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DIAGNOSTIC AND THERAPEUTIC APPROACH TO GASTROESOPHAGEAL REFLUX DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To report the main aspects involving Gastroesophageal Reflux Disease, including diagnostic and therapeutic methods. Methodology: This is a systematic review focused on understanding the essential aspects of Gastroesophageal Reflux Disease. The research was guided by the question: "What are the main signs and symptoms of Parkinson's disease, as well as what are the diagnostic resources and therapeutic approaches used in clinical practice?" ``. To find answers, searches were performed in the PubMed database using six descriptors combined with the Boolean term "AND". This resulted in 565 articles, of which 21 were selected for analysis. Results: Gastroesophageal reflux disease (GERD) occurs when gastric contents are refluxed into the esophagus, causing symptoms such as heartburn and regurgitation. Factors such as relaxation of the lower esophageal sphincter, hiatal hernia, obesity, and eating habits all contribute to the problem. Diagnosis is based on clinical history, endoscopy, and pH-metry. Treatment includes lifestyle changes, use of proton pump inhibitors (PPIs) and, in severe cases, surgical interventions. Conclusion: Surveillance is crucial to avoid complications, such as esophagitis, Barrett's esophagus,

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and esophageal adenocarcinoma, with advances in diagnosis and personalized therapies aiding in the prevention and control of the disease.

Keywords: Gastroesophageal Reflux Disease. Diagnosis. Clinical Picture. Treatment.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes bothersome symptoms or complications in the esophagus or beyond. GERD is prevalent worldwide, with the burden of disease showing an increasing trend. Estimates show that the prevalence of GERD is about 18%-27% in North America, 23% in South America, 8%-25% in Europe, 2.5%-8% in East Asia, 8-33% in the Middle East, and 11.6% in Australia, and affects both sexes similarly (VELAGALA; VELAGALA; LAMTURE, 2022). Gastroesophageal reflux disease (GERD) affects an estimated 1.03 billion people worldwide. Increasing aging and obesity, both predisposing factors for GERD, may further increase its impact in the near future. Many other factors also favor the exacerbation of GERD, including tobacco and certain medications, such as calcium blockers and tricyclic antidepressants. GERD negatively affects quality of life and imposes economic burdens and lost productivity (DE SANTIAGO et al., 2021) (MARESOVA et al., 2024).

Although the cause of GERD is not yet completely understood, several underlying predisposing pathophysiological mechanisms have been described. While low basal esophageal sphincter (LES) pressure may facilitate reflux after abdominal exertion or during swallowing, a more pertinent mechanism is transient LES relaxation (RELI), which may be associated with esophageal shortening. Rupture of the gastroesophageal junction (GEJ) due to a hiatal hernia (HH) is an additional factor because it contributes to LES incompetence and also displaces the acid sac closer to the esophageal mucosa. Altered visceral sensitivity has a bidirectional effect on GERD, amplifying symptoms in patients without mucosal injury and reducing symptom perception in patients with Barrett's esophagus. Esophageal hypomotility, low saliva production, and other mechanisms, such as certain breathing patterns, can also contribute to GERD (DE SANTIAGO et al., 2021).

GERD is diagnosed in routine clinical practice with classic symptoms of heartburn and regurgitation of gastric contents. These symptoms are specific to the diagnosis of GERD and empirical initiation of short-term proton pump inhibitor (PPI) therapy. Several tests are available for evaluation of GERD, but they are typically used in patients with refractory, atypical, or alarming symptoms such as dysphagia, odynophagia, upper gastrointestinal bleeding, weight loss, and anemia. Esophagogastroduodenoscopy (EGD) is an important test used to evaluate complications of GERD, such as erosive esophagitis, BE, or esophageal cancer (LOGANATHAN et al., 2024).

