ADVANCES IN GERD: EXPLORING PATHOPHYSIOLOGY, CONTEMPORARY DIAGNOSIS AND TREATMENT MODALITIES

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ABSTRACT

Gastroesophageal reflux disease is a common condition where stomach contents flow back into the gullet, resulting in various discomforts and possible complications like esophagitis, Barrett's esophagus, and chronic laryngitis. The underlying pathophysiology of Gastroesophageal reflux disease includes critical factors such as temporary relaxation of the lower esophageal sphincter, sliding hiatal hernia, obesity, and slowed gastric motility. Recognizing the full spectrum of symptoms- from common heartburn to unusual presentations like chronic cough and asthma- alongside aggravating factors like dietary habits, smoking, and stress, is crucial for effective management. Diagnosis strategies primarily involve symptom assessment and may include endoscopy, pH monitoring, and PPI trials to evaluate therapeutic responses. While proton pump inhibitors are the mainstay of treating gastroesophageal reflux disease, alternative pharmacologic options such as baclofen, antacids, and prokinetics may also be utilized, particularly in cases of persistent symptoms. Surgical interventions, including Nissen fundoplication and the newer LINX procedure, present additional avenues for patients unresponsive to medical therapy, offering varying degrees of success in symptom relief and maintaining esophageal integrity. This review delineates the complex interplay of the pathophysiological mechanisms governing gastroesophageal reflux disease, highlights contemporary diagnostic approaches, and evaluate both pharmacological and surgical treatment modalities, providing a comprehensive overview essential for healthcare professionals managing this multifaceted condition.

KEYWORDS: chronic cough; aggravating factors; management; diagnosis; surgical therapy

INTRODUCTION

Gastroesophageal reflux disease (GERD) is characterized by the reflux of stomach or duodenum contents flowback into the gullet, which can lead to discomfort or pathologic or physiological consequences [1]. In the stomach the digestive fluids exasperate the lining of food pipe, causing burning sensation known as heartburn [2]. The lower esophageal sphincter malfunctions that result in frequent or extended relaxations, which recirculates stomach acid. Eventually, the gastroesophageal mucous membrane suffers deterioration and deformation due to the presence of gastric fluid. Genetic factors, excess weight and tobacco use are contraindications for those with GERD. If not properly cured it might show other problems such as esophagitis, esophageal strictures, Barrett's esophagus, chronic laryngitis,

hypersalivation. GERD related complications occur in 18%-25% of cases with esophagitis, 7-23% with esophageal structures, and 76.2% with Barett's esophagus [3].

PATHOPHYSIOLOGY

Ever since Heinrich Quincke first identified GERD in 1879, our comprehension of its pathophysiology has gradually deepened and evolved. Various components come up with GERD comprise:

- Transient relaxation of the cardiac sphincter
- Sliding hiatal hernia
- Low LES pressure
- Development of acid pockets due to poor mixing of acid with stomach content
- Increased distensibility at the gastroesophageal junction
- Obesity
- Delayed gastric emptying [4].

LES Normal function: The normal tonic contraction at the distal end of esophagus is maintained by lower esophageal sphincter which consists of smooth muscle and is about 3-4cm longer [5]. The prevention of reflux of food and/ or acid is effectively done by the high-pressure LES barrier [6]. It is one of the two muscular valves at each extremity of the gullet, serving the airway from gastric contents by preventing reflux. The LES needs to be adaptable to prevent reflux in various situations, such as during swallowing, lying down, and abdominal straining. The LES produces a high-pressure zone at rest that varies on the individual and ranges from 15 to 30 mm Hg above intragastric pressures. Breathing, body posture, movement, intra-abdominal pressure, and gastric distention all affect normal LES pressure. Significant diurnal fluctuation is observed in the lower esophageal sphincter pressure (LESP), which peaks at night and troughs its lowest during the day and after meals [7].

