

A Meta-Analysis of GLP-1 After Roux-En-Y Gastric Bypass: Impact of Surgical Technique and Measurement Strategy

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Abstract

Background Roux-en-Y gastric bypass (RYGB) is an effective treatment for diabetes. Glucagon-like peptide-1 (GLP-1) is a gut hormone that is important to glucose homeostasis.

Objective This study aimed to assess GLP-1 level and its predictors after RYGB.

Methods The study design was a meta-analysis. The data sources were MEDLINE, EMBASE, Web of Science, and the Cochrane Databases. The study selection composed of studies with pre- and post-RYGB levels. The main outcomes were as follows: Primary outcome was the change in postprandial GLP-1 levels after RYGB. Secondary outcomes included the changes in fasting glucose, fasting insulin, and fasting GLP-1 levels after RYGB. Meta-regression to determine predictors of changes in GLP-1 levels was performed. Outcomes were reported using Hedge's *g*.

Results Twenty-four studies with 368 patients were included. Postprandial GLP-1 levels increased after RYGB (Hedge's $g = 1.29$, $p < 0.0001$), while fasting GLP-1 did not change ($p = 0.23$). Peak postprandial GLP-1 levels gave the most consistent results ($I^2 = 9.11$). Fasting glucose and insulin levels decreased after RYGB ($p < 0.0001$).

Roux limb length was a significant predictor for amount of GLP-1 increase ($\beta = -0.01$, $p = 0.02$). Diabetes status, amount of weight loss, length of biliopancreatic limb, and time of measurement were not significant predictors ($p > 0.05$).

Conclusion Postprandial GLP-1 levels increase after RYGB, while fasting levels remain unchanged. Shorter Roux limb length is associated with greater increase in postprandial GLP-1, which may lead to better glycemic control in this population.

Keywords RYGB · GLP-1 · Incretin · Diabetes · Metabolic · Bariatric · Mechanism · Obesity

Abbreviations

RYGB	Roux-En-Y Gastric Bypass
GLP-1	Glucagon-Like Peptide-1
BMI	Body Mass Index
NAFLD	Non-alcoholic Fatty Liver Disease
US	United States
SOS	Swedish Obese Subjects
T2DM	Type 2 Diabetes Mellitus
STAMPEDE	Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently
AUC	Area Under The Curve
OGTT	Oral Glucose Tolerance Test
ROBINS-I	Risk Of Bias In Non-Randomized Studies—Of Interventions
NOS	Newcastle-Ottawa Quality Assessment Scale
CI	Confidence Interval
RCT	Randomized Controlled Trial
FXR	Farnesoid X Receptor

Introduction

Obesity has become a growing pandemic. Since 1980, worldwide obesity has doubled [1]. In the USA, more than one third of the adult population were obese (BMI of ≥ 30 kg/m²) in

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2014 [2]. Parallel to this, there has been a rapid increase in obesity-related comorbidities including hypertension, hyperlipidemia, diabetes, coronary artery disease, non-alcoholic fatty liver disease (NAFLD), gallbladder disease, and certain types of cancer. In 2012, approximately 210 billion dollars were spent to treat obesity-related conditions in the USA, accounting for 21% of health care expenditures [3].

Roux-en-Y gastric bypass (RYGB) is a bariatric surgery developed by Mason and Ito in 1967 for the management of obesity [4]. It involves the creation of an upper gastric pouch. A portion of the small intestine is divided at the mid-jejunum, and the distal portion is anastomosed to the gastric pouch to become the Roux limb. The excluded portion of the stomach and the proximal small intestine, also known as the biliopancreatic limb, are anastomosed distally to the distal end of the Roux limb. Ingested nutrients flow down the Roux limb and come in contact with the biliary and pancreatic secretions below the level of the anastomosis in the segment of the small intestine known as the common channel. In the Swedish Obese Subjects (SOS) study, patients who underwent RYGB lost $27 \pm 12\%$ of their baseline weight at 15 years and had a decreased mortality rate compared to the control group [5].

In addition to inducing weight loss, RYGB has been shown to be effective at treating obesity-related comorbidities including type 2 diabetes mellitus (T2DM). In a STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) trial, 150 obese and uncontrolled diabetic subjects were randomized to receive intensive lifestyle therapy and medications or intensive lifestyle therapy and medications and bariatric surgery (RYGB or sleeve gastrectomy). At 3 years, those who underwent RYGB had significant improvement in their glycemic control compared to those who received intensive lifestyle therapy and medications alone. Additionally, more patients in the RYGB arm were able to discontinue their anti-diabetic medications [6]. While the benefits of RYGB on glycemic control is clear, the exact mechanisms remain unknown.

It has been hypothesized that the early delivery of nutrients to the distal gut may lead to improvement in diabetes after RYGB. Also known as the hindgut hypothesis, this theory implies an important role of the incretin hormone glucagon-like peptide-1 (GLP-1) on glycemic control after bypass surgery [7]. Secreted by L-cells in the distal ileum and colon, GLP-1 secretion is stimulated by nutrients within the lumen. It then binds to receptors in the pancreatic beta-cells to promote the release of insulin and therefore plays a key role in glycemic control. In addition, GLP-1 also promotes satiety, delays gastric emptying, increases insulin sensitivity, and decrease glucagon secretion [8].

GLP-1 levels have been shown to increase following gastric bypass surgery in several observational studies. However, a meta-analysis investigating the effect of RYGB on changes

in GLP-1 has not previously been investigated. We therefore present a systematic review and meta-analysis to assess the changes in GLP-1 levels following RYGB. In addition, a meta-regression was performed to assess predictors of changes in GLP-1 levels after gastric bypass.

Methods

Data Sources and Searches

The search strategy, study eligibility criteria, selection process, data collection process, primary and secondary outcomes, and analyses were defined a priori and are described below.

