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REVIEW ARTICLE

Sleeve Gastrectomy and Type 2 Diabetes Mellitus: a Systematic Review of Long-Term Outcomes

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Abstract Long-term T2DM resolution rates are not well established following the laparoscopic sleeve gastrectomy (LSG). The aim of this paper was to systematically review the evidence on the efficacy of the LSG on long-term T2DM resolution. A comprehensive electronic literature search was conducted. Included studies reported 5-year follow-up of T2DM outcomes following the LSG. Eleven studies ($n=1354$) were included in the systematic review. T2DM patients ($n=402$) encompassed 29.7 % of patients. Diabetes prevalence decreased post-operatively to 20.5 % at 5 years, with diabetes resolution occurring in 60.8 % of patients. Mean plasma glucose levels and haemoglobin A1c values fell from 170.3 to 112.0 mg/dL and 8.3 to 6.7 % respectively at the 5-year mark. The LSG is an effective long-term metabolic surgery for patients with T2DM.

Keywords Sleeve gastrectomy · Diabetes · Long-term results · Laparoscopic

Introduction

The rise of worldwide obesity rates has been well established. Of all the comorbidities related to obesity, the link between obesity and type 2 diabetes mellitus (T2DM) is the strongest [1]. Obesity is associated with a sevenfold increase in the risk of development of type 2 diabetes, and approximately 80 % of individuals with type 2 DM are clinically obese [1, 2]. The prevalence of diabetes in patients with class II and III obesity, meeting the criteria for bariatric surgery, ranges from 16 to 18 % and 18 to 44 %, respectively [3]. T2DM contributes significantly to the morbidity associated with obesity, including but not limited to cardiovascular disease and kidney failure [4].

Bariatric surgery has been shown to be the most effective primary management strategy for obesity and its comorbidities compared to lifestyle and medical management [5]. Furthermore, studies have shown a 10–50 % compliance rate associated with long-term antidiabetic diet and pharmacotherapy when enrolled in a multidisciplinary programme [4]. Surgical patients, on the other hand, in the well-established Swedish Obese Subjects study had over a threefold increase in diabetes remission rates at 2 and 10 years compared to non-surgical groups [4]. However, long-term diabetes remission rates decreased from 72 to 37 % at 10 years. Attenuation in weight loss and comorbidity resolution rates after 2 years is not an uncommon observation in bariatric trials [6].

The sleeve gastrectomy (LSG), unlike the Roux-en-Y gastric bypass (RYGB), has limited long-term data as a primary bariatric operation. Originally the first step in a staged weight loss strategy, LSG has promising short- and medium-term results. The lack of long-term weight-loss outcomes has been criticized in the literature, with some authors even concluding that the lack of sufficient evidence limits their conclusions of its overall efficacy in general [7, 8]. At the latest published Consensus Summit on Sleeve Gastrectomy, surgeons with >5 years of experience encompassed only 21.5 % of surgeons (28 out of 130 surgeons in attendance) [9]. Therefore, it is not surprising that there is clear paucity of long-term co-morbidity outcomes and resolution rates post-LSG [10].

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The aim of this paper was to systematically review the evidence on the efficacy of the laparoscopic sleeve gastrectomy on diabetes resolution in the obese population undergoing bariatric surgery.

Methods

Data Sources

A comprehensive literature search was conducted through Medline, Embase, Scopus, Web of Science, Dare, Cochrane library and HTA database. Conference abstracts and registered clinical trials were also searched, along with Google for other type of grey literatures. In addition, the reference lists of all included studies were examined to identify any relevant publications. The search terms used were sleeve gastrectomy, vertical gastrectomy, metabolic surgery and diabetes, T2DM, DM.

Selection Criteria

Due to the scarcity of high-quality evidence, all human randomized controlled trials, non-randomized comparison studies, case series, abstracts and those published in languages other than English from 1946 to October 2015 were considered for inclusion. Case reports, expert's opinions and reviews were excluded. Included studies needed to report 5-year diabetes-focused outcomes on at least five T2DM patients.

The target patient population were adults (>18 years) with type 2 DM who had undergone LSG as a primary procedure or as a first-stage procedure in a staged procedure. All revisional LSG operations were excluded. Abstracts were screened by two independent reviewers.