Transient lower esophageal sphincter relaxations (TLESRs): Series of events that relaxes LES, generally for shorter period, and not involved in peristaltic movement [8,9]. These episodes, which last about 10 to 35 seconds, reduce the LES pressure to match the gastric pressure (7). They are triggered only when vagal nerve i.e., both sensory and motor nerve gets activated in response to the stretching of the stomach [10]. It is regarded as one of the main causes of pathological reflux, even when the resting tone is normal for the patients suffering from GERD. Patients with GERD experience TLESRs just as often as those without GERD. However, a greater proportion of these TLESRs in GERD patients are linked to reflux [11]. The contact of gastric acid with the esophageal lining for prolonged period of time raises the

risk of damaging the oesophagus and causing symptoms to appear. The percentage of reflux episodes caused by TLESRs changes depending on the severity of GERD [12].

Hiatal Hernia: Both GERD and hiatal hernia conditions can occur autonomously. Although, it is acknowledged that a hiatal hernia disrupts many of the natural anti-reflux mechanisms and is considered an independent factor contributing to GERD [13]. The proximal stomach shifts through the diaphragm's hiatus into the chest, and separates the LES from crural diaphragm [14]. The mere presence of the abdominal portion of the esophagus is regarded as an anti-reflux mechanism, as it is subjected to positive abdominal pressure and functions like a valve [15]. Furthermore, TLESRs appear to happen more often when a hiatal hernia is present. Unsurprisingly, hiatal hernia in terms of anatomical and physiological is linked to a weaker LES (due to lack of the diaphragm's pinchcock action), impaired peristalsis, more significant mucosal damage, and increased acid exposure [16]. It is linked with failure of medical treatment for GERD [15].

Enhanced proximal postprandial gastric acid pocket (PPGAP): Apparently, if the food does not blend with stomach's acid, the excess of acid leads to acidity and builds up in the PPGAP below the LES. The PPGAP is not only larger and more acidic, but it also lingers longer compared to those suffering from GERD than normal. Combining with a hiatal hernia pushes up wards through the LES, triggering GERD symptoms [17-19].

Obesity: One of the finest reasons that demonstrates the link between obesity and GERD is, the flow of gastric juice from the stomach into the gullet gets driven by the pressure difference between the abdomen and the chest due to higher intragastric pressure experienced by obese patients as the studies suggested [20,21], and that this pressure is associated with both body mass and waist circumference [22]. Higher intra-abdominal pressure builds up the tension between anti-reflux barrier, promoting hiatal hernia to above level for obese patients. Without any doubt, the reason why physicians say, losing even a small amount of weight (around 1015 pounds) can lower GERD symptoms [23].

Delay in gastric emptying: About 26% of GERD patients have delayed gastric emptying, which increases the risk of reflux by keeping acidic food in the stomach for longer. The symptoms of GERD are exacerbated by delayed gastric emptying because it raises stomach pressure, relaxes the LES, and allows acid to pass into the esophagus [24,25]. By pushing stuff upward, peristalsis shortened the time of reflux; however, contractions may be slowed down by big food boluses or increased viscosity. Food retention or elevated intra-abdominal pressure can prevent reflux. When reflux does happen, though, the esophageal mucosa may be harmed by stomach contents that contain irritants such as bile salts, digestive enzymes, and gastric acid.

Dietary changes can alter these components' production, and undigested food particles may also contribute to reflux by having a variety of effects on the underlying mucosa [26,27].

