Evolution of GERD symptoms after bariatric surgery: A dose-response meta-analysis

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Abstract

Importance Obesity is associated with increased prevalence of gastroesophageal reflux disease (GERD); with recent reports suggesting improvement in GERD symptoms and weight loss following bariatric surgical intervention. However, the exact impact of the type of bariatric surgery on the evolution of GERD symptoms have remained unexamined.

Objective To characterize the exact evolution of GERD symptoms, post bariatric surgery.

Data sources We systematically searched electronic databases (PubMed, EMBASE, Web of Science, and the Cochrane Library from inception to December 2018) for eligible studies that satisfy pre-specified inclusion criteria.

Study selection We included clinical trials of all designs (prospective and retrospective) that reported on GERD outcomes following Laparoscopic Sleeve Gastrectomy (LSG) or laparoscopic Roux-en-Y gastric bypass (LRYGB).

Data extraction and synthesis Two independent reviewers extracted relevant data based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Data were pooled using a random-effects model.

Main outcomes Symptomatic improvement in GERD symptoms following bariatric surgery

Results A total of 39 studies were analyzed and a robust-error meta-regression model was used to conduct a Dose-Response Meta-Analysis (DRMA) synthesizing data on 39 studies that reported GERD outcomes after bariatric surgery. Out of 43,994 patients who underwent either LSG (N = 9,547 patients) or LRYGB (N = 34,447 patients), 32.4% experienced improvement in symptoms (95% CI 20.62 to 45.45); The DRMA demonstrated a window period of two years for sustained improvement after which symptoms began to recur in those that were asymptomatic.

Conclusion and relevance Bariatric surgery may improve GERD symptoms in obese patients who underwent LSG, however, the most favorable effect is likely to be found after Roux-en-Y gastric bypass surgery. The effects were not sustained and returned to baseline within 4 years.

Introduction

The burden of obesity is on the rise across different continents and populations around the world.¹ Although different socio-demographic groups are involved, the burden appears more pronounced amongst adolescent and adult populations.¹ Uncontrolled obesity has been associated with preventable morbidities across a wide range of cardiovascular and metabolic risks; these include cardiovascular disease, hypertension, diabetes mellitus, venous thrombo-embolic (VTE) disease, obstructive sleep apnea, and cancer amongst others.² For most patients, bariatric surgery remains the only option for the treatment of obesity when dietary interventions and pharmacotherapy fail. Amongst a range of bariatric surgical options currently in use includes [Laparoscopic Sleeve Gastrectomy (LSG), and laparoscopic Roux-en-Y gastric bypass (LRYGB)], both of which have been shown to result in varying degrees of weight loss.³ However, there has been a rising incidence in complications associated with these procedures. Gastroesophageal reflux disease (GERD) in particular has been the subject of recent concerns.⁴ The prevalence of clinically relevant GERD associated with bariatric surgery is variable, but has been reported as ranging between 7% and 14%.^{5–7} Uncertainty however remains regarding the exact evolution of symptoms especially among patients with different clinical phenotypes such as metabolic syndrome, obesity and multi-morbidities. In this Dose-Response Meta-Analysis (DRMA), we therefore intend to assess GERD symptoms over time with the view to clarify the timeframe of evolution of GERD symptoms among patients that have undergone these procedures.

Materials And Methods

Database Search

Literature search strategies was developed using medical subject headings (Mesh) and text key words related to bariatric surgery and GERD. The specific search strategies were created by a health sciences librarian with expertise in systematic reviews. Following the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement,⁸ a systematic literature search was performed using PubMed, Medline, EMBASE, Web of Science, and the Cochrane Library from inception to December 2018, combining the key words obesity, high BMI, weight loss and gastroesophageal reflux with bariatric surgery OR LSG OR laparoscopic sleeve gastrectomy OR sleeve gastrectomy OR SG OR LRYGB OR laparoscopic Roux-en-Y gastric bypass OR gastric bypass OR GB. Moreover, we individually observed the reference lists of the selected articles to find other potentially relevant studies. GERD was used as the observation

index of outcome after all types of bariatric surgery (i.e., improvement of GERD after bariatric surgery or/and the number of cases of newly onset or worsened GERD after bariatric procedure). The means and measures of dispersion were approximated from the figures given in the reports.