Data Extraction

Two independent reviewers collected pertinent data from full-text articles, with discrepancies resolved by a third party. The primary outcome of interest was resolution or improvement of type 2 DM. The definition of resolution of DM was heterogeneous: cessation of diabetes medical therapy, HbA1c ≤6.5 % or HbA1c <6.0 %. Improvement was defined as changing from insulin to oral medications, or a reduction in the overall dose or number of diabetes-related medications. Secondary outcomes included basic patient demographics, weight loss results, plasma glucose and A1c levels and follow-up information.

Statistical Analysis

Due to the significant heterogeneity with a systematic review with limited RCTs and control groups, a meta-analysis was not conducted. For the review, syntheses of mean, range and average percentages across studies were used to describe the effectiveness of the intervention.

Results

Search Results

The initial search identified 3191 studies. After removing duplicates, 664 abstracts or full texts remained for review. Of the 664 studies, 627 were removed based on abstract and title screening. The remaining 37 titles were screened by full text. Sixteen papers were excluded based on the lack of primary DM outcome data, <5-year outcomes reported, did not differentiate LSG-specific outcomes identified and not being a primary study. Thus, 11 studies met the inclusion criteria and were included in our systematic review (Fig. 1). This consisted of one randomized controlled trial and nine case series [8, 11–19].

Included Studies

All 11 studies reported T2DM-specific outcomes post-LSG. Baseline patient demographics for the full cohort versus the

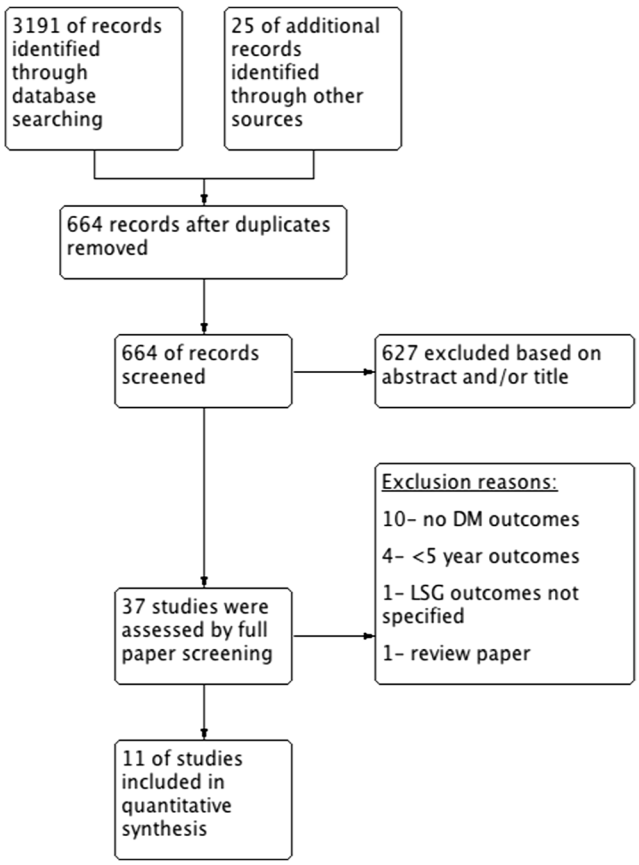

Fig. 1 PRISMA diagram of systematic review synthesis

DM-specific cohort are presented in Table 1. A total of 1354 subjects were included, where DM patients encompassed 29.7 % of patients (402 of 1354 total patients). Individual study enrolment numbers ranged from 30 to 560 total patients and 14 to 156 diabetic patients. Only three studies exclusively enrolled DM patients [11, 12, 14]. The mean age was 45.3 ± 6.9 years for all patients and 51.1 ± 5.9 years for the diabetic patients only. The mean preoperative BMI was 48.4 ± 10.8 and 44.6 ± 11.8 kg/m^2 for all patients and diabetic patients, respectively.

Diabetes prevalence preoperatively was 47.4 % amongst all obese patients. This decreased post-operatively at 5 years to 20.5 %. The primary outcome of interest was diabetes resolution, which occurred in 60.8 % of patients. Within the studies, four studies reported resolution or stability in 100 % of patients [8, 11, 17, 19]. Three studies reported recurrence rates of diabetes in 13.1 % of patients [10, 12, 14].

Post-operative BMI dropped an average of 15.5 to 33.2 ± 4.7 kg/m^2 at 5 years, for all patients. Specific diabetes measurements were limited to only three studies [11, 12, 14]. Mean plasma glucose levels fell from baseline 170.3 mg/dL to a 5-year mean of 112.0 mg/dL (Table 2). Mean A1c fell from baseline of 8.3 % to a 5-year level of 6.7 %. Five-year follow-up data was only reported in 56 % of patients.