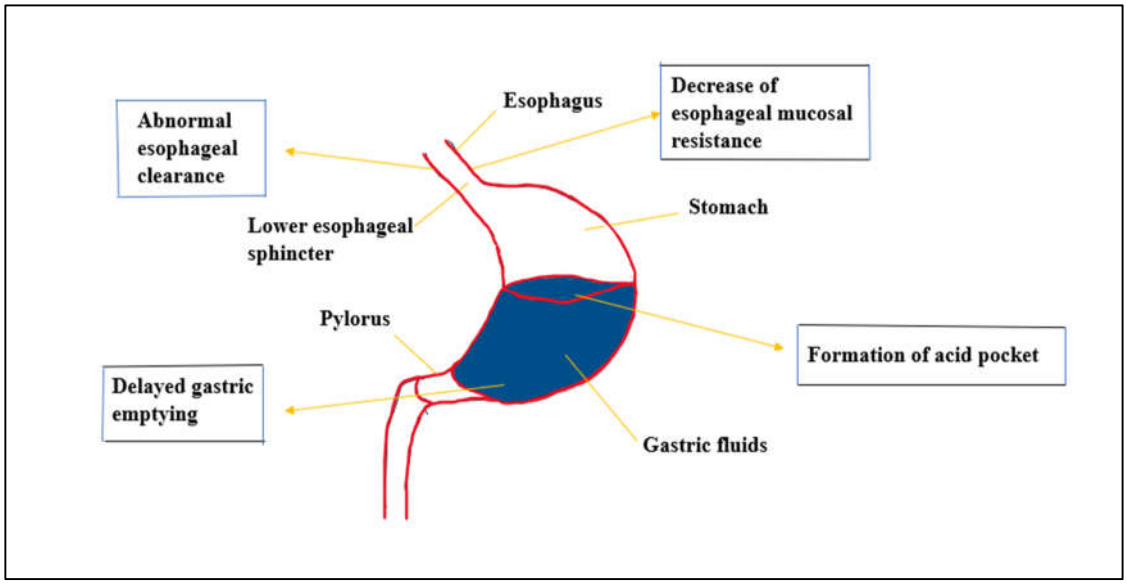

Fig 1: Pathophysiology of Gastroesophageal reflux disease

SIGN AND SYMPTOMS

GERD can be associated with extensive indications, which perhaps further divided into typical, atypical, and gastroesophageal symptoms. Frequently the stomach content flow into the food pipe, or comparatively substantial amount leaks out which is responsible for heartburn or acid reflux in some people. Heartburn manifests as a fiery sensation that radiates from the upper stomach following area of breastbone rising all the way to the throat and might be related with difficulty in swallowing [28]. Additional symptoms are a burning feeling in the throat, an unpleasant taste, and rumbling sounds from the stomach. The most frequent extra esophageal symptoms linked to GERD include non-cardiac chest pain, chronic hoarseness, persistent cough, and asthma [29]. The dental eroding of enamel i.e., tooth decay and throat infections does occur when the acid reaches the mouth as well as throat. Inflammation of the vocal cords can lead to chronic posterior laryngitis and hoarseness [30].

Table 1: Signs and symptoms

Typical symptoms	Heartburn, acid regurgitation
Atypical symptoms	Dyspepsia, epigastric pressure, epigastric fullness, epigastric pain, belching, nausea, bloating
Extra esophageal symptoms	Laryngitis, asthma, dental erosions

AGGRAVATING FACTORS

Key factors believed to contribute significantly to GERD's development include the activation of inflammatory mediators in the gullet, alterations in esophageal mucosal integrity, increased biochemical and mechanical sensitivity in the esophagus, and both peripheral and central sensitization. The symptoms can be significantly worsened by factors such as stress, central sensitization, anxiety, and hypervigilance [31,32]. Moreover, prolonged exposure of acidic substances to the mucosal lining can weaken its protective properties, leading to the onset of GERD symptoms. Dysfunctions in these mucosal lining may significantly contribute to the development of disease [33].

Potential triggers or aggravating factors for GERD encompass dietary and lifestyle elements (such as specified foods, obesity, eating habits, smoking and alcohol intake and sleeping position), in addition to pregnancy, hiatal hernia and certain medications [34].

Dietary factors: For patients with GERD, dietary interventions target not just to reduce weight but also the avoidance of foods that might trigger symptoms. Acidic foods, like those with citrus or tomatoes, have different ingestion dynamics compared to foods with neutral pH, which can worse GERD symptoms [35]. Consuming chocolate, fizzy drinks, and fatty meals may prolong the duration that the esophagus is exposed to acid and increase the production of stomach acid, according to studies [36]. It has been proposed that diets rich in protein and fiber help reduce the symptoms of GERD by improving the tone of the lower esophageal sphincter, which varies significantly during the day and after meals before peaking at night [37].