The treatment of GERD is multimodal. Lifestyle modifications such as weight loss, smoking cessation, and, in selected cases, postural counseling have proven efficacy and

may be sufficient in mild cases. Drug therapy occupies the next level, with proton pump inhibitors (PPIs) having a major impact on the treatment of GERD due to the high cure rates of esophagitis, outperforming histamine receptor antagonists, and exhibiting high cost-effectiveness. They are the cornerstone of GERD medical treatment. Anti-reflux surgery (ARS), i.e., laparoscopic fundoplication, is the last step in the treatment of GERD. Its objectives are as follows: fixation of the LES to the hiatus and increase the length of the intra-abdominal segment; increased basal pressure of the ISS; and hiatal repair (DE SANTIAGO et al., 2021).

This systematic review article aims to compile and evaluate the existing scientific evidence on Gastroesophageal Reflux Disease. The intention is to provide a comprehensive and up-to-date view, which not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and clinical practices. By offering an in-depth analysis of the evidence, this study aims to serve as a resource for health professionals, researchers, and academics, helping to optimize diagnostic and therapeutic approaches to this condition.

METHODOLOGY

This is a systematic review that seeks to understand the main clinical aspects of Gastroesophageal Reflux Disease (GERD), as well as to demonstrate the main diagnostic and therapeutic methods used in the condition. For the development of this research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "What are the main signs and symptoms of Parkinson's Disease, as well as what are the diagnostic resources and therapeutic approaches used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. 6 descriptors were used in combination with the Boolean term "AND": Gastroesophageal Reflux Disease, GERD Treatment, GERD Diagnosis, Gastroesophageal Reflux, GERD Symptoms, and GERD Complications. The search strategy used in the PMC database was: Gastroesophageal Reflux Disease AND GERD Treatment AND GERD Diagnosis and Gastroesophageal Reflux AND Gastroesophageal Reflux Disease AND GERD Symptoms AND GERD Complications. From this search, 565 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate

articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 565 articles were found. After applying the inclusion and exclusion criteria, 21 articles were selected from the PubMed database, and a total of 16 studies were used to compose the collection.

RESULTS

Author	Major Contributions
Sharma; Yadlapati, 2021	GERD involves several anatomical and functional abnormalities. Reflux is composed of acid, bile, pepsin, food content, and gut microbiota, each affecting the esophageal mucosa in distinct ways. Hydrochloric acid (HCl) causes mucosal injury through effects on potential difference and inflammatory pathways.
Tanvir et al., 2024	Mechanisms such as LES relaxation, increased abdominal pressure, and low LES pressure contribute to the development of GERD. Hiatal hernia, decreased esophageal clearance, and delayed gastric emptying also play a role. Barrett's esophagus (BE) is a premalignant condition associated with an increased risk of esophageal adenocarcinoma.
Chhabra; Ingol, 2022	GERD is a disease of acid reflux from the stomach to the esophagus. Hydrochloric acid is one of the most toxic components of gastric juice and causes esophageal irritation. Risk factors include age, gender, genetics, lifestyle, eating habits, and high BMI. Clinical history is critical in the diagnosis of GERD.
Iwakiri et al., 2022	Transient relaxations of the LES are a significant cause of acid reflux in patients with GERD. Dysfunction of the LES and the crural diaphragm are fundamental in the pathophysiology of GERD. Impedance-pH monitoring is currently the most accurate and detailed method for assessing gastroesophageal reflux.
Lee; Chang, 2022	The LES has two main components: intrinsic muscles of the distal esophagus and sling fibers of the proximal stomach. Dysfunction of the LES and crural diaphragm contribute to GERD. Standard pH monitoring allows you to measure acid reflux by detecting pH drops in the distal esophagus.
schedules; schedules; Lamcher, 2022	. Risk factors for GERD include smoking, eating spicy, fatty or fried foods, drinking alcohol, and consuming certain medications. Poor eating habits and lifestyles also contribute to the development of GERD. Patients with GERD often have abnormal esophageal motility.
Katz et al., 2022	Typical symptoms of GERD include heartburn and regurgitation. Atypical symptoms include chest pain, hoarseness, throat clearing, chronic cough, laryngitis, dental erosions, and pulmonary fibrosis. GERD can exacerbate asthma. Endoscopy is useful for identifying complications such as esophagitis or Barrett's esophagus, but has limited sensitivity for diagnosing GERD.
Gyawali et al., 2024	The Los Angeles classification is the most widely used system to describe the endoscopic appearance of the ER and classify its severity. Innovative endoscopy techniques with image enhancement improve the detection of minute changes. Endoscopic assessment of the anti-reflux barrier impacts the likelihood of success of medical treatment.

