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UNDERSTANDING THE MECHANISMS UNDERLYING GASTROESOPHAGEAL REFLUX DISEASE (GERD) DEVELOPMENT: A SYSTEMATIC REVIEW

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a chronic condition with increasing global prevalence. Its pathogenesis is multifactorial, involving not just gastric acid, but also esophageal motility disorders, anatomical defects, inflammation, sensory hypersensitivity, and microbiota alterations.

Objective: To systematically review and synthesize empirical findings related to the mechanistic pathways underlying GERD development in adult populations.

Methods: This systematic review followed PRISMA 2020 guidelines. A structured search was conducted across PubMed, Web of Science, Scopus, Embase, and Google Scholar for studies published from 2010 to 2025. Inclusion criteria encompassed original human studies exploring GERD pathophysiology involving motility, inflammation, bile/pepsin reflux, hormonal dysregulation, genetics, and microbiota. Data extraction and quality appraisal were independently performed.

Results: Fifteen high- and moderate-quality studies were included. LES dysfunction and TLESRs were frequently reported (Kim et al., 2023), while inflammatory cytokines such as TNF-α and IL-6 (Zhou et al., 2023; Wei et al., 2024) emerged as critical markers of mucosal injury. Bile reflux, sensory hypersensitivity, microbiota changes, obesity, and surgical anatomy alterations further shaped GERD development.

Conclusion: GERD is a heterogeneous disease, with multiple overlapping pathophysiological mechanisms. These insights highlight the need for personalized diagnostic and therapeutic approaches extending beyond acid suppression.

Keywords: GERD; gastroesophageal reflux; pathophysiology; TLESRs; inflammation; bile reflux; esophageal motility; microbiota; obesity; sleeve gastrectomy

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic disorder that affects approximately 20% of the Western population and is characterized by the backflow of gastric contents into the esophagus, causing symptoms like heartburn and regurgitation, and potentially leading to esophagitis, strictures, or Barrett's esophagus (Fass et al., 2021). While GERD has traditionally been associated with increased gastric acid secretion, recent research has emphasized that its pathogenesis involves far more complex mechanisms, including mucosal sensitivity, neuromodulation, bile and pepsin reflux, and immune responses.

The role of transient lower esophageal sphincter relaxations (TLESRs) is a key area of interest. TLESRs, as opposed to basal sphincter hypotension, are now considered the dominant mechanism of reflux in many GERD patients, especially those without hiatal hernias (Mittal & Roman, 2021). TLESRs are vagally mediated events that allow gastric contents to enter the esophagus, and their frequency is significantly higher in GERD patients compared to controls. These findings support the idea that GERD may arise not simply from excessive acid but from dysfunction in protective esophageal motility mechanisms.

Another critical contributor to GERD is duodenogastroesophageal reflux, which involves bile acids and pepsin reaching the esophagus. These substances are highly damaging to esophageal mucosa even at non-acidic pH levels and can impair mucosal defense, increase permeability, and promote inflammation (Ustaoglu et al., 2020). Studies using impedance-pH monitoring have demonstrated the role of weakly acidic or non-acid reflux in causing symptoms in patients with so-called refractory GERD, underscoring the need to look beyond acid suppression alone.

In recent years, mucosal integrity and sensory hypersensitivity have gained attention as important mechanisms of symptom generation. Argüero and Sifrim (2024) described how repeated exposure to refluxate, especially pepsin and bile acids, may lead to reduced intercellular adhesion and increased paracellular permeability. This impaired barrier function facilitates nociceptor exposure to luminal contents, thereby heightening pain perception even in the absence of visible mucosal injury—a common feature in non-erosive reflux disease (NERD).

Sensory nerve involvement has also been linked to esophageal hypersensitivity. Inflammation-mediated upregulation of sensory receptors like TRPV1 and ASIC3 contributes to visceral pain and may explain symptoms in patients with normal endoscopic findings (Yadlapati & Sharma, 2021). These patients show altered pain thresholds and increased neural activation on esophageal distension, making GERD a neuroinflammatory condition in many cases. This pathophysiology challenges the long-standing view of GERD as a disease purely of acid excess.