We searched four databases—MEDLINE, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials—from inception to August 1, 2016 without language or study design restriction. An extensive search strategy was employed to find articles that relate to changes in GLP-1 levels after RYGB. For articles related to RYGB, the following were searched by subject heading: *gastric bypass*; and by text words in the title and abstract: *RYGB, Roux en Y gastric bypass, Roux en Y, gastric bypass, stomach bypass, bariatric surgery, obesity surgery, bypass surgery*. For articles related to GLP-1, the following were searched by subject heading: *glucagon like peptide 1*; by text words in the title and abstract: *glucagon like peptide 1, glucagon like peptide, GLP1, GLP-1, GLP 1, incretin**; and by text words in the body of the article: *GLP1, GLP-1, glucagon like peptide*. The final search combined the search parameters for RYGB and GLP-1.

After duplicates were removed, two of the authors (P.J and D.J) independently reviewed titles and abstracts produced by the search. Studies deemed potentially relevant were reviewed in full to determine eligibility. Disagreements regarding final study inclusion were resolved by discussion. If a consensus could not be reached, the senior author (C.T.) served as the final arbiter.

Study Selection

Study Design and Population

Randomized clinical trials, observational cohort studies, and case series were included. Reviews, editorials, case-control studies, and studies using non-human subjects were excluded, as were articles without full text availability or English translation. Only one study from the same research group was selected to preserve independence of observations. Studies which measured GLP-1 levels in the setting of GLP-1 agonist/antagonist were also excluded. Studies were included if patients were adults > 18 years of age, obese with mean body mass index (BMI) ≥ 30 kg/m², underwent RYGB

surgery for weight loss, and received serum GLP-1 measurements pre and postRYGB.

Intervention

The study intervention was defined as RYGB for weight loss. No restrictions were applied to approach (open versus laparoscopic), or technique (length of Roux limb or biliopancreatic limb). Studies were excluded if patients underwent RYGB for indications other than weight loss (e.g., malignancy) or underwent other gastrointestinal surgeries or bariatric interventions without subgroup analysis of RYGB-only patients.

Comparison

All subjects underwent GLP-1 measurement pre and postRYGB and served as their own comparison.

Outcomes

The primary outcome was defined as change in serum postprandial GLP-1 level following RYGB from baseline preRYGB level. No restrictions were applied regarding method of stimulation (mixed meal versus oral glucose tolerance test (OGTT)). Specifically, after consumption of a mixed meal or glucose drink, frequent blood sampling was performed for up to 3 h for analysis of GLP-1. The postprandial levels may then be reported using an average or area under the curve (AUC) GLP-1 level (an average of hormonal levels from different blood draws during the 3-h interval) or peak GLP-1 level (the highest hormonal level during the 3-h interval). Studies reporting one or more of the following were eligible for inclusion: average GLP-1 levels pre and postRYGB, peak GLP-1 levels pre and postRYGB, GLP-1 total area under the curve (AUC) pre and postRYGB, or difference in GLP-1 levels pre to postRYGB.

In instances when more than one postRYGB serum GLP-1 level was reported, the measurement obtained closest to 1-year postRYGB was utilized for quantitative analysis to minimize the possible effect of weight change on GLP-1 levels [5].

Secondary outcomes were defined as changes in fasting glucose, fasting insulin, and fasting GLP-1 levels after RYGB. These were defined as the serum levels of glucose, insulin, and GLP-1 in the morning after an overnight fast.

Data Extraction, Risk of Bias Assessment, and Quality Assessment

A data extraction sheet was constructed to record information on study characteristics, patient characteristics, and predefined outcomes. Risk of bias was assessed using the Cochrane Collaboration's risk of bias in non-randomized studies of interventions (ROBINS-I) tool for observational studies and the

Cochrane Collaboration's tool for assessing risk of bias for randomized clinical trials. The domains assessed were selection bias, consideration of confounders, exposure measurement (performance bias), blinding of outcome (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and bias due to deviations from intended interventions. In this study, publications were deemed low risk of bias if more than 50% of the above domains were judged as low risk.

The quality of observational studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOS). The domains assessed were selection of cohort, ascertainment of exposure/comparator, and assessment of outcome. Quality of randomized clinical trials was assessed using the JADAD score. In this study, high quality was defined as an NOS score of ≥ 6 or a JADAD score of ≥ 3 .

Two authors (P.J. and D.J.) independently extracted data and assessed the risk of bias and study quality for each of the articles. Any disagreements were resolved by discussion and consensus, with the senior author (C.T.) serving as the final arbiter if consensus could not be reached.

Data Synthesis and Analysis

Our primary analysis was a mean difference in GLP-1 levels postRYGB from baseline preRYGB. Hedge's g was used to report the pooled effect size. A pretest-posttest correlation coefficient of 0.5 was used. Traditional forest plots with two-sided 95% CIs were constructed.

Sensitivity analyses were performed. Subgroups were predefined and used to assess the influence of specific factors on the primary outcome. Factors included diabetic status preRYGB (present versus absent), method of postprandial GLP-1 measurement (peak versus area under the curve (AUC)/mean), and different levels of pretest-posttest correlation coefficient (0.1 versus 0.9).

Univariate meta-regression was performed to assess the influence of predefined clinical characteristics on the primary outcome. These included diabetic status preRYGB, length of Roux limb (cm), length of biliopancreatic limb (cm), amount of weight loss postRYGB (% total body weight), and timing of postRYGB GLP-1 measurement (months).

Heterogeneity was assessed for the individual meta-analyses using the χ^2 test and the I^2 statistic. Significant heterogeneity was defined as $p < 0.05$ using the χ^2 or $I^2 > 50\%$. A random-effect model was used except for when statistical heterogeneity was not significant. Differences in subgroups were assessed using an χ^2 test for interaction with a $p < 0.05$ defined as statistically significant. To assess for publication bias, a funnel plot was created and visually inspected for asymmetry. The trim and fill method was used to correct for funnel plot asymmetry and provide an adjusted effect. The classic fail-safe test was also applied to assess risk of bias across studies.

Analyses were performed using comprehensive meta-analysis version 3.0 (Englewood, NJ).

Results

Study Selection

A total of 2680 studies were identified. After removal of duplicates, 1673 abstracts were reviewed. One thousand four hundred twenty-one studies were excluded leaving 252 articles for full manuscript review. After individual review of all manuscripts, 30 studies satisfied all criteria. One of the 30 studies, however, contained relevant discrepancy that could not be reconciled, and therefore was excluded. A total of 29 studies were included in the systematic review and meta-analysis (Fig. 1) [9–37].

