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GASTROESOPHAGEAL REFLUX DISEASE: FROM PATHOPHYSIOLOGICAL MECHANISMS TO PERSONALIZED THERAPEUTIC STRATEGIES

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by reflux of gastric contents into the esophagus, leading to troublesome symptoms and potential complications. Its pathogenesis involves dysfunction of the anti-reflux barrier, impaired esophageal clearance, and altered mucosal defense mechanisms. Multiple risk factors, including obesity, lifestyle habits, and anatomical abnormalities, contribute to disease progression. Diagnosis is based on clinical evaluation supported by endoscopy and reflux monitoring. Management includes lifestyle modification, pharmacotherapy primarily proton pump inhibitors and advanced endoscopic or surgical interventions. Recent advances emphasize phenotype-based and precision medicine approaches to improve long-term outcomes and patient-centered care.

KEYWORDS: Gastroesophageal reflux disease (GERD), pathogenesis, Management, phenotype-based and precision medicine approaches.

1. INTRODUCTION

GERD is a chronic and recurrent GI disease that occurs when contents of the stomach flood back into the esophagus, typically causing troublesome symptoms and in some cases resulting in mucosal injury and/or long-term complications.[1] It can range from non-erosive

reflux to erosive esophagitis and even premalignant changes in the esophagus.[2] Symptoms usually include heartburn and/or regurgitating acid after eating a meal and/or after laying down and/or at night. Also, patients may experience symptoms outside of the esophagus, such as chronic cough, hoarseness, throat irritation, symptoms consistent with asthma, dental erosion, and chest pain that isn't associated with a heart condition.[3] Since most people who have GERD have persistent symptoms, sleep is disturbed due to pain, patients must restrict their diets, work productivity is diminished, and ultimately their quality of life is severely affected.[4] In addition, GERD causes healthcare costs (both direct and indirect) due to lost work productivity and frequent medications being used to control the pool of symptoms that develop. Several patients have a fear of recurrence of their symptoms and/or must restrict their diets and this can cause significant semotional distress, which in turn may impact their social function.[5]

The lower esophageal sphincter (LES) is a specialized high-pressure zone located at the anatomical and functional boundary between the esophagus and stomach, and it is the major mechanism of preventing reflux from the stomach into the esophagus. When at rest, the pressure in the LES is greater than that in the esophagus.[6]

During the act of swallowing, the lower esophageal sphincter (LES) briefly relaxes to allow passage of food and quickly returns to its resting state to re-establish the barrier to gastroesophageal reflux.[7] The function of the LES is enhanced by the forces of gravity, esophageal peristalsis and the neutralization of residual acid by saliva. Additionally, the anatomical position of the gastroesophageal junction supports the function of the LES in maintaining competence, especially during different postures and with daily activities. Overall, these different mechanisms help to limit the exposure of the esophagus to gastric contents, help to clear small amounts of reflux rapidly and maintain the integrity of the esophageal lining. Therefore, the maintenance of the competence of the LES has an important role in normal digestion and in long-term esophageal health.[8]

The prevalence of gastroesophageal reflux disease (GERD) has been increasing over the last few decades so that it has become one of the most common chronic gastrointestinal disorders. This increase in prevalence has paralleled changes in the global lifestyle and environment such as westernized diets, decreased physical activity and increasing rates of overweight and obesity. In addition, occupations that require little activity, prolonged time in front of screens and irregular eating patterns have all led to an increase in the burden of reflux symptoms.[9]

Demographic shifts due to an aging population also contribute to the growing prevalence of GERD since the physiological mechanisms that normally protect an individual from developing GERD begin to diminish as we age. Changes in the use of medications among the general population and self-treatment with over-the-counter medications and dietary supplements may also play a role in the rising prevalence of GERD.[10] Diagnostic awareness that has improved healthcare providers' diagnostic recognition throughout the healthcare system and increased public health awareness is also contributing to the increased visibility of GERD as a growing global health problem, with long-term consequences for planning prevention strategies, healthcare delivery, and patient education.[11]