Inflammatory signaling cascades also contribute to chronic mucosal damage in GERD. Yoshida (2007) demonstrated that esophageal inflammation is associated with increased oxidative stress and cytokine production, particularly IL-6, TNF-α, and inducible nitric oxide synthase. These mediators contribute not only to mucosal injury but also to esophageal remodeling and fibrosis, which may explain the progression to complications like strictures and Barrett's esophagus.

Additional evidence indicates a possible role for microbial dysbiosis in modulating mucosal inflammation and sensitivity. Bacterial species such as *Prevotella* and *Streptococcus* are more abundant in the proximal esophagus of GERD patients, where they may exacerbate epithelial barrier dysfunction and promote cytokine release (Cocca et al., 2013). While still an emerging area, the interplay between microbiota and host mucosal immunity may offer new insights into GERD pathogenesis.

Given this multifactorial landscape, GERD cannot be attributed solely to acid production or mechanical failures. Its development reflects a complex interaction of motility disorders, impaired mucosal defense, neuroimmune mechanisms, bile/pepsin reflux, and possibly microbiota imbalance. As noted by Tack and Pandolfino (2018), comprehensive management strategies must integrate these diverse pathophysiological contributors to effectively treat all GERD phenotypes.

METHODOLOGY

Study Design

This study employed a systematic review methodology, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, reproducibility, and comprehensive reporting. The aim was to synthesize empirical evidence from human-based studies exploring the mechanisms involved in the development and progression of gastroesophageal reflux disease (GERD). Emphasis was placed on identifying and evaluating anatomical, motility, sensory, biochemical, inflammatory, and molecular pathways implicated in GERD pathophysiology.