Study Characteristics and Risk of Bias

Details of the included studies are shown in Table 1. Twenty-five out of 29 studies were cohort studies. Four studies were randomized controlled trials (RCTs) with one of the study arms being an RYGB group. Only the RYGB arm of the RCTs was included in the analysis. Out of 29 studies, 14 reported postprandial GLP-1 levels only, while 10 reported both postprandial and fasting levels. Five studies only reported fasting GLP-1 levels. Only the 24 studies that reported postprandial GLP-1 levels before and after RYGB were included in the meta-analysis.

A total of 24 included studies yielded a total of 368 subjects. Mean age of the subjects included in the studies ranged from 36 to 52 years old. Mean BMI prior to RYGB ranged from 32.1 to 51.9 kg/m². Median time of postRYGB GLP-1 measurement was 6.5 months (range 0.07 to 12).

Fig. 1 PRISMA flow diagram. Search and selection process used for studies included in the meta-analysis

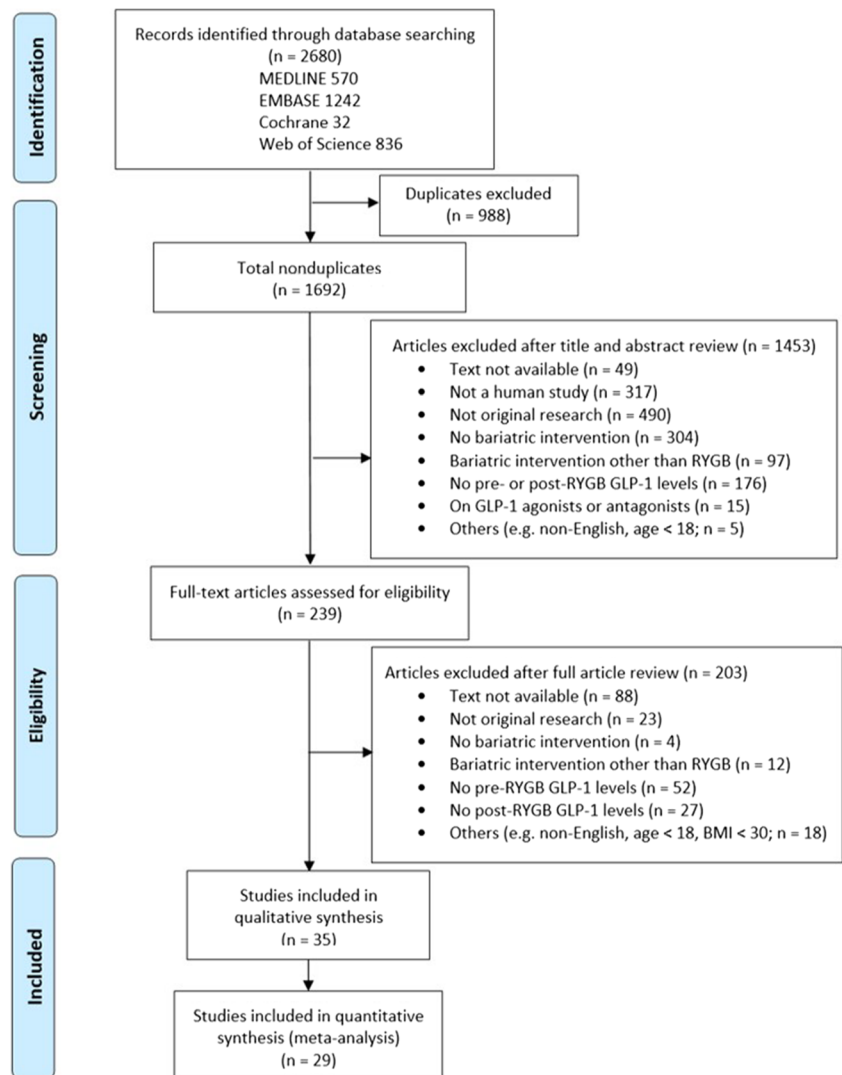


Table 1 Characteristics of studies included in the systematic review and meta-analysis. Data presented as means \pm SD

