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A comprehensive analysis of gastroesophageal reflux disease: Pathophysiology, clinical manifestations, and diagnostic approaches

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***Abstract*---Background:** Gastroesophageal reflux disease (GERD) is a common condition characterized by the reflux of stomach contents, leading to troublesome symptoms and potential complications. The Montreal definition emphasizes symptom severity, while the Lyon Consensus focuses on physiological aspects, and the Rome IV Conference highlights functional syndromes resembling GERD. This article aims to provide a comprehensive analysis of GERD, consolidating various definitions and perspectives. **Aim:** The study seeks to clarify the multifaceted nature of GERD, including its pathophysiology, clinical manifestations, diagnostic approaches, and therapeutic strategies. **Methods:** This narrative review synthesizes existing literature, examining prevalence, morbidity, and mortality associated with GERD, as well as its pathogenesis and the impact of lifestyle factors such as obesity. Data from various studies were analyzed to assess the global prevalence of GERD and its complications. **Results:** GERD prevalence varies globally, from 2.5%

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in China to 51.2% in Greece, with significant associations between obesity and GERD-related complications, including esophageal adenocarcinoma (EAC). The economic burden of GERD is substantial, with significant healthcare costs reported in multiple countries. The review also highlights the dual role of Helicobacter pylori, which may both exacerbate and protect against GERD symptoms. **Conclusion:** GERD is a complex condition necessitating a multidisciplinary approach to diagnosis and management. Understanding its pathophysiology and the factors influencing its prevalence is critical for effective therapeutic strategies. Continued research is needed to optimize GERD management, considering the interplay of various cofactors, including lifestyle and comorbidities.

***Keywords*---**gastroesophageal reflux disease, pathophysiology, prevalence, complications, therapeutic strategies.

Introduction

Gastroesophageal reflux disease (GERD) is conceptualized from multiple viewpoints. The Montreal definition characterizes GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications” [1]. The merit of this definition lies in its straightforwardness, as it consolidates a wide array of seemingly unrelated symptoms and potential complications. Nevertheless, the Montreal definition fails to account for cofactors that may interact with reflux, resulting in atypical phenotypes that fall within this broad categorization. Conversely, the Lyon Consensus definition adopts a physiomorphologic approach, identifying GERD through the occurrence of excessive gastroesophageal reflux, esophageal motility disturbances, and heightened epithelial permeability associated with reflux [2]. However, many of these characteristics are non-specific to GERD. The definition proposed by the Rome IV Conference is symptom-oriented and aims to delineate functional syndromes that exhibit GERD-like features [3]. However, these functional syndromes can resemble GERD even in the absence of reflux causation. Integrating these various definitions presents a challenge. In this review, GERD is characterized as a spectrum of syndromes that are attributable to or worsened by gastroesophageal reflux, manifesting either symptomatically, endoscopically, or through physiological testing, ultimately leading to morbidity due to bothersome symptoms and/or associated risks. As a prevalent condition with a wide range of presentations, GERD is addressed by a multitude of healthcare providers across various specialties, including general practitioners, internists, gastroenterologists, surgeons, emergency department physicians, hospitalists, otolaryngologists, pulmonologists, obstetricians, and pediatricians. This diversity has resulted in a variety of perspectives on management. Numerous topics related to management—such as the use and safety of proton pump inhibitors (PPIs), criteria for endoscopy, recommended dietary changes, and the roles of surgical and endoscopic procedures—have developed in recent years, leading to a considerable volume of literature that can be somewhat overwhelming. This narrative review aims to clarify the often conflicting

information regarding GERD in the adult population for clinicians, scholars, and clinical researchers.

Prevalence and Geographic Distribution:

Gastroesophageal reflux disease (GERD) is a global health issue, with prevalence rates reported to vary significantly, ranging from 2.5% in China to 51.2% in Greece [4][5]. This variation is likely indicative of both actual differences in disease occurrence and methodological disparities in research, as some studies define GERD based on the frequency of weekly heartburn and/or regurgitation, while others focus on the presence of erosive esophagitis. Notably, although the prevalence of GERD symptoms is comparable among different racial groups, complications such as erosive esophagitis and esophageal adenocarcinoma (EAC) are observed more frequently in Caucasians, particularly those with central obesity. Furthermore, reflux symptoms are becoming increasingly prevalent among young adults, with the most significant rise noted in the 30-39 age group [7], and EAC cases are on the rise in individuals under 50 [8].

