Universidade Federal do Rio Grande do Sul

Faculdade de Medicina

Programa de Pós-Graduação em Medicina: Ciências Cirúrgicas

EFEITOS DA GASTRECTOMIA VERTICAL E DO BYPASS GÁSTRICO EM Y DE ROUX NA DOENÇA DO REFLUXO GASTROESOFÁGICO, MEDIDOS DE FORMA OBJETIVA POR MEIO DE ENDOSCOPIA, MANOMETRIA E PHMETRIA ESOFÁGICA: REVISÃO SISTEMÁTICA E METANÁLISE

DIRCEU FELIPE VALENTINI JUNIOR

Porto Alegre, 2023

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Dissertação apresentada como requisito parcial para obtenção do título de Mestre no Programa de Pós-Graduação em Medicina: Ciências Cirúrgicas, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul.

Porto Alegre, 2023

FICHA CATALOGRÁFICA

CIP - Catalogação na Publicação

VALENTINI JUNIOR, DIRCEU FELIPE
EFEITOS DA GASTRECTOMIA VERTICAL E DO BYPASS GÁSTRICO EM Y DE ROUX NA DOENÇA DO REFLUXO GASTROESOFÁGICO, MEDIDOS DE FORMA OBJETIVA POR MEIO DE ENDOSCOPIA, MANOMETRIA E PHMETRIA ESOFÁGICA: REVISÃO SISTEMÁTICA E METANÁLISE / DIRCEU FELIPE VALENTINI JUNIOR. -- 2023.
74 f.
Orientador: RICHARD RICHACHENEVSKY GURSKI.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Medicina: Ciências Cirúrgicas, Porto Alegre, BR-RS, 2023.

1. Doença do Refluxo Gastroesofágico. 2. Cirurgia Bariátrica e Metabólica. 3. Gastrectomia Vertical . 4. Bypass Gástrico em Y de Roux. I. GURSKI, RICHARD RICHACHENEVSKY, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

DEDICATÓRIA

Ao meu grande amor **Marina de Queiroz**, por compartilhar comigo sonhos e incentivar a concretização dos projetos.

Aos meus pais **Dirceu e Nilda**, por sempre estimularem minha formação e por servirem de exemplo de dedicação ao trabalho.

AGRADECIMENTOS

Ao meu orientador **Prof. Dr. Richard R. Gurski,** por compartilhar seus conhecimentos e servir de exemplo de dedicação à Cirurgia, à Pesquisa e à Docência.

Aos colegas **Dr. Guilherme S. Mazzini** e **Vinicius J. Campos**, pelos ensinamentos práticos e teóricos desde o início do meu treinamento como cirurgião.

Ao acadêmico de Medicina e aluno de iniciação científica **Arthur Becker Simões** por ter colaborado em todas as etapas da Revisão Sistemática e Metanálise.

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LISTA DE ABREVIATURAS

DRGE: Doença do Refluxo Gastroesofágico

GV: Gastrectomia Vertical

BGYR: Bypass Gástrico em Y de Roux

TEA: Tempo de Exposição Ácida (pH <4)

DMS: Escore de DeMeester

EDA: Endoscopia Digestiva Alta

EEI: Esfíncter Esofágico Inferior

EE: Esofagite Erosiva

EB: Esôfago de Barrett

HH: Hérnia Hiatal

IMC: Índice de Massa Corporal

IFSO: Federação Internacional para a Cirurgia da Obesidade

ASMBS: Sociedade Americana de Cirurgia Bariátrica e Metabólica

OR: Odds Ratio

RESUMO

Introdução: O potencial surgimento ou agravamento da Doença do Refluxo Gastroesofágico (DRGE) após a realização da Cirurgia Bariátrica e Metabólica é uma das principais preocupações do cirurgião. Este tema tornou-se um tópico central de debate da comunidade científica.

Objetivo: O objetivo dessa Revisão Sistemática e Metanálise é avaliar os efeitos da Gastrectomia Vertical (GV) e do Bypass Gástrico em Y-de-Roux (GBYR) na anatomia da junção esofagogástrica, na exposição ácida do esôfago e na motilidade esofágica.

Métodos: Uma revisão sistemática da literatura, sem restrição de idioma ou de data de inserção, foi realizada nos seguintes bancos de dados: PubMed, Embase, Lilacs, Scopus, Web of Science e Cochrane. Foram selecionados artigos reportando parâmetros objetivos em exames de monitorização do pH esofágico e/ou manometria esofágica e/ou endoscopia digestiva alta antes e depois da realização da cirurgia bariátrica (GV ou GBYR). Os dados foram sumarizados por metanálise, através do modelo de efeitos randômicos, e os resultados apresentados como diferença média ponderada e risco relativo. Os estudos foram divididos em grupos, de acordo com a presença ou ausência de DRGE na avaliação pré-operatória, e uma análise de subgrupo foi realizada.

Resultados: Trinta e nove artigos, com um total de 2318 participantes, relataram dados objetivos dos testes antes e depois da GV. Para RYGB, dezessete estudos, compreendendo 665 pacientes, atenderam os critérios de inclusão. Comparado ao pré-operatório, ocorreu um aumento significativo no Tempo de Exposição Ácida (TEA) e no Escore de DeMeester (DMS) após a GV. Na manometria esofágica,

observou-se uma diminuição na pressão de repouso e no comprimento total do Esfíncter Esofágico Inferior (EEI) no seguimento após a GV. A análise conjunta dos dados demonstrou um aumento significativo da prevalência de Esofagite Erosiva (EE) após a GV. Na avaliação dos estudos que incluíram apenas pacientes sem DRGE no pré-operatório, a GV também foi associada a um aumento da exposição ácida esofágica (TEA e DMS). Neste grupo, a incidência de EE foi de 27.6% e a incidência de Esôfago de Barrett (EB) foi de 5.72%. Após o BYGR, ocorreu uma diminuição no TEA e no DMS. Observou-se uma diminuição na prevalência de EE após o BGYR. Não ocorreu mudança significativa dos parâmetros da manometria quando comparado os valores de antes e depois da realização do BGYR.

Conclusão: A gastrectomia vertical (GV) é associada com um aumento do refluxo ácido, maior risco de EE e de BE, e piora da função motora do esôfago e da junção esofagogástrica. Após Bypass Gástrico em Y de Roux (BGYR) ocorreu uma diminuição o tempo de exposição ácida esofágica e uma diminuição da prevalência de Esofagite Erosiva.

Palavras-chave: Doença do Refluxo Gastroesofágico; Cirurgia Bariátrica e Metabólica; Gastrectomia Vertical; Bypass Gástrico em Y de Roux.

ABSTRACT

Background: The development or worsening in Gastroesophageal Reflux Disease (GERD) is a major concern after Metabolic and Bariatric Surgery.

Objective: The aim of this systematic review and meta-analysis is to assess the effects of Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB) in esophagogastric junction anatomy, esophageal acid exposure and esophageal motility.

Methods: A systematic literature search was carried out in PubMed, Embase, Lilacs, Scopus, Web of Science and Cochrane databases without date and language restrictions. Eligible articles were studies reporting objective parameters in esophageal pH monitoring test and/or esophageal manometry and/or esophagogastroduodenoscopy before and after bariatric surgery (SG or RYGB). A preplanned subgroup analysis based on the presence of GERD in the preoperative assessment was performed.

Results: Thirty-nine studies, with a total of 2318 subjects, reported data of instrumental evaluation before and after SG. For RYGB, seventeen articles, comprising 665 patients, met the inclusion criteria. Compared to the preoperative assessment, there was an increase in Acid Exposure Time (AET) and in DeMeester Score (DMS) after SG. The pooled results also showed a higher risk of Erosive Esophagitis (EE) following SG. Meta-analysis of studies reporting manometric changes, demonstrated a decrease in Lower Esophageal Sphincter (LES) resting pressure and in LES length after SG. In the subgroup of studies that included only patients without preoperative pathologic reflux, SG was associated with an increase in esophageal acid exposure (AET and DMS). In this group, the incidence of

new-onset Erosive Esophagitis (EE) was 27.6% and the incidence of Barrett's Esophagus (BE) was 5.72%. After RYGB there was a decrease in Acid Exposure Time (AET) and in DeMeester Score (DMS). The overall prevalence of EE decreased after RYGB. RYGB did not significantly change the parameters of esophageal manometry.

Conclusion: Sleeve Gastrectomy is associated with an increase in acid reflux, higher risk of EE and BE, and worsening in gastroesophageal motor function. RYGB was associated with improvement in esophageal acid exposure and with an improvement of EE.

Keywords: Gastroesophageal Reflux Disease; Bariatric and Metabolic Surgery; Sleeve Gastrectomy; Roux-en-Y Gastric Bypass.

INTRODUÇÃO

A obesidade está associada a um aumento no risco de desenvolvimento de Doença do Refluxo Gastroesofágico (DRGE), Esofagite Erosiva (EE), Esôfago de Barrett (EB) e Adenocarcinoma da Junção Esofagogástrica.[1,2] Pacientes candidatos à Cirurgia Bariátrica e Metabólica (CBM) tem uma maior prevalência de DRGE (40 - 65%) quando comparados à população geral (10 - 20%).[3,4] Diversos ensaios clínicos demonstraram que a diminuição do excesso de peso tem um efeito positivo na diminuição dos sintomas do refluxo. [5-7]

O tratamento da obesidade severa com a utilização de medicamentos associados a mudanças dietéticas e comportamentais apresenta elevadas taxas de falha e de reganho de peso. Para a maioria dos pacientes, a cirurgia bariátrica permanece sendo a melhor opção para perda de peso sustentada e remissão das comorbidades.[8,9] Atualmente, os dois procedimentos cirúrgicos mais realizados são a Gastrectomia Vertical Laparoscópica (GV*)* e o Bypass Gástrico em Y-de-Roux Laparoscópico (BGYR), representando, respectivamente, 61% e 26% das cirurgias bariátricas realizadas no mundo.[10]

Apesar da bem estabelecida relação entre a obesidade e a DRGE, a associação entre a cirurgia bariátrica e a doença do refluxo é bem mais complexa. Em teoria, ao produzir redução sustentada do excesso de peso, a cirurgia deveria promover melhora dos sintomas e evitar as complicações da DRGE. Contudo, tem se observado que alguns pacientes apresentam piora dos sintomas de refluxo após a cirurgia bariátrica.[11,12] Além disso, alguns grupos descreveram uma alta taxa de incidência de *denovo* DRGE e até mesmo surgimento de Esôfago de Barrett (EB) após o tratamento cirúrgico da obesidade.[13]

Apesar das evidências crescentes no assunto, os mecanismos fisiopatológicos relacionados ao desenvolvimento ou remissão da DRGE após a cirurgia bariátrica não são completamente entendidos. A maioria dos estudos sobre a DRGE após a cirurgia bariátrica baseiam-se exclusivamente em sintomas, e um dos principais problemas da DRGE e das suas consequências é que nem sempre conseguimos encontrar uma boa correlação entre os sintomas reportados pelo paciente e a gravidade da doença.[14,15] Uma avaliação objetiva por meio de exames de monitorização do pH esofágico, manometria esofágica e endoscopia digestiva alta (EDA) é essencial para esclarecer o verdadeiro impacto da Cirurgia Bariátrica e Metabólica na Doença do Refluxo Gastroesofágico.

REVISÃO DA LITERATURA

GASTRECTOMIA VERTICAL e DRGE

A Gastrectomia Vertical Laparoscópica (ou *Sleeve*) provou ser uma modalidade cirúrgica efetiva para o tratamento da obesidade e das comorbidades associadas.[16] Ensaios clínicos randomizados comparando os desfechos da GV e do BGYR demonstraram que as duas técnicas produzem resultados semelhantes na redução do excesso de peso.[17,18] A GV é tecnicamente mais simples e tem um tempo operatório menor do que o BGYR. Devido a essas vantagens, a GV se tornou o procedimento bariátrico mais realizado no mundo.[10] Contudo, à medida que a popularidade da GV continua aumentando, mais evidências de que esta cirurgia pode induzir ou agravar a DRGE têm surgido.[11,12] Ainda assim, alguns grupos relataram melhora dos sintomas de refluxo em pacientes submetidos à GV.[19,20]

Uma revisão sistemática e metanálise publicada recentemente por *Yeung et al* [11] avaliou a prevalência de DRGE, Esofagite Erosiva e Esôfago de Barrett após a realização da Gastrectomia Vertical, totalizando 10718 pacientes. A análise conjunta dos dados identificou uma piora na DRGE em 19% dos pacientes e refluxo *de novo* em 23%. A prevalência de Esofagite Erosiva e de Esôfago de Barrett no longo prazo (acima de 24 meses de seguimento) foi 28% e 8%, respectivamente. Apesar do grande tamanho da amostra, há uma elevada heterogeneidade entre os resultados dos artigos incluídos e a grande maioria dos autores não utilizaram critérios objetivos de avaliação do refluxo.

