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Changes in Time of Gastric Emptying after Surgical and Endoscopic Bariatrics and Weight Loss: A Systematic Review And Meta-Analysis

Eric J. Vargas¹, Fateh Bazerbachi¹, Gerardo Calderon¹, Larry J. Prokop², Victoria Gomez³, M. Hassan Murad⁴, Andres Acosta¹, Michael Camilleri⁵, Barham K. Abu Dayyeh¹

¹Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

²Division of Library Services, Mayo Clinic, Rochester, Minnesota, USA

³Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida USA

⁴Evidence-Based Practice Center, Mayo Clinic, Rochester, Minnesota, USA

⁵Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

Abstract

Background & Aims: Gastric emptying (GE) is involved in regulation of appetite. We compared times of GE after different bariatric endoscopic and surgical interventions and associations with weight loss.

Methods: We performed a comprehensive search of publication databases, through September 14, 2018, for randomized and non-randomized studies reporting outcomes of weight-loss surgeries. Two independent reviewers selected and appraised studies. Outcome of interest was GE $T_{1/2}$ (min), measured before and after the procedure. A random effects model was used to pool the mean change in $T_{1/2}$ (min) after the intervention. We performed meta-regression analysis to find

Corresponding Author: Barham K. Abu Dayyeh MD MPH FASGE, Associate Professor of Medicine Mayo Clinic, Director of Advanced Endoscopy, Director of Metabolic and Bariatric Endoscopy, Division of Gastroenterology and Hepatology, 200 First Street SW Rochester MN 55905, AbuDayyeh.Barham@mayo.edu, Phone 507-266-4739.

AUTHOR CONTRIBUTIONS

Dr. Eric J. Vargas: Study concept and design, acquisition of data, analysis and interpretation, drafting of the manuscript,

Dr. Fateh Bazerbachi: Acquisition of data and drafting of manuscript

Dr. Gerardo Calderon: Acquisition of data and drafting of manuscript

Mr. Larry Prokop : Study concept and design, material support

Dr. Victoria Gomez: Acquisition of data, critical revision of the manuscript

Dr. M. Hassan Murad: Study concept and design, statistical analysis, interpretation of data

Dr. Andres Acosta : Study supervision and critical revision

Dr. Michael Camilleri: Study concept and design, drafting and critical revision of manuscript

Dr. Barham K. Abu Dayyeh: Study concept and design, drafting of manuscript, interpretation of data, study supervision.

DISCLOSURES:

Drs. Vargas, Bazerbachi, Calderon, Gomez, Murad, Acosta and Camilleri as well as Mr. Larry J. Prokop have no relevant disclosures.

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associations between GE and weight loss. Heterogeneity was calculated using the I^2 statistic. Methodological quality was assessed.

Results: From 762 citations, the following studies were included in our analysis: 9 of sleeve gastrectomy, 5 of intragastric balloons, and 5 of antral botulinum toxin. After sleeve gastrectomy, the pooled mean reduction in GE $T_{1/2}$ at 3 months was a 29.2 minutes (95% CI, reductions of 40.9 to 17.5 min; $I^2=91\%$). Fluid-filled balloons increased GE $T_{1/2}$ by 116 minutes (95% CI, 29.4 to 203.4 min; $I^2=58.6\%$). Air-filled balloons did not produce a statistically significant difference in GE $T_{1/2}$. Antral botulinum injections increased GE $T_{1/2}$ by 9.6 min (95% CI, 2.8–16.4 min; $I^2=13.3\%$). Placebo interventions reduced GE $T_{1/2}$ by 6.3 min (95% CI, reductions of 10 to 2.6 min). Changes in GE were associated with weight loss after sleeve gastrectomy and intragastric balloons but not botulinum toxin injections.

Conclusions: In a systematic review and meta-analysis, we found that sleeve gastrectomy reduces GE $T_{1/2}$ whereas fluid-filled balloons significantly increase GE $T_{1/2}$. Air-filled balloons do not significantly change the time of GE, which could account for their low efficacy. Antral botulinum toxin injections produced small temporary increases in GE time, which were not associated with weight loss. Changes in GE time after surgical and endoscopic bariatric interventions correlate with weight loss and might be used to select interventions, based on patients' physiology.

Keywords

IGB; motility; stomach; food

INTRODUCTION:

Obesity has reached epidemic proportions with close to 60% of Americans being overweight or obese. (1, 2) This rise has led to a similar increase in excess weight-related comorbidities such as hypertension, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD) and cancer.(3, 4) While the cornerstones of obesity treatment remain lifestyle and behavioral interventions, many individuals fail to reach the levels of weight loss necessary for effective reduction of comorbidity with these approaches.(5) Bariatric surgery has been shown to be the most effective treatment for initial and long term weight loss with improvements in comorbidities, quality of life and incidence of cancer.(6-9) The mechanisms involved in the success of bariatric surgery are multifactorial, including restrictive, partially malabsorptive and hormonal changes that synergistically lead to weight loss.(9-11) Endoscopic bariatric therapies, such as intragastric balloons, small intestine bypass liners and stomach remodeling techniques have been developed to reduce net caloric intake by mimicking the perturbations generated by bariatric surgery.(12, 13)

The regulation of food intake however remains complex, involving both appetite and orexigenic signals that arise from multiple areas in the central nervous system and gastrointestinal tract. Central to appetite regulation are two important gastrointestinal traits, satiation and satiety, which are in part regulated by rates of gastric emptying and the stomach accommodation volume. (14, 15) Abnormalities in these traits, such as accelerated gastric emptying, have been implicated in obesity, but the effects of bariatric surgery and

endoscopic bariatric procedures on gastric emptying are variable in the published literature. Our general hypothesis is that each bariatric surgery and endoscopic bariatric intervention has a specific effect on gastric emptying that in turn regulates post-interventional appetite, tolerance and weight loss. Our specific aim was to perform a systematic review and meta-analysis of the effects on gastric emptying of sleeve gastrectomy, Roux-en-Y gastric bypass, adjustable gastric banding and endoscopic bariatric therapies such as intragastric balloons, botulinum toxin injections, implantable small bowel bypass liners and stomach remodeling techniques and investigate their associations with weight loss.