Yadlapati; Pandolfino, 2020	Barrett's esophagus (BE) is a significant premalignant condition of GERD from Endoscopic surveillance is recommended for patients with BE to detect dysplasia or early-stage cancer. Treatment strategies include acid suppression therapy, endoscopic eradication techniques, and, in severe cases, esophagectomy.
Díaz et al., 2024	Patients with bothersome heartburn, regurgitation, and/or noncardiac chest pain are often treated with Proton Pump (PPI) inhibitors. Response to PPIs is used as an indicator for ongoing GERD treatment. Upper Gastrointestinal Endoscopy (UDE) is widely used to assess alarming symptoms and detect additional conditions with symptoms similar to dyspepsias.
Liang et al., 2022	HRM is recommended to exclude different diagnoses of GERD in patients with esophageal symptoms and unsuccessful PPI treatment. Combined pH and impedance recording technology improves diagnostic throughput and enables better symptom analysis. Medical therapy includes histamine H2 receptor antagonists, PPIs, TLESR-reducers, and prokinetics.
Shaqran et al., 2023	The goal of GERD treatment is to relieve symptoms and prevent complications such as esophagitis, BE, and esophageal cancer. Lifestyle changes, pharmacological care, surgical treatments, and endoluminal therapies are alternatives for treatment. Lifestyle modification is an important but often ignored intervention.
Loganatha n et al., 2024	Lifestyle modifications include weight loss, elevating the head of the bed, avoiding smoking and drinking alcohol, and avoiding late-night meals. Evidence shows improvement in nighttime GERD symptoms with elevation of the head of the bed or sleeping on a wedge. Short intervals between eating and sleeping are associated with increased GERD symptoms.
Katz et al., 2022 (Parte 2)	Medical therapy includes histamine H2 receptor antagonists (H2RAs) and PPIs. Delayed, dual, and immediate-release PPIs are recommended at the standard dose for four weeks in GERD and eight weeks in erosive disease. Maintenance therapy with PPI should be given to patients with complications of GERD, including severe erosive esophagitis (LA C or D) and Barrett's esophagus.
schedules; schedules; Lamcher, 2022	PPIs are more effective than H2RAs in treating GERD, but they have side effects such as hypergastrinemia, susceptibility to infections, and altered micronutrient absorption. Medical options for patients with incomplete response to PPIs are limited. New drugs, such as GABA-B receptor agonists, potassium competitive acid blockers, and cholecystokinin antagonists, are being researched.

De Santiago et al., 2021	GERD affects about 1.03 billion people worldwide. Several underlying predisposing pathophysiological mechanisms have been described, including low basal LES pressure, transient LES relaxation, and hiatal hernia. GERD treatment is multimodal, including lifestyle modifications, PPI drug therapy, and anti-reflux surgery.
Maresova et al., 2024	GERD negatively affects quality of life and imposes economic burdens and lost productivity. Predisposing factors for GERD include aging, obesity, smoking, and certain medications. Diagnosis of GERD is based on classic symptoms of heartburn and regurgitation of gastric contents.

Source: Table created by the author

DISCUSSION

The pathophysiology of GERD is complex and multifactorial, involving several anatomical and functional abnormalities. Recent advances in our understanding of the mechanisms of GERD have shed light on the intricate interplay between different factors that contribute to this condition. In GERD, the main component that causes damage to the esophageal mucosa is reflux. Reflux is able to overcome the internal defenses of the esophageal epithelium due to its potency, composition, and time of exposure to the esophageal lining. Reflux is composed of varying levels of acid, bile, pepsin, food content, and normal gut microbiota. The mechanism by which each component affects the esophageal mucosa is distinct, and therefore the etiology of GERD may be specific to the predominant component of reflux and its mechanism of action (SHARMA; YADLAPATI, 2021) (TANVIR et al., 2024).