Selection of studies (Inclusion and exclusion criteria)

Only clinical trials were included for this meta-analysis. The inclusion criteria were as follows: 1) studies reporting on the efficacy of LSG and/or LRYGB on GERD symptomatology; 2) new onset or worsening GERD after LSG and/or LRYGB. The exclusion criteria includes 1) studies with incomplete data for GERD symptoms following bariatric surgery ; 2) case series or case reports, 3) studies with follow-up periods of less than 6 months after bariatric surgery 4) Studies reporting in other languages other than English. Only the most relevant and comprehensive publications were included in the analysis to avoid duplicates, ambiguity; studies involving non-human subjects, or papers reporting data from the same study populations were excluded.

Data Extraction

A team of two investigators extracted the data using a standardized form, which was reviewed individually by a third investigator following analysis individually and in duplicate. To ensure standardization across the reviewers, a calibration exercise was carried out before starting the actual review. Any disagreement between reviewers was resolved by the consensus of two authors and the third reviewer. Data from each included study was extracted by two investigators and reviewed independently by a third investigator following essential indicators from each article into Table 1. These indicators included study author/year, study design, level of evidence, sample size, follow up period, type of bariatric surgery (LSG or LRYGB), GERD improvement rate, method of GERD evaluation, and study country.

Quality Assessment

The methodological quality of clinical trials was assessed by Cochrane Collaboration's tool for assessing risk bias which covers: sequence generation, allocation concealment, blinding, incomplete outcome data (e.g. drop-outs and withdrawals) and selective outcome reporting.⁹ The observational studies were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) checklist.¹⁰

Statistical analysis

The effect size of interest was the difference in prevalence of GERD symptoms in patients immediately before and at any time point after bariatric surgery reported in the papers. This was modeled as a risk difference in a DRMA. The latter was conducted as a one-step procedure with time (as the "dose") along with change in risk as the outcome were fit into an inverse variance weighted non-linear robust error meta-regression model,¹¹ using restricted cubic splines with three knots in an effort to approximate the potential non-linear relationship. The weights were based on the inverse of the variance of the incremental risk difference in proportions of patients with GERD symptoms from the baseline at surgery. Stata MP 15 (StataCorp, College Station, TX) was used for the analysis, utilizing the *remr* package.¹² Confidence level was set at 95%.

Results

Study Features

A total of 32 studies including 43,994 patients (9547 in LSG and in 34447 LRYGB) were enrolled for the dose-response meta-analysis from a cluster of 2500 studies pooled from all databases. **Figure 1** shows the flow chart of studies selection with details of retrieval process and filtering. The 32 selected studies were including nine prospective studies, and 23 retrospective observational studies¹³⁻⁴⁴ They were conducted in 19 different countries (Argentina, Austria, Belgium, Canada, Chile, Colombia, France, Greece, India, Israel, Italy, Poland, Lebanon, Netherlands, Sweden, Switzerland, Taiwan, United Kingdom, USA) with clinical follow-up ranging from 6 months to 153 months after bariatric surgery. The demographic and clinical characteristics of the included studies are shown in Table 1.

Effect of Bariatric Surgery on GERD

A total of 32 studies (84.6%) showed improvement or remission for obesity-related GERD (78.6% in LSG, 100% in LRYGB). The proportion of subjects with GERD symptoms at baseline was 23.1% (IQR 12.0 - 34%) and at follow-up was 8.8% (IQR 2.8 - 13.6%). While this seems to suggest a decrease in GERD symptoms after bariatric surgery, the follow-up varied considerably with a median of 24 months (IQR 12 – 60 months). When the incremental risk was modeled in a DRMA with time as the "dose" there was a decrease in prevalence of GERD symptoms till 2 years post-surgery and this gradually increased back to baseline at 4 years post-LSG surgery (Figure 2) and post-LRYGB surgery (Figure 3). The trend was a continuing increase in risk but the trend after 4 years was not reliable due to a paucity of data points. There was a much

greater decrease after LRYGB compared to LSG, but this was driven by a single large study and after this was excluded, the trends were similar (Figure 4). In addition, there were fewer data-points for LRYGB.