METHODS:

This systematic review and meta-analysis was reported following the PRISMA statement guidelines with a priori-developed protocol. PRISMA CHECKLIST is available in the appendix

Data Sources and Search Strategy

A comprehensive search of several databases from each database's inception date to September 14th, 2018 was conducted. The databases included Ovid MEDLINE Epub Ahead of Print, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian (L.J.P) with input from the study's investigators (E.J.V, F.B., B.A.D.) Controlled vocabulary supplemented with keywords was used to search for the effects of bariatric surgery and endoscopic bariatric therapies on gastric emptying in English language. The actual search strategy included the following key words gastric emptying, obesity, bariatric surgery, intragastric balloon, botulinum toxin, endoscopy, sleeve, bypass, adjustable gastric band is included in the appendix.

Study Selection

This systematic review and meta-analysis included randomized clinical trials and observational studies that investigated patients 18 years or older who underwent bariatric surgery (Roux-en y gastric bypass, adjustable gastric band and sleeve gastrectomy), intragastric balloons, endoscopic botulinum toxin antral injections, small bowel bypass liner placement or stomach remodeling techniques for the treatment of obesity. Studies involving patients who underwent bariatric surgery for reasons other than obesity were excluded. Only studies that assessed both pre- and post-intervention gastric emptying of solids were included to allow for quantitative analysis. Placebo/sham arms from interventional studies were also pooled for analysis to represent a control arm. Any abstracts found on the initial search were re-searched for full published text during the analysis phase until September 18, 2018.

Two independent reviewers (E.J.V and G.C) working in pairs screened the titles and abstracts for initial eligibility criteria and final eligible references. Any discrepancies during the process between the independent reviewers were discussed. If no consensus was reached, an independent third reviewer was asked to settle the discrepancy. Kappa statistic was

calculated to assess agreement beyond chance.(16) The study selection flow diagram appears in figure 1.

Measurement of Gastric Emptying

For each study, the gastric emptying methodology was compared to the consensus guidelines that set to standardize the measurement of gastric emptying(17). Details regarding the type of meal (solid vs. semisolid), total calories, fat content (% of calories), scintigraphy vs. breath testing, and duration of testing were collected. Gastric emptying studies were graded optimal vs suboptimal as recently recommended in the literature, based on the use of a solid meal, at least 30% fat, monitoring for at least 3 hours (18), absence of confounding medications as well as documented pre and post $T_{1/2}$ (minutes) with standard deviation.

Data Extraction

A priori data collection form was developed prior to data abstraction. The following information was abstracted from each study: author, year, study design, patient characteristics, type of gastric emptying assessment, time of pre- and post- intervention gastric emptying assessment, and mean/median $T_{1/2}$ (minutes), as the measures of gastric emptying. The information was collected in duplicate. Any missing data was handled by contacting the first and/or corresponding author via electronic means with limited responses(19) For the endoscopic bariatric techniques, we collected the type of endoscopic procedure and device indwelling time, and gastric emptying data as above. Data expressed in median and interquartile range were converted using the Cochrane handbook guidelines. Weight loss after each intervention in percent excess body weight lost (%EWL) and %percent total body weight lost (%TBWL) was collected for surgical and endoscopic interventions, respectively

Methodological Quality Assessment

The methodological quality of randomized trials was assessed using the Cochrane Collaboration risk assessment tool. This assessment focused on how the randomization sequence was generated; how allocation was concealed, whether there were important imbalances at baseline; which groups were masked (patients, care givers, data collectors, outcome assessors, data analysts); attrition rate; whether the analyses was by intention to treat; how was missing outcome data dealt with. The methodological quality of non-randomized studies (which applied to the majority of studies) was done using the Newcastle-Ottawa quality assessment tool as per the Cochrane Handbook.(20) This tool includes assessment of how the participants represented the population of interest, how the comparative group was selected, and how outcome was assessed, as well as length and adequacy of follow-up when applicable. Any discrepancy was resolved by a third independent reviewer. Results were compiled into a single bias assessment graph.

Main Outcome Measure

The main outcome of interest for this systematic review and analysis was a *priori* defined mean difference in $T_{1/2}$ (expressed in minutes) after the intervention, which is the amount of time it takes for 50% of solid contents to empty from the stomach. Liquid emptying was not

assessed as the emptying of solids or semi-solid represents the typical food ingested day to day and since it is conceivable that the interventions might enhance delivery of food from the proximal stomach to the distal stomach, or the interventions might interfere with the trituration of solid food. Other measures of gastric emptying, such as percent emptied or retained at 2 and 4 hours were inconsistently reported in surgical studies; therefore, $T_{1/2}$ was selected as the main outcome measure. A negative mean difference in (post minus pre-procedure) GE $T_{1/2}$ indicates acceleration, whereas a positive mean difference in GE $T_{1/2}$ indicates a gastric emptying delay following the intervention.

STATISTICAL ANALYSES

We conducted a meta-analysis to pool the mean difference in $T_{1/2}$ (minutes) after the interventions using the DerSimonian and Laird random effects model to account for heterogeneity between and within studies.(21, 22) The I-squared statistic was used to estimate the percentage of total between-study variation due to heterogeneity rather than chance(23). The I-square ranges from 0-100%, with values of 25%, 25-50% and 50% indicating low, moderate and high heterogeneity, respectively. A priori determined sensitivity analysis based on the timing of post intervention gastric emptying assessment (< 1 months or > 1 months) was conducted to explore sources of heterogeneity. For the endoscopic bariatric therapies, a priori determined sensitivity analysis was performed by type of endoscopic device (fluid vs. gas filled balloon). Meta-regressions to assess the role of baseline gastric emptying rate and optimal vs. suboptimal gastric emptying measurement methods on the final mean difference after the intervention were also performed. In order to explore the association between changes in gastric emptying and weight loss, a meta-regression was performed for each intervention separately. Statistical evaluation of publication bias and construction of funnel plots was not feasible due to the heterogeneity and small number of included studies.(24, 25) Thus, the impact of publication bias on certainty in the evidence remains unclear. All meta-analyses were performed using STATA 15 software. All values are two-tailed with an alpha level set at 0.05.

RESULTS

Description of Included Studies

A total of 762 citations were identified through database searches. After removing duplicates, 569 citations were reviewed. Only 94 conference abstracts and full manuscripts went to full review after excluding animal studies, reviews, studies involving non-obesity interventions such as cancer. Data abstraction was performed in a total of 19 studies (Figure 1). Chance adjusted agreement (Kappa statistic) for final inclusion in the list of manuscripts to be reviewed was 0.974.