Morbidity and Mortality:

While GERD itself is not classified as a fatal condition, it can lead to serious complications, including EAC, bleeding, esophageal rupture, aspiration, lung transplant rejection, aspiration pneumonia, and complications from medical interventions such as surgery and dilation. The estimated annual mortality rate directly attributable to GERD in Canada was approximately 65 patients [9]. A population study conducted in Sweden reported an annual death rate of 0.20 per 100,000, caused primarily by hemorrhagic esophagitis (51.9%), aspiration pneumonia (34.6%), perforated esophageal ulcers (9.6%), and spontaneous esophageal rupture (3.9%) [10]. The societal costs associated with GERD are considerable. In Canada, the direct annual cost of managing GERD was estimated at CAD 52,235,910 (approximately £30.2 million or €33.4 million) in 2004-05 [9]. In the United States, GERD accounted for 8,863,568 physician visits, 65,634 hospitalizations, and an estimated expenditure of $12.3 billion on upper endoscopies within a single year [11]. In Japan, the average medical cost for GERD patients aged 20-59 reached $266 per patient per month in 2014, which is roughly 2.4 times higher than the mean national healthcare expenditure [12].

Pathogenesis:
Obesity and the Western Lifestyle:

Numerous studies have identified a correlation between obesity and GERD, with a particularly strong association between central adiposity and GERD-related complications such as EAC [13]. A meta-analysis encompassing 107 international studies revealed a relative risk of 1.73 for experiencing at least weekly GERD symptoms among obese individuals, although this analysis exhibited considerable heterogeneity across studies [5]. Another meta-analysis involving 40 studies indicated that individuals with central adiposity had a relative risk of 1.87 for erosive esophagitis (95% confidence interval, 1.51 to 2.31) and a 1.98-fold risk of developing Barrett's esophagus, even after controlling for body mass index [13]. The underlying mechanism involves increased intra-abdominal and intragastric

pressure from central adiposity, which challenges the anti-reflux barrier and contributes to the formation of hiatal hernias. Additionally, obesity is often associated with overeating, leading to gastric distension and transient relaxations of the lower esophageal sphincter (LES) [14]. Metabolic consequences of central obesity may further exacerbate GERD; even in the absence of pathological reflux, the distal esophageal epithelium in obese patients demonstrates increased permeability, suggesting a compromised epithelial barrier [15].

Helicobacter pylori:

Though relatively recently discovered, *Helicobacter pylori* has been infecting humans for at least 50,000 years [16]. Its strongest associations are with the promotion of peptic ulcers and gastric cancer. Interestingly, this infection may also confer protective effects against GERD. Epidemiological data indicate an inverse relationship between *H. pylori* infection and the occurrence of erosive esophagitis, Barrett's esophagus, and EAC [17][18]. The proposed mechanism for this protective effect suggests that chronic *H. pylori* gastritis can lead to atrophic gastritis and a state of relative hypochlorhydria, subsequently reducing the acidity of gastroesophageal reflux. Supporting this hypothesis, proton pump inhibitors (PPIs) are reported to be more effective in patients with *H. pylori* infection, likely due to the pre-existing reduction in gastric acid secretion [19]. However, findings from two large randomized controlled trials comparing *H. pylori* eradication to placebo did not reveal a significant increase in reflux symptoms two years post-eradication [20][21], suggesting that the observed inverse correlation between *H. pylori* infection and GERD may not be causal.