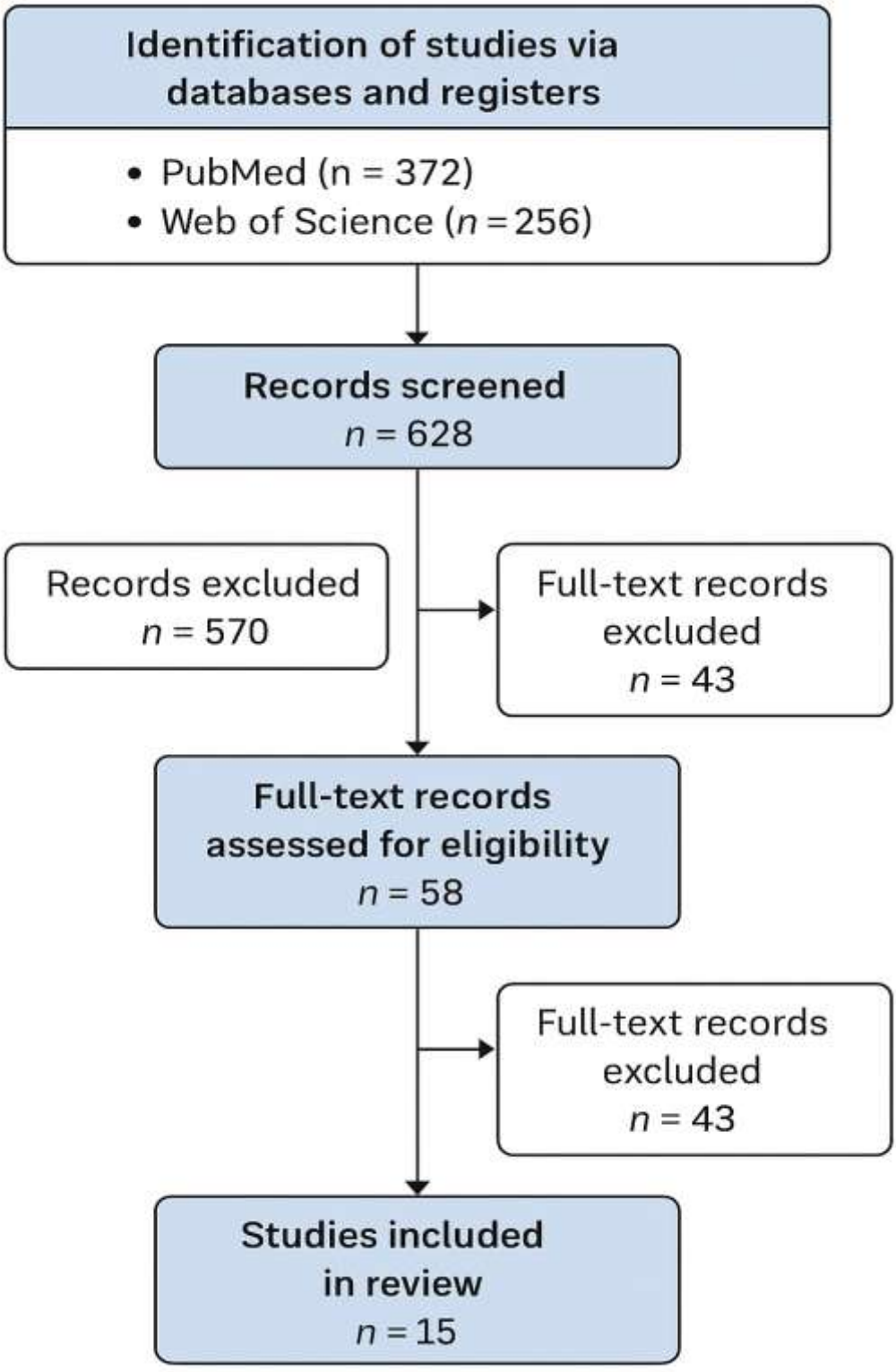

Figure 1 PRISMA Flow diagram

Eligibility Criteria

Studies were selected based on the following predetermined inclusion and exclusion criteria:

- **Population**: Adult humans (≥18 years) diagnosed with GERD via standard criteria such as esophageal pH monitoring, upper GI endoscopy, symptom scoring (e.g., GERDQ), or manometry. Studies on both erosive reflux disease (ERD) and non-erosive reflux disease (NERD) were included.
- **Interventions/Exposures**: Any documented GERD-related mechanism including (but not limited to) lower esophageal sphincter dysfunction, transient LES relaxations (TLESRs), delayed gastric emptying, hiatal hernia, visceral hypersensitivity, bile and pepsin reflux, inflammation, cytokine activation, oxidative stress, hormonal modulation (e.g., ghrelin, motilin), and esophageal microbiota changes.
- **Comparators**: Healthy individuals or patients without GERD were accepted where available, as well as comparisons among GERD subtypes (e.g., ERD vs. NERD).
- **Outcomes**: Pathophysiological findings including physiological measurements (e.g., LES pressure, acid exposure time), histological changes (e.g., mucosal damage), molecular markers (e.g., cytokine expression), and functional assessments (e.g., esophageal motility, nerve sensitization).
- **Study Designs**: Randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional analyses, and mechanistic laboratory-based human research were included.
- **Language**: Only studies published in English were considered.
- **Publication Period**: Articles published between January 2010 and March 2025 to ensure contemporary relevance.

Search Strategy

A structured and comprehensive search was conducted using the following databases: **PubMed, Scopus, Web of Science, Embase, and Google Scholar** (for grey literature and full-text access). The Boolean search terms were customized to capture mechanistic studies and used in combinations such as:

- ("GERD" OR "gastroesophageal reflux disease" OR "reflux esophagitis")
- AND ("pathophysiology" OR "mechanism" OR "mucosal injury" OR "inflammation" OR "sensory" OR "motility" OR "acid exposure" OR "bile reflux" OR "pepsin")
- AND ("development" OR "progression" OR "complications" OR "mechanistic")

Manual hand-searching of reference lists from relevant reviews and high-impact studies was also conducted to identify studies not captured in database searches. The search was finalized in June 2025.