Discussion

As per current literature, this is the first systematic review to look primarily at long-term diabetes results of LSG. We report diabetes resolution at 5 years was 60.8 %; however, recurrence of T2DM was reported in 13 % of diabetic patients.

While there has been paucity in the literature as to the long-term effects of LSG on T2DM resolution, the short-term outcomes have already been well established. Recent systematic reviews of short- and intermediate-term LSG-associated outcomes reported 66.2 to 70 % of patients had resolution of T2DM [20, 21]. Gill et al., in a review of 28 primary studies, observed 97.1 % of patients had either improvement or resolution of T2DM, at a mean of only 13.1 months [21]. In comparison to other bariatric procedures at all follow-up intervals, the duodenal switch is the most effective procedure for diabetes management (resolution, 98.9 %; resolution or improvement, 76.7 %) followed by RYGB (resolution, 83.7 %; resolution or improvement, 93.2 %), and then gastric banding (resolution, 47.9 %; resolution or improvement, 80.9 %) [22].

RYGB has been consistently supported as the standard of care for T2DM management in the severely obese [17, 19]. In a review focused on longer-term follow-up, Puzziferri et al. reviewed RYGB studies with follow-up >2 years and found that the DM remission rates was 66.7 %, with mean HbA1c levels dropping by 2.2 % [7]. This absolute value is well within the findings of our LSG study. In a randomized controlled trial between the two procedures, Peterli et al. reported that while RYGB patients had an early augmented insulin response, both procedures were effective in achieving euglycemia. In the latest 2015 systematic comparison of LSG and RYGB, T2DM resolved more often with RYGB (OR = 1.27, CI 0.95–1.69); however, the difference was not significant [23]. Overall, it appears that LSG can achieve T2DM resolution results in the range of RYGB although it is not equivalent. However, LSG offers the advantage of a technically simpler procedure without malabsorption consequences [23].

Table 1 Baseline characteristics within included studies for systematic review

Investigator, year	Patients (*n*), T2DM (*n*)	Mean age (year)	Gender (% female)	Mean BMI (kg/m^2)	Surgery	Pre-op prevalence of DM (%)	FU period (months)
Abbatini, 2013 [11]	33, 33	49.3 ± 8	69.7	52.1 ± 8.5	LSG	100	60
Braghetto, 2012 [19]	560, 156	NR	NR	38.4 ± 5.1	LSG	27.8	60
Brethauer, 2013 [12]	23, 23	57.7 ± 10.2	74	50.7 ± 10.6	LSG	100	>60
Catheline, 2013 [8]	53, 15	41.8 ± 11.3	77	49.9 ± 9.1	LSG	28.3	60
Eid, 2012 [13]	74, 35	50	52	66.0 ± 7.0	LSG	47.2	>60
Lee, 2014 [14]	30, 30	46.4 ± 8.1	68.8	46.4 ± 8.1	LSG	100	60
Lemanu, 2015 [10]	55, 14	46.9	81.8	31 ± 2.8	LSG	25.4	60
Musella, 2013	175, 26	38.2	58	47.9	LSG	14.9	60
Rawlins, 2013 [16]	55, 19	55	70	65	LSG	34.5	60
Sieber, 2014 [17]	68, 21	43.1 ± 10.1	78	43.0 ± 8.0	LSG	30.2	>60
Zachariah, 2013 [18]	228, 30	34.7 ± 10.1	63.5	37.4 ± 4.8	LSG	13.1	60
Total	1354, 402	45.3 ± 6.9	69.3	48.4 ± 10.8	LSG	47.4	>60