Physiology: The Lyon Consensus:

The Lyon Consensus evaluated the significance of physiological testing in diagnosing GERD. It concluded that the primary factor in the pathophysiology of GERD is the incompetence of the esophagogastric junction (EGJ), characterized by the separation of the crural diaphragm from the LES, as seen in hiatus hernia, and a low EGJ contractile index, which is calculated from sphincter pressure over time via high-resolution manometry. Traditionally, research focused on low LES pressure as an indicator of reflux barrier dysfunction; however, the EGJ contractile index expands this understanding to include both the crural diaphragm and the LES. A diminished EGJ contractile index is frequently observed in patients with erosive esophagitis and Barrett's esophagus. Many individuals with GERD have an EGJ contractility index within the normal range but still experience excessive acid reflux due to transient LES relaxation—an intrinsic physiological mechanism involved in belching. These transient relaxations are triggered by a vago-vagal reflex initiated by stomach distension. The key difference between GERD patients and healthy individuals is the higher frequency of transient LES relaxations associated with acid reflux rather than merely gas venting. This phenomenon is compounded by increased compliance of the EGJ, allowing for wider openings and greater reflux volumes during relaxation [23-26].

Hiatus Hernia: The Co-Conspirator:

Axial or sliding hiatal hernia is closely linked to GERD, especially in cases of peptic esophagitis and its complications, to the extent that both patients and healthcare providers often conflate hiatal hernia with GERD. While this perspective is misleading, the role of a hiatal hernia in GERD pathophysiology is substantial and multifaceted. One primary effect is the physical separation of the LES and the crural diaphragm, reducing their collaborative effectiveness as a barrier to reflux events and impeding esophageal acid clearance after reflux episodes. Additionally, hiatal hernia may reposition the "acid pocket," which forms postprandially as newly secreted acid overlays ingested food, creating a reservoir for postprandial reflux. In the presence of a hiatal hernia, the acid pocket can move into the hernia compartment, exposing the distal esophageal epithelium to gastric acid during any period of LES relaxation, including those associated with swallowing or secondary peristalsis. The mechanism by which alginate compounds are thought to alleviate GERD symptoms may involve creating a protective gelatinous raft that caps the acid pocket and displaces it from the LES. The Lyon Consensus recognized the importance of hiatal hernia in the pathophysiology of GERD, particularly when its size exceeds 3 cm [27-29].

The Inflammation Hypothesis:

The traditional "burn hypothesis" of reflux esophagitis suggests that the damaging effects of hydrochloric acid, combined with enzymatic degradation by pepsin, cause injury to the esophageal epithelium from the lumen inward. However, recent studies have challenged this view, proposing instead that much of the damage results from chronic inflammation mediated by chemokines. In experiments involving rats, reflux esophagitis was induced, leading to lymphocyte infiltration starting in the submucosa and advancing to the epithelial surface. This lymphocytic response was associated with the secretion of IL-8 and IL-1β, resulting in injury patterns that persisted for weeks. A similar process was observed in patients with high-grade esophagitis, who initially responded well to PPIs but subsequently experienced recurrent esophagitis upon discontinuation of the medication. These findings imply that alternative pharmacological strategies, independent of acid suppression, may be viable for the treatment of esophagitis [30-31].

Diagnostic Testing: Endoscopy, Reflux Monitoring, Motility Testing:

Endoscopy serves as the primary diagnostic modality for suspected gastroesophageal reflux disease (GERD) syndromes, attributed to its accessibility, relative safety, capability for biopsy, therapeutic potential, and specificity regarding potential findings. The Los Angeles Classification delineates four severity grades of esophagitis (A-D), categorized by the extent of erosions (mucosal breaks) in the distal esophagus. The Lyon Consensus recognizes only Los Angeles grades C and D esophagitis as definitive evidence of GERD; however, we propose the inclusion of Los Angeles grade B esophagitis, provided it is accurately graded. In contrast, Los Angeles grade A esophagitis occurs in 5-7% of normal individuals and does not constitute definitive evidence of GERD. Other clinically pertinent findings may include peptic strictures, Barrett's metaplasia, and hiatal hernia.