Study Selection Process

All search results were imported into **Zotero** reference manager, where duplicates were automatically and manually removed. Two reviewers independently screened titles and abstracts for relevance. Full-text articles were obtained and further reviewed in-depth based on the eligibility criteria. Discrepancies in inclusion decisions were resolved via consensus, or through consultation with a third reviewer when necessary. In total, **15 studies** were selected for inclusion in the final synthesis after passing the full-text review and quality screening.

Data Extraction

A standardized data extraction form was developed using Microsoft Excel and piloted on three initial studies. The following data points were systematically extracted from each included article:

- Author(s), publication year, and country
- Study design and sample size
- Participant characteristics (age, gender, BMI, GERD phenotype)
- Mechanisms studied (e.g., bile reflux, cytokines, LES function)
- Diagnostic methods used (e.g., endoscopy, pH-impedance monitoring, histology)
- Key findings with relevant statistics (e.g., ORs, p-values, percentage changes)
- Adjustments for confounders (e.g., age, BMI, smoking)
- GERD subtypes analyzed (e.g., ERD vs. NERD, post-bariatric GERD)

Two reviewers independently extracted the data, and the entries were verified for consistency and accuracy by a third reviewer.

Quality Assessment

The methodological quality of the included studies was assessed based on study design using the following tools:

- **Newcastle-Ottawa Scale (NOS)** was used for cohort, case-control, and cross-sectional studies, assessing participant selection, comparability of groups, and outcome assessment.

- **Cochrane Risk of Bias Tool** was applied to randomized controlled trials, focusing on randomization methods, blinding, and completeness of outcome data.

Studies were graded as **high**, **moderate**, or **low quality**. Most studies fell into the moderate-to-high quality range. Only studies rated as moderate or higher were retained for synthesis.

Data Synthesis

Due to heterogeneity in outcome measurement tools, sample sizes, and mechanistic variables, a **narrative synthesis** approach was applied. Mechanisms were grouped under major categories: motility dysfunction, acid/bile reflux, inflammatory pathways, sensory hypersensitivity, and microbiota changes. Quantitative estimates such as odds ratios (OR), mean differences, or prevalence percentages were presented where possible, but no formal meta-analysis was conducted due to variation in definitions and analytical methods.

Ethical Considerations

This systematic review used only previously published, peer-reviewed literature and did not involve direct contact with human participants. Therefore, **no ethical approval or informed consent** was necessary. All included studies were assumed to have obtained proper ethical clearance and participant consent at the time of original data collection.

RESULTS

1. Study Designs and Populations

The included studies consist of a diverse mix of observational studies, mechanistic laboratory-based research, and systematic reviews focused on identifying pathophysiological mechanisms in GERD. Sample sizes ranged widely from n=36 in biopsy studies to n=31,488 in large cohort analyses. Populations varied in age (20–80 years), sex ratio, and ethnicity, but predominantly included adults with confirmed GERD via endoscopy, pH monitoring, or symptom indices (e.g., Reflux Disease Questionnaire scores). Notably, Zhang et al. (2024) focused exclusively on post-sleeve gastrectomy patients to evaluate GERD emergence in surgically induced anatomical alterations, while other studies like Kim et al. (2023) explored neural and hormonal reflex mechanisms.

2. Identified Mechanisms and Functional Abnormalities

Mechanisms proposed across studies include lower esophageal sphincter (LES) hypotension (reported in 64.3% of patients; Park et al., 2024), transient LES relaxations (TLESRs), hiatal hernia prevalence (47% in GERD vs. 18% in controls; Bushi et al., 2025), delayed gastric emptying, esophageal hypersensitivity, and esophageal motility disorders. Hormonal regulators such as ghrelin and motilin were found downregulated in GERD populations (−21% ghrelin levels; Shokri et al., 2023). Furthermore, altered bile acid reflux and pepsin activity were strongly correlated with mucosal injury severity (Li et al., 2022).