Methodology of Gastric Emptying Measurement

Out of the 19 studies, only 8 studies collected gastric emptying measurements for at least 3 hours. Of these, 1 used a semi-solid meal. The remaining 11 studies collected measurements anywhere from 1 through 2.5 hours, with 2 studies using a semi-solid meal. Overall, the caloric content of the meals, and the percent derived from fat varied between studies. The

majority (15/19) studies reported used scintigraphy and the remainder used breath-based testing. (Table 1-2)

Using the recommendations in the literature, only 8/19 studies were initially judged to be of optimal quality based on the duration of testing (>3 hours) with 7 using a solid meal. Overall, studies with optimal methodology and solid meal testing, involved 2 sleeve gastrectomy, 2 intragastric balloon, and 4 with antral botulinum toxin injections.

Methodological Quality Assessment:

The 19 studies in this meta-analysis were assessed for bias using the Newcastle Ottawa scale for cohort studies and the Cochrane Collaboration risk assessment tool for randomized studies.(20, 26)

Sleeve Gastrectomy—For sleeve gastrectomy, 8 out of 9 studies were non-randomized trials; therefore, the risk of bias was high for randomization, allocation, and masking (blinding) for these studies, whereas the single randomized clinical trial was still biased on assessment of the outcome due to the lack of masking (blinding). The risk of bias graph and summary are available in Supplementary Figure 8. The non-randomized studies were considered to be of medium quality on the Newcastle Ottawa Scale Assessment.

Intragastric Balloons—All 5 intragastric balloon studies were judged to be of low randomized quality except the one randomized clinical trial which was considered to be of medium quality. The RCT was downgraded from high to medium quality due to lack of allocation concealment, masking (blinding) and masking during the outcome assessment (Supplementary Figure 9). On the Newcastle Ottawa Assessment scale, they were judged to be high to medium quality.

Endoscopic Botulinum Toxin Antral Injections—Among the studies using botulinum toxin injections, the majorities (80%) were double-blind randomized clinical trials and were judged to be of medium to high quality. One study was non-randomized and was considered poor quality on the Cochrane risk assessment tool, but medium to high quality in the Newcastle Ottawa Assessment Scale. (Supplementary Figure 10)

Studied Interventions

Sleeve Gastrectomy—A total of 25 laparoscopic sleeve gastrectomy studies, with only 9 meeting full inclusion criteria comparing pre- and post-surgery T1/2 outcomes were found (n=233 patients) (19, 27-34). For the 1 randomized clinical trial, each of the two arms of the study was treated as a separate study in the metaanalysis phase as opposed to pooling their values (27). The remaining studies were single arm pre- and post- intervention gastric emptying assessments. Only 2 studies had optimal (3 hour) and solid meal testing.

Roux-en-Y Gastric Bypass—There were no studies reporting both pre- and post-Roux-en-Y changes in gastric emptying of solids, and 2 only reported post-surgical changes (35, 36). Therefore, changes after RYGB were excluded from the meta-analysis.

Laparoscopic Adjusted Gastric Banding—Two individual adult studies with the laparoscopic adjustable gastric band (LAGB) and solid gastric emptying measurements were found. Only 1 study had pre- and post-surgery gastric emptying assessments and was therefore not included in the meta-analysis.(37)

Intragastric Balloons—A total of 11 studies using an intragastric balloon for obesity were identified. Only 5 reported pre and post intervention GE $T_{1/2}$ for solid meals (38-42). The studies included 3 fluid-filled balloons and 2 gas-filled balloons. All studies performed a gastric emptying assessment within 3 months of balloon placement. Only 1 study with a fluid-filled balloon utilized optimal gastric emptying methodology. No studies with present day available gas-filled balloons or dual fluid-filled balloons were found. The placebo arm from 1 intragastric balloon studies was included in the meta-analysis phase.

Endoscopic Botulinum Toxin Antral Injections—Only 4 studies of endoscopic botulinum toxin injections for obesity reported pre- and post-intervention GE $T_{1/2}$ and one study reported mean difference with standard deviation. Therefore, a total of 5 studies were included in the meta-analysis phase (43-47), with 4/5 using optimal gastric emptying measurement methodology. Three studies reported changes in gastric emptying for the sham group (control injection) and were studied in the analysis phase with the 2 placebo arms to represent the control group.

Other Endoscopic Interventions—A total of 3 studies using the small bowel implantable device were found. One of the studies reported changes in $T_{1/2}$, %2 hour and %4 hour retention (48). The remaining two studies only reported either %2hr retention or %4hr retention and thus were excluded from the meta-analysis. In 2 studies involving differing stomach remodeling techniques, (1 Endoscopic Sleeve Gastroplasty using Apollo Endosurgery's OverStitch Device and 1 Primary Obesity Surgery Endolumenal procedure using the USGI's Incisionless Operating Platform), changes in gastric emptying were found (49, 50). Given the differences in technique and device, these studies were excluded from the meta-analysis. The final studies included in the meta-analysis along with details by intervention are included in Tables 1-2.

Change in Gastric Emptying ($T_{1/2}$) and Association with Weight Loss

Sleeve Gastrectomy—There were a total of 9 studies included in the meta-analysis (n=233 patients). Using a random effects model, the pooled change in gastric emptying 3 months after sleeve gastrectomy was a mean acceleration of -29.2 minutes (95% CI -40.9 to -17.5) (Supplementary Figure 1). There was high heterogeneity in the results ($I^2=91.4\%$). Sensitivity analysis excluding studies in which the gastric emptying assessment was performed less than 1 month post intervention, heterogeneity decreased to 77.8%, with a mean acceleration of -25.5 minutes (95% CI: -34.8 to -16.3). Subgroup analysis by optimal (n=2 studies) vs suboptimal gastric emptying (n=4 studies) methodology using only pure solid-meal testing (6/8 studies), resulted in decrease in heterogeneity from 91.4% to 0% and 50.5%, respectively. In the optimal testing group, sleeve gastrectomy accelerated gastric emptying by -8.3 minutes (95% CI: -16.5 to -0.05 minutes) and in the suboptimal testing group, by -41.1 minutes (95% CI: -49.6 to -32.6 minutes) Supplementary Figure 2)

On meta-regression examining the relationship between change in GE and %EWL at 12 months (n=6 studies), no significant association was found (p=0.986). However, when examining the post sleeve gastrectomy T_{1/2} association with weight loss, lower (faster) post-LSG T_{1/2} was associated with more %EWL at 12 months (p=0.009) (Figure 2). We then performed a meta regression assessing the relationship between baseline gastric emptying and final mean difference in gastric emptying T_{1/2} after the intervention, suggesting slower baseline GE was associated with faster post SG (coefficient -0.61;p=0.051) (Supplementary Figure 3).