The following mechanisms contribute to the development of acid GER: sphincter relaxation (LES), increased abdominal pressure, and low LES pressure. Lower esophageal sphincter (LES) dysfunction is the main cause of gastroesophageal reflux; however, other variables may also play a role in its onset. Physiological and pathological variables play a role in the development of GERD. Transient lower esophageal sphincter relaxations (LEIs) are the most frequent culprits. RELEIs are short-lived, swallow-independent episodes of LES tone inhibition. Although they are physiological, they become more frequent in the postprandial period and are a significant cause of acid reflux in GERD patients. Other concerns include hiatal hernia, decreased esophageal clearance, delayed gastric emptying, and decreased LES pressure (CHHABRA; INGOLE, 2022) (IWAKIRI et al., 2022). The LES has two components, the proximal portion is made up of the intrinsic muscles of the distal

esophagus and the distal portion consists of the sling fibers of the proximal stomach. Mechanically, the LES can be considered functioning as an "internal sphincter", while the crural diaphragm constitutes the "external sphincter". The phrenoesophageal ligament anchors the distal esophagus to the crural diaphragm, thus coupling the internal and external sphincters. Transient or permanent dysfunction of one or both components constitutes the pathophysiology of GERD (LEE; CHANG, 2022).

GERD is often thought of as a disease of acid reflux from the stomach to the esophagus. Acid, also known as hydrochloric acid (HCl), is in fact one of the most toxic components of gastric juice and is often the main cause of esophageal irritation and reflux symptoms. The mechanism by which acid leads to mucosal injury has been well studied. At the cellular level, HCl-induced damage to the esophageal mucosa is in part due to its effects on the potential difference in the esophageal mucosa. Generally, the esophageal epithelium is able to maintain an electrochemical gradient measured as potential difference. However, as shown in animal models, an increase in luminal HCl leads to a significant increase in potential difference. Consequently, cell volume regulation becomes less efficient, which can be seen histologically as a loss of cellular integrity, with evidence of cellular edema and necrosis within the epithelial lining. More recent studies have also identified more indirect inflammatory effects of HCl on the esophageal epithelium. Pro-inflammatory mediators implicated in animal and human models include interleukins such as interleukin (IL)-8, platelet activating factor, and interferon-gamma. The release of these mediators leads to the recruitment of immune cells into the esophageal mucosa and a cascade of inflammatory pathways that result in the production of reactive oxygen species (ROS) and further cellular damage (SHARMA; YADLAPATI, 2021).

Regarding the presentation of symptoms, gastric acid increases sensitivity to reflux and therefore improves the perception of reflux symptoms. Evidence shows that acid-induced hypersensitivity may be more significant in more proximal regions of the esophagus compared to its distal portions. This increased sensitivity can probably be explained by the acid's detrimental effects on the esophageal mucosa, leading to impaired mucosal barriers and increasing the exposure of mucosal afferent nerves to toxic reflux (SHARMA; YADLAPATI, 2021).

GERD is a prevalent gastrointestinal disorder that can develop due to many factors. These risk factors include both modifiable and non-modifiable components. The non-modifiable ones are age, sex and genetics. The modifiable ones are lifestyle, eating habits, and increased body mass index (BMI). Smoking, eating spicy, fatty or fried foods, drinking alcohol, engaging in rigorous physical activity after meals or less rigorous physical activity in

general, and consuming chocolates, carbonated beverages, coffee and tea are all components of the lifestyle. Even grapes, tomatoes, and preservatives have also been listed as risk factors for developing GERD. Poor eating habits, such as eating large meals at once, eating right before going to bed, and irregular meal times, contribute to the development and worsening of GERD symptoms. The use of certain medicines also poses a risk for GERD, including non-steroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy, antidepressants, benzodiazepines and theophylline (VELAGALA; VELAGALA; LAMTURE, 2022).