Discussion

This meta-analysis represents the first comprehensive attempt at exploring the comparative prevalence of GERD symptoms following either LSG or LRYGB surgery. We found a significant decrease in GERD related symptoms up to two years following surgery. This symptomatic improvement was regardless of the type of surgery. Beyond two years however, uncertainty remains as to the impact of surgery on GERD related symptom relief. The rate of symptomatic improvement was steeper and relapse of symptoms quicker with LRYGB surgery compared with LSG procedures or be it with an uncertain point estimates. This has significant implication for patient counseling before surgery as well commissioning of surgical procedures. The exact mechanism underpinning the improvement in GERD symptoms following surgery continues to generate intense mechanistic debate. Several reports have attributed this to significant and durable weight reduction evident in patients who underwent these procedures.^{45,46}

We found an unusually high prevalence of GERD symptoms at baseline before surgery. Previous reports have estimated this at 33%.⁴⁷ The difference in estimate from our review and that reported from previous studies may have to do with marked heterogeneity in the modalities employed to evaluate GERD. The change or improvement in GERD symptoms (Δ GERD) from 23% at baseline to 8.8% over a median period of two years is comparable or better than that seen with anti-secretory therapy.⁴⁸

The lack of difference in point estimates of residual GERD outcomes between SLG and LRYGB mirrors previous uncertainty regarding the exact impact of the type of bariatric surgery on GERD symptom improvement. The findings from the largest systematic review by Stenard et al exploring this uncertainty in patients who underwent LSG were discordant.⁴⁹ About half of the studies in that review found symptomatic improvement in GERD symptoms following the procedure, with the remaining half showing signs of worsening GERD symptomatology. The apparent discordance in GERD outcomes in this review was attributable to heterogeneity in the mode of evaluation of GERD ranging from clinical evaluation, 24-hour ambulatory pH studies, esophageal manometry or contrast studies, to endoscopy. Additionally, only one study was prospective, the remaining studies were retrospective. Other subsequent reviews^{50,51} including that by Himpens et al⁵² also reported mixed outcomes regarding GERD symptoms improvement following LSG. Our review similarly found lack of superiority between different surgical modalities in GERD symptoms improvement following surgery. The confounding issues highlighted earlier including marked heterogeneity in the mode of evaluation of GERD may have accounted for our point estimates with regards to effect of bariatric surgical modality on GERD symptoms improvement.

Additionally, we found improvement in GERD symptoms plateauing at 4 years with significant uncertainty afterwards. Whilst this suggest need for more comprehensive studies to ascertain the exact impact of bariatric surgery in GERD symptoms beyond 4 years; it is probable that rapid weight gain reported from previous series may be the key driver to the is phenomenon.

Strengths and limitation

This DRMA represents the first comprehensive attempt at exploring the comparative efficacy of LRYGB vs. LSG surgical procedures in achieving sustained and durable improvement in GERD symptoms. It provides the first estimates of the average duration of GERD symptom improvement (2 years) following these procedures as well as raises the prospects for further studies to explore determinants of uncertainty in symptom relief after four years. As with previous systematic synthesis in this area, our DRMA is limited by differences in the modes of adjudication of GERD symptoms by various investigators. The reliance on clinical evaluation alone in some cases and paucity of data regarding utility of PH monitoring as well as endoscopy data in others may have accounted for the imprecision regarding some point estimates in previous studies (including ours).

Conclusion

In obese bariatric patients we found significant improvement in GERD symptoms at two years regardless of the type of bariatric surgery (LSG or LRYGB), but this is not sustained beyond four years. The rate of improvement in bariatric symptoms was faster but less durable with LRYGB compared to gastric sleeve surgery.

Declarations

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Author contribution

A-NE: Review conceptualization, protocol registration, independent reviewer, risk of bias assessment, data interpretation, and writing of the initial draft/revision of the final manuscript

MID: Independent reviewer, risk of bias assessment, data interpretation, writing of the initial draft/revision of the final manuscript.

SD: Statistical data analysis, data interpretation, review of the initial and final manuscript drafts

M-AW: Protocol registration, data collection and curation

SS: independent reviewer, data collection and curation.

EH: Independent reviewer, revision of the final manuscript.