Author	Year	Country	Number	BMI prior to RYGB (kg/m ²)	DM status prior to RYGB	Fasting versus postprandial	Δ in GLP-1	PreRYGB GLP-1 (pmol/L)	PostRYGB GLP-1 (pmol/L)	Δ in GLP-1 (pmol/L)	Time of postRYGB GLP-1 measurement (months)
Anderwald ¹¹	2012	Austria	6	49.0 \pm 3.0	–	Postprandial	Increase	2.3 \pm 2.6	5.5 \pm 2.0	3.2 \pm 2.3	7
Borg ¹²	2006	UK	6	48.3 \pm 1.4	–	Postprandial	Increase	34.9 \pm 11.7	94.0 \pm 60.5	59.1 \pm 36.1	6
Bose ¹³	2010	USA	11	45.1 \pm 8.2	DM	Fasting Postprandial	Unchanged Increase	33.2 \pm 11.5 15.4 \pm 5.8	21.8 \pm 5.4 143.0 \pm 85.1	–11.4 \pm 8.5 127.6 \pm 45.5	12
Breitman ¹⁴	2011	USA	30	43.3 \pm 4.1	DM/no DM	Fasting	Unchanged	3.4 \pm 4.4	3.3 \pm 5.5	–0.1 \pm 5.0	2
Bryant ¹⁵	2013	Sweden	12	45.3 \pm 1.9	No DM	Postprandial	Increase	12.8 \pm 7.0	77.6 \pm 35.2	64.8 \pm 21.1	12
Campos ¹⁶	2010	USA	12	48.4 \pm 6.8	No DM	Postprandial	Increase	5.1 \pm 4.1	16.7 \pm 6.7	11.6 \pm 5.4	6
Chronaiou ¹⁷	2012	Greece	12	46.1 \pm 2.2	–	Fasting	Unchanged	23.0 \pm 11.2	27.0 \pm 9.9	4.0 \pm 10.5	12
Evans ¹⁸	2011	USA	10	45.6 \pm 7.6	DM	Postprandial	Increase	25.9 \pm 7.0	98.1 \pm 49.3	72.2 \pm 28.2	0.5
Falken ¹⁹	2011	Denmark	12	45.5 \pm 1.9	No DM	Fasting Postprandial	Unchanged Increase	18.7 \pm 7.3 18.3 \pm 9.0	18.5 \pm 7.0 233.0 \pm 103.9	–0.2 \pm 7.2 214.7 \pm 56.5	12
Fellici ²⁰	2014	Brazil	36	32.1 \pm 0.3	DM	Postprandial	Increase	1.7 \pm 11.6	12.0 \pm 11.6	10.3 \pm 11.6	12
Gandolfini ²¹	2015	France	34	46.3 \pm 5.9	–	Postprandial	Increase	3.4 \pm 2.9	62.5 \pm 48.6	59.1 \pm 25.8	12
Hansen ²²	2011	USA	9	51.9 \pm 6.0	–	Fasting	Unchanged	1.5 \pm 1.2	1.9 \pm 1.8	0.4 \pm 1.5	1.5
Jorgensen ²³	2012	Denmark	25	42.3 \pm 4.9	DM/no DM	Postprandial	Increase	13.7 \pm 11.2	28.5 \pm 22.4	14.9 \pm 16.8	12
Korner ²⁴	2009	USA	28	48.0 \pm 1.0	–	Fasting	Unchanged	10.5 \pm 3.0	14.1 \pm 6.3	128.5 \pm 35.1	12
Lips ²⁵	2014	Netherlands	31	43.9 \pm 1.0	DM/no DM	Postprandial	Increase	5.8 \pm 7.4	5.9 \pm 7.4	0.1 \pm 7.4	0.75
Morinigo ²⁶	2006	Spain	34	49.1 \pm 1.9	DM/no DM	Fasting	Unchanged	2.5 \pm 1.8	2.2 \pm 1.9	–0.3 \pm 1.9	1.5
Nosso ²⁷	2016	Italy	14	42.6 \pm 6.0	DM	Postprandial	Increase	11.5 \pm 8.2	11.9 \pm 8.0	0.4 \pm 8.1	12
O'Brien ²⁸	2013	USA	22	45.7 \pm 6.5	–	Fasting	Unchanged	7.0 \pm 6.0	47.0 \pm 22.2	40.0 \pm 14.0	12
Peterli ²⁹	2012	New Zealand	12	47.6 \pm 6.8	No DM	Postprandial	Increase	4.7 \pm 4.5	4.5 \pm 3.7	–0.2 \pm 4.1	12
Promintzer-Schiffner ³⁰	2016	Austria	6	49.3 \pm 3.2	No DM	Postprandial	Increase	9.5 \pm 7.1	54.6 \pm 44.0	45.1 \pm 25.6	12
Rubino ³¹	2004	USA	10	46.3 \pm 4.3	DM/no DM	Postprandial	Increase	3.4 \pm 2.8	21.2 \pm 19.4	17.8 \pm 11.3	7
Salinari ³²	2013	Italy	14	42.9 \pm 4.7	DM/no DM	Fasting	Unchanged	4.0 \pm 1.2	24.8 \pm 10.3	20.8 \pm 5.8	0.75
Samat ³³	2013	USA	9	46.0 \pm 1.8	DM	Postprandial	Increase	18.8 \pm 7.1	27.0 \pm 14.2	8.2 \pm 10.7	1
Steven ³⁴	2016	UK	27	42.2 \pm 1.0	DM/no DM	Postprandial	Increase	16.0 \pm 9.1	31.8 \pm 15.1	15.8 \pm 11.4	12
Umeda ³⁵	2011	Brazil	10	39.7 \pm 1.9	DM	Fasting	Unchanged	3.3 \pm 2.1	8.9 \pm 6.1	5.5 \pm 4.1	2
Yan ³⁶	2014	USA	20	45.5 \pm 2.1	DM/no DM	Postprandial	Increase	2.7 \pm 1.8	1.9 \pm 2.2	–0.8 \pm 2.0	3
Yip ³⁷	2014	New Zealand	11	42.6 \pm 4.2	DM	Postprandial	Increase	5.0 \pm 1.4	12.8 \pm 4.9	7.7 \pm 3.1	3
Youssef ³⁸	2013	UK	10	45.0 \pm 1.5	No DM	Postprandial	Increase	0.6 \pm 1.4	26.7 \pm 14.8	26.1 \pm 8.1	3
Zhang ³⁹	2015	China	9	32.9 \pm 2.0	DM	Fasting	Unchanged	8.8 \pm 10.1	5.6 \pm 2.4	–3.2 \pm 6.3	3
						Postprandial	Increase	9.4 \pm 8.3	84.1 \pm 86.2	74.7 \pm 47.3	0.07
						Postprandial	Increase	2.3 \pm 4.0	6.3 \pm 4.3	4.0 \pm 4.2	3
						Postprandial	Increase	7.1 \pm 3.3	32.4 \pm 10.2	25.3 \pm 6.8	3
						Fasting	Unchanged	4.5 \pm 1.6	5.8 \pm 3.8	1.3 \pm 2.7	3
						Postprandial	Increase	3.5 \pm 1.0	5.1 \pm 1.0	1.6 \pm 1.0	3
						Fasting	Increase	2.7 \pm 1.2	3.3 \pm 1.2	0.6 \pm 1.2	3

BMI body mass index, RYGB Roux-en-Y gastric bypass, DM diabetes, GLP-1 glucagon-like peptide-1, kg kilogram, m meter, pmol/l picomole/l, UK United Kingdom, USA United States of America