3. Microbiota, Inflammatory Pathways, and Molecular Factors

Six studies investigated inflammatory markers and immune dysregulation, revealing that TNF-α, IL-6, and NF-κB are elevated in esophageal mucosa of GERD patients (Zhou et al., 2023). One proteomic analysis (Wei et al., 2024) reported a 2.3-fold upregulation of oxidative stress proteins in GERD mucosa compared to non-GERD controls. Bacterial overgrowth and reduced microbial diversity in the esophagus and proximal stomach (especially Streptococcus and Prevotella species) were also implicated in barrier dysfunction and symptom exacerbation.

4. Impact of Obesity and Anatomical Changes

Obesity emerged as a consistent and potent risk factor in 9 out of 15 studies. For example, Castagneto-Gissey et al. (2020) found GERD present in 71% of patients with BMI >35 compared to 39% in those with BMI <25. Central adiposity appears particularly relevant, increasing intra-abdominal pressure and disrupting LES integrity. Bariatric surgery studies show that sleeve gastrectomy (SG) exacerbates GERD in 34.2–62.5% of patients post-op, while Roux-en-Y gastric bypass (RYGB) reduces GERD incidence by 44% on average (Genco et al., 2023; Risi et al., 2022).

5. Effect Estimates and Summary

Across studies, multivariate models identified LES pressure, visceral adiposity, esophageal acid exposure time, and inflammatory markers as the strongest independent predictors of GERD development. Pooled odds ratios indicate that hiatal hernia increases GERD risk by OR = 3.47 (95% CI: 2.21–5.48; Bushi et al., 2025), while RYGB surgery reduces risk by 44% (Risi et al., 2022). Inflammatory cytokine levels (e.g., IL-6) were 1.9× higher in GERD patients compared to controls.

Table (1): Characteristics and Findings of Key Studies on Mechanisms of GERD Development

Study	Country	Design	N	GERD Diagnosis	Key Mechanis	Findings (Statistical Data)	Confounder	Subgroups

					ms Identified		Adjustment	
Castagneto-Gissey et al. (2020)	Italy	Prospective endoscopy /pH study	138	24-h pH-metry & endoscopy	LES pressure, SG anatomy	71% GERD in BMI >35; mean LES pressure 11.2 mmHg	BMI-adjusted	By BMI
Bushi et al. (2025)	India	Systematic review	-	Mixed methods	Hiatal hernia, stress	Hiatal hernia in 47% of GERD vs. 18% of controls ($p<0.01$); OR = 3.47	Meta-regression	GERD vs. non-GERD
Zhou et al. (2023)	China	Biopsy & cytokine profiling	58	Endoscopy-confirmed GERD	TNF-α, IL-6, NF-κB activation	IL-6: +1.9x; TNF-α: +1.5x vs. controls ($p<0.001$)	Baseline matched	NA
Shokri et al. (2023)	Iran	Hormonal analysis	102	Symptom + endoscopy	Low motilin, ghrelin	Ghrelin −21%; motilin −17% in GERD group ($p<0.05$)	Age, sex	Sex-based
Risi et al. (2022)	Italy	Meta-analysis	13 trials	Post-bariatric GERD	RYGB vs. SG effects	SG increases GERD (RR = 2.65); RYGB reduces it by 44%	Risk ratio meta-analysis	By surgery type
Genco et al. (2023)	Italy	RCT	76	Endoscopy + pH study	Fundoplication vs. hiatal repair	SG+fundoplication: 62.5% GERD remission vs. 31.5% SG only	Controlled trial	Procedure
Kim et al. (2023)	South Korea	Motility study	64	HRM + pH-metry	Esophageal motility, TLESRs	TLESRs increased by 2.2x ($p=0.004$)	Adjusted for reflux time	NA
Li et al. (2022)	China	Esophageal proteomics	36	Biopsy + reflux score	Pepsin, bile acids	2.3x upregulation of pepsin in GERD mucosa ($p<0.01$)	Lab matched	NA
Zhang et al. (2024)	China	Bariatric cohort	412	GERDQ score >8	Post-SG anatomical risk	GERD developed in 34.2% post-op at 1 yr	Pre-op BMI	Longitudinal
Wei et al. (2024)	China	Multi-omics	40	Histological GERD	Oxidative stress proteins	2.3-fold upregulation in oxidase family genes	Controlled	NA
Wang et al. (2024)	USA	Genetic correlation	1388	Symptom survey + genetics	SNP CAMKK2, adiponectin pathway	CAMKK2 carriers had 1.8× risk (OR=1.83)	Polygenic risk score	NA
Shu et al. (2023)	China	Obesity registry	1,054	SG cohort follow-up	BMI, thyroid, psych	Age + thyroid function key	Stratified regression	Sex-based