Toxic habits: Tobacco and alcohol use known to have directly triggering symptoms of GERD. This is because of the relaxation of the LES caused by consumption of tobacco and alcohol, as studies have shown acid exposure prolonged and multiple times in individuals. Quitting tobacco smoking has been significantly linked to improve symptoms in individuals with a normal BMI who are undergoing antisecretory therapy, as shown in cohort study of 29610 individuals [38]. In fact, smoking has been linked to more frequent reflux events, often triggered by deep inspiration and coughing. Smoking delays acid clearance by reducing saliva secretion [39] and raises direct esophageal injury.

Eating habits: Food, especially large meals, triggers TLESRs. Eating meals 2- 3 hours before bedtime (triggering nighttime acid availability), consumption of alcohol with meals, increase the likelihood of nocturnal reflux [30]. Mechanoreceptors activates due to gastric distention that boost TLERs frequency. Eating heavy meal causes the gastric area to expand, leading to distention. This leads to more frequent transient relaxations of the LES, making reflux more

likely. So, it is suggested that after having a meal at least for 3 hours' people should avoid going to sleep [8].

Pregnancy: GERD, most often caused during pregnancy, usually presents as symptomatic GERD (commonly heartburn) rather than esophagitis [40]. The development of GERD is believed to involved multiple factors, the primary mechanism behind GERD in pregnancy likely involves reduced LES pressure due to the impact of estrogen and progesterone on LES function [40,41]. The two hormones seem to work in tandem, with progesterone mediating the relaxation of LES smooth muscle and estrogen priming the LES for relaxation [42]. For most patients with mild symptoms, lifestyle and dietary changes can effectively manage GERD.

Medication: Various medication can exacerbate GERD symptoms by impacting gastric acid emptying and lowering LES pressure, which promotes reflux [43]. Worsening of symptoms often comes with the use of sedatives, antidepressant drugs, that leads to change saliva secretion, LES tone and even motility of esophagus. Painkillers, often described as NSAIDs, such as salts of potassium (Diclofenac potassium) and alendronate causes inflammation of oesophagus [30] as the tissue resistance and even severe case of esophagitis is caused by long term use of NSAIDs [44]. As NSAIDs are commonest among conditions like osteoporosis, leads to esophageal related problems specifically due to toxicity produced by medication [45].

DIAGNOSIS OF GERD

Diagnosing GERD involves identifying typical and atypical symptoms. The GERD questionnaire (GERDQ) can help guide the diagnosis. Patients without warning signs (such as weight loss, dysphagia, upper gastrointestinal haemorrhage, anaemia or persistent vomiting) can begin a PPI trial [46]. Upper gastrointestinal endoscopy should be considered for individuals whose reflux symptoms have not improved with a PPI trail. If an upper gastrointestinal endoscopy reveals no abnormalities, pH monitoring should be conducted for further insight. [47].

Endoscopy and biopsy: Endoscopy is preferred for screening individuals with suspected GERD syndrome due to its effectiveness in diagnosis, safety, ability to obtain biopsies, therapeutic options, and specificity [48,49]. However, endoscopy has not shown to be significantly advantageous.The biopsy is done for the diagnosis of adults remains to be fully defined. Its limitations include being time-intensive, expensive, and having lower sensitivity. Nevertheless, it proves advantageous when there is a high anticipated risk of GERD and when endoscopy does not provide substantial positive findings [50]. Additionally, the site of the esophageal biopsy is crucial, as abnormalities are more frequently detected in the esophageal quadrant adjacent to the lesser curvature of the stomach [51].