Segundo o consenso de Lyon, publicado em 2018, a aplicação de questionários de sintomas e a resposta ao uso de terapia anti-secretora não podem ser considerados evidências conclusivas da presença de DRGE.[21] A Endoscopia

Digestiva Alta e os testes de monitorização do pH esofágico são fundamentais na investigação da DRGE. Além da baixa sensibilidade e especificidade para o diagnóstico, a avaliação clínica isolada não é suficiente para predizer a gravidade da doença. Esta concepção moderna, reforçou a necessidade da produção de novos dados sobre a relação entre a GV e a DRGE, a partir de uma avaliação instrumentalizada com testes objetivos.

No estudo publicado por *Thereaux e colaboradores*,[22] os pacientes candidatos a GV foram submetidos a avaliação da exposição ácida esofágica, através realização de pHmetria de 24h, antes do procedimento e 6 meses depois da cirurgia. A partir dos dados obtidos na avaliação pré-operatória, a coorte foi dividida em dois grupos: pacientes com DRGE e pacientes sem DRGE. No grupo de pacientes sem refluxo patológico no pré-operatório, ocorreu um aumento significativo no Tempo de Exposição Ácida (TEA). Dos 29 pacientes que tinham pHmetria normal antes da cirurgia, 20 apresentaram refluxo patológico no exame de reavaliação. No grupo de pacientes que tinham DRGE no pré-operatório, não houve melhora dos índices de exposição ácida após a GV.

Estudos que realizaram Endoscopia antes e depois da GV sugerem que a cirurgia está relacionada a elevadas taxas de incidência de Esofagite Erosiva e de Hérnia Hiatal.[23,24] Uma revisão da literatura reportou uma alarmante taxa de 11,6% de prevalência de Esôfago de Barrett após a Gastrectomia Vertical.[13] Devido ao aumento do risco de desenvolvimento de EB, a Federação Internacional para a Cirurgia da Obesidade (IFSO) recomenda a realização de endoscopias de rastreio durante o acompanhamento dos pacientes submetidos à Gastrectomia Vertical.[25]

Múltiplos mecanismos parecem contribuir para o aumento do refluxo após a GV.[26,27] A cirurgia modifica a anatomia da junção esofagogástrica, o que pode

prejudicar o funcionamento da barreira anti-refluxo: a dissecção do ângulo de His pode danificar as fibras do cárdia resultando em fraqueza do Esfíncter Esofágico Inferior (EEI);[28,29] a ruptura do ligamento frenoesofágico pode facilitar a ocorrência de hérnia de hiato.[30] Outros autores têm descrito que o formato estreito e tubular do estômago após a cirurgia produz um aumento da pressão intragástrica.[31] Além disso, dados obtidos em exames de manometria demonstram uma piora da peristalse do corpo esofágico, o que pode dificultar a capacidade de depuração do conteúdo ácido.[32-34]

BYPASS GÁSTRICO EM Y DE ROUX e DRGE

O Bypass Gástrico em Y de Roux (BGYR) por muito tempo foi considerado a técnica "padrão-ouro" no tratamento cirúrgico da obesidade. É um procedimento bastante estudado e seus desfechos no longo prazo são bem conhecidos.[35,36] Entretanto, devido ao seu componente disabsortivo e as modificações na anatomia do intestino delgado, nem todos os portadores de obesidade são candidatos ao BGYR. Além disso, a realização desta cirurgia requer mudanças significativas nos hábitos alimentares e no estilo de vida, e muitos pacientes não desejam submeter-se à esta técnica.

Em relação aos efeitos do BGYR em pacientes com DRGE, diversos grupos demonstraram que a técnica está associada a um adequado controle dos sintomas do refluxo.[17,18] Em um estudo prospectivo, *Madalosso e colaboradores* [37] investigaram 53 pacientes com a utilização de pHmetria esofágica de 24h, endoscopia digestiva alta e manometria esofágica antes e após três anos da realização de BGYR. Observou-se diminuição do refluxo ácido (a média do Escore de DeMeester diminuiu de 28.6 para 1.2) e melhora ou resolução da EE em 83.4%

dos pacientes. Apesar do adequado controle da DRGE, a avaliação manométrica demonstrou uma diminuição significativa na pressão do EEI e uma piora na amplitude das ondas de contrações peristálticas no esôfago distal.

Rebecchi e colaboradores [38] estudaram um grupo de 72 pacientes com a realização de impedâncio-pHmetria, manometria esofágica e EDA antes e após 5 anos da realização do BGYR. Os participantes foram divididos em dois grupos, de acordo com a presença ou ausência de refluxo ácido patológico na pHmetria pré-operatória. Os resultados demonstraram que no grupo de pacientes com refluxo ocorreu uma normalização da exposição esofágica ao refluxo ácido e diminuição dos sinais macroscópicos de Esofagite Erosiva na Endoscopia. Apesar da diminuição significativa do Escore de DeMeester e do Tempo de Ácida mesmo nos pacientes que já estavam com estas medidas normais antes da operação, observou-se um aumento no número de episódios de refluxo fracamente ácido neste grupo.

A revisão sistemática publicada por *Gu L et al.*[12] reuniu 23 estudos, incluindo 6 ensaios clínicos randomizados, que compararam diretamente os efeitos do Bypass Gástrico em Y-de-Roux e da Gastrectomia Vertical na DRGE. A metanálise revelou uma incidência de refluxo *de novo* em 9,3% dos pacientes submetidos a GV e em apenas 2,3% dos pacientes submetidos a BGYR (OR: 5.1 $p < 0.001$). Na comparação entre os dois procedimentos, o BGYR teve um efeito melhor no tratamento da DRGE (OR: 0.19 $p < 0.001$).

Diante das evidências atuais, o BGYR tem sido recomendado como a técnica de escolha em pacientes com obesidade (IMC ≥ 35) e sinais de DRGE severa.[39, 40] Contudo, ainda não há consenso sobre como deve ser realizada a investigação do refluxo nos pacientes candidatos à cirurgia bariátrica.

JUSTIFICATIVA

O desenvolvimento ou a agravamento da Doença do Refluxo Gastroesofágico após a cirurgia bariátrica tornou-se uma das maiores preocupações dos cirurgiões, tendo em vista o número crescente de estudos demonstrando que a GERD após os procedimentos bariátricos está associada não apenas com a piora na qualidade de vida dos pacientes, mas também com um risco aumentado de Esôfago de Barrett (EB) e de Adenocarcinoma da Junção Esofagogástrica.

A avaliação objetiva da exposição ácida esofágica e um melhor entendimento dos efeitos da Gastrectomia Vertical e do Bypass Gástrico em Y de Roux na função da barreira anti-refluxo poderão esclarecer quais exames devem ser realizados na investigação pré-operatória e o quanto os resultados destes testes podem influenciar na escolha da técnica cirúrgica.

OBJETIVO

OBJETIVO GERAL

Por meio de uma Revisão Sistemática da literatura descrever os efeitos anatômicos, fisiológicos e funcionais da Gastrectomia Vertical e do Bypass Gástrico em Y de Roux no esôfago e na junção esofagogástrica.

OBJETIVOS ESPECÍFICOS

Conduzir uma Metanálise para sintetizar as mudanças em parâmetros objetivos nos seguintes testes: monitorização de 24h do pH esofágico, manometria esofágica e endoscopia digestiva alta. Os resultados dos estudos encontrados na Revisão Sistemática foram combinados e os valores medidos antes da cirurgia foram comparados com os obtidos após o procedimento.

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ARTIGO ORIGINAL EM INGLÊS

SLEEVE GASTRECTOMY IS ASSOCIATED WITH SIGNIFICANT INCREASE IN ESOPHAGEAL ACID REFLUX, DECREASE IN LOWER ESOPHAGEAL SPHINCTER FUNCTION AND ESOPHAGEAL DISMOTILITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Running Title

Bariatric Surgery and Gastroesophageal Reflux Disease

Keywords: Gastroesophageal Reflux Disease; Bariatric and Metabolic Surgery; Sleeve Gastrectomy; Roux-en-Y Gastric Bypass.

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Conflict of Interest:

None of the authors have any conflict of interest.

ABSTRACT

Background: The development or worsening of Gastroesophageal Reflux Disease (GERD) is a major concern after Metabolic and Bariatric Surgery.

Objective: The aim of this systematic review and meta-analysis is to assess the effects of Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB) in esophagogastric junction anatomy, esophageal acid exposure and esophageal motility.

Methods: A systematic literature search was carried out in PubMed, Embase, Lilacs, Scopus, Web of Science and Cochrane databases without date and language restrictions. Eligible articles were studies reporting objective parameters in esophageal pH monitoring test and/or esophageal manometry and/or esophagogastroduodenoscopy before and after bariatric surgery (SG or RYGB). A preplanned subgroup analysis based on the presence of GERD in the preoperative assessment was performed.

Results: Thirty-nine studies, with a total of 2318 subjects, reported data of instrumental evaluation before and after SG. For RYGB, seventeen articles, comprising 665 patients, met the inclusion criteria. Compared to the preoperative assessment, there was an increase in Acid Exposure Time (AET) and in DeMeester Score (DMS) after SG. The pooled results also showed a higher risk of Erosive Esophagitis (EE) following SG. Meta-analysis of studies reporting manometric changes demonstrated a decrease in Lower Esophageal Sphincter (LES) resting pressure and in LES length after SG. In the subgroup of studies that included only patients without preoperative pathologic reflux, SG was associated with an increase in esophageal acid exposure (AET and DMS). In this group, the incidence of new-onset Erosive Esophagitis (EE) was 27.6% and the incidence of Barrett's

Esophagus (BE) was 5.72%. After RYGB there was a decrease in Acid Exposure Time (AET) and in DeMeester Score (DMS). The overall prevalence of EE decreased after RYGB. RYGB did not significantly change the parameters of esophageal manometry.

Conclusion: Sleeve Gastrectomy is associated with an increase in acid reflux, higher risk of EE and BE, and deterioration of gastroesophageal motor function. RYGB was associated with improvement in esophageal acid exposure and with an improvement of EE.

INTRODUCTION

Obesity is associated with increased risk of Gastroesophageal Reflux Disease (GERD), Erosive Esophagitis (EE), Barrett's Esophagus (BE) and Esophageal Adenocarcinoma (EAC).[1,2] Patients eligible for Bariatric and Metabolic Surgery (BMS) have a higher prevalence of GERD (40 to 65%) in comparison to the general population (10 to 20%).[3,4] Several clinical trials have demonstrated that weight reduction has a positive and continuous effect on reflux symptom improvement.[5–7]

Bariatric surgery is the most effective treatment for severe obesity and obtains the best long-term outcomes in sustained weight loss and control of obesity-related comorbidities.[8,9] Laparoscopic Sleeve Gastrectomy (SG) and Laparoscopic Roux-en-Y Gastric Bypass (RYGB) are the two most common bariatric procedures performed worldwide, representing, respectively, 61% and 26% of all bariatric procedures.[10]

Despite the well-known association between obesity and GERD, and the consistent weight loss associated with bariatric surgery, the relationship between obesity surgical therapy and GERD seems to be more complex. GERD can worsen following bariatric surgery, and some groups reported a high incidence of new-onset GERD after surgery, depending on the type of the procedure.[11,12] This issue has become a major concern and a central topic of debate, since GERD following bariatric surgery is associated not only with impaired quality of life, but also with a higher risk for Barrett's Esophagus (BE) and Esophageal Adenocarcinoma (EAC).[13,14]

Most of the published studies on GERD after bariatric surgery relies on clinical symptoms, and part of the problem with GERD and its consequences is that sometimes we cannot find a good correlation between self-reported reflux symptoms

and the severity of the disease.[15–17] An instrumental assessment through esophageal 24h-pH monitoring tests, esophageal manometry and esophagogastroduodenoscopy is essential to clarify the impact of Bariatric and Metabolic Surgery in Gastroesophageal Reflux Disease.[18,19]

The aim of this systematic review and meta-analysis is to evaluate the anatomical, physiological, and functional effects of Sleeve Gastrectomy and Roux-en-Y Gastric Bypass in the esophagus and esophagogastric junction.

MATERIALS AND METHODS

A systematic review and meta-analysis was performed. This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[20] The study protocol was registered into the International Prospective Register of Systematic Reviews (PROSPERO), under the Identification Number CRD42021235233.

SEARCH STRATEGY

A comprehensive literature search was performed without date and language restrictions. The search strategy was designed by a reference librarian and it was carried out in PubMed, Embase, Lilacs, Scopus, Web of Science and Cochrane databases with inceptions up to March 2022. Controlled vocabulary supplemented with keywords and MeSH Terms were used to search for Esophageal Manometry, Esophageal pH monitoring tests, Esophagogastroduodenoscopy and Esophageal Radiography/imaging in patients who underwent Bariatric Surgery: Sleeve Gastrectomy and Roux-en-Y Gastric Bypass. The detailed search strategy is available in **Supplementary file 1**.