Prolonged ambulatory esophageal reflux monitoring (via pH or combined pH-impedance) serves three primary functions in GERD management: (1) quantifying abnormal esophageal acid exposure in the absence of esophagitis; (2) determining the correlation between a patient's symptoms and reflux events; and (3) assessing whether gastroesophageal reflux (acidic or weakly acidic, as indicated by pH impedance studies) is effectively managed through therapy. This assessment becomes particularly relevant when evaluating atypical symptoms or persistent symptoms despite seemingly adequate pharmacological and/or surgical interventions. Confirming a physiologically defined disease state is also crucial when considering procedural interventions for GERD. High-resolution manometry is capable of identifying physiological abnormalities associated with GERD, such as a diminished esophagogastric junction (EGJ) contractility index, the presence of a hiatal hernia, or weak/absent peristalsis; however, it lacks utility in treatment definition. The exception arises when procedural treatments are being considered, necessitating manometry to detect unrecognized achalasia and to ensure that peristaltic function is sufficiently preserved for the planned intervention [32-35].

GERD Phenotypes:

Implicit in the Montreal definition is the notion that GERD can be characterized by either endoscopic features or a symptom complex resulting from gastroesophageal reflux. This duality poses management challenges, as the factors leading to mucosal injury differ from those contributing to symptomatology, making it imprudent to assume that treatment strategies should remain uniform. The emerging perspective is that rather than existing as a continuum of disease with esophagitis merely representing a more severe form of non-erosive reflux disease (NERD), GERD encompasses distinct phenotypes, each exhibiting unique and overlapping characteristics. Supporting this concept are two decades of longitudinal data indicating that the progression from NERD to severe esophagitis, strictures, or Barrett's esophagus is infrequent. Moreover, patients with severe esophagitis or Barrett's esophagus exhibit significant predispositions, often being white, male, centrally obese, and possessing a family history of the condition. In contrast, NERD does not demonstrate any discernible racial or gender bias. The extent to which esophageal hypersensitivity contributes to pathophysiology also varies significantly among phenotypes. The Rome IV classification addresses this variability within the NERD cohort by subdividing it into “true NERD,” reflux hypersensitivity, and functional heartburn, with reflux as the dominant symptom determinant at one end and hypersensitivity predominating at the other (functional heartburn). In conclusion, while gastroesophageal reflux is a contributing factor across all these syndromes (except possibly functional heartburn), its influence as a pathophysiological determinant varies markedly [36-37].

Barrett’s Esophagus and Esophageal Adenocarcinoma:

The most severe potential outcome of GERD is esophageal adenocarcinoma (EAC), a malignancy whose incidence has surged dramatically in Western populations over the past three decades, mirroring trends in GERD prevalence. A seminal epidemiological study has established a dose-dependent relationship, indicating

that patients experiencing severe reflux symptoms (greater than three times per week for over five years) face a sixteen-fold increased risk of developing EAC. Furthermore, the majority of EAC cases are diagnosed at an advanced stage, associated with poor prognoses and low five-year survival rates. This reality has led to the establishment of screening endoscopy protocols aimed at detecting either early EAC, which offers significantly better survival outcomes, or more frequently, the precursor lesion of Barrett's metaplasia. Consequently, societal guidelines (which exhibit considerable variability) have proposed employing symptom burden as a criterion for endoscopic screening and subsequent surveillance for Barrett's esophagus. While this approach remains contentious, a systematic analysis of retrospective case-control studies suggests that Barrett's surveillance programs facilitate earlier diagnoses of EAC and potentially improve mortality rates. It is noteworthy that up to 40% of EAC patients present without a significant history of reflux symptoms, and approximately 80-95% of EAC patients are diagnosed de novo. Thus, only a minority of EAC patients exhibit a symptom burden severe enough to justify endoscopic screening within Barrett's surveillance programs [38-49].