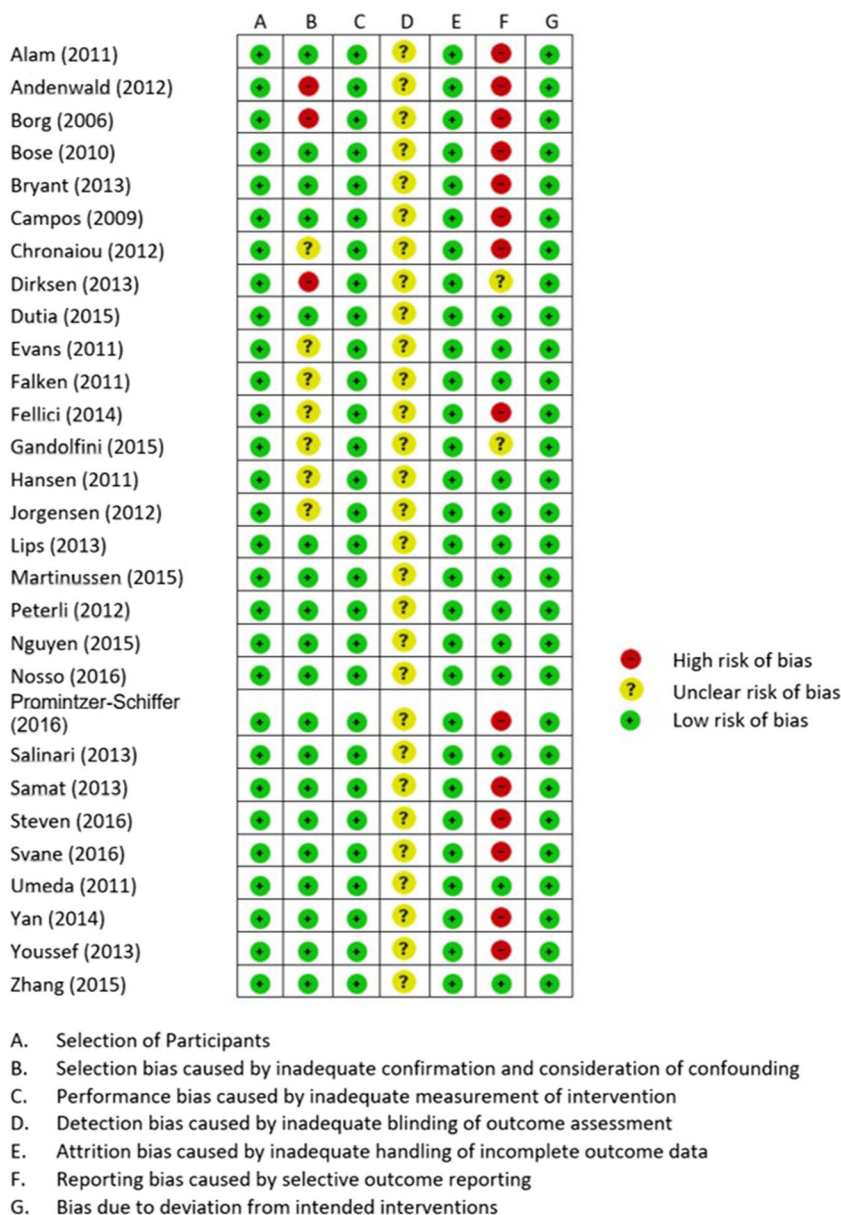
All included studies were deemed to be of high quality and low risk of bias (Fig. 2). Risk of bias across studies was assessed using a funnel plot. Visual inspection demonstrated that smaller and statistically insignificant studies appeared to be missing likely due to publication bias (Fig. 3a). Duval and Tweedie’s trim and fill method resulted in a smaller increase in postprandial GLP-1 levels after RYGB. However, the increase in postprandial GLP-1 levels after RYGB remained significant (Fig. 3b). Specifically, Hedge’s *g* decreased from 1.29 [1.15, 1.43] to 1.17 [1.04, 1.30]. The classic fail-safe method yielded 2124 studies that would be required to show no difference in preRYGB and postRYGB postprandial GLP-1 levels.

Primary Outcome

All of the 24 studies that reported postprandial results demonstrated an increase in postprandial GLP-1 levels after RYGB with Hedge’s *g* of 1.29 [1.15, 1.43] ($p < 0.0001$) (Fig. 4). Heterogeneity across studies was low with I^2 of 32.27 ($p < 0.067$) and Q -value of 33.96.

A sensitivity analysis showed that postprandial GLP-1 levels after RYGB were significantly higher than the preRYGB levels regardless of diabetic status prior to RYGB. Specifically, Hedge’s *g*’s were 1.76 [1.36, 2.17], 1.39 [1.17, 1.61], and 1.25 [0.99, 1.49] in the non-diabetic, mixed, and diabetic groups, respectively ($p = 0.106$).

