EBMIL after GBP and SG (overall difference, 10.6 % (−4.2, 25.5)) at 1 year. Although not statistically significant, there was a suggestion of greater reduction of %EBMIL after GBP than SG in the Taiwanese study [12] by 19.3 % (−3.8, 42.4) with a lower mean baseline BMI (30.3 kg/m²) but not in the American study [13] with a mean baseline BMI of 36.6 kg/m².

Discussion

This study has systematically reviewed all available evidence for T2D remission following GBP and SG in the last five year period during which SG have been commonly used as a standalone bariatric procedure. A significant number of studies were not eligible for analysis due to lack of documentation regarding glucose lowering medications and HbA_{1c} thresholds used to define T2D remission. Of the available studies, we found similar T2D remission and weight loss in the first year after both GBP and SG when using comparable glycemic thresholds and time points of assessment. Both GBP and SG caused substantial early T2D remission (67 and 56 % at 3 months), with modest additional T2D remission at 12 months (76 and 68 %) despite substantially greater weight loss at 12 compared with 3 months (72.5 versus 45.9 % after GBP and 45.9 versus 25.9 % after SG). We did not detect a significant difference between the two procedures based on the assessed RCTs or other studies in the short term (within 3 years).

T2D remission defined by HbA_{1c} of <6 % was 59 and 51.2 % after GBP and SG, respectively, for all studies with outcome reported at less than 2 years. This is much lower than that reported by a recent meta-analysis for studies with follow-up of less than 2 years [4] (82.3 % after GBP by remission criteria of HbA_{1c} of <6 %); however, SG was not examined in this study. A systematic review on T2D outcomes after SG [5] reported T2D remission to be 93.1 % after SG (based

Table 1 Baseline characteristics of reported data from included studies

	GBP (n=998)	SG (n=179)
Duration of type 2 diabetes (years)	6.88±4.53	7.39±2.75
% females	65.3±16.9	68.7±8.1
% patients treated with insulin	27.1±30.2	23.8±13.3
Baseline BMI (kg/m ²)	43.99±5.55	43.32±6.57