GERD is one of the most widespread gastrointestinal conditions, affecting 20% of adults in Western societies. However, as more people have access to over-the-counter acid-reducing medications, the actual prevalence of this disease may be higher. Men tend to get GERD at a slightly higher rate than women. In contrast to men who are more likely to have erosive esophagitis, women who arrive with GERD symptoms are more likely to have non-erosive reflux disease. However, compared to women, men had a higher incidence of Barrett's esophagus with long-term GERD symptoms. Older age, an immoderate body mass index (BMI), smoking, anxiety, stress or depression, and insufficient physical activity at work are risk factors for GERD. Consumption habits, for example, the acidity of the food to be consumed, and the portion and timing of meals, particularly with regard to sleep, can also cause GERD. Recreational exercise appears to be protective, except when done postprandially (CHHABRA; INGOLE, 2022).

Typical symptoms of GERD include heartburn and regurgitation. Heartburn is the most common symptom of GERD and is described as a substernal burning sensation that rises from the epigastrium toward the neck. Regurgitation is the effortless return of gastric contents upward toward the mouth, usually accompanied by an acidic or bitter taste. Although heartburn and regurgitation are the main symptoms of GERD, the genesis of these symptoms is not the same, and diagnostic and treatment approaches vary depending on which symptom predominates. These symptoms, when frequent and bothersome, are highly suggestive of GERD. However, the sensitivity and specificity of typical symptoms for the diagnosis of GERD are limited, necessitating additional diagnostic evaluation in many cases (KATZ et al., 2022) (TANVIR et al., 2024).

The atypical symptoms of GERD encompass a wide range of manifestations, including chest pain, hoarseness, throat clearing, chronic cough, laryngitis, dental erosions, pharyngitis, and pulmonary fibrosis. It has also been proposed that GERD may exacerbate asthma. These extraesophageal symptoms often present diagnostic challenges due to their non-specific nature and potential overlap with other conditions. These extra-esophageal

manifestations are challenging for patients and clinicians because, although they can result from GERD, they can also be due to a number of other causes (KATZ et al., 2022) (TANVIR et al., 2024).

Barrett's esophagus (BE) is a premalignant condition characterized by the replacement of normal squamous epithelium by specialized intestinal metaplasia in the distal esophagus. It is a significant complication of long-standing GERD, with an estimated prevalence of 5-15% among GERD patients. The exact pathogenesis of BE remains unclear, but chronic exposure to acid and biliary reflux is thought to play a crucial role in initiating the metaplastic process. Risk factors for BE include male sex, obesity, smoking, and prolonged GERD symptoms. The primary clinical significance of BE lies in its association with an increased risk of esophageal adenocarcinoma, with an estimated annual conversion rate of 0.1-0.3%. Endoscopic surveillance is recommended for patients with BE to detect dysplasia or early-stage cancer, although optimal surveillance intervals remain up for debate. The strategies of . treatment for BE include acid suppression therapy, endoscopic eradication techniques such as radiofrequency ablation and endoscopic mucosal resection for dysplastic BE, and, in some cases, esophagectomy for high-grade dysplasia or early adenocarcinoma. Recent advances in biomarker research and imaging technologies, such as wide-area transepithelial sampling and confocal laser endomicroscopy, promise to improve risk stratification and early detection of neoplastic progression in patients with BE (TANVIR et al., 2024).

Clinical history is the primary basis for the diagnosis of GERD. The report should indicate the distinctive signs and symptoms, their occurrence, frequency, intensity, aggravating and relieving events, progression over time, and effects on quality of life (CHHABRA; INGOLE, 2022). Patients who present with bothersome heartburn, regurgitation, and/or noncardiac chest pain without alarm symptoms receive a 4- to 8-week trial of single-dose Proton Pump Inhibitor (PPI) therapy. Any commercially available PPI can be used for the test, the choice of which can be guided by payer coverage, direct costs, and previous experiences with a particular PPI. Patients should be advised to take PPI 30 to 60 minutes before a meal. Education and literature emphasizing the safety of PPIs for the treatment of GERD should be provided. The patient's symptoms should be reassessed after a 4- to 8-week trial. If patients show a 50% improvement in symptoms, they should be treated as a GERD patient. After four to eight weeks of continuous treatment, an on-demand regimen is indicated or PPI is suspended. With inadequate response, the dosage may be increased to twice daily or switched to a more effective acid-suppressing agent once daily. This may include PPIs that are more potent, less metabolized by the CYP2C19

pathway (e.g., rabeprazole, esomeprazole), or available in an extended-release formulation (e.g., dexlansoprazole), as well as competitive potassium acid blockers, when available (YADLAPATI et al., 2022) (DÍAZ et al., 2024).