Proton pump inhibitor trail: Proton pump inhibitors (PPIs) are considered the primary treatment for alleviating symptoms and promoting the healing of erosive esophagitis. Research has demonstrated that PPIs provide superior healing rates and lower relapse rates in patients suffering from erosive esophagitis compared to H2 receptor antagonists (H2RAs). An empirical trial of PPIs as a diagnostic tool for GERD in patients with heartburn has indicated a sensitivity of 71% and a specificity of only 44%, when compared to the combination of endoscopy and pH monitoring [52,53]. When it comes to atypical symptoms, the response rates to PPIs are considerably lower than for heartburn, which diminishes the usefulness of this diagnostic method [54]. A significant restriction is the considerable impact that esophageal hypersensitivity has on symptom variation [55,56]; additionally, there are variations in PPI dosage and the length of the test [57]. Despite having low specificity and a high rate of placebo response [58], opting for empirical PPI treatment is more cost-effective than undergoing diagnostic testing [59]; however, it likely leads to overdiagnosis and an unnecessary increase in PPI usage.

Ambulatory reflux monitoring: It can establish the presence of GERD in individuals who have normal endoscopic findings, exhibit atypical symptoms, or are contemplating Anti-reflux Surgery (ARS). Reflux monitoring illustrates the repercussions of GERD pathophysiology, such as prolonged esophageal acid exposure time (AET) or the number of reflux episodes, rather than elucidating the underlying mechanisms responsible for them. The primary outcome of a 24-hour pH-metry assessment is the AET. Extending the duration of recording to 48 or 96 hours with a wireless pH monitoring device improves diagnostic capabilities and the reliability of the test. This approach is especially useful when a trans-nasal catheter was not well tolerated or yielded a negative result, even in the presence of strong indications of GERD. Additionally, pH-impedance monitoring serves as an alternative reflux assessment technique that analyses reflux events through a pH electrode alongside multiple impedance electrodes. This technique detects all types of refluxes and determines flow direction, thus considered the gold standard [60-66].

Impedance pH monitoring: AET may accurately predict the response to both medicinal and surgical reflux treatment [67,68] and is the most constant and reliable of all the pH monitoring metrics [69]. It is also generated from automated analysis. Recent research has shown that it is a useful technique for assessing reflux and offers better way to examine the symptoms [66]. Regardless of acidity, the pH-impedance measurements may identify if the reflux content is liquid, gaseous, or mixed. When a liquid flows across an electrode, its low resistance causes the impedance to drop. Furthermore, during hiccups, the low ionic density of air causes an

increase in impedance to gas movement and a high resistance to electrical currents. Using this information, a pH impedance catheter probe equipped with an impedance electrode measures the frequency of prograde motion after swallowing and retrograde motion during reflux to determine the direction of pill movement inside the gullet lumen [70]. When trans-nasal catheters are intolerable or there is a high probability that a prior GERD diagnosis was negative, it is helpful [61,65]. By combining impedance and esophageal pH monitoring, reflux may be efficiently classified as acid reflux, weak acid reflux, or alkaline reflux [71].

Other impedance parameters

Narrow-band imaging: To improve contrast and show mucosal patterns and microvasculature, NBI uses spectral narrow band filters. Because of this, it is feasible to identify modest alterations in the mucosal microvasculature of GERD patients, such as altered squamous-columnar junctions, micro erosions, and enhanced vascularity at the villous mucosal surface [72]. Thus, NBI is used to diagnose gastroesophageal reflux and monitor its improvement following PPI therapy. In 82 patients, NBI found inflammatory lesions in the lesions, which were associated with a favorable response to PPI therapy [73]. Although NBI is not the main technique for diagnosing GERD, given the expense of endoscopy, it can be used in conjunction with other methods to diagnose the condition and monitor response to PPI medication.

Mean nocturnal baseline impedance (MNBI): Another important marker that utilizes nighttime impedance values is MNBI, which are more reliable compared to daytime values that can be affected by swallowing [74]. According to research, in healthy people, lower MNBI levels can distinguish between different kinds of coughs, esophagitis, NERD (non-erosive reflux disease), functional heartburn, and GERD/NERD [75-77]. It has been demonstrated that in patients with inconclusive GERD, impaired esophageal mucosal integrity, as indicated by a low MNBI, improves the diagnostic yield of impedance-pH. It can be used in conjunction with AET to evaluate how well anti-reflux medication is working [78].