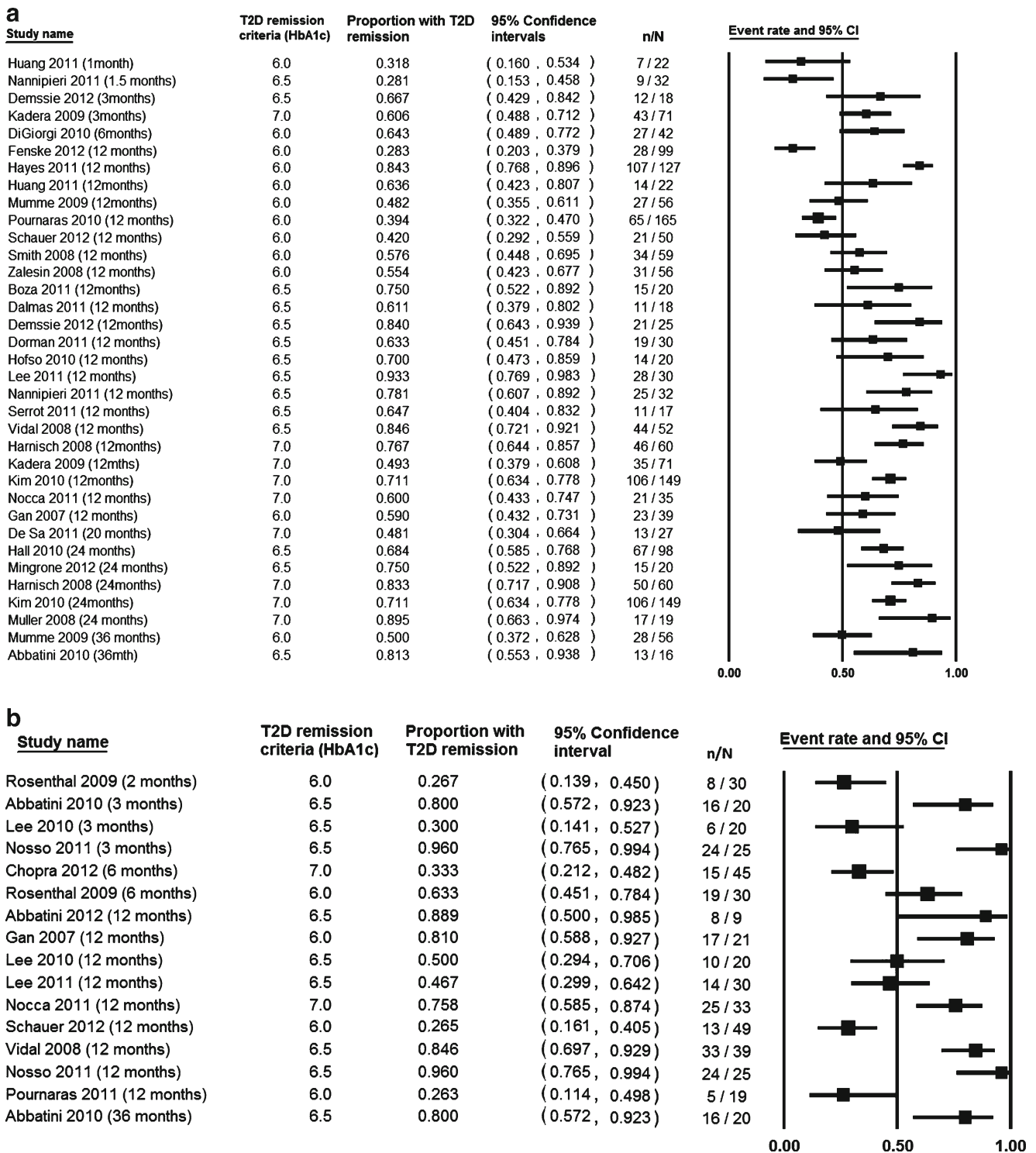


Fig. 2 Proportion of patients with remission of T2D **a** after GBP and **b** SG in ascending order of follow-up time after surgery

on studies with various follow-up time period with mean of 13.1 months) but remission criteria of individual studies were not examined. For weight loss outcomes, we found a mean %EWL of 65 % after GBP at 12 months similar to 67.1 % as previously reported [4]. We found %EWL to be 66.8 % at 12 months after

SG which is higher than that reported at 47.3 % after SG with a mean follow-up of 13.1 months [5].

Discrepancies between the present study and earlier reviews may be explained by selection of different studies with different baseline characteristics, heterogeneity in defining diabetes remission, and the pooling of

Percentage of patients with diabetes remission after GBP and SG (by criteria HbA_{1c} <6.5%)

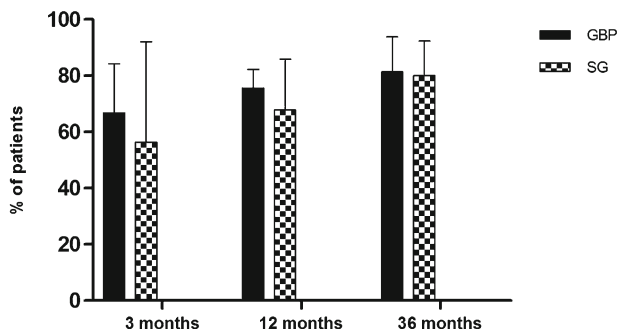


Fig. 3 Proportion of patients with T2D remission after GBP and SG by criteria of HbA_{1c} at <6.5 % at 3, 12, and 36 months follow-up after surgery

studies with different follow-up time points. Glycemic thresholds for diabetes remission (or ‘cure’ or ‘resolution’) are generally defined using similar thresholds to those used to diagnose diabetes or pre-diabetes, unlike ‘improvement’ which is not able to be quantified or compared easily. Even so, these diabetes remission thresholds are controversial because their impact on risk of recurrence of diabetes, or progression of microvascular and macrovascular disease following bariatric surgery is not clear, leading to heterogeneity in glycemic threshold outcomes chosen between studies. However, seemingly small differences in glycemic thresholds used to define diabetes remission after surgery can have a significant impact on proportions achieving this threshold, making comparisons between studies difficult. This combined with the fact that diabetes remission is closely (but perhaps not solely) linked to weight loss after surgery, which follows a typical time course, we have made comparisons of efficacy between studies giving attention to both equivalent diabetes remission criteria and time points of assessment.