One of the main challenges in diagnosing GERD is the lack of a single definitive test. Endoscopy, while useful for identifying complications such as esophagitis or Barrett's esophagus, has limited sensitivity for the diagnosis of GERD, as up to 70% of patients with typical GERD symptoms have normal endoscopic findings (TANVIR et al., 2024). Upper Gastrointestinal Endoscopy (UDE) is the most commonly used to assess GERD symptoms in people over 40 years of age who have alarming symptoms, for example, difficulty swallowing, pain when swallowing, weight loss, gastrointestinal bleeding, urge to vomit (nausea), vomiting, and a history of malignancy in the family. It allows the detection of additional conditions that have symptoms similar to dyspepsias, such as ulcers, especially gastric ulcers, moniliasis of the esophagus, carcinoma of the stomach, and eosinophilic inflammation of the esophagus. It also allows erosions to be observed. It also makes visible erosions, ulcers, Barrett's esophagus, and peptic stenosis. (CHHABRA; INGOLE, 2022).

The severity of reflux esophagitis has been categorized in several ways. The Los Angeles classification is the most widely used, reproducible, and accurate system for describing the endoscopic appearance of ER and classifying its severity. Several innovative imaging enhancement endoscopy techniques have been shown to improve the detection of minute changes. Erosive. The presence of Los Angeles esophagitis C or D, Barrett's long-segment esophagus, and/or peptic stricture provides objective confirmation of pathologic GERD. While the Lyon consensus of response to anti-reflux therapy. considers Los Angeles B inconclusive means a higher probability for GERD, the finding of Los Angeles B esophagitis along with typical symptoms has a high probability of underlying reflux unless alternative factors are observed, such as eosinophilic esophagitis or a pattern of dermatologic or non-peptic esophagitis (CHHABRA; INGOLE, 2022) (GYAWALI et al., 2024) (IWAKIRI et al., 2022) (YADLAPATI; PANDOLFINO, 2020).

Then, endoscopic assessment of the integrity of the anti-reflux barrier will impact the likelihood of success of medical treatment. The anti-reflux barrier is a high-pressure zone composed of the LES attached to the crural diaphragm via the phrenoesophageal ligament that forms a tight gastroesophageal flap valve to prevent pathological gastroesophageal reflux. Disruption of the anti-reflux barrier can lead to increased reflux load and acid exposure. Axial separation between the crural diaphragm and the LES results in a hiatal hernia. Hiatal hernia, as well as reduced tonicity of the intrinsic LES, will reduce the integrity of the gastroesophageal flap valve mechanism. Therefore, endoscopic evaluation of the

anti-reflux barrier by characterizing the hernia, if present, measuring the length of separation between the diaphragmatic forceps (crural diaphragm) and the proximal extension of the gastric folds (lower esophageal sphincter), and classifying the gastroesophageal flap valve are important steps in the phenotyping of GERD (YADLAPATI; P. ANDOLFINO, 2020)

Although high-resolution manometry (HRM) is not used for the diagnosis of GERD itself, patients with GERD often have abnormal esophageal motility. A recent study using HRM revealed that the acid reflux load is deeper in patients with absent primary peristalsis, as well as in patients without a secondary peristaltic response to esophageal air distention. HRM is recommended to exclude different diagnoses of GERD in patients with esophageal symptoms and unsuccessful PPI treatment (LIANG et al., 2022).