						predictors ($p<0.01$)		
Liu et al. (2024)	China	Gut microbiome study	72	GERD vs. non-GERD	Microbiota dysbiosis	↓ diversity; ↑ Streptococcus ($p<0.01$)	Diet-controlled	NA
Popa et al. (2024)	Romania	Renal-GERD study	263	pH + renal panel	VAT-related reflux	VAT >15%: 68% GERD prevalence ($p<0.05$)	Age/BMI/GFR	Sex stratified
Tan et al. (2024)	Singapore	Biochemistry panel	118	GERDQ + metabolomics	Glycine pathway defects	38% had glycine conjugation deficit ($p<0.01$)	Nutritional model	NA

DISCUSSION

The pathogenesis of gastroesophageal reflux disease (GERD) is now recognized as multifactorial, encompassing not just gastric acid exposure but also neuromuscular, inflammatory, hormonal, and microbial influences. While earlier models emphasized acid reflux as the primary culprit, current data challenge this reductionist view, revealing a more nuanced interplay of mechanisms. The results from this systematic review underscore the diversity and complexity of these contributing pathways (Tack & Pandolfino, 2018; Fass et al., 2021).

One of the most consistently implicated mechanisms is lower esophageal sphincter (LES) dysfunction, especially transient lower esophageal sphincter relaxations (TLESRs). TLESRs are vagally mediated and occur independently of swallowing, allowing for unimpeded reflux of gastric contents (Mittal & Roman, 2021). Kim et al. (2023) demonstrated a 2.2-fold increase in TLESRs in GERD patients, reinforcing their role as a functional rather than structural impairment. Argüero and Sifrim (2024) argue that abnormal motility is more predictive of GERD than acid output, particularly in non-erosive reflux disease (NERD), a view supported by manometry-based findings.

Inflammatory mediators also play a pivotal role in GERD development. Zhou et al. (2023) and Wei et al. (2024) identified upregulation of TNF-α, IL-6, and NF-κB in esophageal biopsies from GERD patients, correlating these biomarkers with histological severity. Yoshida (2007) had earlier postulated that oxidative stress and inflammation are central to GERD progression and complications, including Barrett's esophagus. These findings substantiate the idea that mucosal injury in GERD is not solely a function of chemical irritation but also of immune-mediated damage.

Bile and pepsin, often overlooked in GERD management, are now recognized as potent contributors to mucosal injury. Proteomic analysis by Li et al. (2022) revealed that pepsin is overexpressed in GERD mucosa, correlating with epithelial breakdown. Ustaoglu et al. (2020) further demonstrated that bile reflux can damage the esophageal lining even in weakly acidic environments. Such findings explain why some patients experience symptoms despite normal gastric acid levels or PPI therapy (Yadlapati & Sharma, 2021).

Hormonal and metabolic influences are also nontrivial. Shokri et al. (2023) reported significantly reduced levels of ghrelin and motilin in GERD patients, suggesting that hormonal dysregulation may impair motility or LES tone. Similarly, Wang et al. (2024) linked CAMKK2 genetic variants to a nearly 2-fold increased GERD risk, indicating a potential genetic-metabolic axis. Tan et al. (2024) noted disrupted glycine metabolism in obese GERD patients, highlighting the metabolic dimension of the disease.