Two investigators (D.F.V.J. and A.B.S.) independently reviewed the eligibility of the retrieved articles. Studies identified by the search strategy above were screened for inclusion using a two-step process. First, the titles and abstracts of each study were assessed. Secondly, the full text was assessed for studies which were thought to be potentially relevant. References of the selected articles were also manually reviewed for identification of additional relevant studies. Any disagreement was resolved by discussion and consensus with a third investigator (R.R.G).

INCLUSION AND EXCLUSION CRITERIAS

The eligible studies were clinical trials, retrospective or prospective cohort studies that fulfill the inclusion criteria:

- Adult patients (>18 years-old) that underwent Bariatric and Metabolic Surgery: Sleeve Gastrectomy or Roux-en-Y Gastric Bypass.
- Esophageal pH monitoring Test and/or Esophageal Manometry and/or Esophagogastroduodenoscopy were performed **before** and at least one month **after surgery**. The study must have reported at least one **objective** parameter in one of these tests, both before and after surgery.

Reviews, meta-analysis, case reports, editorial letters and conference abstracts were excluded from the analysis. In addition, studies were excluded if: a) GERD evaluation was solely based on symptoms; b) Test was done only before or only after the surgery; c) Reassessment was performed only in selected patients; d) Systematic presence of associated procedures added to the standard surgical technique (such as fundoplication or omentopexy in SG).

When more than one retrieved study reported duplicated data from the same group of patients, only the study with the most comprehensive information was

selected for inclusion. Authors were contacted when the data presented in the included articles was not adequate for inclusion within a meta-analysis.

QUALITY ASSESSMENT

Two authors (V.S.G and J.B.O.A) independently assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale (NOS) for cohort studies.[21] According to the NOS, each individual study was evaluated in three parts: a) the selection of the patients; b) the comparability of the groups; and c) the completeness of the reported outcomes. The maximum score attributable to each article is nine points.

DATA EXTRACTION

Data was independently extracted by two authors (D.F.V.J. and A.B.S.) using a standardized form organized by the first author`s name and year of publication, and stored in the Microsoft Excel® (Microsoft Corporation, Redmond, Washington, USA). The following data was extracted from each study:

a) General information: Authors names, year of publication, study design, country of origin, language, title, journal, type of surgery, type of test performed, number of participants.
b) Patient Demographics: age, sex, pre and postoperative Body Mass Index (BMI).
c) Outcomes: Pre and postoperative parameters of the performed tests.

The included studies were further classified into three groups, according to the presence or absence of pathologic reflux in the preoperative assessment.

Gastroesophageal Reflux Disease (GERD) definition was based on endoscopic and pHmetric findings, regardless of typical GERD symptoms:

Group 1: Studies that included only patients **without** preoperative GERD;

Group 2: Studies that included only patients **with** preoperative GERD;

Group 3: Studies that included patients **with and without** preoperative GERD;

OUTCOMES

The outcomes were changes in objective parameters, comparing pre and postoperative measured values, of the following tests:

- **Esophageal pH Monitoring**: Total Esophageal Acid Exposure Time (AET) (percentage of total time where pH is < 4); DeMeester Score (DMS).
- **Esophageal Manometry**: Lower Esophageal Sphincter (LES) Resting Pressure (mmHg); LES Length (cm); Esophageal Body Amplitude (mmHg); Intragastric Pressure (mmHg).
- **Esophagogastroduodenoscopy (Endoscopy/EGD):** Erosive Esophagitis according to the Los Angeles Classification[22]; Hiatal Hernia; Barrett's Esophagus.

STATISTICAL ANALYSIS

Statistical Analysis was conducted in R software® version 4.0.3, using the meta package version 4.9-2.[23,24] Results were summarized and presented as weighted mean difference (MD) for continuous variables, and risk ratio (RR) for categorical variables. All statistics were calculated using a 95% confidence interval (CI). Given the expectation of heterogeneity in estimates across the included articles,

the random effects model (inverse variance) was used. Sensitivity analyses were performed according to the subgroup division outlined above. Differences between subgroups were assessed with a test for interaction.[25]

Heterogeneity was quantified using the I^2 statistic, with the values of 25%, 50%, and 75% corresponding to the limits of low, moderate, and high statistical heterogeneity, respectively.[26] Publication bias was quantified using Egger's regression model and visual evaluation was undertaken by assessing symmetry of the funnel plot for each outcome.[27] Data not summarized in the meta-analysis will be presented descriptively.

RESULTS

LITERATURE SEARCH RESULTS

The search strategy retrieved 5189 potentially relevant articles, and 5 additional records were identified through manual search within the references. After removing duplicated studies, 2728 unique records had their title and abstract screened. Of these, 97 articles were selected for possible inclusion and had their full text reviewed. Finally, 52 studies were included. The PRISMA flow-chart is presented in **Figure 1.**

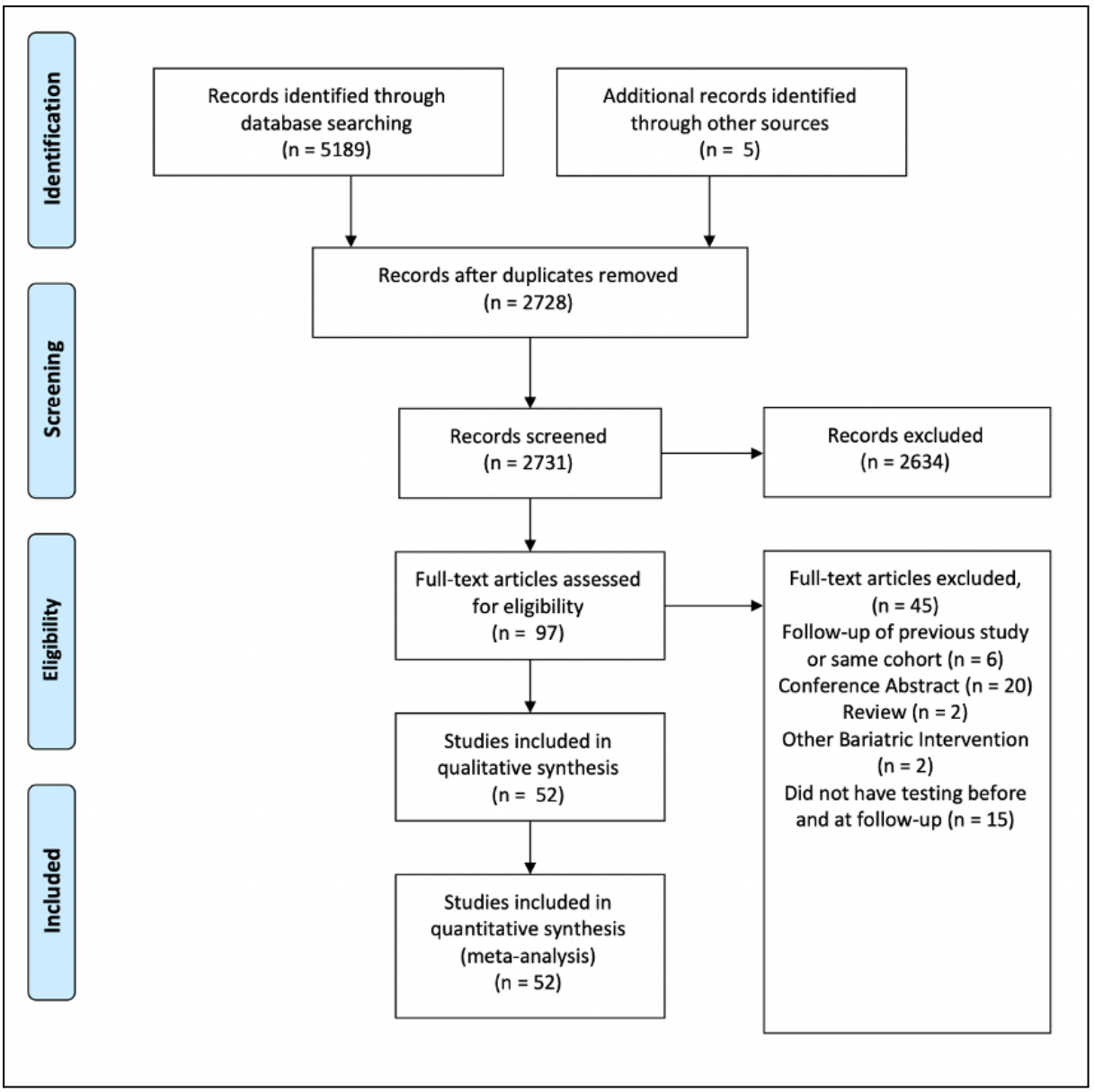


Figure 1: Preferred reporting items for systematic review and meta- analysis (PRISMA) flow diagram.[20]

STUDY CHARACTERISTICS

Almost all included articles were retrospective or prospective cohort studies. There were only two prospective trials directly comparing effects of Sleeve Gastrectomy with Roux-en-Y Gastric Bypass.[28,29] Thirty-nine studies [28–66], with a total of 2318 subjects, reported data of instrumental evaluation before and after Sleeve

Gastrectomy. For Roux-en-Y Gastric Bypass (RYGB), 17 articles [28,29,51,52,64,67–78] , with a total of 665 subjects, were included in the meta-analysis

The interval between surgery and postoperative tests reassessment ranged from 2 to 78 months. All studies include both male and female participants. The mean age ranged from 31.9 to 50.5 years. The mean preoperative BMI ranged between 36.6 – 48.9 kg/m^2 for SG and between 40.3 – 54.5 kg/m^2 for RYGB. Postoperative mean BMI ranged between 25.8 – 40.7 kg/m^2 and 27 – 37.8 kg/m^2 for SG and RYGB, respectively.

The baseline GERD status varied across the included studies. In some studies, the presence of pathologic reflux before surgery was an exclusion criterion, while in others, only patients with objectively confirmed preoperative GERD were selected. Although the definition of GERD was not equal for all authors, the use of gold-standard diagnostic tests for gastroesophageal reflux diagnosis (24-pHmetry and Endoscopy)[15] allowed us to further classify the selected articles into three groups, according to the subjects' preoperative GERD status. For categorization, we followed the same definition of pathologic reflux provided by each study. Most of the included studies considered a DeMeester score > 14.72 and/or pH less than 4 for at least 4.2% of the total time during 24h esophageal pH monitoring, or endoscopic findings of Erosive Esophagitis as diagnostic of GERD.

Five studies [37,39,41,47,75] previously divided the subjects into two different cohorts, based on the presence or absence of preoperative pathological reflux, and reported separate data for each group. The characteristics of the included studies are presented in **table 1** and **table 2**. The assessments of quality based on NOS are shown in **supplementary file 2**.