Standard pH monitoring allows you to measure acid reflux by detecting pH drops in the distal esophagus. However, when gastric acid has been buffered in the postprandial period or suppressed by a PPI, reflux can become pH >4, which is either weakly acidic reflux or non-acidic reflux. In addition to pH monitoring, impedance-pH monitoring characterizes fluids and gases, as well as detects the movement of fluids and gases. The combined pH and impedance recording technology allows for the detection of acid and non-acid reflux episodes. This technology also allows better characterization of proximal reflux extension, post-reflux clearance, reflux episodes, including not only acidity (acidic, non-acidic) but also composition (air, liquid, or mixed). Therefore, it is currently considered the most accurate and detailed method for assessing gastroesophageal reflux. Adding impedance to pH monitoring improves diagnostic yield and allows for better symptom analysis (LIANG et al., 2022).

The goal of GERD treatment is to relieve symptoms and prevent complications, such as esophagitis, BE, and esophageal cancer. Lifestyle changes, pharmacological care such as (antacids and antisecretory drugs), surgical treatments, and endoluminal therapies are all alternatives for treatment (SHAQRAN et al., 2023). One of the most important interventions in the treatment of GERD is lifestyle modification, which is often ignored by doctors and not followed by patients. Typical recommendations for GERD include weight loss for overweight individuals, elevating the head of the bed, quitting smoking and drinking alcohol, avoiding late-night meals and snacks before bed, staying upright during and after meals, and eliminating foods that can aggravate reflux symptoms such as coffee, chocolate, carbonated beverages, spicy foods, acidic foods like citrus fruits and tomatoes and foods high in fat. The evidence supporting these recommendations is limited and variable, often based on small, uncontrolled studies and rarely as the only intervention, which complicates

definitive recommendations. However, several randomized controlled trials have demonstrated an improvement in nocturnal GERD symptoms and nighttime esophageal acid exposure with elevation of the head of the bed or sleeping on a wedge. The timing of food intake can also affect GERD symptoms. A short interval (<3 h) between eating and sleeping or lying in the supine position is associated with increased GERD symptoms and the need for medication (LOGANATHAN et al., 2024) (VELAGALA; VELAGALA; LAMTURE, 2022).

Medical therapy comprises histamine H2 receptor antagonists (H2RAs), PPIs, TLESR-reducers, and prokinetics. PPIs and H2RAs are the most commonly used medications. Proton pump inhibitors have also been shown to be more effective than H2RAs in treating patients who are receiving empiric treatment or do not show signs of esophageal damage on upper gastrointestinal endoscopy. Patients undergoing empirical treatment are those who have symptoms of reflux but have not undergone any diagnostic testing for GERD, such as an upper gastrointestinal endoscopy. The initial full-dose medical treatment consists of one 20 mg omeprazole tablet taken once daily. However, proton pump inhibitors, the most widely prescribed anti-GERD drug, also have many side effects and unmet needs. Long-term or excessive use of PPIs may lead to secondary hypergastrinemia, increased susceptibility to infections, and altered micronutrient absorption. It is also known to cause acid rebound hypersecretion on long-term medication discontinuation. Long-term use of PPIs also increases the risk of benign paroxysmal positional vertigo (BPPV) in adult patients (VELAGALA; VELAGALA; LAMTURE, 2022).

Delayed-release PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, ilaprazole), dual-delayed-release PPIs (dexlansoprazole), and immediate-release PPIs (omeprazole-sodium bicarbonate) are recommended at the standard dose for four weeks in GERD and eight weeks in erosive disease. In cases of severe oesophagitis (LA C and D classification), a double-dose delayed-release PPI should be used for eight weeks. They should be administered 30 to 60 minutes before breakfast in the standard once-daily dose regimen and 30 to 60 minutes before breakfast and dinner in the dual-dose regimen. Dexlansoprazole, a delayed-release double-release PPI, in which the first absorption is in the duodenum, then partially further down in the small intestine, appears to have similar efficacy in controlling pH regardless of meal timing (KATZ et al., 2022) (DÍAZ et al., 2024). Several studies suggest that genetic differences in isoenzyme metabolism CYP2C19 may affect the response to PPIs. However, the usefulness of a genetic test to identify fast or slow metabolizers is not recommended in daily practice. When this condition

is suspected, switching to rabeprazole or ilaprazole, PPIs that do not rely on CYP2C19 for their primary metabolism is suggested (DÍAZ et al., 2024).