Real-time magnetic resonance imaging (MRI): To address GERD, a real time MRI method is potentially better as suggested in a study report. Modern ultrafast MRI sequences can detect the esophageal and gastroesophageal junction, enabling dynamic reflux assessment during repeated Valsalva manoeuvres, with high tissue contract and up to 20 ms temporal resolution [79,80]. For individuals exhibiting GERD symptoms, the best diagnostic performance for detecting GERD compared to invasive pH measurements and impedance is Real-time MRI. Real- time MRI images can reveal both acidic and non- acidic reflux, and identify patients with non- acidic reflux that is unidentified by other methods. Currently, there is no evidence to

replace existing diagnostic methods with real- time MRI. However, it can be used as an additional diagnostic tool, especially for those who cannot tolerate 24-hour esophageal monitoring [81].

TREATMENT

When lifestyle changes fail to manage GERD symptoms effectively, pharmacologic treatment can be beneficial for patients. The primary approach to treating GERD with medication is acid suppression. Traditional therapeutic agents encompass not only acid suppressants like PPIs, histamine type 2 receptor antagonists (H2RAs) and antacids, but also medication such as prokinetics and baclofen that can affect gastrointestinal motility [82].

MEDICATION

Baclofen: Baclofen, effectively agonising the γ-aminobutyric acid type-B receptor, has a history of being used to treat spastic muscular disorders and is now also applied in the management of refractory gastric reflux disease [53,83]. Research indicates that taking baclofen at bedtime significantly reduces postprandial reflux events, lowers sleep- related reflux instances and greatly enhances both objective and subjective sleep metrics compared to a placebo. It has been found to lower acid exposure to mucosal layer as well in both healthy individuals and GERD patients by preventing temporary relaxation of the lower esophageal sphincter, which is causing reflux events [84]. Regrettably, the aftereffects frequently hinder prolonged usage, with common issues including same as that occurs during the administration of anti-allergic drugs such as drowsiness, vertigo, weakness, and fatigue [85].

Antacids and alginates: Antacids work locally by neutralizing gastric or esophageal hydrochloric acid, offering temporary relief for patients with pyrosis. However, this relief is short- term, and symptoms may quickly return. Alginates like sucralfate create a thick layer that lines the gullet temporarily, preventing gastric fluids directly from contacting the esophageal tissue [86]. On combining antacid with alginate preparations proves particularly effective in reducing postprandial esophageal acid exposure [87]. Formulations with alginate, sodium bicarbonate, and calcium carbonate provide symptom relief regardless of the stimulus (acid, pepsin, bile). They can be used alongside PPIs, leading to satisfactory therapeutic outcomes [88,89].

Histamine Type 2 Receptor Antagonists: H2 antagonists, or H2 blockers, are medication that work by inhibiting histamine, which play role in production of stomach acid, thus reducing pepsin output and volume of gastric acid. Cochrane systemic reviews have shown that they are being effectively utilized in managing GERD either with or without esophagitis [90]. H2RAs are quite effective in alleviating heartburn symptoms and act quickly. If heartburn continues

after 6 weeks of H2RA treatment, it's unlikely that extending the treatment or increasing the dosage will provide additional benefits [91,92]. H2RAs availability on the market is also good include cimetidine, famotidine, nizatidine, and ranitidine. When administered in respective doses, these four drugs are considered equally effective. The efficacy of H2RAs at controlling baseline acid secretion than postprandial secretion and ought to be taken 30 to 60 minutes prior to meals [93,94].

Proton pump inhibitors (PPIs): They are the most effective class of drugs for the management of GERD (95). It operates by blocking the final stage of acid secretion, targeting the H^+/K^+-ATPase pump which leads to K^+ absorption and H^+ secretion. Compared to H2RAs and placebos, PPIs offer quicker and more effective symptom relief and are more superior in treating erosive esophagitis [54,94].