It has been hypothesised that GBP is superior to SG for achieving T2D remission prior to significant weight loss based on the foregut and hindgut hypotheses. The ‘foregut hypothesis’ suggests that by excluding food contact with the proximal gut there is reduced secretion of unknown factors that usually increase insulin resistance [16]. The ‘hindgut hypothesis’ proposes an increased secretion of gut hormones such as glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and peptide YY (PYY) occurs when there is expedited delivery of food to the hindgut [17]. GLP-1 has an insulinotropic effect whereby glucose-dependent insulin secretion is increased by GLP-1 acting directly on pancreatic beta cells as well as inducing satiety, and slowing gastric emptying [18]. Increases in GLP-1 early after GBP have been shown to occur before significant weight loss [19, 20]. Likely from accelerated stomach emptying, GLP-1 also increases after SG but to a lesser

degree than after GBP [20]. GIP also acts on pancreatic beta cells to increase insulin secretion, although reports on its changes have been varied after GBP and SG [21]. PYY is co-secreted with GLP-1 from the distal ileum to promote satiety and has been shown to increase early after GBP [22] and to a lesser extent after SG [23]. Ghrelin is an orexigenic hormone secreted in the gastric fundus that inhibits insulin secretion and stimulates release of counter-regulatory hormones, as well as stimulating appetite by acting on the hypothalamus [24]. Long-term reduction of ghrelin through stomach resection (after SG [25]) or loss of contact with food (GBP) [26] may play a role in T2D remission after bariatric surgery.

Despite these theories, our analysis of studies to date suggest that SG is as effective as GBP, as both GBP and SG caused substantial early T2D remission (67 and 56 % at 3 months), with modest additional T2D remission at 12 months (76 and 68 %) despite substantially greater weight loss at this later time point. This may be explained by the contribution of acute caloric restriction in achieving early T2D remission in both GBP and SG [27] and shortened bowel transit times [28] leading to increased incretin hormones. It is possible that GBP is more effective in achieving T2D remission for certain patient groups, such as those less obese (BMI, <35 kg/m²) as in the Taiwanese RCT [12], despite similar weight loss to SG.

Our review is limited by the paucity of published randomised controlled studies comparing GBP with SG using standard criteria to define T2D remission; hence, most included studies in this review were based on non-randomised observational data. Of the two available RCTs comparing GBP and SG, one showed a superior effect of GBP on T2D remission defined by HbA_{1c} of <6.5 % [12] while the other showed no significant difference using HbA_{1c} of <6 % [13] at 12 months follow-up. This is potentially explained by a different mean baseline BMI (30.3 versus 36.6 kg/m²) as well as other characteristics such as duration of diabetes and insulin treatment which was only reported in one of the RCT studies. The impact of differing glycemic criteria used to define T2D remission, on the relative efficacy of GBP compared with SG on T2D remission is unknown as the two RCT did not present data using both HbA_{1c} thresholds. A previous study found the effect of different glycemic thresholds on redefining diabetes remission rates to be greatest with GBP compared with SG [29].

The American Diabetes Association released a consensus statement in 2009 recommending the use of partial remission (defined by HbA_{1c} of <6.5 % and fasting glucose 100–125 mg/dL (5.6–6.9 mmol/L)) and complete remission (HbA_{1c} in normal range of <5.6 % and fasting glucose of <5.6 mmol/L), provided each of these assessments were persistent for at least 1 year in

Table 2 Proportion of patients with remission of T2D, %EWL, and %EBMIL according to time after surgery and criteria for T2D remission, indicating overall effect with random effect models and 95 % confidence intervals in brackets