Atypical and Extraesophageal Manifestations:

Gastroesophageal reflux has been associated with a variety of atypical and extraesophageal conditions, including laryngitis, pharyngitis, chronic cough, postnasal drip, non-cardiac chest pain, bronchiectasis, poorly controlled asthma, globus sensation, cardiac arrhythmias, laryngeal cancer, subglottic stenosis, vocal fold granulomata, halitosis, dental erosion, hiccups, aspiration pneumonia, pulmonary fibrosis, lung transplant rejection, sleep apnea, burning tongue, dysgeusia, and chronic sinusitis. The strength of evidence supporting the link between reflux and these conditions varies widely, from speculative to substantiated by treatment trials (50). The accurate attribution of these conditions to gastroesophageal reflux disease (GERD) is complicated by proposed pathogenic mechanisms that differ from those affecting esophageal syndromes. This fosters the hypothesis that physiologic or "silent" reflux may cause harm. Symptoms such as cough or arrhythmias might arise from overlapping neural pathways activated by reflux but may not reach the threshold necessary to provoke esophageal symptoms. It is also suggested that when structures such as vocal folds come into contact with gastric contents, the absence of a robust mucosal defense leads to damage, even with reflux parameters that would be considered normal in the esophagus. Thus, diagnosing these atypical syndromes is challenging, as esophageal reflux testing often lacks sensitivity and coexisting endoscopic abnormalities are rare (51). Additionally, proposed methods for assessing pepsin or acid reflux in a supraesophageal distribution have not been validated. Given these limitations, most relevant data are derived from uncontrolled medical or surgical treatment studies. The few randomized controlled trials involving proton pump inhibitors (PPIs) in patients with poorly controlled asthma, reflux laryngitis, and postnasal drip have either yielded completely negative results or, in the case of postnasal drip, only marginally positive outcomes in a highly selective population.

As indicated in the preceding analysis, the management of suspected atypical GERD syndromes is fraught with uncertainties concerning diagnosis, causality,

and treatment effectiveness. Nevertheless, several overarching principles can be discerned. First, while reflux can lead to atypical syndromes, it is rare for it to be the primary cause in patients who do not exhibit typical esophageal symptoms. For instance, in a randomized controlled trial evaluating esomeprazole for posterior laryngitis that intentionally excluded patients with frequent heartburn, the placebo response outperformed the esomeprazole response (41). Although reflux may be a significant etiological factor in laryngitis, numerous potential cofactors or alternative explanations exist, such as excessive voice use, visceral hypersensitivity, environmental irritants, and postnasal drip. Thus, if patients do not respond to PPI therapy, effective management typically necessitates a multidisciplinary approach aimed at identifying causal cofactors and adjunctive therapies, and such syndromes should not automatically require referral to gastroenterology. A second key point is that reflux testing (pH-metry or pH impedance monitoring) is more valuable when it is negative, effectively ruling out reflux as a cause, rather than when the results are ambiguous or positive, which merely leaves the possibility of a reflux cause open without confirming it. A third noteworthy observation is that although fundoplication successfully eliminates reflux, no high-quality evidence supports its efficacy in atypical syndromes that do not respond to high-dose PPI therapy. For example, in a controlled study involving patients unresponsive to PPIs, no improvement was observed in laryngeal symptoms among those subsequently treated with surgical fundoplication. In conclusion, atypical and extraesophageal manifestations of GERD present a management dilemma informed by expert opinion, with differing views among specialists from various disciplines. From a gastroenterology perspective, the Clinical Practice Updates Committee of the American Gastroenterological Association recommends a therapeutic trial of aggressive acid suppression for six to eight weeks, focusing on the response of extraesophageal symptoms and using reflux testing primarily to exclude rather than confirm a reflux-related cause. In the same document, they advise against the use of unvalidated tests to implicate GERD and the surgical management of atypical syndromes unresponsive to PPI therapy (50).