RESULTS FOR SLEEVE GASTRECTOMY

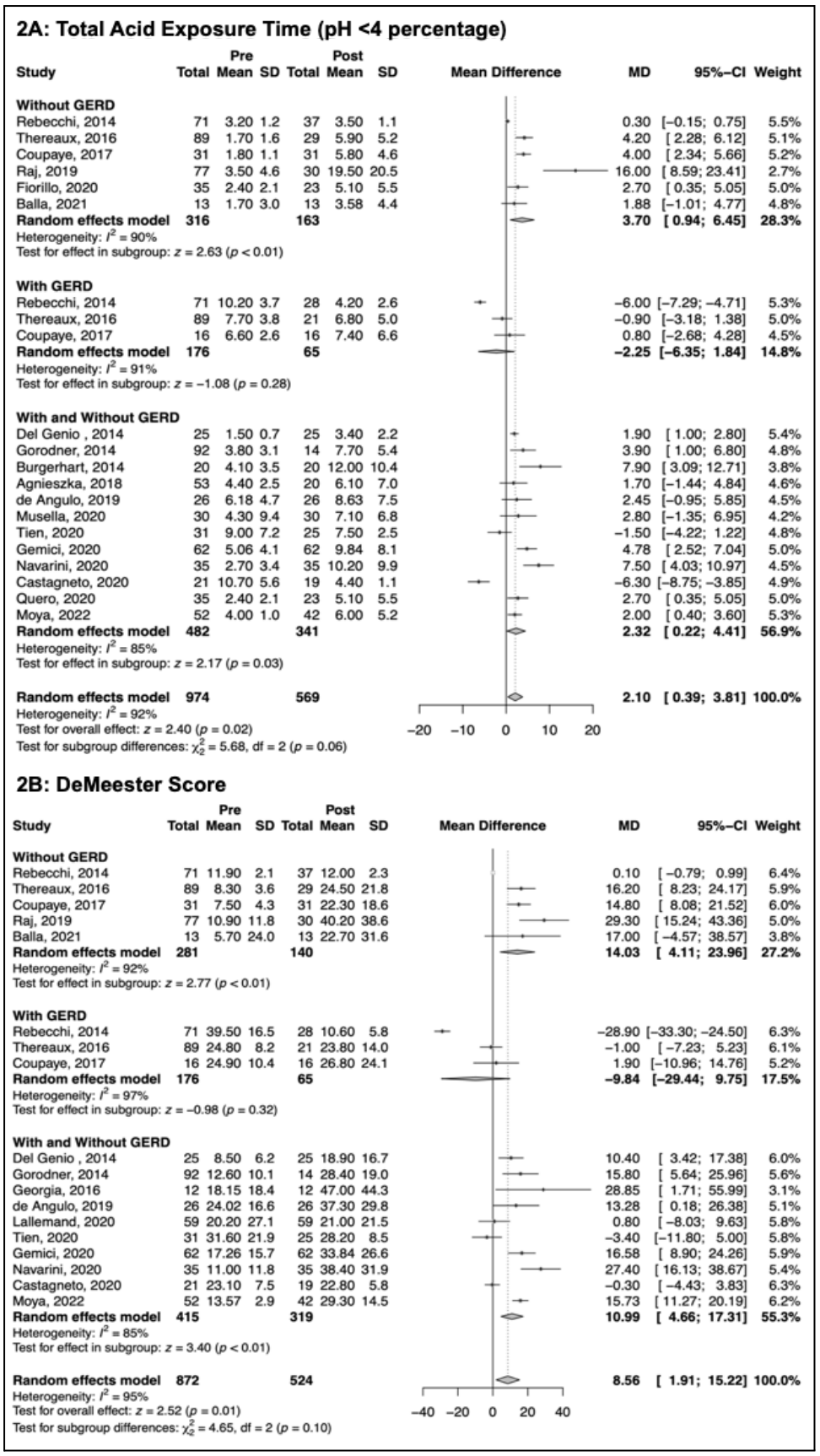
24h-Esophageal pH-monitoring

A total of 20 articles [28,29,33–35,37–39,41,44,53,55–61,64,66] reported changes in esophageal pH-monitoring parameters after Sleeve Gastrectomy. In the overall cohort, the total percentage of Acid Exposure Time (AET) increased, MD 2.10 (95% Confidence Interval 0.39 – 3.81; I^2: 92%). DeMeester Score equally increased after SG, with a weighted mean difference of 8.56 (95% CI 1.91 – 15.22; I^2: 95%) **(Figure 2)**.

In subgroup analysis of the studies including only subjects without preoperative pathologic reflux, Acid Exposure Time (AET) and DeMeester increased after SG, MD 3.7 (95% CI 0.94 – 6.45; I^2: 90%) and 14.03 (95% CI 4.11 – 23.96; I^2: 91%), respectively. In the analysis of studies that included solely patients with preoperative pathologic reflux, SG was not associated with improvement in any of the phmetric parameters evaluated.

The results for the group of studies that included patients with and without preoperative pathologic reflux were in the same direction of those in the overall cohort. Acid Exposure Time (AET) and DeMeester Score increased following SG, MD 2.32 (95% CI 0.22 – 4.41; I^2: 85%) and 10.99 (95% CI 4.66 – 17.31; I^2: 85%), respectively.

Figure 2: Forest plot of changes in esophageal pH monitoring after Laparoscopic Sleeve Gastrectomy. 2A: *Total Acid Exposure Time (pH <4 percentage)* 2B: *DeMeester Score*

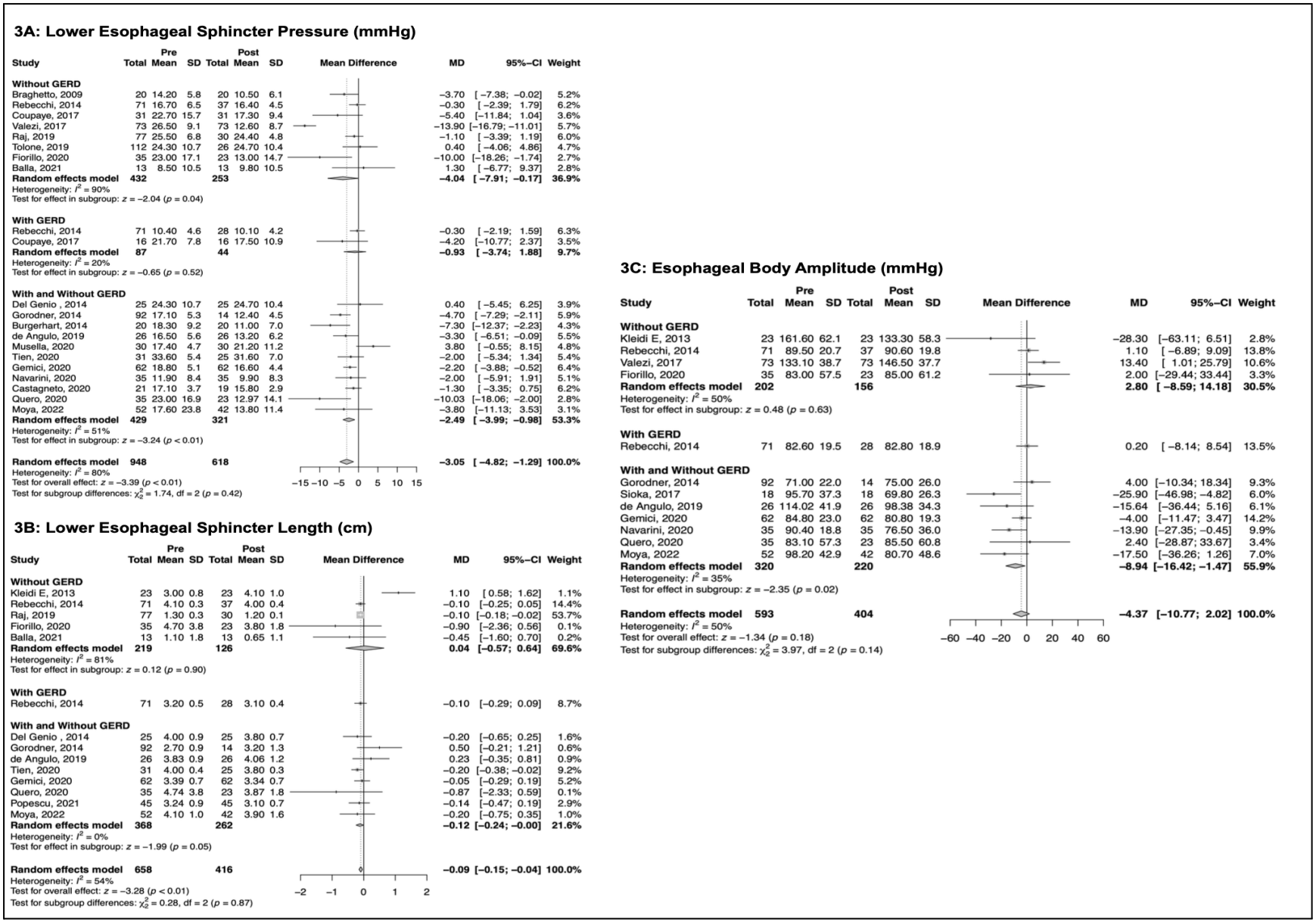


Esophageal Manometry

Twenty-three articles [28–31,33–35,37,40–42,52,53,55,57–61,63,64,66] provided information on esophageal manometric changes after Sleeve Gastrectomy. In the overall cohort, Lower Esophageal Sphincter (LES) resting pressure and LES length significantly decreased after SG, MD - 3.05 (95% CI – 4.82 to – 1.29; I^2: 80%) and - 0.09 (95% CI -0.15 to – 0.04; I^2: 54%), respectively. Esophageal body amplitude and intragastric pressure did not change, MD = - 4.37 (95% CI – 10.77 to 2.02; I^2: 50%) and MD = 2.02; 95% CI – 4.42 to 8.45; I^2: 98%), respectively **(Figure 3)**.

In subgroup analysis, considering studies that included patients with and without GERD, the pooled results were more consistent with less heterogeneity: LES resting pressure decreased, MD – 2.49 (95% CI – 3.99 to – 0.98; I^2:51%) and LES length reduced after surgery MD - 0.12 (95% CI -0.24 to – 0.00; I^2: 0%). In addition, in the analysis of this group, Esophageal Body Amplitude (mmHg) significantly decreased after Sleeve Gastrectomy: MD – 8.94 (95% CI – 16.42 to – 1.47; I^2: 35%).

Figure 3: Forest plot of manometric changes after Laparoscopic Sleeve Gastrectomy. 3A: Lower Esophageal Sphincter Pressure (mmHg) 3B: Lower Esophageal Sphincter Length (cm) 3C: Esophageal Body Amplitude (mmHg)

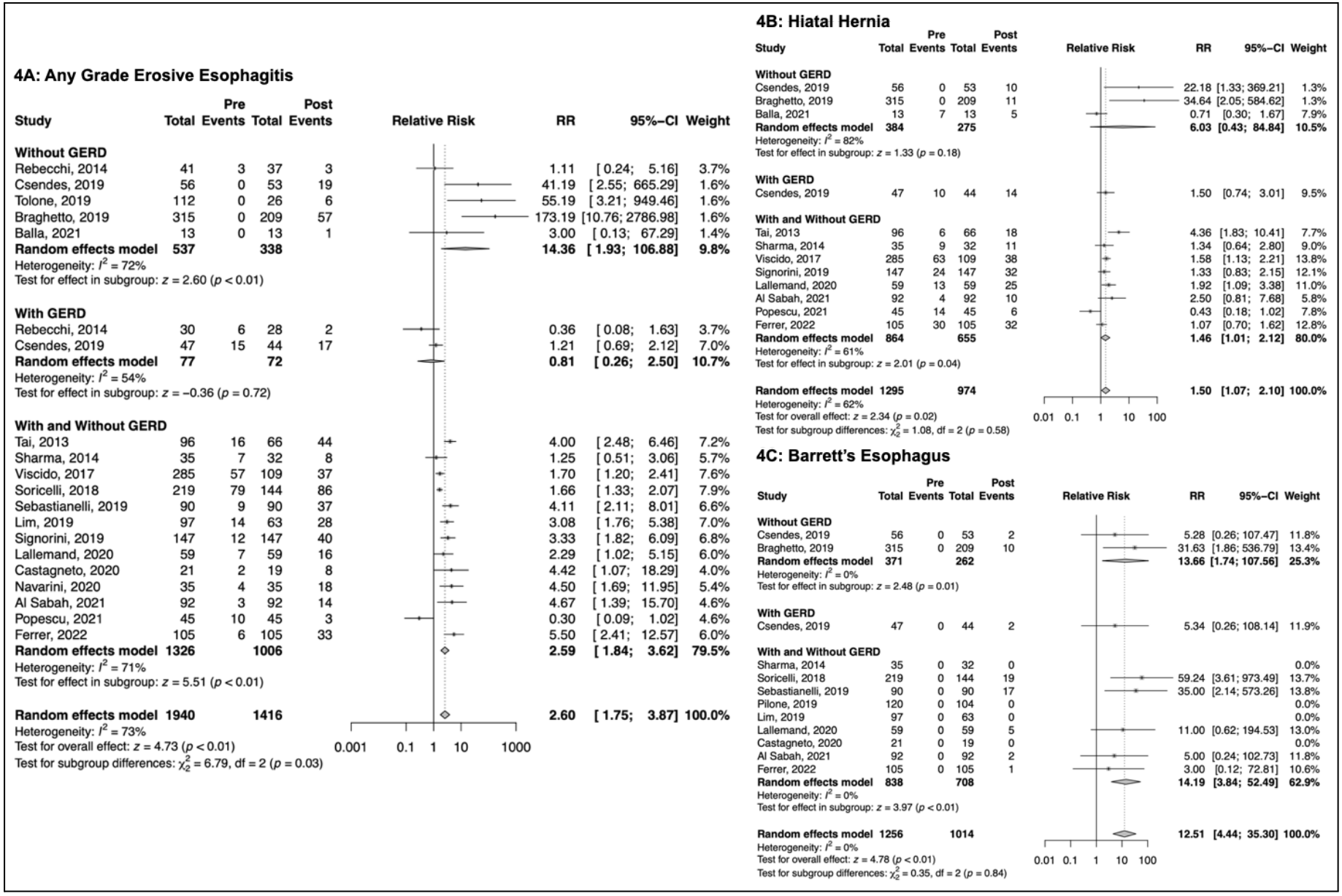


Endoscopic Findings

The pooled number of patients submitted to endoscopic evaluation before and after Sleeve Gastrectomy was 1755, comprehending 20 studies [28,32,36,37,43,45–47,50–52,56,60,62–65] In the overall cohort, the Relative Risk (RR) of any grade Erosive Esophagitis (EE) was 2.6 greater after Sleeve Gastrectomy (95% CI 1.75 – 3.87; I^2: 73%). The prevalence of hiatal hernia on endoscopy also increased after the surgery, RR of 1.5 (95% CI 1.07 – 2.10; I^2: 62%) **(Figure 4A-B).**

Five articles [37,46,47,52,64] reported data on Erosive Esophagitis in patients without preoperative GERD. In this group, the incidence of new-onset Erosive Esophagitis after surgery was 27.6%. In the analysis of studies that included patients regardless of the preoperative GERD status, the prevalence of Erosive Esophagitis was 17% before and 37% after Sleeve Gastrectomy, with a pooled RR for any grade EE of 2.59 (95% CI 1.84 – 3.62; I^2: 71%). All cases of preoperative Erosive Esophagitis were grade A or B. After surgery, 10.3% of the patients with EE had grade C or D Erosive Esophagitis. Eleven studies [36,45–50,56,60,62,65] , comprehending 1014 patients, reported information on Barrett's Esophagus (BE) **(Figure 4C)**. In the postoperative endoscopic assessment, the pooled prevalence of BE was 5.72%. Since there were no patients with BE *prior* to surgery, all cases are *denovo* Barrett`s Esophagus.