Intragastric Balloons—A total of 5 studies were included in the initial meta-analysis (n=66). The pooled mean change in gastric emptying was a non-significant delay of 42.7 minutes (95% CI: -0.83 to 86.2). Heterogeneity was high (I²=85%) (Figure 3). In the subgroup analysis comparing gas vs. fluid-filled balloons, fluid-filled balloons delayed gastric emptying by a mean 116.4 minutes (95% CI: 29.4 to 203.4) whereas air-filled balloons non-significantly altered gastric emptying by a mean -2.9 minutes (95% CI: -21.7 - 15.9). Heterogeneity decreased from the overall 85% for all 5 studies to 51.5% (I²=51.5%), and 57.8% (I²=57.8%), in the air and fluid-filled balloon analyses, respectively (Figure 3). When examining the association between GE and weight loss (n=5 studies), meta-regression revealed greater changes (produced delays) in gastric emptying was associated with more %TBWL at 6 months (p=0.05). Additionally, slower post-IGB GE was also associated with more weight loss at 6 months (p=0.04). (Figure 4)

Endoscopic Botulinum Toxin Injections for Weight Loss—5 studies were included in the meta-analysis separated in a total 12 arms by study dose. The mean change in gastric emptying post intervention was a mean 9.6 minute delay (95% CI: 2.8-16.4) Heterogeneity was low at 13.3% (I²=13.3%). (Supplementary Figure 4) On sensitivity analysis by study dose (<300 units or 300 units Botulinum Toxin), low doses were associated with a non-significant delay of 5.6 minutes (95% CI: -3.5 to 14.6), and higher doses were associated with a statistically significant delay of 9.6 minutes (95% CI: 2.8-16.4). Heterogeneity remained low at 17.3% and 13.3%, respectively. On subgroup analysis using only optimal gastric emptying testing, antral botulinum toxin injections <300 units delayed emptying by 13.2 minutes (95% CI 2.7-23.7 minutes) and doses 300 units delayed emptying by 14.6 minutes (95% CI: 7.5-21.7 minutes) with low heterogeneity (I²=0.0%). (Supplementary Figure 5) On meta regression, changes in GE were not associated with absolute weight loss at an average 4 months after the botulinum toxin injections.

Placebo—A total of 4 placebo/sham arms from botulinum toxin and intragastric balloon studies were pooled to investigate the changes in gastric emptying. The mean change in gastric emptying was a mean acceleration of -6.1 minutes (95% CI: -9.8 to -2.4). Heterogeneity was low at 0%. (Supplementary Figure 6). Supplementary Figure 7 contains all the studies by intervention in the meta-analysis.

DISCUSSION

In this systematic review and meta-analysis on the effects of bariatric surgery and endoscopic treatments on gastric emptying, there were several important findings. First, in

endoscopic and bariatric interventions are modifying the body's existing food regulation pathways facilitating weight loss with greater perturbations associated with more weight loss per our analysis.

The observed accelerated gastric emptying after sleeve gastrectomy and association with weight loss is likely multifactorial. After sleeve gastrectomy, the proximal portion of the stomach and the majority of the greater curvature is resected, reducing Ghrelin production, reducing stomach accommodation, increasing intraluminal pressure, and promoting content delivery to the antrum. However, by leaving the lesser curvature intact, antral innervation remains functional, promoting faster gastric emptying through the pylorus, promoting early nutrient delivery to the intestine. As a result, through the increased intragastric pressure, reduced Ghrelin production and changes in bile acid metabolism through earlier nutrient delivery, weight loss ensues (59). In contrast, fluid-filled balloons markedly delay gastric emptying through an outlet obstruction mechanism, while also promoting a sense of fullness by stimulating stretch receptors by the food and the balloon itself without any increases in Ghrelin.(41) Early studies investigating fluid-filled balloons found a reduction in food intake with increasing fluid volume, but were unable to identify delays in gastric emptying.(60, 61) Subsequent studies with air-filled balloons showed initial promise for weight loss, but were abandoned due to the high rates of distal intestinal obstruction and poor efficacy in weight loss.(39, 42) Our results suggest air-filled balloons do not alter gastric emptying, providing a possible explanation for the decreased efficacy in induction of weight loss, though there is improved tolerability of the newer commercially available air-filled balloons.(51, 62) Air-filled balloons likely fail to delay gastric emptying as they tend to float in the stomach, whereas the fluid-filled balloons delay gastric emptying through an obstructive physiology and stronger stretch receptor stimulation. This obstructive mechanism with fluid-filled IGBs is likely responsible for the increased nausea, vomiting and reflux experienced early on during device residency, which improves over time. Predictably, this improvement parallels the weight loss plateau seen with fluid-filled balloons around 3 months, when patient's accommodating volume has likely increased/improved, behavioral change fatigue ensues, or hormonal adaptations begin to occur. However, changes in stomach accommodating volume *during* IGB use have not been investigated. Indeed, early studies have shown that impaired accommodation leads to earlier meal-induced satiation in the presence of an obstruction, providing a putative factor contributing to weight regain.(63) With botulinum toxin injections to the antrum, the transient delays in GE are likely a consequence of inhibiting the cholinergic neurons that control antral contractility and the interstitial cells of Cajal, which likely increase intragastric pressure and antrum distention leading to weight loss. However, the short duration of botulinum toxin's action on cholinergic neurons likely explains the failure to produce sustained weight loss in the absence of repeated injections, thus the lack of association between changes in GE with weight loss in our analysis.

Our study has many limitations, including the small number of studies available for all interventions, low methodological quality of the trials, and absence of direct comparisons on gastric emptying between the interventions. Additionally, we were limited by the significant amount of clinical and statistical heterogeneity across the studies largely due to their non-randomized nature and different methods of gastric emptying assessment. Varying meal size, fat content, duration of testing and type of assessment (breath vs. scintigraphy) likely

explain the heterogeneity between studies as determined in our subgroup analyses. with different surgical techniques in the laparoscopic sleeve gastrectomy (bougie size, distance from the antrum) likely explaining the remaining heterogeneity.