Currently marketed FDA approved PPIs include pantoprazole, rabeprazole, lansoprazole, omeprazole, and esomeprazole as a once-daily administration in their respective dosage forms, which are sufficient to treat most patients [54]. With few significant side effects, these drugs are generally well tolerated [96]. PPIs have a plasma half-life of just 60-90 minutes, but their inhibitory effect on gastric acid secretion persists for about 24 hours due to their covalent binding to the pump [97]. Since meals trigger proton pumps, taking a dose 15- 60 minutes before eating is most effective for acid suppression [57]. Thus, it is advised that patients on a daily dose of PPI regimen take their dose prior to breakfast [98].

Tenatoprazole is a new type of PPIs, offers a longer plasma half- life, resulting in extended acid inhibition and reduced nocturnal acid breakthrough [99,100]. Despite of having an approximately seven times longer half-life than other PPIs, it is still regarded as an effective alternative for patients whose once-daily PPI treatment is ineffective [101].

Prokinetics: A gastroprokinetic agent functions as a selective 5HT4 agonist, boosting ACh release from parasympathetic nerve endings, which then enhance bowel movement, accelerates gastric emptying [102] and increase the LES basal pressure. Conventionally, medications like mosapride and cisapride, which are 5-HT_4 antagonists, combined with selective dopamine-2 antagonists such as metoclopramide and domperidone for synchronicity. Sadly, the after effects restrict their usage, particularly since 5HT4 antagonists have been linked to heart related issues. Mosapride citrate being a $5HT_4$ receptor agonist and a $5HT_3$ receptor antagonist has notably reduced acid reflux and known to improve GERD symptoms, mainly when used as an conjuvant therapy [103].

Itopride: Itopride capacities as a dopamine (D_2) receptor opponent and restrains AChss esterase. It incorporates a proton pump inhibitor and a prokinetic specialist. This sedate has

been illustrated to ease GERD indications and lower esophageal corrosive levels in patients with gentle EE [104]. Itopride decreases TLESRs without strikingly affecting esophageal peristalsis [104,105]. It requires a higher dosage to enhance gastrointestinal motility compared to cisapride, metoclopramide and domperidone [106].

Cisapride: Cisapride was the pioneering serotonergic drug employed as prokinetic agent. It functions as a non- selective 5-HT4 receptor agonist, exhibiting a relatively weak antagonist effect on 5-HT3 receptors [107]. The medication shows prokinetic effects in the distal esophagus, stomach, jejunum, and colon, and has proven effective for various gut functional or motor disorders. It is used in GERD because it enhances the strength of esophageal contractions, increase LES pressure, and speeds up both gastric emptying and orocecal transit [108,109]. But as the event of cardiac arrhythmias and early death occur, this medication has been taken out from most of markets.

Pumosetrag (DDP733): It could be a halfway 5HT3 receptor agonist with gastrointestinal prokinetic properties. In exploratory creature models, DDP733 raises basal weight. Besides, DDP733 eminently diminished the recurrence of reflux occasions and upgraded the normal plentifulness of distal esophageal withdrawals in sound people, without changing LES basal weight [110,111].

Metoclopramide: Metoclopramide has direct fractional agonist properties at the 5-HT4 receptor and antagonistic properties at the 5-HT3 receptor [112]. The drug's enactment of 5-HT4 receptor is accepted to improve its gastrointestinal prokinetic impacts by expanding the discharge of acetylcholine (Ach) from natural cholinergic neurons [113]. Metoclopramide works as a dopaminergic adversary, upgrading LES weight, supporting esophageal peristalsis, and quickening gastric purging [114]. The essential restriction to the standard utilizes of this pharmaceutical is its side effects profile. All prokinetics with central D2 receptor adversary properties have been appeared to cause extrapyramidal responses. These impacts can restrain the utilize of metoclopramide in up to 30% of patients. Side effects such as laziness, tumult, crabbiness, weakness, and dystonic responses [115].