Figure 4: Forest plot of endoscopic findings after Laparoscopic Sleeve Gastrectomy. 4A: Any Grade Erosive Esophagitis 4B: Hiatal Hernia 4C: Barrett's Esophagus



RESULTS FOR ROUX-EN-Y GASTRIC BYPASS

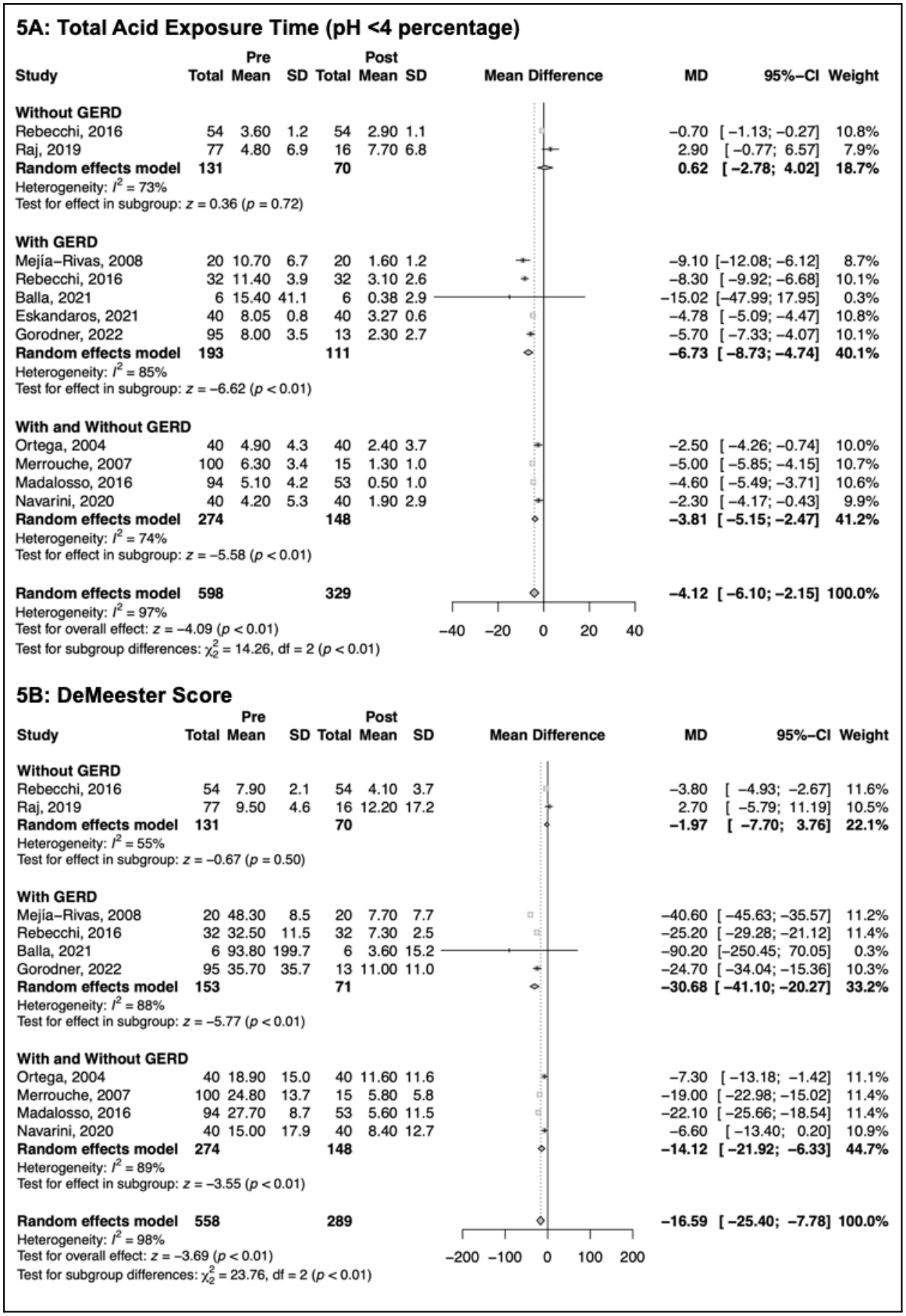
24h-Esophageal pH-monitoring

A total of 10 articles [28,29,64,68–70,72,75,77,78] reported changes in esophageal pH-monitoring parameters after Roux-en-Y Gastric Bypass. In the overall pooled results, Acid Exposure Time (AET) significantly decreased after RYGB, MD - 4.2 (95% CI -6.10 to -2.15; I^2: 97%). DeMeester Score also decreased in the postoperative evaluation, MD - 16.59 (95% CI -25.4 to -7.78; I^2: 98%) (**Figure 5**).

Subgroup analysis of studies that include only patients with preoperative pathologic reflux, both pHmetric parameters decreased after RYGB: Acid Exposure Time (MD = -6.73; 95% CI -8.73 to -4.74; I^2: 85%) and DeMeester Score (MD = -30.68; 95% CI – 41.10 to – 20.27; I^2: 88%). Two articles [29,75] reported data for patients without preoperative pathologic reflux, and there was no significant change in the pHmetric parameters evaluated.

In the analysis of the group of studies that included patients with and without preoperative pathologic reflux, there was also a similar decrease in both Acid Exposure Time (MD = -3.81; 95% CI -5.15 to -2.47; I^2:74%) and DeMeester Score (MD = -14.12; 95% CI – 21.92 to – 6.33; I^2: 89%).

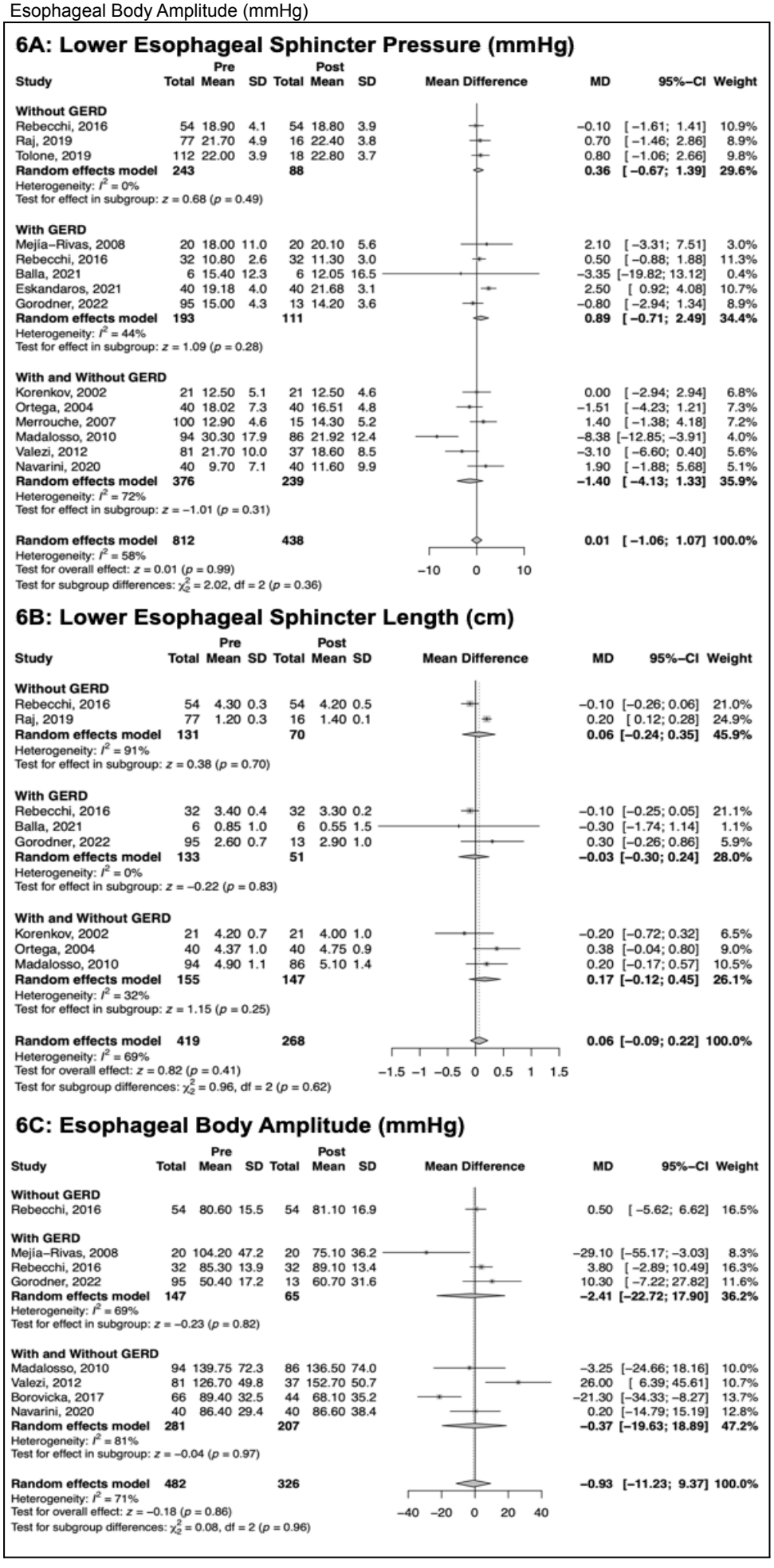
Figure 5: Forest plot of changes in esophageal pH monitoring after Roux-en-Y Gastric Bypass. 5A: *Total Acid Exposure Time (pH <4 percentage)* 5B: *DeMeester Score*



Esophageal Manometry

Fourteen studies [28,29,52,64,67–70,73,75–79] provided data on Esophageal Manometry before and after RYGB. Lower Esophageal Sphincter (LES) resting pressure and LES length did not change after surgery: MD 0.01mmHg (95% CI -1.01 to 1.07; I^2: 58%) and MD 0.06cm (95% CI -0.09 to 0.22; I^2: 69%). Esophageal body amplitude was also not altered after RYGB (MD = -0.93; 95% CI -11.23 to 9.37; I^2: 71%). The subgroup analyses based on preoperative GERD status equally demonstrated no difference between pre and postoperative manometric results, still with less heterogeneity **(Figure 6).**

Figure 6: Forest plot of manometric changes after Roux-en-Y Gastric Bypass. 6A: Lower Esophageal Sphincter Pressure (mmHg) 6B: Lower Esophageal Sphincter Length (cm) 6C: Esophageal Body Amplitude (mmHg)