Fig. 2 Risk of bias of included studies



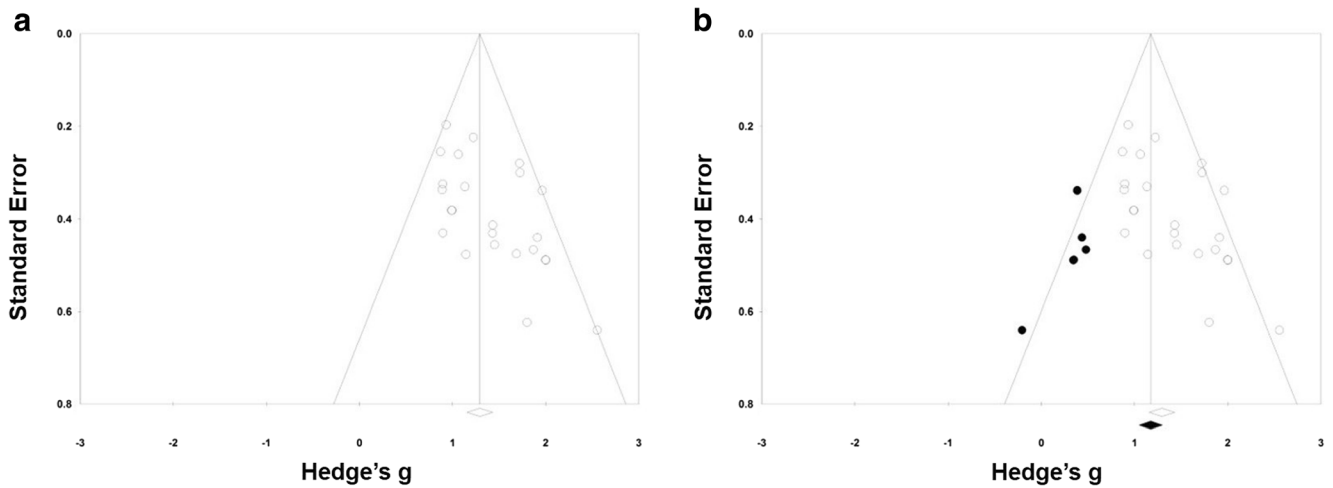
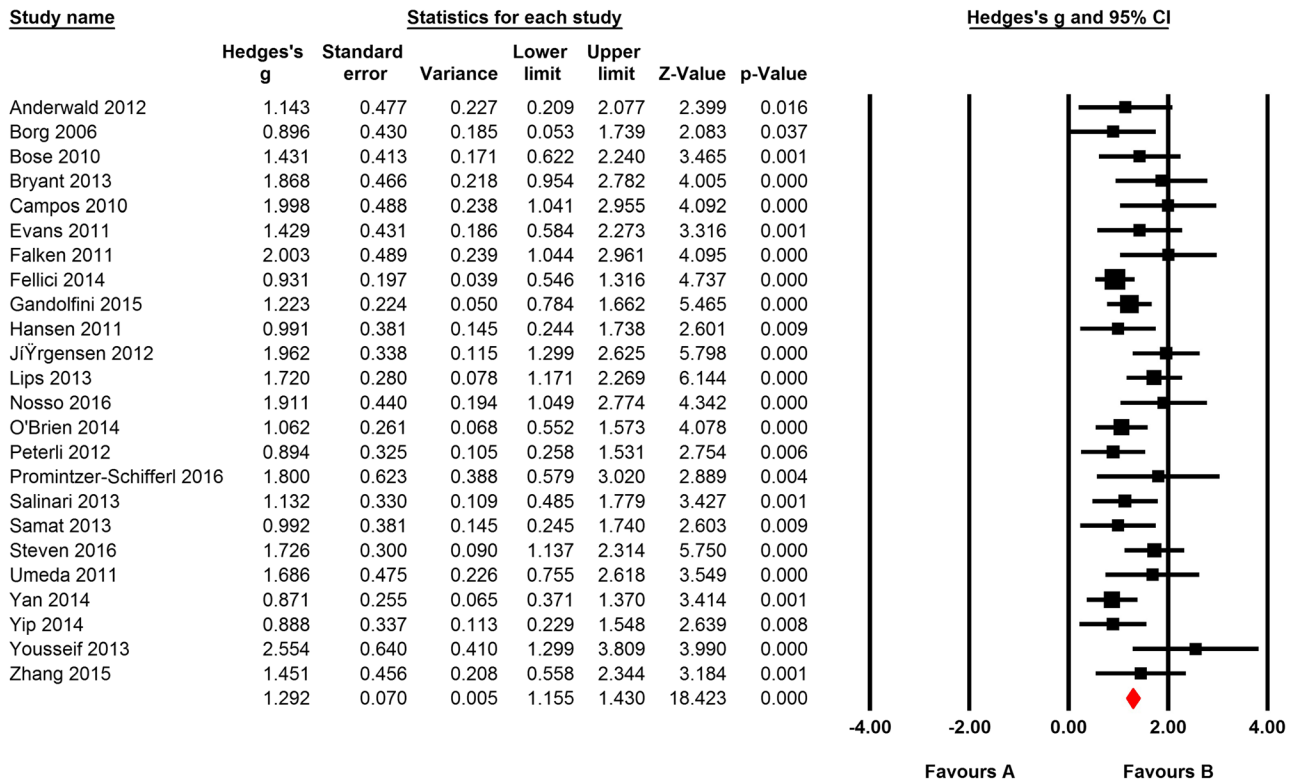


Fig. 3 a Funnel plot of changes in postprandial GLP-1 levels after RYGB. **b** Funnel plot with Duval and Tweedie’s trim and fill method. A white circle represents a study, while a black circle represents an unpublished study. Visual inspection demonstrates a publication bias with small, non-significant studies missing. With the Duval and Tweedie’s trim

and fill method, the Hedge’s *g* of postprandial GLP-1 levels decreases from 1.29 [1.15, 1.43] to 1.17 [1.04, 1.30], although overall, the Hedge’s *g* remains positive suggesting a significant increase in postprandial GLP-1 levels after RYGB

Meta Analysis



Meta Analysis

Fig. 4 Forest plot of studies assessing the changes in postprandial GLP-1 levels after RYGB. Hedge’s (fixed effect) = 1.29 [1.15, 1.43] ($p < 0.0001$). Heterogeneity $I^2 = 32.27$ ($p < 0.067$) and Q -value = 33.96

Similarly, the primary outcome remained the same regardless of how postprandial GLP-1 levels were reported (peak versus mean versus AUC) ($p = 0.162$). However, the heterogeneity across studies was the lowest when peak postprandial levels were used (I^2 of 9.11 versus 48.95 for peak versus AUC levels, respectively). In studies that assessed both peak and AUC postprandial GLP-1 levels, peak levels occurred at a median of 30 (range 20–60) min after glucose or meal stimulation. When the pre-post correlation coefficient was changed from 0.5 to 0.1 and 0.9, postRYGB GLP-1 levels remained higher than the preRYGB levels (Hedge's $g = 1.66$ [1.42, 1.89] ($p < 0.0001$) and Hedge's $g = 0.82$ [0.71, 0.93] ($p < 0.0001$), respectively).

Secondary Outcomes

Fifteen out of 24 studies reported pre and postRYGB fasting glucose and insulin levels. Fasting glucose levels decreased after RYGB (Hedge's $g = -0.85$ [-0.98, -0.71] ($p < 0.0001$)). Heterogeneity across studies was low with I^2 of 22.68 ($p = 0.20$) and Q -value of 18.11. Similarly, fasting insulin levels were lower after RYGB compared to the preRYGB levels (Hedge's $g = -0.97$ [-1.31, -0.63] ($p < 0.0001$)). Heterogeneity across studies was however high with I^2 of 78.54 ($p < 0.0001$) and Q -value of 65.22.