Despite these limitations, this is the first study aimed at evaluating the effects of different bariatric interventions on gastric emptying and its relationship with weight loss, showing larger perturbations in gastric emptying being associated with more weight loss and opposite effects of fluid-filled IGBs and sleeve gastrectomy surgery on gastric emptying suggesting a different mechanism of action targeting different gastric and small intestinal physiology.

The obesity management tools box is expanding to include multiple medical, endoscopic, and surgical interventions. Individual patients' response to these interventions, however, varies and follows a traditional Bells curve distribution with low, average, and high responders, given the heterogeneity of obesity as chronic multifactorial disease with varying pathophysiologic and behavioral etiologies. This meta-analysis synthesizes the available data revealing an association between gastric emptying and weight loss after sleeve gastrectomy and fluid-filled IGBs, suggesting gastric emptying can be utilized to tailor obesity management across interventions and measure response to such. Overall, patients with slower gastric emptying at baseline may not tolerate fluid-filled IGBs, and maybe better candidates for sleeve gastrectomy surgery or air-filled gastric balloon. On the other hand, patients with accelerated gastric emptying at baseline might be more responsive to an intervention that significantly delays gastric emptying, such as fluid-filled IGBs. This physiologically tailored and personalized approach to bariatric intervention, have shown promise in proof-of-concept prospective trials both with obesity pharmacotherapies and IGBs (55, 64, 65) Therefore, we recommend patients with obesity should undergo a standardized gastric emptying of solids assessment in order to personalize their approach with medications, endoscopic devices and bariatric surgery, reducing the number of non-responders, maximizing device efficacy and health care resources.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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prisma 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations;	2

Section/topic	#	Checklist item	Reported on page #
		conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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Need to Know

Background:

We performed a systematic review and meta-analysis of times of gastric emptying (GE) after different bariatric endoscopic and surgical interventions and associations with weight loss.

Findings:

In a systematic review and meta-analysis, we found that sleeve gastrectomy reduces GE $T_{1/2}$ whereas fluid-filled balloons significantly increase GE $T_{1/2}$. Air-filled balloons do not significantly change the time of GE, and antral botulinum toxin injections produced small temporary increases in GE time. Changes in GE time after surgical and endoscopic bariatric interventions correlate with weight loss.

Implications for Patient Care:

Changes in GE time after bariatric procedures might be used to select interventions for weight loss, based on patients' physiology.

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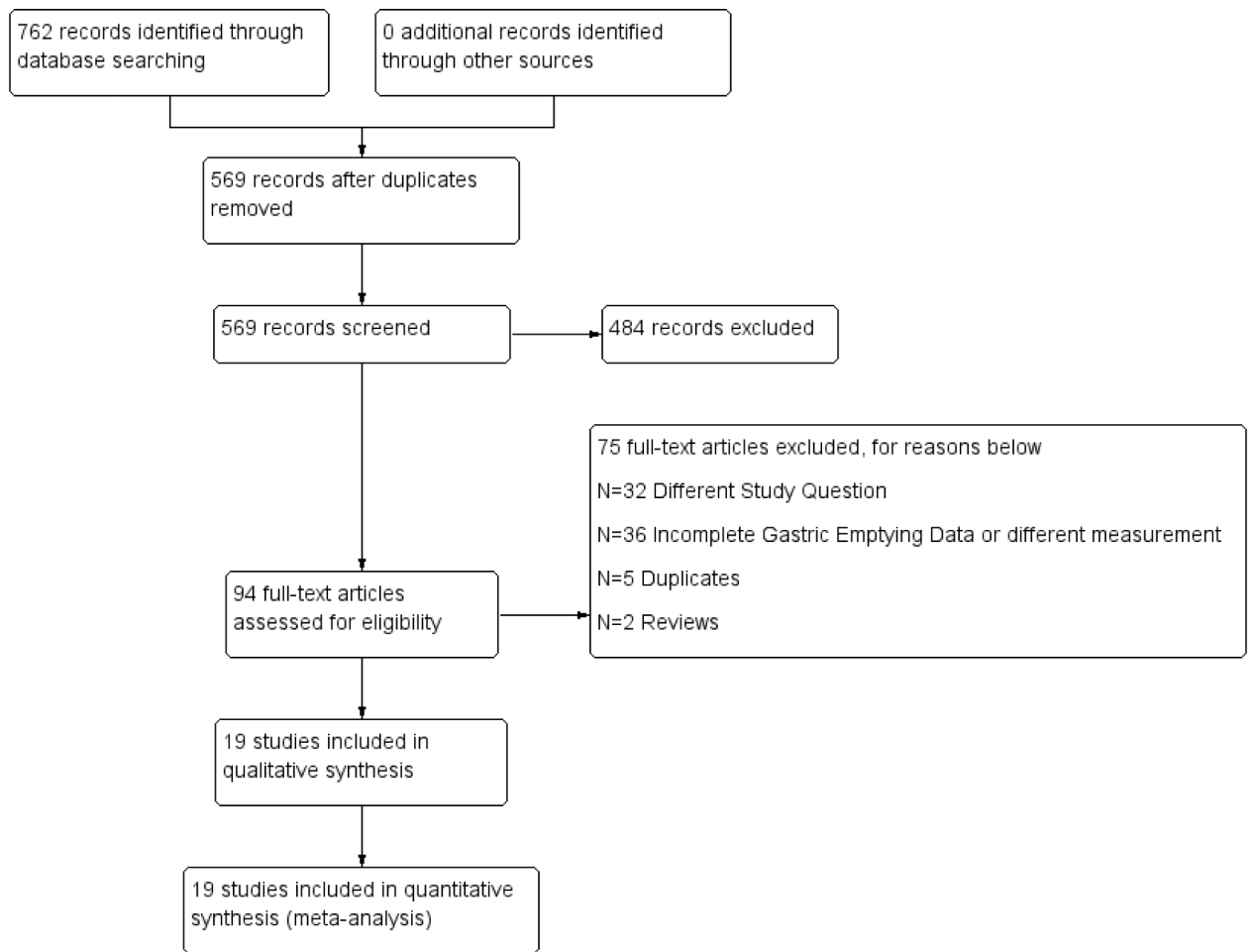