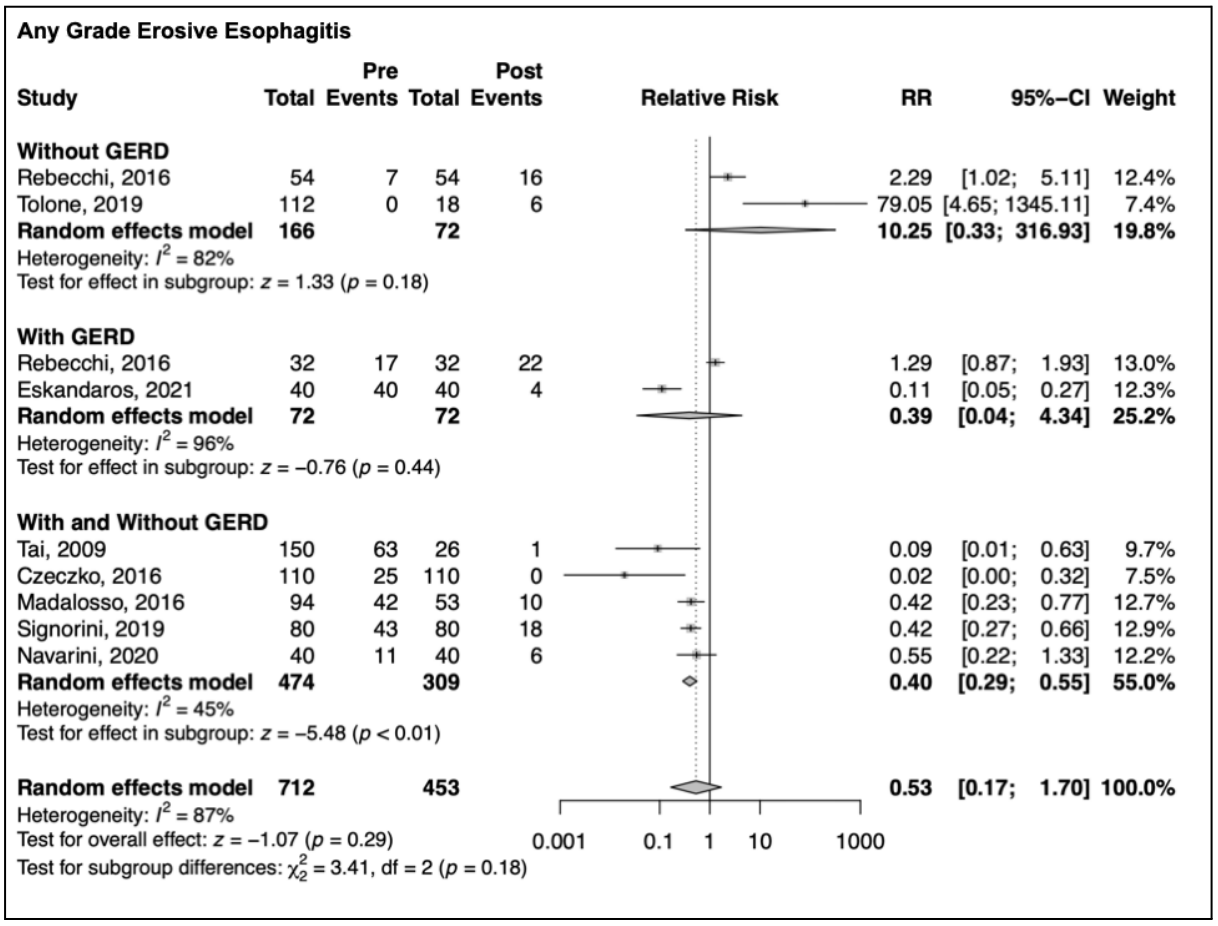


Endoscopic Findings

Eleven studies [28,51,52,70–72,74–79] described findings in esophagogastroduodenoscopy (EGD) before and after Roux-en-Y Gastric Bypass (RYGB). A total of 516 patients underwent endoscopic reassessment after surgery. In the overall cohort, the prevalence of Erosive Esophagitis (EE) was 38.8% before and 11.3% after RYGB. In subgroup analysis, for studies that included patients with and without GERD, the Relative Risk (RR) of EE significantly decreased after surgery (RR 0.40; 95% CI 0.29 – 0.55; I^2: 45%) **(Figure 7)**.

Five articles [51,64,71,74,75] reported data about hiatal hernia before the surgery, but only three [51,64,74] described the findings at postoperative assessment. In all these 3 studies, there was a decrease in the prevalence of hiatal hernia after RYGB. There was no identification of *denovo* Barrett's Esophagus in the included studies. *Signorini* [51] reported a prevalence of BE of 7,5% before and 5% after RYGB (p= 0.001).

Figure 7: Forest plot of endoscopic findings of any grade Erosive Esophagitis after Roux-en-Y Gastric Bypass.



DISCUSSION

SLEEVE GASTRECTOMY and GERD

Laparoscopic Sleeve Gastrectomy (SG) has proved to be an efficient standing-alone procedure for the treatment of obesity and obesity-related co-morbidities.[80–82] It is technically easier and has a shorter operative time in comparison to Laparoscopic Roux-en-Y Gastric Bypass (RYGB). Due to these advantages, SG has become the most performed bariatric procedure worldwide.[10] However, as the popularity of SG continues to increase, more evidence showing that the surgery may induce or aggravate GERD has arisen.[11,12] Currently, GERD is the

most common indication for revisional surgery after SG.[81] Nevertheless, some groups reported improvement of reflux symptoms after Sleeve Gastrectomy.[37,83]

In the analysis of cohorts including only subjects without preoperative pathologic reflux, we found a significant increase in all pHmetric parameters evaluated. Also, in this group, the incidence of new-onset Erosive Esophagitis in endoscopy was 27,6%. These results suggest that SG is associated with the development of *denovo* reflux. When analyzing studies that included only patients with preoperative pathologic reflux, SG was not able to reduce the acid reflux reaching the distal esophagus.

Most of the included studies admitted patients with and without preoperative pathologic reflux. This group can be considered a representation of the overall population seeking bariatric surgery. As previously discussed, a higher prevalence of GERD in patients with obesity is expected.[84] Nevertheless, it is important to know that although including patients with GERD, all the studies reporting outcomes of SG excluded subjects with severe GERD (large hiatus hernia, severe esophagitis, or Barrett's Esophagus). The pooled results confirmed that SG produces an increase in Acid Exposure Time (AET) and an increase in DeMeester Score.

We found a significant increase in overall prevalence of Erosive Esophagitis after Sleeve Gastrectomy. Besides, while all the cases of EE before SG were grade A or B, some patients presented with grade C or D in the postoperative assessment. Likewise, we identified a high incidence rate of Barrett's Esophagus (BE) in the follow-up: 5.9%. Others previously published meta-analysis aimed to assess the incidence of BE after SG found a similar rate.[14]

Multiple mechanisms seem to contribute to reflux after SG.[18,19] This surgery modifies the anatomy of the gastro-esophageal junction and may impair the

anti-reflux barrier: dissection of the angle of His can damage the sling fibers resulting in weakness of the LES;[30,34] disruption of the anchoring architecture by dissection of the phreno-esophageal ligament can increase the rates of hiatal hernia following the surgery.[85] The narrow stomach has been related with increased intragastric pressure and with reduced gastric compliance after oral intake, leading to further increase in gastroesophageal pressure gradient.[86] Lastly, SG can be associated with a higher risk of ineffective peristalsis, which results in impaired esophageal clearance.[87–89]

To assess the potential mechanisms related with pathologic reflux after SG, we analyzed the changes in esophageal manometry. In the overall pooled cohort, we found a decrease in Lower Esophageal Sphincter (LES) resting pressure and LES length. The analysis of the group of studies that included patients regardless of preoperative GERD showed a consistent result with a lower heterogeneity. Besides, there was a decrease in Esophageal Body Amplitude (mmHg) in this group.

ROUX-EN-Y GASTRIC BYPASS and GERD

Roux-en-Y Gastric Bypass (RYGB) has long been accepted as a reflux-protective bariatric surgery.[72,90,91] In our analysis, RYGB resulted in a significant decrease in Acid Exposure Time and DeMeester Score, both in studies that included solely patients with preoperative pathologic reflux and in the overall cohort. For patients without preoperative pathologic reflux, RYGB was not associated with increase in esophageal acid exposure.

The pooled data of endoscopic assessment showed a high prevalence of Erosive Esophagitis in the preoperative evaluation (38%) with a much lower prevalence on follow-up endoscopy (11.3%). In manometric evaluation, no changes

in Lower Esophageal Sphincter (LES) resting pressure, LES length and Esophageal body amplitude after RYGB were found.

Our results suggest that RYGB is associated with GERD control. We found more evidence that RYGB did not change the function of the gastro-esophageal anti-reflux system and did not impact the esophageal motor function. Some others anatomical and physiological changes produced by RYGB are hypothesized to be contributory to the improvement of GERD: the small size of the new gastric pouch and a patent gastrojejunostomy reduces the volume of content disposable for regurgitation; most parietal cells are excluded from the gastric pouch, decreasing the amount of acid produced near the esophagus; the Roux-en-Y diversion avoids the bile reflux.[92,93]

SLEEVE GASTRECTOMY versus ROUX-EN-Y GASTRIC BYPASS

In our systematic review, we identified 45 articles [28,29,32–39,41,43–66,68–72,74–78] reporting data of gastroesophageal reflux evaluation by means of Endoscopy and/or 24-pHmetry. Unfortunately, only two studies were designed to compare the effects of Sleeve Gastrectomy and Roux-en-Y Gastric Bypass on GERD.[28,29] This lack of controlled double-arms trials did not allow us to directly compare the outcomes of the two procedures, and it was the main responsible for the overall poor quality of the included studies. Notwithstanding, we aimed to assess the impact of each surgery, comparing with the baseline characteristics of the subjects submitted to each bariatric procedure. Herein, the results we found were reliable and coherent with the current literature.

A previous meta-analysis published by *Gu L et al.*[12] pooled the data of 23 studies, including 6 RCTs, that directly compared the results of RYGB and SG on

GERD. This study revealed an incidence of new-onset GERD of 9,3% following SG and of 2,3% after RYGB (OR: 5.1 $p < 0.001$). According to them, RYGB had a better effect on GERD (OR: 0.19 $p < 0.001$). The main limitation of their meta-analysis is that most studies included relied on symptoms and drug efficacy without an objective evaluation.

The majority of expert surgeons consider the presence of severe GERD a contraindication for Sleeve Gastrectomy. [94] Indeed, this fact affected the selection of patients with GERD suitable to perform SG in the studies, since all the authors excluded from their protocols subjects with severe GERD. On the other hand, the pooled data of the studies following RYGB, comprehended patients with signs of severe reflux, even with Barrett's Esophagus. This difference in the selection process could be a source of bias, but, surprisingly, the results showed a significant improvement in pHmetric and endoscopic parameters following RYGB, and a worsening in those parameters following SG. Even knowing that further prospective randomized clinical trials may provide higher quality information, our study suggests that RYGB should be the surgery of choice in all the cases of GERD, including mild GERD [91,94].

Our results showed, through objective assessment, that SG is associated with the development of new-onset GERD. Nevertheless, although pragmatic, the worsening in pHmetric, manometric and endoscopic parameters found after SG could be less clinically relevant in the subset of patients without preoperative GERD, and the benefits of the surgery may overcome the risk.

In our opinion, patients presenting for Bariatric and Metabolic Surgery should be carefully assessed for the presence of GERD by a standardized clinical and instrumental evaluation. Patients must be aware of the potential risks of each

procedure. If SG is performed, a screening endoscopy should be performed at 1 year postoperatively, and then every 2-3 years, as advised in the most recent position statement of the IFSO.[14]

STRENGTH AND LIMITATIONS

The preplanned subgroup analysis allowed us to better understand the impact of bariatric surgery in patients with and without preoperative pathologic reflux, as well as it helped to reduce the heterogeneity between the studies. However, this study has several limitations. First, although we used objective parameters, the definition of GERD varied a lot among the authors. Even gathering all available studies describing instrumental assessment of pathologic reflux after SG and RYGB, the absolute report of each measured outcome was relatively small. Many other factors could contribute to the high heterogeneity in some of the parameters analyzed: differences of follow-up and re-assessment time, variation on surgical technique (bougie size, distance of gastrectomy from the pylorus, pouch size), methods used for evaluation (type of manometry or pH-monitoring).

CONCLUSIONS

We summarized the effects of Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB) on esophageal acid exposure and on changes in esophagogastric junction anatomy and function. Our conclusion is that SG is associated with an increase in acid reflux, higher risk of EE and BE, and worsening of gastroesophageal motor function. Conversely, RYGB was associated with improvement in pathologic acid reflux in 24-h pHmetry and in improvement of erosive esophagitis on endoscopy. The presence of preoperative GERD and its

complications should be extensively assessed during the preoperative work-up, as it might aid the surgeon in choosing the most suitable treatment for the patient. Finally, high-quality studies could help to elucidate whether there are any predictive and modifiable factors that can lead to a lower development of *denovo* GERD after SG.