	Follow-up (months)	T2D remission criteria by HbA _{1c}	Overall effect (%)	Number of studies	Number of subjects	I ² (p value)	
GBP	Proportion with remission of T2D	3	<6.5 %	66.7 (42.9, 84.2)	1	18	–
			<7 %	60.6 (48.8, 71.2)	1	71	–
		6	<6 %	64.3 (48.9, 77.2)	1	42	–
		12	<6 %	56.5 (41.0, 70.8)	8	634	90.9 (<0.001)
			<6.5 %	75.5 (67.3, 82.2)	9	244	39.6 (0.103)
			<7 %	65.5 (55.2, 74.5)	4	315	71.2 (0.008)
		24	<6.5 %	69.4 (60.5, 77.1)	2	118	0.0 (0.558)
			<7 %	79.3 (68.7, 86.9)	3	228	62.2 (0.071)
		36	<6 %	50.0 (37.6, 52.8)	1	56	–
			<6.5 %	81.3 (55.3, 93.8)	1	16	–
		<24 overall 0.636 (0.569, 0.699)	<6 %	54.5 (42.4, 66.1)	10	737	88.1 (<0.001)
			<6.5 %	74.1 (67.6, 79.7)	9	314	72.7 (<0.001)
			<7 %	65.5 (55.2, 74.5)	5	413	65.8 (0.007)
		≥24 overall 0.726 (0.629, 0.805)	<6 %	50.0 (37.6, 52.8)	1	56	–
			<6.5 %	70.6 (62.3, 77.8)	3	134	0.0 (0.530)
			<7 %	79.3 (68.7, 86.9)	3	228	62.2 (0.071)
		%EWL	3	31.160 (29.823, 32.497)	2	88	87.9 (0.004)
			12	68.863 (64.698, 73.027)	6	515	91.6 (<0.001)
		%EBMIL	3	45.953 (33.804, 58.102)	2	87	0.0 (0.805)
		12	72.521 (65.440, 79.602)	14	812	88.6 (<0.001)	
SG	Proportion with remission of T2D	3	<6.5 %	56.3 (12.6, 92.0)	3	65	88.2 (<0.001)
		6	<6 %	63.3 (45.1, 78.4)	1	30	–
			<7 %	33.3 (21.2, 48.2)	1	45	–
		12	<6 %	44.0 (15.3, 77.4)	3	89	87.4 (<0.001)
			<6.5 %	67.8 (42.1, 85.9)	5	123	80.3 (<0.001)
			<7 %	75.8 (58.5, 87.4)	1	33	–
		36	<6.5 %	80.0 (57.2, 92.3)	1	20	–
		<24 Overall 51.2 (46.3, 74.3)	<6 %	43.9 (23.7, 66.3)	4	149	83.7 (<0.001)
			<6.5 %	75.4 (50.2, 90.3)	5	188	81.3 (<0.001)
			<7 %	55.1 (16.9, 88.1)	2	78	92.1 (<0.001)
		≥2 years Overall	<7 %	80.0 (57.2, 92.3)	1	20	–
		%EWL	3	36.300 (33.145, 39.455)	2	45	96.3 (<0.001)
			12	67.099 (60.204, 73.995)	4	104	47.0 (0.129)
	%EBMIL	3	25.940 (–3.507, 55.386)	2	68	0.0 (0.452)	
		12	66.744 (47.753, 85.735)	6	142	73.2 (0.002)	

GBP Roux-en-Y gastric bypass, SG sleeve gastrectomy, T2D type 2 diabetes, EBML excess BMI loss, EWL excess weight loss

the absence of active pharmacological therapy. Additionally, they defined prolonged remission if these conditions were met for at least 5 years [30]. Only a few studies reported on partial remission using this criteria [13, 15, 31–40] and none reported on complete remission. The most commonly reported criteria were HbA_{1c} of <6.5 [7, 12, 14, 41–53] and <7 % and fasting glucose of 6.9 mmol/L [54–60]. One study found a significantly lower proportion of patients fulfilled T2D remission defined by new criteria compared with other

older definitions [29]. We did not detect a significant impact of different HbA_{1c} thresholds for T2D remission in the first 3 months, but thereafter, a greater proportion of patients generally met less stringent criteria for T2D remission.

There was a paucity of outcome data on weight loss and T2D remission after GBP and SG beyond 3 years with adequate follow-up rates. By excluding studies with follow-up rate of less than 50 % to reduce attrition bias, longer term follow-up data had to be excluded.