FU follow-up, *NR* not reported

Table 2 Laparoscopic sleeve gastrectomy outcomes—systematic review

Investigator, year	Glucose level (mg/dL)		Hb A1c (%)		Post-op mean BMI (kg/m^2)	T2DM outcomes			
	Pre	Post	Pre	Post		Resolved	Improved	Stable	Recurrence
Abbatini, 2013 [11]	143.2 ± 47.9	101.6 ± 15.3	7.3 ± 1.4	5.9 ± 2.1	36.4 ± 2.2	76.9		23.1	
Braghetto, 2012 [19]					29.9	63	35.7		
Brethauer, 2013 [12]	137		7.8 ± 1.6	7.0		31	52	17	17
Catheline, 2013 [8]					35.3 ± 7.4	64		36	
Eid, 2012 [13]						37.1	40	70	
Lee, 2014 [14]	230.6 ± 85.3	122.4 ± 11.9	9.9 ± 1.8	7.1 ± 1.2		6.7	30	70	
Lemanu, 2015 [10]					39.8	42.9	35.7		7.1
Musella, 2013					29.7	65.3		19.3	15.4
Rawlins, 2013 [16]					35	100			
Sieber, 2014 [17]					43.0 ± 8.0	85		15	
Zachariah, 2013 [18]					27.9 ± 4.1	96.6		3.33	
Total	170.1	112.0	8.3	6.7	33.2 ± 4.7	60.8	39.4	25.1	13.1

Weight recidivism is a concern for all bariatric operations, especially for the restrictive-type procedures. Beginning after the second post-operative year, about 20 % of LSG patients can expect significant weight regain, with 5–10 % of these patients requiring a second unplanned revisional bariatric operation for weight regain [24, 25]. A concern with weight regain is the return of previously resolved co-morbidities, including DM. It appears that diabetes resolution rates drop off slightly in the long term but 13 % of patients can expect a recurrence of their diabetes. However, resolution rates are relatively maintained in the long term (60 % resolution rates from our long-term study compared to 66 % from Gill et al. at 13 months) [21].

Weight loss alone has been shown to be the strongest predictor of diabetes remission following surgery; however, the mechanism behind the success of LSG in obese patients in glucose homeostasis is multifactorial [14]. An augmented glucagon-like-peptide-1 (GLP-1) response, reduction in the diabetogenic effects of ghrelin and increases in both peptide YY and cholecystokinin initiate the immediate weight-*independent* improvement in DM while the substantial weight loss in the following months post-operatively maintain weight-*dependent* long-term DM resolution [17, 26].

The gut hormone modulation theory explains why diabetes amelioration occurs immediately in the post-operative period, prior to any significant weight loss [3]. To explain further, while attenuated incretin effect with DM2 is well described, post-LSG, there is an increased incretin GLP-1 release [14]. This increased GLP-1 release promotes insulin release, which can be synergistically coupled with a simultaneous reduction in insulin resistance, modulated by peptide YY [18, 27]. Peptide YY, a satiety factor, also induces a dose-dependant loss in appetite [28]. In addition, the resection of the greater curvature of the stomach, the primary site of ghrelin release, leads to both a decreased hunger drive and a marked improvement in glucose homeostasis, as it suppresses insulin release [29].

One of the difficulties in determining the response of patients after bariatric surgery is the fact that type 2 DM is also a heterogeneous disease state. The contributions of beta cell dysfunction and insulin resistance to the disease state can be quite variable from patient to patient [30]. In addition, other patient factors can contribute to whether or not a patient has resolution or improvement in their diabetes. In their meta-analysis of predictive factors, Wang et al. found that older age, long duration of diabetes, insulin use and poor glycemic control were associated with failure of diabetes remission in the post-operative time period [31]. One of the main drivers of the phenomenon is impaired beta cell function. Long-standing diabetes is associated with deterioration of beta cell function reflected by lower preoperative C-peptide levels, a measurement to assess insulin secretion, and therefore has limited beta cell function to maximize after bariatric surgery [31, 32].

Limitations

A few limitations exist in this systematic review. First, the definition of DM resolution was heterogeneous and defined differently by the primary studies. For instance, cut-points of glycosylated haemoglobin included both 6.0 and 6.5 [14, 16]. As well, the reporting of diabetic objective markers, notably plasma glucose levels and A1c levels, was sparse, which is not ideal. Lastly, the majority of the primary studies that encompassed this systematic review were non-controlled case series, with only one randomized controlled trial. Therefore, the overall

heterogeneity between the studies was expectantly significant, and consequently, a meta-analysis was not performed.

Conclusion

In this review, it appears that LSG is an effective long-term metabolic surgery for patients with T2DM, with 5-year resolution rates of approximately 60 %. However, recurrence of comorbidities following any restrictive bariatric surgery, including the LSG, is a concern, with 13 % of patients in our review having a recurrence of their diabetes at 5 years. While LSG is still in its infancy as a bariatric procedure, more long-term studies will become available in the next few years to further strengthen its efficacy as a primary metabolic and bariatric procedure.

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