Analysis of the 15 studies that reported fasting GLP-1 showed that there was no significant change in fasting GLP-1 levels before and after RYGB (Fig. 5). Specifically, Hedge's g was 0.10 [-0.06, 0.27] ($p = 0.23$). Heterogeneity across studies was low with I^2 of 46.16 ($p = 0.03$) and Q -value of 26.00.

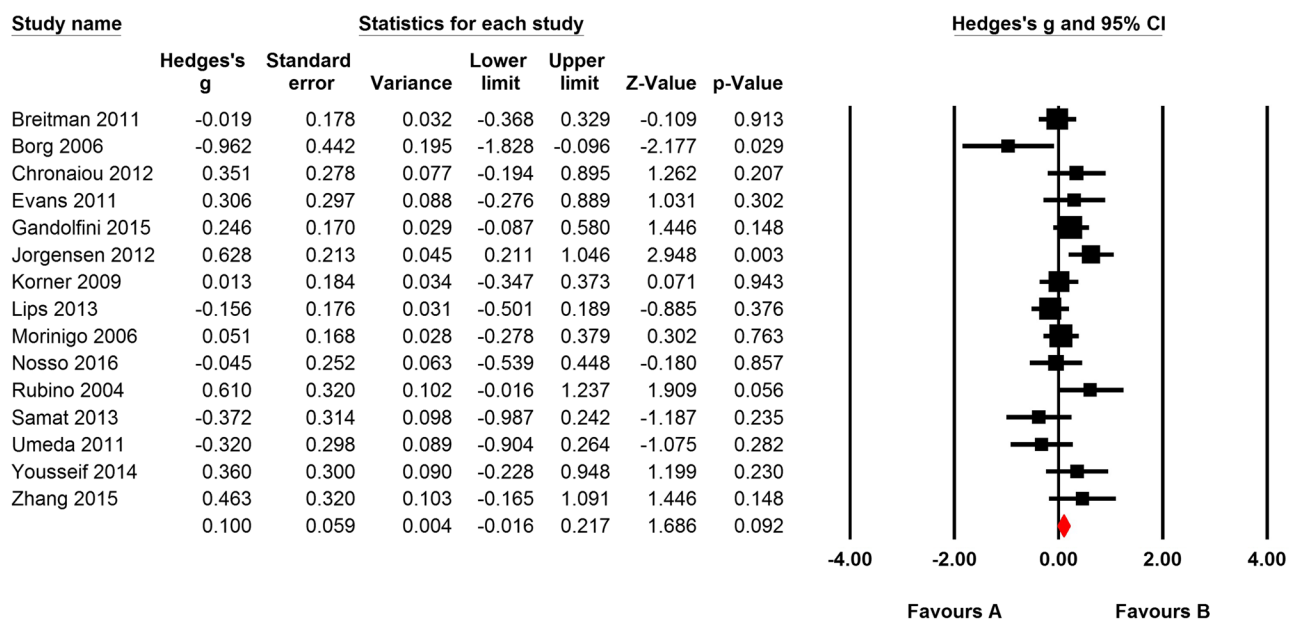
Meta-Regression Analysis

Meta-regression analysis showed that length of Roux limb was a significant predictor of the amount of change in postprandial GLP-1 levels after RYGB ($\beta = -0.01$, $R^2 = 0.69$, $p = 0.02$) (Table 2). Diabetes status prior to RYGB, the amount of weight loss, the length of biliopancreatic limb, and time from RYGB were not significant predictors of the amount of GLP-1 increase after RYGB ($p > 0.05$ in all) (Table 2).

Discussion

This systematic review and meta-analysis demonstrate that postprandial GLP-1 levels increase after RYGB, while fasting levels do not change. In addition, measurement of peak postprandial GLP-1 levels, which occurs at 30 min after meal or glucose stimulation, appears to give the most consistent results and should be used as a standard measurement. Meta-regression analysis shows that

Meta Analysis



Meta Analysis

Fig. 5 Forest plot of studies assessing the changes in fasting GLP-1 levels after RYGB. Hedge's g (fixed effect) = -0.85 [-0.98, -0.71] ($p < 0.0001$). Heterogeneity $I^2 = 22.68$ ($p < 0.20$) and Q -value = 18.11

Table 2 Meta-regression of predictors of GLP-1 level increase after RYGB

Moderator	Coefficient β	95% CI	<i>p</i> value	<i>R</i> ²
DM status prior to RYGB (DM versus no DM)	0.44	[- 0.08, 0.97]	0.10	0.35
Roux limb length (cm)	- 0.01	[- 0.02, - 0.01]	0.02*	0.69
Biliopancreatic limb length (cm)	0.00	[- 0.01, 0.01]	0.69	0.00
Amount of weight loss (% TBW)	- 0.01	[- 0.03, 0.01]	0.19	0.12
Time of postGLP-1 measurement (months)	0.00	[- 0.04, - 0.03]	0.91	0.00

CI confidence interval, DM diabetes, RYGB Roux-en-Y gastric bypass, cm centimeter, TBW total body weight, GLP-1 glucagon-like peptide-1

*represents statistical significance ($p < 0.05$)

shorter Roux limb length appears to be associated with higher postprandial GLP-1 levels, which may lead to better glycemic control. Diabetic status prior to gastric bypass, amount of weight loss, length of biliopancreatic limb, and time from RYGB are not associated with increased GLP-1 levels after RYGB. These results suggest that bariatric surgical techniques may be individualized by adjusting Roux limb length based on diabetic status and monitored using postprandial GLP-1 to achieve optimal glycemic results.

GLP-1 is a gut hormone that is secreted by L-cells in the distal ileum and colon. It belongs to a group of hormones called incretins, which play an important role in glycemic control [38]. Also known as the incretin effect, oral glucose administration stimulates incretin secretion, which leads to greater insulin release from the pancreas compared to an equal amount of glucose administered intravenously. The postprandial elevation in GLP-1, along with the decrease in fasting insulin and glucose levels, demonstrated in this meta-analysis highlights the importance of postprandial GLP-1 amplification as a mechanism of T2DM treatment following RYGB.