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TABLE 1: CHARACTERISTICS OF INCLUDED ARTICLES OF SLEEVE GASTRECTOMY

AUTHOR, YEAR	COUNTRY	PREOPERATIVE GERD	GERD DEFINITION	*N* AT F/U	AGE (year)	BASELINE BMI (kg/m2)	F/U BMI (kg/m2)	ENDOSCOPY	TYPE OF MANOMETRY	TYPE OF PH MONITORING	TIME OF F/U TEST (month)
Braghetto, 2009 [30]	Chile	Without GERD	Endoscopic Erosive Esophagitis	20	37.6	38.3	28.2	-	Conventional Manometry	-	6
Kleidi E, 2013 [31]	Greece	Without GERD	Endoscopic Erosive Esophagitis	23	38.5	47.9	40.7	-	Conventional Manometry	-	2
Tai, 2013 [32]	Taiwan	w/wo GERD	Endoscopic Erosive Esophagitis	66	37.2	36.3	25.8	YES	-	-	12
Burgerhart, 2014 [33]	Netherlands	w/wo GERD	NR - phmetric values	20	43	47.6	37.9	-	High-resolution Manometry	24-hours Impedance pHmetry	3
Del Genio, 2014 [34]	Italy	w/wo GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	25	42	47	36.2	-	High-resolution Manometry	24-hours Impedance pHmetry	13
Gorodner, 2014 [35]	Argentina	w/wo GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	14	42	40	NR	-	Conventional Manometry	24-hours pHmetry	14
Sharma, 2014 [36]	India	w/wo GERD	Endoscopic Erosive Esophagitis	32	35.8	47.8	NR	YES	-	-	6
Rebecchi, 2014 [37]	Italy	Without GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	37	43.1	44.4	30.6	YES	Conventional Manometry	24-hours pHmetry	24
Rebecchi, 2014 [37]	Italy	With GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	28	41.8	44.	31.5	YES	Conventional Manometry	24-hours pHmetry	24
Georgia, 2016 [38]	Greece	w/wo GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	12	39.7	49	30.2	-	-	24-hours Impedance pHmetry	12
Thereaux, 2016 [39]	France	Without GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	29	40.5	40.7	NR	-	-	24-hours pHmetry	6
Thereaux, 2016 [39]	France	With GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	21	46.3	43.4	NR	-	-	24-hours pHmetry	6
Sioka, 2017 [40]	Greece	w/wo GERD	NR	18	40.7	46.3	31.1	-	Conventional Manometry	-	7
Coupaye, 2017 [41]	France	Without GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	31	41	42.7	30.6	-	High-resolution Manometry	24-hours pHmetry	12
Coupaye, 2017 [41]	France	With GERD	DMS > 14.72	16	41.3	44.7	32.1	-	High-resolution Manometry	24-hours pHmetry	12
Valezi, 2017 [42]	Brazil	Without GERD	Endoscopic Erosive Esophagitis	73	40.2	41.1	NR	-	Conventional Manometry	-	12
Viscido, 2017 [43]	Argentina	w/wo GERD	Endoscopic Erosive Esophagitis	109	40	47.8	29.3	YES	-	-	18
Agnieszka, 2018 [44]	Poland	w/wo GERD	pH < 4 in > 4,2% total time, or > 73 episodes of acid reflux	20	43.3	46.6	38.3	-	-	24-hours pHmetry	12
Soricelli, 2018 [45]	Italy	w/wo GERD	Endoscopic Erosive Esophagitis	144	NR	45.8	28.9	YES	-	-	66
Braghetto, 2019 [46]	Chile	Without GERD	pH < 4 in > 4,2% of total time or DMS > 14.72; Endoscopic Erosive Esophagitis	209	NR	38.4	29.9	YES	-	-	NR
Csendes, 2019 [47]	Chile	Without GERD	Endoscopic Erosive Esophagitis	53	38.6	38.6	28.6	YES	-	-	NR
Csendes, 2019 [47]	Chile	With GERD	Endoscopic Erosive Esophagitis	44	38	37.4	NR	YES	-	-	NR
Lim, 2019 [48]	Singapore	w/wo GERD	Endoscopic Erosive Esophagitis	63	38.2	42.1	30.2	YES	-	-	13.3
Pilone, 2019 [49]	Italy	w/wo GERD	Endoscopic Erosive Esophagitis	120	37.5	44.2	35.4	YES	-	-	26.4
Sebastianelli, 2019 [50]	France and Italy	w/wo GERD	Endoscopic Erosive Esophagitis, BE	90	41	46	34	YES	-	-	78

Signorini, 2019 [51]	Argentina	w/wo GERD	Endoscopic Erosive Esophagitis, BE	147	44.9	NR	NR	YES	-	-	12
Tolone, 2019 [52]	Italy	Without GERD	pH < 4 in > 6% total time, >4,2% in upright or > 80 episodes of acid reflux	18	39	42	30	YES	High-resolution Manometry	24-hours Impedance pHmetry	12
de Angulo, 2019 [53]	Espanha	w/wo GERD	NR - phmetric values	26	45.3	46.6	NR	-	Conventional Manometry	24-hours pHmetry	12
Raj, 2019 [29]	India	Without GERD	DMS > 14.72	30	37.8	45.2	27.4	-	Conventional Manometry	24-hours Impedance pHmetry	6
Ferraz, 2020 [54]	Brazil	w/wo GERD	Endoscopic Findings	459	40.4	39.7	28	YES	-	-	20.8
Fiorillo, 2020 [55]	France	Without GERD	pH < 4 in > 6% total time, or > 80 episodes of acid reflux	23	36	42.4	32.8	-	High-resolution Manometry	24-hours Impedance pHmetry	4
Lallemand, 2020 [56]	France	w/wo GERD	DMS > 14.72	59	45.2	45.2	37.4	YES	High-resolution Manometry	24-hours pHmetry	60
Musella, 2020 [57]	Italy	w/wo GERD	NR - phmetric values	30	NR	47.5	30	-	High-resolution Manometry	24-hours Impedance pHmetry	12
Quero, 2020 [58]	France	w/wo GERD	pH < 4 in > 6% total time	23	36	41.9	32.8	-	High-resolution Manometry	24-hours pHmetry	7.5
Tien, 2020 [59]	Australia	w/wo GERD	DMS > 14.72	25	45.7	43.2	32.7	-	High-resolution Manometry	24-hours Impedance pHmetry	6
Castagneto, 2020 [60]	Italy	w/wo GERD	DMS > 14.72	19	41.6	41.2	26.8	YES	High-resolution Manometry	24-hours pHmetry	14.3
Gemici, 2020 [61]	Turkey	w/wo GERD	DMS > 14.72	62	40.3	47.9	38	-	Conventional Manometry	24-hours pHmetry	3
Navarini, 2020 [28]	Brazil	w/wo GERD	pH < 4 in > 6% total time, Endoscopic Erosive Esophagitis	35	40	40.3	26.8	-	Conventional Manometry	24-hours pHmetry	12
Al Sabah, 2021 [62]	Kuwait	w/wo GERD	Endoscopic Erosive Esophagitis, BE	92	34.9	46.8	NR	YES	-	-	60
Popescu, 2021 [63]	Romania	w/wo GERD	Endoscopic Erosive Esophagitis, BE	45	49.7	46.7	37.2	YES	High-resolution Manometry	-	8.4
Balla, 2021 [64]	Italy	Without GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	13	42	41	28	YES	Conventional Manometry	24-hours pHmetry	12
Ferrer, 2022 [65]	Spain	w/wo GERD	NR	105	49.7	46.6	37.2	YES	-	-	62
Moya, 2022 [66]	Spain	w/wo GERD	pH < 4 in >6% total time, or > 80 episodes of acid reflux, Endoscopic EE	42	45	45	29.4	-	Conventional Manometry	24-hours pHmetry	18

GERD: Gastroesophageal Reflux Disease; w/wo: with and without; DMS: DeMeester Score; *N*: number of patients; F/U: Follow-up; BMI: Body Mass Index; BE: Barrett`s Esophagus; EE: Erosive Esophagitis

TABLE 2: CHARACTERISTICS OF INCLUDED ARTICLES OF ROUX-EN-Y GASTRIC BYPASS

AUTHOR, YEAR	COUNTRY	PREOPERATIVE GERD	GERD DEFINITION	*N* AT F/U	AGE (year)	BASELINE BMI (kg/m2)	F/U BMI (kg/m2)	ENDOSCOPY	TYPE OF MANOMETRY	TYPE OF PH MONITORING	TIME OF F/U TEST (month)
Korenkov, 2002 [67]	Germany	w/wo GERD	NR	21	38.7	54	NR	-	Conventional Manometry	-	12
Ortega, 2004 [68]	Spain	w/wo GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	40	36	54.5	34	-	Conventional Manometry	24-hours pHmetry	12
Merrouche, 2007 [69]	France	w/wo GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	15	38.4	45.1	32.5	-	Conventional Manometry	-	9.5
Mejía-Rivas, 2008 [70]	Mexico	with GERD	pH < 4 in > 4,2% of total time	20	38.9	46.5	33.2	YES	Conventional Manometry	24-hours pHmetry	6
Tai, 2009 [32]	Taiwan	w/wo GERD	Endoscopic Erosive Esophagitis	26	31.8	43.6	28.5	YES	-	-	12
Madalosso, 2010, 2016 [72,79]	Brazil	w/wo GERD	pH < 4 in > 4,2% of total time or Endoscopic Erosive Esophagitis	53	38	46	30	YES	Conventional Manometry	24-hours pHmetry	39
Valezi, 2012 [73]	Brazil	w/wo GERD	NR	37	44.6	44.9	NR	-	Conventional Manometry	-	13
Czeczko, 2016 [74]	Brazil	w/wo GERD	Endoscopic Erosive Esophagitis	110	37.3	40.3	NR	YES	-	-	NR
Rebecchi, 2016 [75]	Italy	without GERD	N of total, acid, and weakly acid reflux episodes > 75, 50, and 33 in 24 hours	54	40.8	44.2	31.5	YES	Conventional Manometry	24-hours Impedance pHmetry	60
Rebecchi, 2016 [75]	Italy	with GERD	N of total, acid, and weakly acid reflux episodes > 75, 50, and 33 in 24 hours	32	40.8	44.4	30.6	YES	Conventional Manometry	24-hours Impedance pHmetry	60
Borovicka, 2017 [76]	Switzerland	w/wo GERD	Endoscopic Erosive Esophagitis	44	41.2	44.9	37.8	YES	High-resolution Manometry	-	4.1
Raj, 2019 [29]	India	without GERD	DMS > 14.72	16	39.2	44.1	27.1	-	Conventional Manometry	24-hours Impedance pHmetry	6
Tolone, 2019 [52]	Italy	without GERD	pH < 4 in > 6% total time, >4,2% in upright or > 80 episodes of acid reflux	18	39	42	30	YES	High-resolution Manometry	24-hours Impedance pHmetry	12
Signorini, 2020 [51]	Argentina	w/wo GERD	Endoscopic Erosive Esophagitis	80	44.9	NR	NR	YES	-	-	12
Navarini, 2020 [28]	Brazil	w/wo GERD	pH < 4 in > 6% total time, Endoscopic Erosive Esophagites B or more	40	39	42.7	27.5	YES	Conventional Manometry	24-hours pHmetry	12
Balla, 2021 [64]	Italy	with GERD	pH < 4 in > 4,2% of total time or DMS > 14.72	6	50.5	44.4	29.5	-	Conventional Manometry	24-hours pHmetry	12
Eskandaros, 2021 [77]	Egypt	with GERD	pH < 4 in > 6% total time, or > 80 episodes of acid reflux	40	36	50	30.2	YES	Conventional Manometry	24-hours pHmetry	12
Gorodner, 2022 [78]	Argentina	with GERD	pH < 4 in > 4,5% of total time or DMS > 14.72	13	40	41	27	YES	Conventional Manometry	24-hours pHmetry	15

GERD: Gastroesophageal Reflux Disease; w/wo: with and without; DMS: DeMeester Score; *N*: number of patients; F/U: Follow-up; BMI: Body Mass Index

SUPPLEMENTARY FILE 1: Search Strategy

PubMed

((Esophagus[mh] OR Esophagogastric Junction[mh] OR Esophag*[tiab] OR Oesophag*[tiab] OR Stomach[mh] OR stomach*[tiab])
AND
(Bariatric surgery[mh] OR bariatric surger*[tiab] OR Gastrectomy[mh] OR Gastrectom*[tiab])
AND
(Endoscopy, Gastrointestinal[mh:noexp] OR Esophagoscopy[mh] OR Gastrointestinal Endoscop*[tiab] OR Esophagoscop*[tiab] OR Esophagogastroduodenoscop*[tiab] OR Gastroscopy[tiab] OR Manometry[mh] OR Esophageal manometry[tiab] OR Esophageal pH Monitoring[mh] OR Esophageal pH[tiab] OR Radiography[mh] OR Esophagus/diagnostic imaging[mh] OR Radiograph*[tiab]))

Embase

((Esophagus/exp OR 'gastroesophageal junction'/exp OR Esophag*:ti,ab OR Oesophag*:ti,ab OR Stomach/exp OR stomach*:ti,ab)
AND
('Bariatric surgery'/exp OR 'bariatric surger*':ti,ab OR Gastrectomy/exp OR Gastrectom*:ti,ab)
AND
('gastrointestinal endoscopy'/de OR Esophagoscopy/exp OR 'Gastrointestinal Endoscop*':ti,ab OR Esophagoscop*:ti,ab OR Esophagogastroduodenoscop*:ti,ab OR Gastroscopy:ti,ab OR Manometry/exp OR 'Esophageal manometry':ti,ab OR 'Esophageal pH Monitoring'/exp OR 'Esophageal pH':ti,ab OR Radiography/exp OR ('Esophagus'/exp AND 'diagnostic imaging'/exp) OR Radiograph*:ti,ab))