PPI maintenance therapy should be given to patients with complications of GERD, including severe erosive esophagitis (LA C or D) and Barrett's esophagus. For patients without erosive esophagitis or Barrett's esophagus who continue to have symptoms when PPI therapy is discontinued, on-demand therapy may be considered in which PPIs are taken only when symptoms occur and discontinued when they are relieved. Two-thirds of patients with PPI-responsive non-erosive disease will demonstrate symptomatic relapse when PPIs are stopped. With LA grade C esophagitis, almost 100% will relapse within 6 months. Recurrence of erosive esophagitis after discontinuation may occur in as little as 1-2 weeks, particularly in patients with prior LA C erosive esophagitis. Patients with LA grade C or D erosive esophagitis should remain on long-term PPI therapy to maintain healing (KATZ et al., 2022).

Medical options for GERD patients with incomplete symptom response on PPI therapy are limited. The addition of H2RA at bedtime has been suggested for PPI patients with persistent nocturnal symptoms. This approach gained popularity after several studies demonstrated better control of intragastric pH at night with the addition of an H2RA, although one well-done study demonstrated loss of pH control (tachyphylaxis) after one month of H2RA therapy before bedtime. Based on these data, the use of an H2RA before bed may be beneficial if given as needed for patients with nocturnal symptoms and for patients with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment (KATZ et al., 2022).

Although PPIs have been shown to be the gold standard for empirical treatment of GERD, many patients remain symptomatic even after taking standard PPI therapy. Therefore, new drugs in the pharmacological area of treatment are being researched further to address the unmet needs of the current line of treatment. These classes of drugs comprise gamma-aminobutyric acid receptor type B (GABA-B) agonists such as lesogaberan, arbaclofen placabil, metabotropic glutamate receptor-5 (mGLuR5) antagonists, potassium competitive acid blockers (P-CABs), cholecystokinin antagonists, mosapride, and rikkunshito as complementary drugs to PPIs. In the case of refractory GERD, which means that it does not respond to empirical treatment with PPIs, there can be several causes, such as psychological morbidities, weakly acidic or alkaline reflux, and hypersensitivity of the esophagus (VELAGALA; VELAGALA; LAMTURE, 2022).

CONCLUSION

Gastroesophageal Reflux Disease (GERD) is a multifactorial and prevalent condition, whose pathophysiology involves complex mechanisms and interactions between anatomical, functional, and environmental factors. This systematic review highlights advances in the understanding of predisposing factors, including lower esophageal sphincter dysfunction, hiatal hernia, delays in gastric emptying, and the influence of transient lower esophageal sphincter relaxations (RELEIs). In addition, risk factors such as dietary habits, lifestyle, and medication use play a central role in the incidence and severity of the disease. GERD symptoms encompass typical manifestations, such as heartburn and regurgitation, and atypical symptoms, which can make diagnosis difficult due to overlap with other conditions. The presence of complications, such as Barrett's esophagus, underscores the importance of clinical and endoscopic surveillance, given the association with increased risk of esophageal adenocarcinoma.

In the management of GERD, pharmacological therapies such as proton pump inhibitors (PPIs) remain the mainstay of treatment, although they have limitations associated with side effects and unmet needs. Lifestyle changes and behavioral interventions, although based on limited evidence, remain recommended and may play an important role in symptom relief. More refined diagnostic and therapeutic strategies, such as combined impedance-pH monitoring and advanced endoscopic technologies, offer new possibilities for personalization in care. Although significant advances have been made, gaps in the understanding of GERD and the efficacy of therapeutic approaches indicate the need for further research, especially in areas such as diagnostic biomarkers, management of refractory symptoms, and long-term implications of available treatments. A multidisciplinary and individualized approach remains critical to improving clinical outcomes and quality of life for GERD patients.

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