Figure 1:
Study Selection Flow Diagram

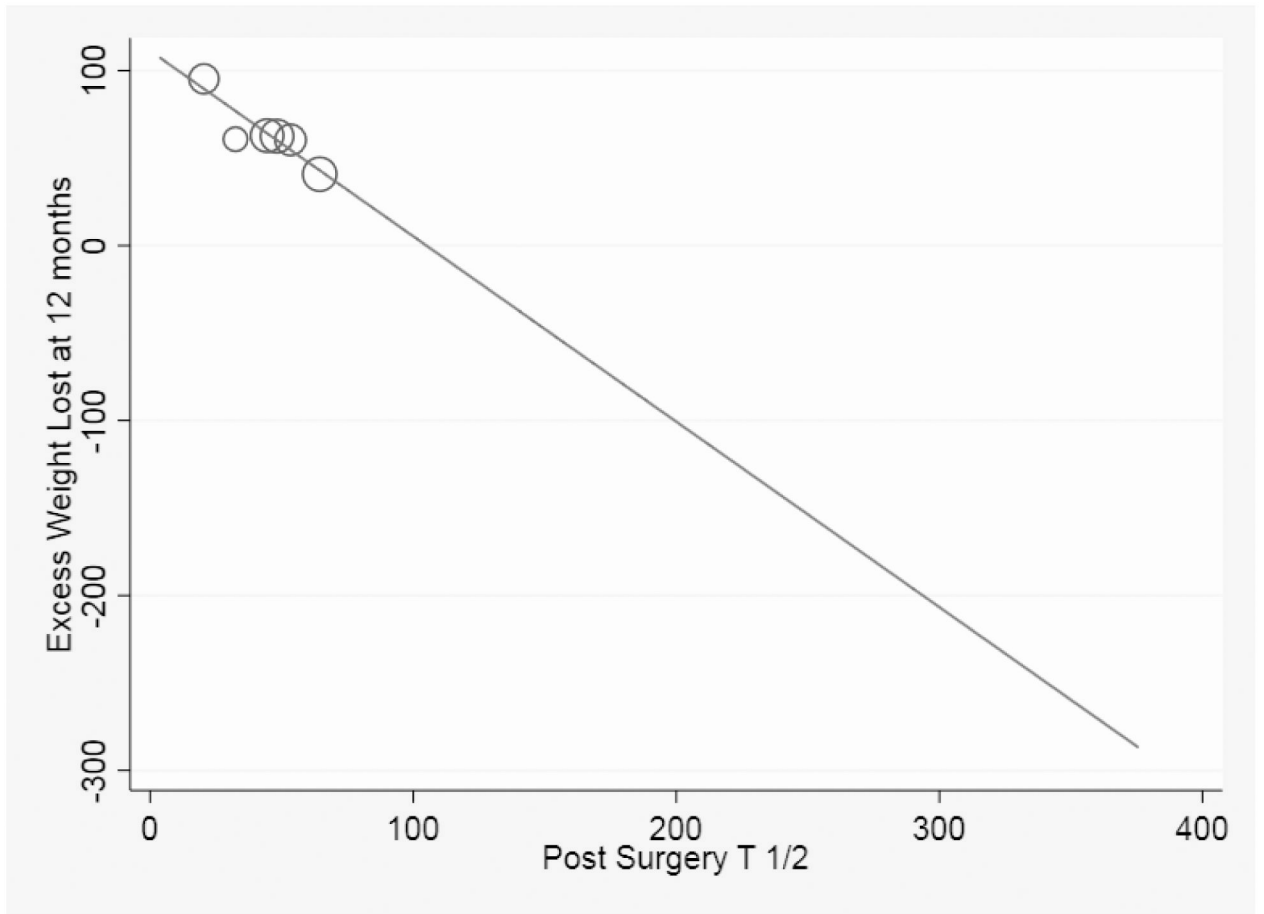


Figure 2:
Association between Post SG T 1/2 and Excess Weight Loss at 12 months

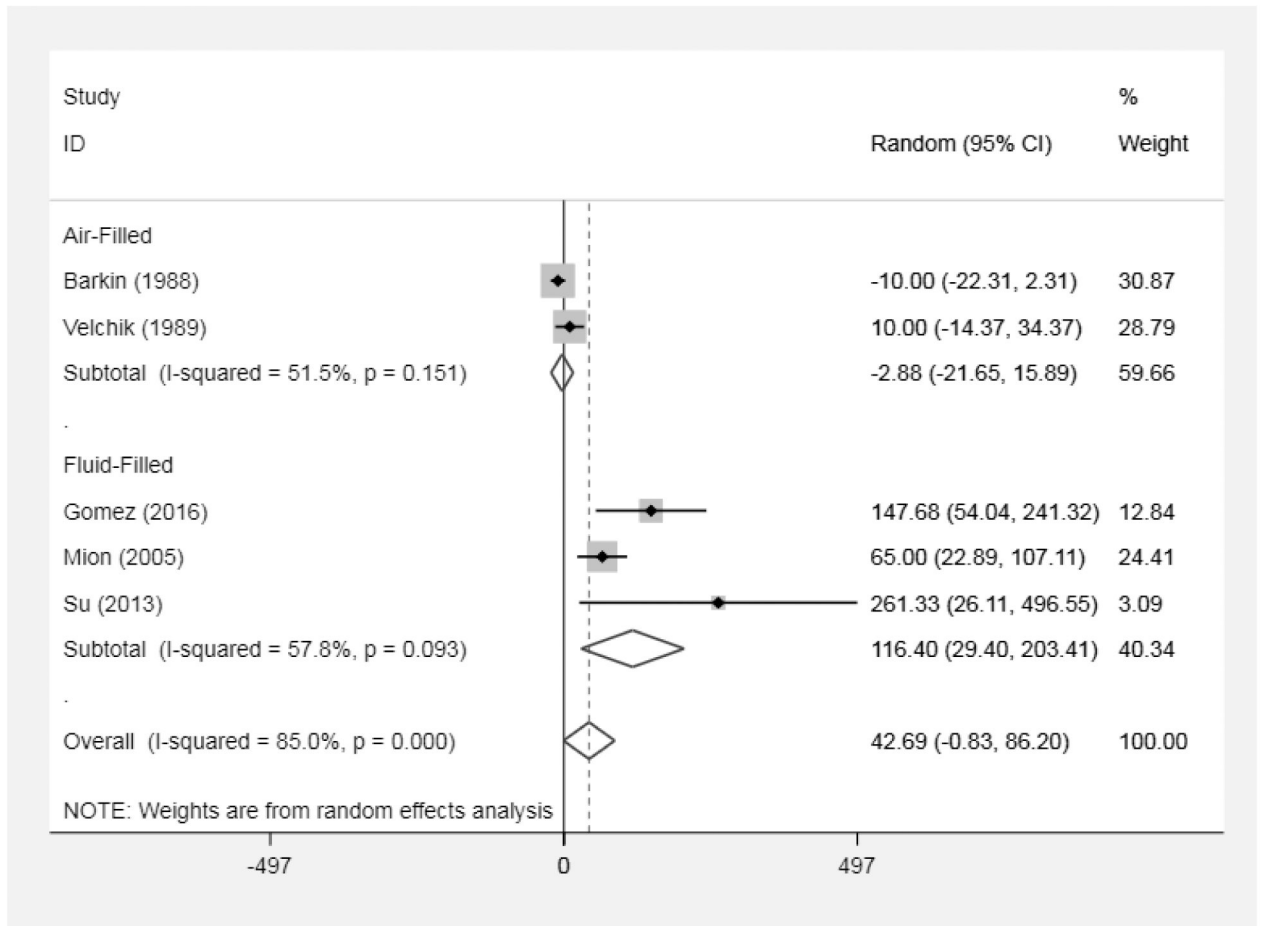