LILACS

((mh:(Esophagus OR Esophagogastric Junction OR Stomach)) OR (ti:(Esophag* OR Oesophag* OR stomach* OR "Unión Esófago-Gástrica" OR "Junção Gastroesofágica")) OR (ab:(Esophag* OR Oesophag* OR stomach* OR "Unión Esófago-Gástrica" OR "Junção Gastroesofágica")) AND (mh:("Bariatric surgery" OR Gastrectomy)) OR (ti:(bariatric surger* OR Gastrectomy)) OR (ab:(bariatric surger* OR Gastrectomy))
AND
(mh:("Endoscopy, Gastrointestinal" OR esophagoscopy OR manometry OR "Esophageal pH Monitoring" OR radiography)) OR (mh:(esophagus AND sh:("diagnostic imaging"))) OR (mh:((esôfago) AND sh:(cintigrafia OR cintigrafia OR cintilografia OR "diagnóstico por raios X" OR "diagnóstico por ultrassom" OR "diagnóstico ultrassônico" OR ecocardiografia OR ecografia OR ecotomografia OR "imagem por raios X" OR "medicina nuclear" OR radiografia OR "raio X" OR "raios X" OR "ressonância magnética" OR "ressonância magnética nuclear" OR

roentgenografia OR ultrassom OR ultrassonografia OR "varredura por radioisótopos" OR "diagnóstico por rayos X" OR "diagnóstico por ultrasonido" OR "diagnóstico por ultrasonidos" OR "diagnóstico ultrasónico" OR "escanografía nuclear" OR gammagrafía OR "gammagrafía con radioisótopos" OR "imagen por radionúclidos" OR "imagen por rayos X" OR "rastreo por radioisótopos" OR "rayo X" OR "rayos X" OR "resonancia magnética" OR "resonancia magnética nuclear" OR ultrasonido OR ultrasonografía))) OR (ti:(gastrointestinal endoscop* OR esophagoscop* OR esophagogastroduodenoscop* OR gastroscopy OR "Esophageal manometry" OR esophageal ph OR radiograph* OR "Endoscopia Gastrintestinal" OR "Procedimentos Cirúrgicos Endoscópicos Gastrointestinais" OR "Procedimientos Endoscópicos Quirúrgicos Gastrointestinales" OR "Procedimientos Quirúrgicos Endoscópicos Gastrointestinales" OR "Procedimentos Cirúrgicos Esofagoscópicos" OR "Procedimientos Quirúrgicos Esofagoscópicos" OR tonometria OR "Monitoramento Ambulatorial do pH Esofágico" OR "Monitoreo del pH Esofágico" OR "Monitorización Ambulatoria del pH Esofágico" OR "Diagnóstico por Raios X" OR "Diagnóstico Radiológico por Raios X" OR roentgenografia OR "Diagnóstico por Rayos X" OR "Diagnóstico Radiológico por Rayos X")) OR (ab:(gastrointestinal endoscop* OR esophagoscop* OR esophagogastroduodenoscop* OR gastroscopy OR "Esophageal manometry" OR esophageal ph OR radiograph* OR "Endoscopia Gastrintestinal" OR "Procedimentos Cirúrgicos Endoscópicos Gastrointestinais" OR "Procedimientos Endoscópicos Quirúrgicos Gastrointestinales" OR "Procedimientos Quirúrgicos Endoscópicos Gastrointestinales" OR "Procedimentos Cirúrgicos Esofagoscópicos" OR "Procedimientos Quirúrgicos Esofagoscópicos" OR tonometria OR "Monitoramento Ambulatorial do pH Esofágico" OR "Monitoreo del pH Esofágico" OR "Monitorización Ambulatoria del pH Esofágico" OR "Diagnóstico por Raios X" OR "Diagnóstico Radiológico por Raios X" OR roentgenografia OR "Diagnóstico por Rayos X" OR "Diagnóstico Radiológico por Rayos X")))

Scopus

TITLE-ABS("Esophagogastric Junction" OR esophag* OR oesophag* OR stomach*) AND TITLE-ABS ("bariatric surgery" OR "bariatric surger*" OR gastrectom*) AND TITLE-ABS ("Gastrointestinal Endoscopy" OR esophagoscopy OR "Gastrointestinal Endoscop*" OR esophagoscop* OR esophagogastroduodenoscop* OR gastroscopy OR manometry OR "Esophageal manometry" OR "Esophageal pH Monitoring" OR "Esophageal pH" OR radiograph*)

Web of Science

TS=(Esophagus OR "Esophagogastric Junction" OR Esophag* OR Oesophag* OR stomach*)
AND

TS=("bariatric surger*" OR Gastrectom*)
AND
TS=(Gastrointestinal Endoscopy OR Esophagoscopy OR "Gastrointestinal Endoscop*" OR Esophagoscop* OR Esophagogastroduodenoscop* OR Gastroscopy OR Manometry OR "Esophageal manometry" OR "Esophageal pH Monitoring" OR "Esophageal pH" OR Radiography OR "Esophagus/diagnostic imaging" OR Radiograph*)

Cochrane
ID Search Hits
#1 MeSH descriptor: [Esophagus] explode all trees 1379
#2 MeSH descriptor: [Esophagogastric Junction] explode all trees 485
#3 MeSH descriptor: [Stomach] explode all trees 3297
#4 (Esophag* OR Oesophag* OR stomach*):ti 10686
#5 (Esophag* OR Oesophag* OR stomach*):ab 20593
#6 #1 OR #2 OR #3 OR #4 OR #5 25405
#7 MeSH descriptor: [Bariatric Surgery] explode all trees 1138
#8 MeSH descriptor: [Gastrectomy] explode all trees 1119
#9 (bariatric surger* OR Gastrectom*):ti 3322
#10 (bariatric surger* OR Gastrectom*):ab 5102
#11 #7 OR #8 OR #9 OR #10 6389
#12 MeSH descriptor: [Endoscopy, Gastrointestinal] this term only 815
#13 MeSH descriptor: [Esophagoscopy] explode all trees 486
#14 MeSH descriptor: [Manometry] explode all trees 1146
#15 MeSH descriptor: [Esophageal pH Monitoring] explode all trees 124
#16 MeSH descriptor: [Radiography] explode all trees 21737
#17 MeSH descriptor: [Esophagus] explode all trees and with qualifier(s): [diagnostic imaging - DG] 86
#18 (Gastrointestinal Endoscop* OR Esophagoscop* OR Esophagogastroduodenoscop* OR Gastroscopy OR Esophageal manometry OR Esophageal pH OR Radiograph*):ti 3825
#19 (Gastrointestinal Endoscop* OR Esophagoscop* OR Esophagogastroduodenoscop* OR Gastroscopy OR Esophageal manometry OR Esophageal pH OR Radiograph*):ab 24212
#20 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 45320
#21 #6 AND #11 AND #20 128

SUPPLEMENTARY FILE 2: Quality assessment of the included studies

AUTHOR, YEAR	COUNTRY	TYPE OF SURGERY	TYPE OF STUDY	SELECTION 1 2 3 4	COMPARABILITY 5	OUTCOMES 6 7 8	TOTAL SCORE	ASSESSMENT
Korenkov, 2002 [68]	Germany	RYGB	Prospective	*-*-	--	***	5	Poor
Ortega, 2004 [69]	Spain	RYGB	Prospective	*-*-	--	**-	4	Poor
Merrouche, 2007 [70]	France	RYGB.	Prospective	*-*-	--	**-	4	Poor
Mejía-Rivas, 2008 [71]	Mexico	RYGB	Prospective	*-*-	--	*-*	4	Poor
Braghetto, 2009 [35]	Chile	SG	Prospective	*-**	--	*-*	5	Poor
Tai, 2009 [72]	Taiwan	RYGB	Prospective	***-	-*	**-	6	Poor
Madalosso, 2010-16 [73]	Brazil	RYGB	Prospective	*-*-	--	*-*	4	Poor
Valezi, 2012 [74]	Brazil	RYGB	Prospective	*-*-	--	**-	4	Poor
Kleidi E, 2013 [36]	Greece	SG	Prospective	*-**	--	*-*	5	Poor
Tai, 2013 [37]	Taiwan	SG	Prospective	*-*-	--	**-	4	Poor
Burgerhart, 2014 [38]	Netherlands	SG	Prospective	*-*-	--	*-*	4	Poor
Del Genio, 2014 [39]	Italy	SG	Prospective	*-**	--	***	6	Poor
Gorodner, 2014 [40]	Argentina	SG	Prospective	*-*-	--	**-	4	Poor
Sharma, 2014 [41]	India	SG	Prospective	*-*-	--	***	5	Poor
Rebecchi, 2014 [30]	Italy	SG	Prospective	*-**	--	***	6	Poor
Georgia, 2016 [42]	Greece	SG	Prospective	*-**	--	***	6	Poor
Czeczko, 2016 [75]	Brazil	RYGB	Retrospective	*-**	--	*-*	5	Poor
Rebecchi, 2016 [31]	Italy	RYGB	Prospective	*-**	--	***	6	Poor
Thereaux, 2016 [33]	France	SG	Prospective	*-**	--	*--	4	Poor
Sioka, 2017 [43]	Greece	SG	Prospective	*-**	--	*-*	5	Poor
Coupaye, 2017 [32]	France	SG	Prospective	*-**	--	***	6	Poor
Valezi, 2017 [44]	Brazil	SG	Prospective	*-**	--	***	6	Poor
Viscido, 2017 [45]	Argentina	SG	Prospective	*-*-	--	**-	4	Poor
Borovicka, 2017 [76]	Switzerland	RYGB	Prospective	*-*-	--	*--	3	Poor
Agnieszka, 2018 [46]	Poland	SG	Prospective	*-**	--	***	6	Poor
Soricelli, 2018 [47]	Italy	SG	Prospective	*-*-	--	**-	4	Poor
Braghetto, 2019 [48]	Chile	SG	Prospective	*-**	--	**-	5	Poor
Csendes, 2019 [34]	Chile	SG	Prospective	*-**	--	***	6	Poor
Lim, 2019 [49]	Singapore	SG	Retrospective	*-*-	--	**-	4	Poor
Pilone, 2019 [50]	Italy	SG	Prospective	*-*-	--	***	5	Poor
Sebastianelli, 2019 [51]	France and Italy	SG	Prospective	*-**	--	***	6	Poor
de Angulo, 2019 [54]	Espanha	SG	Prospective	*-*-	--	***	5	Poor
Raj, 2019 [29]	India	SG and RYGB	Prospective	*-**	--	*--	4	Poor
Tolone, 2019 [53]	Italy	SG and RYGB	Prospective	****	*-	**-	7	Fair
Signorini, 2019 [52]	Argentina	SG and RYGB	Retrospective	*-*-	--	**-	4	Poor
Ferraz, 2020 [55]	Brazil	SG	Retrospective	*-*-	--	***	5	Poor
Fiorillo, 2020 [56]	France	SG	Prospective	*-**	*-	*--	5	Poor
Lallemand, 2020 [57]	France	SG	Prospective	*-*-	--	**-	4	Poor
Musella, 2020 [58]	Italy	SG	Prospective	*-**	--	***	6	Poor
Quero, 2020 [59]	France	SG	Prospective	*-**	--	*--	4	Poor
Tien, 2020 [60]	Australia	SG	Prospective	*-*-	--	*-*	4	Poor
Castagneto, 2020 [61]	Italy	SG	Prospective	*-*-	--	***	5	Poor
Gemici, 2020 [62]	Turkey	SG	Retrospective	*-*-	--	*-*	4	Poor
Navarini, 2020 [28]	Brazil	SG and RYGB	Prospective	*-*-	--	***	5	Poor
Al Sabah, 2021 [63]	Kuwait	SG	Retrospective	*-*-	--	***	5	Poor
Popescu, 2021 [64]	Romania	SG	Prospective	*-*-	--	*-*	4	Poor
Balla, 2021 [65]	Italy	SG and RYGB	Prospective	*-**	--	**-	5	Poor
Eskandaros, 2021 [77]	Egypt	RYGB	Prospective	*-**	--	***	6	Poor
Ferrer, 2022 [66]	Spain	SG	Prospective	*-*-	--	***	5	Poor
Moya, 2022 [67]	Spain	SG	Prospective	*-*-	--	***	5	Poor
Gorodner, 2022 [78]	Argentina	RYGB	Retrospective	*-*-	--	**-	4	Poor

RYGB: Roux-en-Y Gastric Bypass; SG: Sleeve Gastrectomy