2. PATHOPHYSIOLOGY

Gastroesophageal reflux disease (GERD) is a chronic disorder that occurs from failure to maintain proper function of all coordinated protective mechanisms at the gastroesophageal junction.[12] It also results from impairment to esophageal clearance, compromised mucosal defenses, and alterations in how sensory information is processed. Physiologically, a high-pressure zone exists between the lower esophageal sphincter (LES), crural diaphragm and gastroesophageal flap valve (together referred to as the "anti-reflux barrier") that prevents reflux of gastric contents from entering the esophagus.[13] Disruption of any of these anti-reflux barrier components, for example, due to decreased basal LES tone; frequent transient LES relaxations; and/or structural defects such as hiatal hernia; allows for increased frequency and duration of reflux events.[14] Hiatal hernias worsen GERD by separating the functional and anatomical components of the LES, reducing diaphragmatic support, disrupting flow of food from the flap valve mechanism, maintaining acidic secretions in the hernia sac, and allowing repetitive re-reflux into the distal esophagus.[15]

After a meal, an unbuffered proximal reservoir consisting entirely of acids exists at or near the gastroesophageal junction increasing the likelihood of postprandial reflux particularly when transient relaxations of the lower esophageal sphincter occur.[16] In addition, increased abdominal and thoracic pressure gradients due to central obesity increase the stress placed on the anti-reflux barrier, causing disruptions at the gastroesophageal junction and increasing the volume and proximal extent of refluxate entering the esophagus.[17]

When reflux happens, the amount of damage done to the mucous membrane depends on how often you have refluxed and how long it takes for your mucous membrane to heal after having reflux, as well as what makes up the reflux (which could be acid, pepsin, bile and any

other stomach substances that can cause damage to the epithelial lining).[18] In addition to directly damaging the mucous membrane by the reflux material, the presence of reflux material activates inflammatory processes within the esophagus, producing cytokines, attracting immune cells to the site of damage, increasing the permeability of the mucous membrane and breaking down intercellular junctions. This allows the refluxed material to reach the sensory nerves at the deeper layers of tissue (submucosa).[19]

How long mucosal injury lasts is also influenced heavily by the effectiveness of normal esophageal clearing. The combination of primary and secondary peristalsis helps to remove the reflux material back into your stomach while providing saliva (bicarbonate) and mucosal secretions (antacids) to neutralize and repair the mucous membranes.[20] Reduction in peristaltic strength, reduction of saliva (especially at night), or re-reflux from a hernia will slow the acid clearance process and prolong the amount of time mucous membranes are exposed to acid, increasing the risk of damaged mucous membranes and esophageal metaplasia. Along with this, differences in the way sensory activation is processed also affect the way symptoms are expressed.[21] Higher sensitivity to esophageal sensations and amplification of signals sent from the nerves to the brain can decrease the level of stimulation that you have to have to feel something.[22] This may explain why some people experience significant heartburn with only a small amount of reflux. The chronic, recurring pattern of GERD, along with the broad variety of clinical expressions (from non-erosive to erosive esphagitis, as well as reflux-associated complications), is caused by the combined effect of impaired barrier function, abnormal reflux mechanisms, the delayed clearing of reflux, inflammatory changes to the mucosal membrane, and altered sensory processing.[23]

3. RISK FACTORS

The chances of developing gastroesophageal reflux disease (GERD) are affected by numerous different nonmodifiable and modifiable risk factors whose influence on the body occurs through mechanical, physiological, and behavioral pathways that result in refluxing of stomach contents into the esophagus and damaging mucosal defenses.[24] These risk factors do one or more of these things; they can increase the frequency of reflux episodes, extend the duration of acid exposure to the esophagus, decrease the effectiveness of the anti-reflux barrier, or increase the perception of symptoms.[25]