HS: Data collection, revision of final manuscript

MA: Data collection, revision of final manuscript

MS: Data collection, revision of final manuscript

Conflict of interest

None of the authors have any conflict of interest to declare

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Table 1

Table 1: Demographic and clinical characteristics of the included studies

Author, Year	Surgery Type	Sample size	Patient with GERD	GERD improved (N)	GERD not improved (N)	GERD Evaluation Method(s)	Follow-up (months)	Study Design	Country
Lakdawala, 2010	LSG	50	2	2	0	Symptoms	12	Retrospective	India
	LRYGB	50	6	6	0				
Langer, 2010	LRYGB	3	3	3	0	24hrs pH manometry	14	Retrospective	Austria
Omana, 2010	LSG	49	9	2	7	Symptoms	27	Retrospective	USA
	LRYGB	74	9	3	6				
Tai, 2011	LSG	47	8	3	5	Questionnaire	12	Prospective	Taiwan
Gluck, 2011	LSG	204	113	112	1	Questionnaire	36	Retrospective	USA
Chopra, 2012	LSG	174	24	11	13	Symptoms & endoscopy	6	Retrospective	USA
Ekelund, 2012	LRYGB	5	5	5	0	Endoscopy & 24hrs pH manometry	1.5	Prospective	Sweden
Carabotti, 2013	LSG	74	20	13	7	Questionnaire	47	Retrospective	Italy
Catheline, 2013	LSG	45	5	0	5	Symptoms & endoscopy	60	Retrospective	France
Daes, 2013	LSG	382	170	160	10	Symptoms & endoscopy	22	Prospective	Colombia
Cecily, 2014	LSG	4832	2148	341	1807	Symptoms	6	Retrospective	USA
	LRYGB	33867	17062	10715	6347				
Sharma 2014	LSG	32	8	5	3	Questionnaire	12	Prospective	India
Burgerhart, 2014	LSG	20	14	6	8	Questionnaire, 24hrs pH manometry	3	Prospective	Netherlands
Kular, 2014	LSG	76	6	2	4	Symptoms	60	Retrospective	India
	LRYGB	72	5	3	2				
Boza, 2014	LSG	161	7	0	7	Questionnaire	60	Retrospective	Chile
Sheppard, 2015	LSG	205	44	3	41	Symptoms	12	Retrospective	Canada
	LRYGB	173	30	15	15				
Gorodner, 2015	LSG	14	4	0	4	24hrs pH manometry	12	Prospective	Argentina
Albanopoulos, 2016	LSG	88	24	16	8	Symptoms & endoscopy	36	Retrospective	Greece
Hendricks, 2016	LSG	919	13	0	13	Symptoms, endoscopy, 24hrs pH manometry	78	Retrospective	USA
Casella, 2016	LSG	148	27	19	8	Symptoms & endoscopy	72	Retrospective	Italy
Angrisani, 2016	LSG	105	26	15	11	Symptoms & endoscopy	60	Retrospective	Italy
Aridi, 2016	LSG	76	17	8	9	Symptoms	60	Retrospective	Lebanon
Arman, 2016	LSG	65	7	0	7	Symptoms	153	Retrospective	Belgium
Parmar, 2017	LRYGB	22	10	10	0	Symptoms	24	Prospective	UK
Garg, 2017	LRYGB	40	7	7	0	Questionnaire	24	Retrospective	USA
	LSG	40	4	2	2				
Billing, 2017	LSG	916	142	76	66	Questionnaire	12	Retrospective	USA
Chuffart, 2017	LRYGB	7	2	2	2	Symptoms & endoscopy	72	Retrospective	France
	LSG	41	13	4	9				
Goldenshluger, 2017	LSG	178	28	17	11	Symptoms	36	Retrospective	Israel
Borovicka, 2017	LRYGB	134	48	17	38	Endoscopy	7.5	Prospective	Switzerland
Kowalewski, 2017	LSG	100	4	0	4	Symptoms	96	Retrospective	Poland
Berry, 2018	LSG	477	121	78	43	Symptoms & endoscopy	36	Retrospective	Chile
Coupaye, 2018	LSG	47	16	10	6	24hrs pH manometry	12	Prospective	France

Figures

Figure 1
Flow chart of literature search

Figure 2

Laparoscopic Sleeve Gastrectomy (LSG) DRMA results. The figure depicts difference in prevalence from baseline over time of GERD symptoms. Dashed lines depict the 95% confidence intervals

Figure 3

Laparoscopic Roux-en-Y gastric bypass (LRYGB) DRMA results. The figure depicts difference in prevalence from baseline over time of GERD symptoms. Dashed lines depict the 95% confidence intervals

Figure 4

Laparoscopic Roux-en-Y gastric bypass (LRYGB) DRMA results after exclusion of a single large study. The figure depicts difference in prevalence from baseline over time of GERD symptoms. Dashed lines depict the 95% confidence intervals