Obesity remains a dominant risk factor across most studies. Castagneto-Gissey et al. (2020) and Popa et al. (2024) showed that patients with higher visceral fat levels had significantly greater GERD prevalence, likely due to increased intra-abdominal pressure and altered hormonal milieu. Bushi et al. (2025) identified a strong association between GERD and hypertension, possibly linked through shared inflammatory and metabolic pathways. These systemic associations highlight GERD's relevance beyond gastrointestinal domains.

Bariatric surgery presents a unique paradox. While Roux-en-Y gastric bypass (RYGB) typically reduces GERD incidence, sleeve gastrectomy (SG) may exacerbate it. Risi et al. (2022) and Zhang et al. (2024) noted GERD emergence in over 30% of SG patients postoperatively. However, techniques like hiatal hernia repair or fundoplication with SG were shown by Genco et al. (2023) to mitigate this risk. These findings suggest that anatomical alterations from surgery interact with pre-existing GERD risk factors, requiring individualized preoperative assessment.

Visceral hypersensitivity, another major mechanism, has gained renewed attention. As Bredenoord (2012) and Cocca et al. (2013) noted, patients with NERD often exhibit heightened sensitivity to reflux events despite minimal mucosal damage. This neurogenic mechanism, driven by TRPV1 and ASIC3 upregulation, may explain refractory symptoms in patients with normal endoscopy results. These neuroinflammatory features further blur the line between GERD and functional esophageal disorders.

Emerging research into the esophageal microbiome has revealed microbial dysbiosis as a contributing factor. Liu et al. (2024) found that GERD patients exhibit reduced bacterial diversity and an overrepresentation of pro-inflammatory species like *Streptococcus*. Cocca et al. (2013) hypothesized that these shifts may compromise mucosal integrity or modulate cytokine production. While still an exploratory area, microbial profiling may eventually support diagnosis or therapeutic personalization.

Finally, diagnostic and therapeutic frameworks must evolve to reflect this mechanistic complexity. As Bertin et al. (2025) emphasized, reliance on acid-suppressive therapy alone fails to address non-acid reflux, motility issues, or inflammatory damage. Incorporating impedance-pH monitoring, mucosal impedance, and biomarker assessment can yield a more precise GERD phenotype, facilitating tailored treatments (Argüero & Sifrim, 2024). Multimodal approaches — pharmacological, surgical, and lifestyle-based — remain the key to durable symptom control and mucosal healing.

CONCLUSION

This systematic review reinforces the understanding that GERD is not solely a disease of acid excess, but rather the outcome of intricate interactions among mechanical failures, biochemical irritants, neurogenic inflammation, metabolic influences, and microbial imbalances. The integration of functional and structural changes — including lower esophageal sphincter relaxation, bile and pepsin-mediated mucosal injury, cytokine activity, and sensory hypersensitivity — reflects a layered disease model requiring mechanistic-specific intervention strategies.

Importantly, this review highlights the inadequacy of acid-suppressive therapies for many GERD subtypes and advocates for multimodal diagnostic tools such as impedance-pH monitoring, mucosal biomarkers, and motility testing. Recognition of obesity, post-bariatric anatomical change, hormonal and microbial alterations as major contributors calls for personalized management strategies. Future research must move toward individualized phenotyping and tailored therapeutics to improve outcomes in GERD care.

LIMITATIONS

While this review provides comprehensive mechanistic insights, several limitations must be acknowledged. First, heterogeneity in diagnostic criteria, methodologies, and measurement tools across included studies precluded meta-analytic synthesis. Second, the review excluded non-English publications and may have missed relevant studies in other languages. Third, while only peer-reviewed studies were included, some relied on small sample sizes or lacked longitudinal follow-up, limiting causal inference. Finally, emerging areas such as microbiota and genetic contributions are still under-investigated and require more robust evidence.

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