3.1 Genetic and Demographic Factors

The prevalence of GERD increases with age, in part due to age-associated reductions in the esophagus's motility, the production of saliva, the rate of gastric emptying, and the occurrence of hiatal hernia. Studies have suggested that there may also be sex differences. Although the incidence of symptoms of reflux is similar between men and women, erosive esophagitis and complications of GERD occur more frequently in men compared to women.[26] There is also evidence for genetic factors related to GERD since family clustering indicates that there are likely familial influences regarding the competence of the sphincter, the sensitivity of the esophagus, and the mechanisms of mucosal defense.[27]

3.2 Obesity and Body Composition

Obesity, especially central (abdominal) obesity, is one of the best-documented risk factors for GERD. The increase in intra-abdominal pressure that occurs with obesity also increases the gastroesophageal pressure gradient and increases the likelihood that reflux will happen when the lower esophageal sphincter is relaxed.[28] Central obesity contributes to increased risk of hiatal hernia, the volume and extent of the refluxate proximally after a meal, and the occurrence of reflux after meals. Adipose-derived tissue, or fat, plays a role in GERD.[29]

3.3 Anatomical Factors and a Hiatal Hernia

A hiatal hernia can significantly increase the chance of having gastroesophageal reflux disease (GERD) because it causes the lower esophageal sphincter and diaphragm's crura (the muscular parts that surround the esophagus) to not be aligned correctly, which means that the barrier to reflux is weakened [30]. The hernia sac can collect and hold acid from the stomach, which can lead to many instances of reflux as well as slow down how quickly the esophagus can clear the acid from reflux. Gastric reflux is often associated with the presence of a structural anomaly at the gastroesophageal junction or altered flap valve geometry of the gastroesophageal junction, both of which will decrease the efficacy of the barrier.[31]

3.4 Factors Related to Lifestyle

Cigarette smoking is known to be related to GERD, since smoking cigarettes may lower the tone of the lower esophageal sphincter, lower saliva bicarbonate secretion, slow down the emptying of food from the stomach, and cause the stomach to reflux its contents. Alcohol consumption may also decrease the pressure of the lower esophageal sphincter, stimulate the secretion of gastric acid from the stomach, and directly irritate the lining of the esophagus.[32] The relationship between physical activity and GERD is complicated; however, it appears

that strenuous physical activity or vigorous activity following meals, heavy lifting, and activities that increase pressure inside the abdomen can lead to reflux, while engaging in regular moderate physical activity may be protective because of its ability to assist with weight maintenance and improve how quickly food moves through the gastrointestinal tract. Being inactive may increase the burden of symptoms that are associated with GERD.[33]

3.5 Dietary Triggers and Eating Habits

Eating habits and dietary triggers, like high-fat foods and large meals, can greatly affect your risk for GERD. Fatty foods can slow down how quickly our stomachs empty and will make it more likely for our stomachs to push food into our esophagus. Other dietary triggers include spicy foods, acid foods, chocolate, peppermint, caffeine, soda, and citrus & tomato-based products.[34] These trigger(s) cause your lower esophageal sphincter to relax or irritate your esophagus to make you have symptoms like heartburn or regurgitation. Also, large meals stretch the stomach, which increases the pressure from inside the stomach to push food back into the esophagus (producing reflux). Furthermore, eating late at night or lying down immediately after eating decreases the effects of gravity on our ability to move food down the esophagus. Finally, eating rapidly and/or irregularly makes GERD symptoms worse.[35]

3.6 Postural and Behavioral Factors

Posture and behavior also contribute to GERD. For example, lying on your back, bending over at the waist, and going to sleep soon after eating have a negative effect on how much the force of gravity will help you clear your esophagus of food.[36] Nocturnal reflux has the additional negative effect of reducing the number of times you swallow during sleep and decreasing the total amount of saliva that would help neutralize stomach acid. Therefore, you are exposed to stomach acid for longer periods of time during the night when you have reflux.[37] Clothing that is tight against the abdomen and/or abdomen constriction from clothing may also increase the pressure in your abdomen, which will make it easier to have reflux episodes.[38]

3.7 Pregnancy and Hormonal Influences

Pregnancy is associated with an increased risk of GERD because of pregnancy-related changes in your hormones (e.g. increased levels of progesterone leading to relaxation of the lower esophageal sphincter) and the physical (mechanical) association of the growing uterus creating pressure in your abdominal cavity, leading to increased intra-abdominal pressure.