Azithromycin: In the macrolide category, azithromycin stimulates serotonin receptors, increases acetylcholine release, and functions as a motilin agonist (5HT3). According to measurements made using high-resolution manometry, the most recent study found that azithromycin reduced the size of hiatal hernias as well as the frequency of acid reflux episodes. Compared to mildly acidic and nonacidic reflux episodes, the average size of the hiatal hernias was larger during acidic reflux episodes. Furthermore, the acid pocket was commonly located distal to the diaphragm [116]. Additionally, it has been demonstrated that prucalopride, a highly

selective 5-HT4 agonist authorized for the treatment of constipation, shown to reduce AET and promote gastric emptying at high doses (e.g., 4mg/day) in healthy participants [117]. Because of its pharmacodynamic properties, this drug could be beneficial for GERD patients.

Levosulpiride: Being a derivative of benzamides, it is a selective antagonist of D2 receptors, with additional emergence with 5-HT4 receptors more and lesser to 5-HT3 receptors. The serotonergic component of levosulpiride is believed to enhance its therapeutic effectiveness in stimulating gastric and small bowel motility [118,119]. In fact, a multicentre, double-blind, controlled study demonstrated that this drug outperformed in treating patients with functional dyspepsia (FD) compared to domperidone, metoclopramide and placebo [120]. Furthermore, levosulpiride was shown to speed up gastric emptying rate, alleviating both FD and GI diseases related conditions [121,122].

SURGICAL THERAPY

Additionally, surgical intervention should be considered as alternative if the medical therapy does not produce significant changes. The Nissen fundoplication became widely recognized in the 1970s and has since become the most frequently performed anti-reflux surgery, but very first performance of this was already done in 1955 by Dr. Rudolph Nissen. To restore the LES barrier, the hiatal hernia needs to be reduced, and the gastric fundus should be wrapped around the lower esophagus, either partially or completely [123]. Symptomatic recurrence following fundoplication can result from incomplete preoperative evaluation, or insufficient surgical techniques [16].

The Linx treatment (magnetic sphincter augmentation) is a less invasive option. This procedure involves laparoscopically placing a magnetic bead around the LES, allowing food to pass through while preventing acid reflux. This has been linked to better symptom scores and a decreased reliance on PPI therapy, although it does not consistently lower esophageal acid exposure [123,124].

Alternatively, the Stretta procedure involves an endoluminal technique making low radiofrequency energy and its impact on the gastroesophageal junction seen after the application of radiofrequency and the LES was observed to be thicken, which may reduce TLERS frequency, reflux episodes and sensitivity to acid exposure [125]. This providing positive outcomes in improving gastroparesis, minimising gastric emptying time, and alleviating regurgitation symptoms over an extended period [126].

Another surgical treatment is Roux-en-Y gastric bypass treatment for individuals with morbid obesity. A potential study involving 53 patients demonstrated significant improvement and

halting the symptoms of GERD up to 3 years including reflux esophagitis, and acid exposure [127].

CONCLUSION

The understanding of GERD has significantly evolved since its initial identification, encompassing a range of physiological mechanisms that contribute to its pathophysiology, including transient lower esophageal sphincter relaxations, hiatal hernias, delayed gastric emptying and the impact of obesity. Grasping these mechanisms is critical in both diagnosing and treating GERD effectively. Effective diagnosis of GERD relies on a combination of symptom evaluation, diagnostic questionnaires, and a variety of testing modalities, including ambulatory pH monitoring and endoscopy. Treatment typically begins with lifestyle modifications aimed at reducing aggravating factors, followed by pharmacological interventions when necessary. Medications range from antacids from immediate relief to PPIs and H2 receptor antagonists that offer more sustained symptom management. Surgical options like fundoplication, magnetic sphincter augmentation, and other procedures, offer viable pathways to improve symptoms as alternative to the medical therapies not suitable for patients. Overall, the increased awareness of GERD's etiology and its impact on patients underscores the importance of a thorough and personalized management plan. This comprehensive approach is not only essential for symptom relief but also crucial in preventing complications that can significantly impair a patient's quality of life. Continued research into the underlying mechanisms, diagnostic techniques, and therapeutic strategies for GERD is critical to optimize patient outcomes. Hence, a collaborative effort among healthcare providers, patients, and researchers is essential in addressing the challenges posed by GERD and enhancing the well-being of those affected.

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