Figure 3:
Forest Plot with All Intragastric Balloon Studies

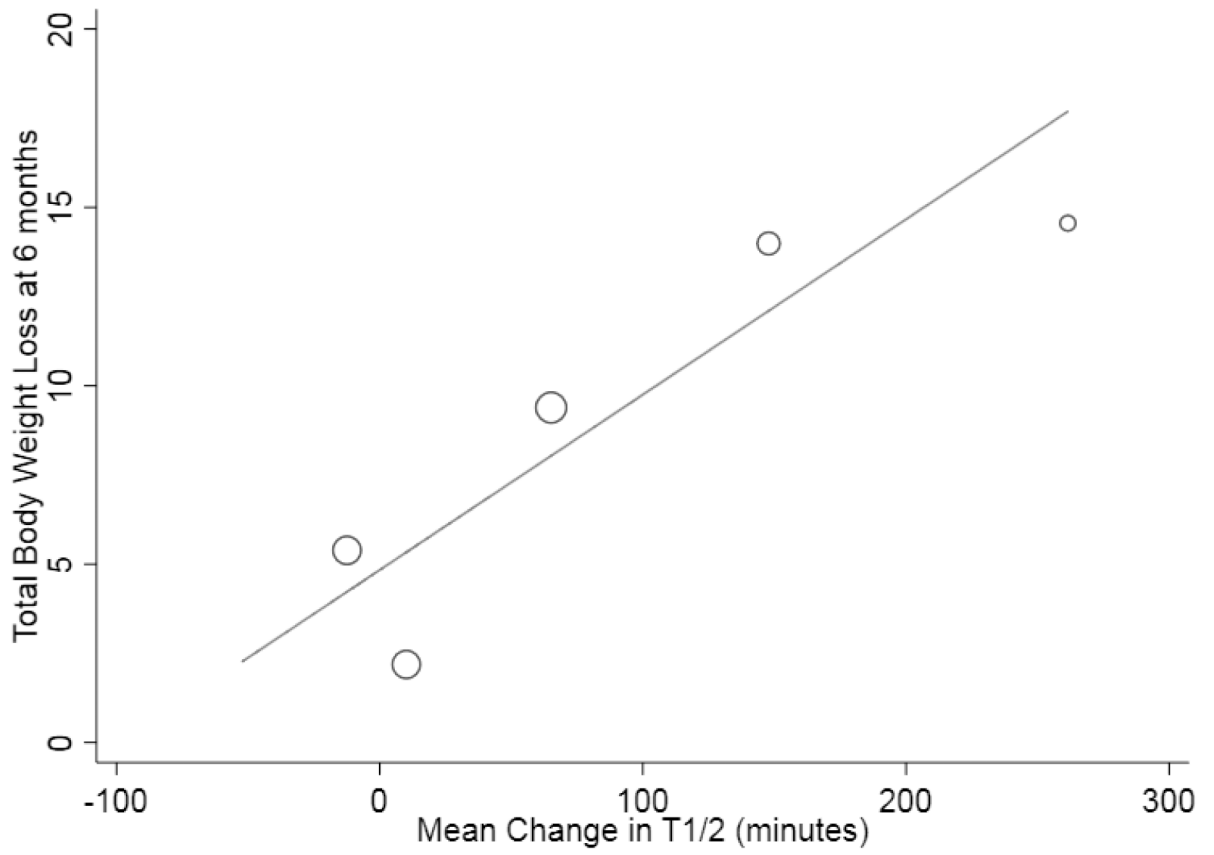


Figure 4:
Association between post IGB T1/2 and %TBWL at 6 months

Table 1:

Characteristics of included Sleeve Gastrectomy and Intra-gastric Balloon Studies

Study (Year)	Study Type	Interventions	Sample size	Age, years	Sex, female (%)	BMI, kg/m ² (mean±s.d.)	Pre-TI/2, min (mean ±s.d.)	Time of 2nd	Post-TI/2, min (mean ±s.d.)	Length	Type of Test	Type of Meal
Melissas (2007)	Single arm	LSG	11	41.5±10.7	72.7%	48±5.9	94.3 ± 15.4	6 months	47.6 ± 23.2	1.5	Scintigraphy	Solid 390 calories, (52% fat, 32% protein, 16% CHO)
Bernstine (2009)	Single arm	LSG	21	35(Range 19-58)	85.7%	45	62.4 ± 19.8	3 months	56.8±18.7	4	Scintigraphy	Solid 230 kcal (35% fat, 18% protein 47% CHO)
Michalsky (2013)	Single arm	LSG	4	N/A	N/A	N/A	57.5±12.7	3 months	32.3±17.3	1.5	Scintigraphy	Solid Unknown kcal (2 slices of bread, 2 eggs, 250 ml black tea)
Pilone (2013)	Single arm	LSG	45	N/A	N/A	N/A	80.4±33.1	3 months	64.3±40	4	Scintigraphy	Semi-solid 230 kcal (35% fat 18% protein 47% CHO)
Melissas (2013)	Single arm	LSG	21	38	N/A	46.8 (Range 35.8-62.5)	63.7±16.5	4 months	53.2±20.1	4	Scintigraphy	Solid 358 kcal (50% fat, 20% protein, 30% CHO)
Kandeel (2015)	Single arm	LSG	45	32.5±8.1	80%	49.1±7.1	74.9±7.1	1 month	28.4±8.3	2	Scintigraphy	Solid 2 meals, pre 2 egg sandwich, post LSG 1 egg
Vigneshwaran (2016)	Single arm	LSG	20	41.6±9.5	45%	33.4±1.2	38.4±13	3 - 6 months	20.3±7.6	N/A	Scintigraphy	Semi-solid Unknown Kcal. Grounded rice
Vives (2017) ^{3cm^a}	RCT	LSG	30	51.3±12.1	73.3%	51±5.2	96.5±78.9	6 months	44.3±21.1	1	Scintigraphy	Semi-solid 400 kcal (30% fat, 15% protein 55% CHO)
Vives (2017) ^{8cm^a}	RCT	LSG	30	50.5±10.6	70%	51.3±7.2	99.9±71.4	6 months	48.1±21.6	1	Scintigraphy	Same as above
Sista (2017)	Single arm	LSG	26	40.9±12.5	69.2%	46.7±4.2	68.7±25	3 months	33.5±18	2	Scintigraphy	Solid 80-82 calorie boiled egg
Barkin (1988)	Single arm	IGB- Air	26	37	58%		100±25	0.5 month	90 ± 10	2.5	Scintigraphy	Solid 2 eggs, 2 pieces of white toast, followed by 300 ml of clear juice.
Velchik(1989)	Single arm	IGB- Air	10	36	100%		57± 27.8	1 month	67 ± 27.8	2	Scintigraphy	Solid 300 kcal egg white sandwich (20% fat)
Miton (2005)	Single arm	IGB- Fluid	15	34.9	86%	34.4±0.7	92±45	1 month	157 ± 70	4	Breath	Solid 250 kcal 1 egg 2 slices bread 5g

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Study (Year)	Study Type	Interventions	Sample size	Age, years	Sex, female (%)	BMI, kg/m ² (mean±s.d.)	Pre-TI/2, min (mean ±s.d.)	Time of 2nd	Post-TI/2, min (mean ±s.d.)	Length	Type of Test	Type of Meal
Su (2013)	Single arm	IGB-Fluid	3	36.8±9.2	66.7%	40.9±15.2	114±18.5	3 months	375.3 ± 207	2	Scintigraphy	margarine [13C]- octanoic acid Solid 260 kcal egg white sandwich
Gomez (2016)	RCT	IGB-Fluid/ Placebt	13	38.1±8.8	87%	34.7±3.4	64.7±39.79	4 months	212.4±167.6	2	Scintigraphy	Solid 255 kcal egg white sandwich with jam and 120 ml of water

Characteristics of Included Botulinum Toxin Injection Studies

Table 2:

Study (Year)	Study type	N	Age, years	Sex, female (%)	BMI, kg/m ² (mean ± s.d.)	Botox Dose	Injection Location	Pre-T1/2, min (mean ± s.d.)	Time of 2nd	Post-T1/2, min (mean ± s.d.)	Length	Type of Test	Type of Meal
Junior(2006)	Prospective	12	N/A	67%	46.2 ± 4.3	Mix		140.9 ± 18.8		144.2 ± 15.1	4	Breath	Solid ~270 kcal (35% fat) 1 egg, two slices white bread 5g margarine (¹³ C Octanoic Acid)
I -200		3			52.5±6.9	200	Antrum 8	147.3±23.9	3 months	144.7 ± 26			
II-200		3			46.7 ± 2.8	200	Antrum 16	144.3 ± 5.5	3 months	154.3±16			
III-300		3			43.8 ± 1.8	300	Antrum 16	134.7 ± 23.2	3 months	145.7 ± 8.7			
IV-300		3			44.5 ± 1.1	300	Antrum 24	148.3 ± 31	3 months	140.7 ± 16.8			
Gui (2006)	RCT	14				Mix					2	Scintigraph	Solid 420 kcal (28% fat) 2 eggs, 100 g bread and water
I – 133		6	46 ± 12	50%	49.4±7	133	Antrum 8	71±16.8	0.5 months	71.8±18.3			
II – 200		4	43 ± 8	25%	49.4±7	200	Antrum 8	82.8±13.1	0.5 months	75.3±6.4			
III- Placebo		4	34±11	50%	44.5±7.3	placebo	Antrum	70.8±12.8	0.5 months	62.5±13.7			
Foschi(2008)	RCT	18/30	40.6±3.5	83%	44.6±1.4	200	Antrum and Fundus	83.4±3.9	2 months	101.6 ± 9.9	3	Breath	Solid 378 kcal standard bun(33.3% fat) (¹³ C Octanoic Acid)
II- Placebo		12/30	45.2±3.7	75%	44.5±7.3	Placebo		103.4±4.5	2 months	96.6 ± 5.6			
Li (2012)	RCT	19	35.7±10.7	52%	34.9±5.9	200	Antrum Body and Fundus	147.2±34.6	1 month	177.8±47.2	4	Breath	Solid 260 kcal (18% fat) 50g flour, 1 egg 150 ml of water (¹³ C OctanoicAcid)
I - 200		9			33.6±6	200	Antrum Body and Fundus	153.2±42.2	1 month	188.4±48.3			
II - 300		10			36.1±6	300	Antrum Body and Fundus	141.8±27.2	1 month	168.5±46.6			
Topazian (2013)	RCT	45/60	49	87%	37.9						4	Scintigraphy	Solid 296 kcal 35% fat egg, toast, and milk
I - 100		15				100	Antrum		0.5 months	MD: 14±29			
II-300		15				300	Antrum		0.5 months	MD: 24±39			

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Study (Year)	Study type	N	Age, years	Sex, female (%)	BMI, kg/m ² (mean ± s.d.)	Botox Dose	Injection Location	Pre-TI/2, min (mean ±s.d.)	Time of 2nd	Post-TI/2, min (mean± s.d.)	Length	Type of Test	Type of Meal
III- 500		15				500	Antrum		0.5 months	MD: 14±27			
IV- Placebo		15				Placebo	Antrum		0.5 months	MD: 0.8±24			