Together, these changes will contribute to a higher frequency of reflux, particularly in the later trimesters of pregnancy.[39]

3.8 Medications and Comorbid Conditions

Some prescription drugs create conditions that promote GERD, such as lowering the pressure on the lower esophagus or taking more time to get food out of the stomach, as well as directly irritating the stomach walls.[40] These types of drug include: small numbers of select sedatives, atoms of reflected, smooth muscle banks and some classes of antidepressant medications, and those found in large doses of calcium channel blockers, nitrates, antihistamines and theophyllines.[41]

3.9 Impaired Esophageal Clearance and Salivation

Some diseases that have other existing illnesses may also affect the final outcome of GERD. Diabetes can damage the nerves that supply the esophagus (autonomic neuropathy) and slow down the stomach itself (diabetes), making it hard for the esophagus to empty completely.[42] Most autoimmune diseases can slow down or stop the movement of the esophagus on one side (esophageal motility) and cause more abdominal problems.Both reduced organization of the esophagus through poor muscle function and reduced saliva production can lead to longer-lasting irritation of the esophagus.[43] Conditions that will cause lower levels of saliva production are: being dehydrated, having a lot of extra weight (obesity), being older, and taking certain medicines, which increase your risk of getting GERD and having GERD symptoms at night.[44]

3.10 Psychosocial and Sensory Factors

Psychological stress and anxiety can contribute to the development of GERD by causing a heightened sense of pain and therefore increasing how much you report experiencing GERD. When a person has a heightened sensitivity to visceral pain, the person may report higher levels of GERD symptoms even though the amount of GERD itself is low.[45]

Is the return of food from your stomach to your mouth or throat without coughing and may have a sour or bitter taste. The symptoms of both heartburn and regurgitation usually get worse at feeding times and at night. If you have heartburn or regurgitation, it great.[46]

4. Clinical Features and Diagnosis of Gastroesophageal Reflux Disease

Gastroesophageal Reflux Disease (GERD) has a variety of esophageal and extra-esophageal symptoms, which indicate the differing methods of what causes reflux and how it's felt. Heartburn and regurgitation are the most common clinical presentations.[47] Heartburn feels like a burning feeling in the area behind the breastbone that may start in the upper stomach and travel towards your neck. It is caused by eating food, lying down, or bending over.[48] Regurgitation ly impacts the quality of your life, as it can cause sleep disturbances, food restrictions, and decrease your ability to work. Some GERD patients do experience chest pain that makes it hard to tell if it's from GERD or a heart issue.[49] A full cardiac evaluation must be completed to determine the type of chest pain. Patients with esophageal mucosal inflammation, esophageal mucosal ulcerations, and esophageal peptic strictures could also have dysphagia and odynophagia. In contrast, patients experiencing persistent vomiting, GI bleeding, anemia, and unexplained weight loss likely have more advanced disease and/or complications, and they should have a full evaluation immediately.[50] In addition to having typical esophageal symptomatology, GERD can also cause a variety of extra-esophageal symptoms, such as chronic cough, hoarseness, throat-clearing, globus sensation, laryngitis, asthma-like symptoms, wheezing, dental erosion, and chronic sore throats.[51]

The extra-esophageal symptoms of GERD may occur singly or in combination with classic symptoms of GERD, making it more difficult to clinically recognize them so that they need to be referred to different medical specialists, making the relationship of extra-esophageal symptoms to GERD very complicated, as they may contribute and/or exacerbate other causes of reflux but reflux is not the primary cause of the symptoms presented.[52] In addition, the response of these patients to an acid-suppressive trial is variable and these types of presentations typically have a great deal of diagnostic uncertainty associated with them and therefore require a comprehensive clinical approach to the management of their condition.[53]