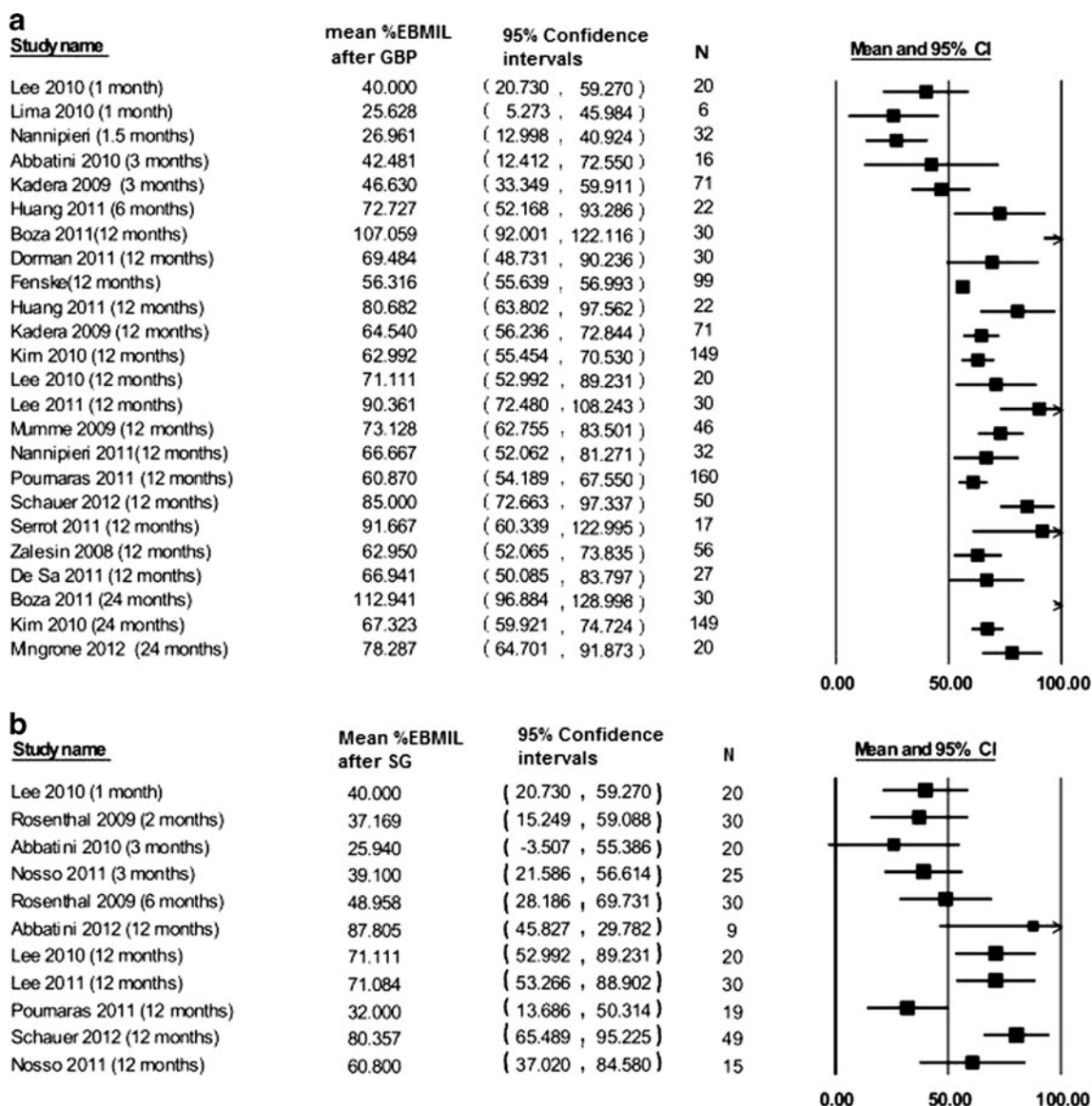


Fig. 4 %EBMIL after GBP and SG in ascending order of follow-up time after surgery

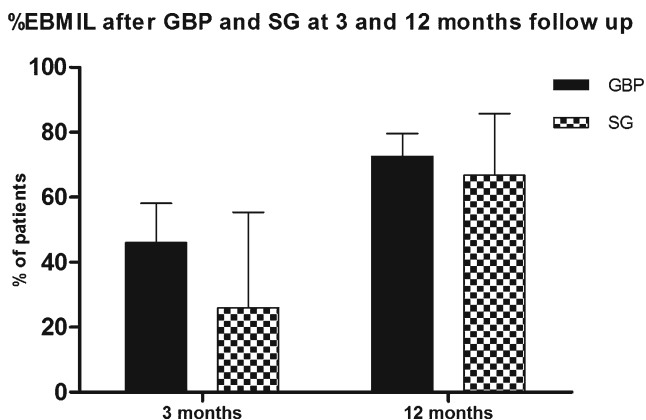


Fig. 5 %EBMIL after GBP and SG at 3 and 12 months after surgery

Finally, non-uniform reporting of weight loss (including both timing of pre-operative weight measurements and types of measurements reported) limited comparison between studies. Assessment of weight loss by %EWL or %EBMIL is dependent on the definition of ideal body weight which may be based on Metropolitan Life Insurance Company height and weight tables and the use of BMI of 25 kg/m² [61] or other formulae. One study demonstrated that %EWL could range from 65 to 82 % by simply using different methods of calculation [62].

Conclusions

This systematic review suggests both SG and GBP are equally effective in causing T2D remission and weight loss,

at least as long as 3 years of follow-up. Further randomised studies comparing SG and GBP reporting long-term data using ADA criteria to define T2D remission with adequate follow-up, using standardised reporting of weight change are required to determine which surgical procedure is better for patients with T2D in the long term.

Conflict of Interest The authors Shelley Yip, Lindsay Plank, and Rinki Murphy declare that they have no conflict of interest.

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