Conclusion

Gastroesophageal reflux disease (GERD) represents a significant global health issue, characterized by a spectrum of clinical manifestations that necessitate a nuanced understanding of its underlying mechanisms and implications. The diverse definitions and perspectives surrounding GERD, from symptom-based categorizations to physiological analyses, highlight the complexity of the disease and its management. This comprehensive analysis underscores the need for healthcare providers to adopt a multifactorial approach when diagnosing and treating GERD, recognizing the interplay between lifestyle factors, such as obesity, and the physiological changes that occur in the esophagogastric junction (EGJ). The review illustrates that the prevalence of GERD symptoms varies widely, influenced by geographical, racial, and methodological factors. The increasing incidence of GERD, particularly among younger populations, necessitates urgent attention to public health strategies aimed at addressing lifestyle modifications. Additionally, the relationship between obesity and GERD-related complications, including esophageal adenocarcinoma (EAC), emphasizes the importance of managing obesity as a risk factor in GERD patients. Economic

implications associated with GERD are profound, leading to substantial healthcare expenditures and resource allocation in various healthcare systems. Understanding these financial burdens can inform policymakers and healthcare providers in developing targeted interventions and improving patient care. Moreover, the role of Helicobacter pylori in the context of GERD illustrates the need for further research to delineate its complex relationship with reflux symptoms and esophageal conditions. The divergent findings regarding its protective and exacerbating effects on GERD underscore the necessity for ongoing investigation into the pathogen's influence on gastric physiology and its implications for treatment. In summary, effective management of GERD requires an integrated approach, considering both the clinical and economic aspects of the disease. Future research should focus on refining diagnostic criteria, optimizing therapeutic strategies, and promoting preventive measures, thereby improving patient outcomes and reducing the overall burden of GERD on healthcare systems.

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تحليل شامل لمرض الارتجاع المعدي المريئي: الفيزيولوجيا المرضية، الأعراض السريرية، وطرق التشخيص

الملخص:

الخلفية :يُعتبر مرض الارتجاع المعدي المريئي (GERD) حالة شائعة تتسم بارتجاع محتويات المعدة، مما يؤدي إلى أعراض مزعجة ومضاعفات محتملة. يُبرز تعريف مونتريال شدة الأعراض، بينما يركز إجماع ليون على الجوانب الفيزيولوجية، وتُسلط مؤتمر روما IV الضوء على المتلازمات الوظيفية التي تشبه GERD. تهدف هذه المقالة إلى تقديم تحليل شامل لـGERD ، موحدةً بين التعريفات ووجهات النظر المختلفة.

الهدف :يسعى هذا الدراسة إلى توضيح الطبيعة متعددة الأبعاد لـGERD ، بما في ذلك الفيزيولوجيا المرضية، الأعراض السريرية، طرق التشخيص، واستراتيجيات العلاج.

الطرق :تستند هذه المراجعة السردية إلى الأدبيات الحالية، حيث تفحص انتشار المرض، والمراضة، والوفيات المرتبطة بـGERD ، بالإضافة إلى آلية حدوثه وتأثير العوامل الحياتية مثل السمنة. تم تحليل بيانات من دراسات متنوعة لتقييم الانتشار العالمي لـ GERD ومضاعفاته.

النتائج :يختلف انتشار GERD على مستوى العالم، حيث يتراوح من 2.5% في الصين إلى 51.2% في اليونان، مع ارتباطات كبيرة بين السمنة ومضاعفاتGERD ، بما في ذلك سرطان المريء الغدي (EAC). العبء الاقتصادي لـ GERD كبير، مع تكاليف صحية مهمة تم الإبلاغ عنها في عدة دول. كما تسلط المراجعة الضوء على الدور المزدوج لبكتيريا *Helicobacter pylori*، التي قد تفاقم أعراض GERD أو تحمي منها.

الخلاصة :يُعتبر GERD حالة معقدة تتطلب نهجًا متعدد التخصصات في التشخيص والإدارة. إن فهم الفيزيولوجيا المرضية والعوامل المؤثرة على انتشاره أمر حاسم لاستراتيجيات العلاج الفعالة. هناك حاجة إلى مزيد من البحث لتحسين إدارةGERD ، مع الأخذ في الاعتبار التفاعل بين العوامل المشتركة المتنوعة، بما في ذلك نمط الحياة والأمراض المصاحبة.

الكلمات المفتاحية :مرض الارتجاع المعدي المريئي، الفيزيولوجيا المرضية، الانتشار، المضاعفات، استراتيجيات العلاج