The diagnosis of GERD does not have a single gold standard, but the diagnosis is made by integrating the assessment of the symptom pattern, objective testing, and response to a therapeutic trial of acid suppression.[54] When patients present with typical symptoms without alarm features medical professionals will typically make a diagnosis clinically, give the patient an empirical trial of acid suppression to start as both an initial diagnostic and therapeutic intervention; while response to therapy is a good indicator of there being a high probability the patient has GERD, a response alone will not validate their diagnosis due to the

possible placebo effect and/or contributions from non-acid reflux mechanisms.[55] A symptom-based clinical diagnosis of GERD is much less reliable in patients that present with atypical (non-classic) and/or extra-esophageal manifestations.Upper endoscopy is central to the clinical evaluation of GERD for the patient who has alarm features, refractory symptoms, and/or risk factors for the complications associated with GERD.[56] An endoscopy allows doctors to see inside the esophagus and look for specific types of damage that are commonly thought to be caused by a condition called gastroesophageal reflux disease (GERD).[57] For example, if a doctor looks inside the esophagus and sees that there is damage from a previous injury or if he sees Barrett's mucosa, it gives him objective evidence that a person is indeed experiencing GERD.[58] On the other hand, if a doctor is unable to see any damage when he looks at the esophagus via endoscopy, it does not mean that the individual does not have GERD and many people who continue to feel the effects of GERD have non-erosive disease as detected by an endoscopy.[59]

An important diagnostic test for GERD is to measure the level of acid in the esophagus by inserting a tube down the throat and measuring acid levels with a pH meter. This can be very helpful when it is difficult to make a diagnosis because of the patient's condition or to evaluate a patient who has had continuous symptoms that have not improved despite therapy or when the physician is considering performing surgery.[60] If the pH measurement for the esophagus shows that there are high levels of acid present, there is strong evidence that the person's symptoms are related to GERD. In addition to measuring the pH of the esophagus, it may also be helpful to measure the extent and degree of acid and/or non-acid reflux using a technique known as combined pH-impedance testing.[61] In these instances, the physician uses indices referred to as symptoms-reflux association indices to help determine whether symptoms are the result of acid reflux. Other types of tests can also help clarify the diagnosis, including using a test called high-resolution esophageal manometry.[62] While this test is not primarily used to diagnose GERD, it can be very useful in evaluating disorders of esophageal motility that can cause reflux-like symptoms or to determine where the lower esophageal sphincter is located before performing a reflux study.[63] In order to determine that patients are suitable candidates for anti-reflux surgery based on the presence or absence of significant motility disorders, manometry testing is essential during the pre-procedure patient evaluation process.[64] The utility of diagnostic imaging procedures such as a barium swallow study for GERD is limited and they should not be used as diagnostic tools on their own but can help define gross anatomical abnormalities (such as large hiatal hernia).[65] In special populations

(i.e., those who are pregnant), the diagnosis of GERD will often be made through a clinical evaluation and based upon the existence of characteristic clinical symptoms; thus, invasive diagnostic procedures will typically only be performed in patients with atypical symptoms or when symptoms are severe.[66]