To date, the exact mechanism by which GLP-1 levels increase after RYGB remains unclear. In the hindgut hypothesis, secretions and nutrients reach the distal ileum and colon more quickly following gastric bypass, which may lead to more stimulation of L-cells and therefore a higher level of GLP-1 [39]. Alternatively, the foregut hypothesis proposes that an exclusion of the duodenum and proximal jejunum after RYGB may prevent the secretion of a yet unidentified inhibitory product (i.e., anti-incretin factor) [40]. Therefore, a higher level of incretin is observed as a result of less inhibition by the proximal small bowel. More recently, it has also been observed that RYGB alters both the levels and composition of bile acids, which may play a key role in glucose metabolism. Specifically, RYGB bypasses the foregut and therefore increase digestate-free bile acids delivered to the distal gut. This leaves more bile acids free for ileal reuptake, which leads to increased serum bile acids after gastric bypass. Increased

free ileal bile acids activate TGR-5 and FXR leading to increased GLP-1 production and equilibration of glucose homeostasis [41, 42]. Additionally, a higher conjugated to unconjugated bile acid ratio has been observed after RYGB in some studies, which are thought to directly induce more GLP-1 secretion [43, 44].

In our study, the length of Roux limb is a significant negative predictor of the amount of GLP-1 increase after RYGB. This finding suggests that RYGB patients with a shorter Roux limb may have a better glycemic control compared to those with a longer Roux limb (as supported by a higher increase in GLP-1 levels in the former group). While there are some studies assessing the effect of limb lengths on the amount of weight loss (most of which showed varied results) [45–48], there have been only a few small studies that evaluated the effect of limb lengths on T2DM remission [49, 50]. Gupta et al. showed that a shorter common channel limb (< 600 cm) appeared to be associated with a higher chance of T2DM remission. In contrary, Kaska et al. suggested that a longer biliopancreatic limb (> 100 cm) improves diabetic effect of RYGB. As far as we know, no studies have previously reported an association between the Roux limb length and glycemic effect after gastric bypass. These results may be due to small sample size.

Possible explanations for the beneficial effects of a shorter Roux limb on glycemic control include changes in bile acid metabolisms and intestinal transit time. By adjusting the length of Roux limb, the location of where bile acids (which travel down the biliopancreatic limb) meet the nutrients (which travel down the Roux limb) is affected. This may lead to changes in bile acid metabolism and an increase in GLP-1 secretion. Furthermore, different Roux limb lengths may have varied intestinal transit time.

In previous rat models, it has been demonstrated that a shorter Roux limb is associated with faster transit time [51, 52]. Therefore, RYGB patients with a shorter Roux limb may have a shorter bowel transit time than those with a longer

Roux limb, which likely cause the nutrients to reach the ileum sooner and therefore a higher spike in GLP-1. Further studies on the effect of Roux limb length on GLP-1 levels and glycaemic control after RYGB are warranted.

This study is the first systematic review and meta-analysis that explores the change in GLP-1 levels after RYGB. In addition to showing that postprandial GLP-1 levels increase after RYGB, the study also demonstrates that fasting glucose and fasting insulin levels decrease, likely as a result of improved insulin sensitivity. The meta-analysis shows that fasting GLP-1 levels do not change after gastric bypass. A likely explanation for this is that RYGB affects the rate that nutrients and bile acids reach L-cells in the distal ileum and colon rather than affecting L-cells directly, only changes in postprandial and not fasting basal GLP-1 levels are observed. In addition, our study also reveals that method of GLP-1 measurement remains relatively varied from one study to another. Specifically, to measure postprandial GLP-1, patients may be fed with a standardized meal or oral glucose administration. The GLP-1 levels may be measured using a peak level, a mean level, or an area under the curve (AUC) over different time periods (ranging from 90 to 180 min in the included studies). Nevertheless, regardless of the methods of stimulation or measurement, postRYGB GLP-1 levels remain significantly higher compared to preRYGB levels. In our analysis, measurement of peak GLP-1 levels postprandially appears to give the most consistent results as supported by the smallest heterogeneity score (I^2 and Q -value). Based on the studies that measured both peak and AUC postprandial levels, the peak levels occur at a median of 30 min after glucose or meal stimulation. Therefore, moving forward, standardizing GLP-1 measurement using a peak level at 30 min may be considered instead of an AUC level, which requires blood draw every 15 to 30 min for at least 1.5 to 3 h.

This study has a few limitations. First, the included studies remain quite heterogenous. This is likely explained by different GLP-1 assays used across studies. To control for this heterogeneity, Hedge's g and random-effect models are therefore used to report the pooled effect. Additionally, our analysis only includes the studies with high quality and low risk of bias. The criteria used to assess the quality and risk of bias are relatively objective with an Ottawa score of ≥ 6 or a JADAD score of ≥ 3 and low risks of bias in more than 50% of the Cochrane criteria. Additionally, not all of the included studies report diabetes status prior to RYGB, amount of weight loss, length of Roux limb, or biliopancreatic limb of the included subjects. Therefore, this may limit our power at detecting the effect of these other factors on change in GLP-1 after gastric bypass. In our study, a shorter Roux limb length is associated with a greater increase in postprandial GLP-1, which may lead to better glycaemic control in this

population. Further prospective studies to confirm this finding should be considered before any specific recommendation on the optimal length of the Roux limb can be made for patients with concomitant T2DM and obesity.

Conclusion

This systematic review and meta-analysis demonstrate that RYGB is associated with an increase in postprandial GLP-1 level. This change appears to parallel a decrease in fasting insulin and fasting glucose levels. Additionally, the study also reveals that measuring postprandial GLP-1 using a peak level appears to result in a more consistent result than an average or AUC level, and that a shorter Roux limb length may predict a greater increase in postprandial GLP-1. Moving forward, postprandial GLP-1 levels may serve several useful purposes. They may be useful in assessing patient response to therapy, may serve as a guide to modifying or adding pharmacologic therapy, and may help in the development of new procedures. To date, bariatric procedures have been designed primarily to treat obesity, with T2DM efficacy being a fortunate secondary effect. We now have an opportunity to fine-tune existing surgeries and develop new devices to emphasize T2DM treatment outcomes.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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