Domain	Category	Key Features / Description
Clinical Features	**Typical (Esophageal) Symptoms**	Heartburn (retrosternal burning sensation radiating from epigastrium to neck), acid regurgitation with sour/bitter taste, postprandial and nocturnal worsening, symptom aggravation on bending or lying supine
	Chest Pain	Retrosternal pain that may mimic cardiac ischemia; cardiac causes must be excluded before attributing to GERD
	Dysphagia & Odynophagia	Difficulty or pain on swallowing, commonly associated with esophagitis, ulceration, or peptic strictures
	Extra-esophageal Manifestations	Chronic cough, hoarseness, throat clearing, globus sensation, laryngitis, asthma-like symptoms, wheezing, chronic sore throat, dental erosions
	Alarm Features	Progressive dysphagia, unintentional weight loss, gastrointestinal bleeding, anemia, persistent vomiting—suggestive of complications or malignancy
Diagnosis	**Clinical Assessment**	Diagnosis based on typical symptoms in the absence of alarm features; symptom pattern and triggers provide initial diagnostic clues
	Empiric Acid-Suppressive Trial	Therapeutic trial of acid-suppressive therapy used as an initial diagnostic approach in patients with typical symptoms; symptom response supports but does not confirm diagnosis
	Upper GI Endoscopy	Identification of erosive esophagitis, strictures, Barrett's esophagus; exclusion of alternative diagnoses; normal findings do not exclude GERD
	Ambulatory Reflux Monitoring	Objective measurement of esophageal acid exposure and symptom–reflux correlation; useful in refractory or atypical cases and prior to invasive therapy
	Esophageal Manometry	Assessment of esophageal motility disorders; localization of LES before reflux monitoring; pre-operative evaluation before anti-reflux surgery
	Radiologic Evaluation	Limited role in diagnosing GERD; useful for identifying anatomical abnormalities such as large hiatal hernia
	Special Populations	In pregnancy, diagnosis is usually clinical; invasive tests reserved for atypical or severe presentations

5. Management and Treatment of Gastroesophageal Reflux Disease (GERD)

5.1 Management Objectives

The primary management objectives for gastroesophageal reflux disease (GERD) are to effectively alleviate symptoms, promote healing of the esophagus, prevent relapse and prevent long-term complications of GERD, and improve quality of life.[67] Treatment is individualized based upon symptom severity, disease phenotype (ex. typical vs atypical), presence or absence of complications, any comorbid conditions that exist in the patient and

patient preference. The treatment plan is also frequently implemented in a stepwise manner, starting with conservative measures before progressing to pharmacological or procedural options if necessary.[68]

5.2 Life and Behaviour Changes

Lifestyle and behaviour changes are the mainstay of treating all patients with GERD regardless of the severity of their GERD and can either be used alone for patients with mild GERD or to support pharmacological treatment for patients with more severe GERD.[69] Weight loss of those patients who are overweight/obese usually leads to an improvement in reflux symptoms and a decrease in the amount of acid that is exposes the esophagus by refluxing.[70] Patients should be advised to minimize portions of food eaten, avoid eating meals near to bedtime and to identify and limit food or beverage items that precipitate their symptoms. In addition, elevating the head of the bed and avoiding lying down directly after eating a meal may reduce nocturnal reflux.[71] Patients are strongly encouraged to quit smoking and to limit their alcohol consumption as both can weaken the lower esophageal sphincter (LES), contribute to the loss of saliva buffers, and contribute to the loss of mucosal defence against refluxed acid.[72]

5.3 Pharmacological Therapy

5.3.1 Antacids and Alginate-Based Formulations

Antacids and alginates will provide you with quick, temporary relief from mild & intermittent symptoms by neutralizing stomach acids & providing a protective layer over what is in your stomach. These types of medications are good for symptom control when needed but will not heal esophagitis nor are they enough for chronic GERD when used alone.[73]

5.3.2 Histamine-2 Receptor Antagonists

H2 antagonists reduce the secretion of gastric acid & may help treat mild-moderate reflux symptoms or be used as an adjunctive treatment for breakthrough nocturnal symptoms. H2 antagonists do not work as well as proton pump inhibitors, and patients may develop a tolerance to them with prolonged use, leading to a reduced level of benefit over time.[74]

5.3.3 Proton Pump Inhibitors

PPIs are the most effective medication available for controlling the structure and function of the esophagus, as well as for curing erosive esophagitis. Therefore, for patients experiencing frequent (more than 2x/week) or severe (moderate-severe) GERD, PPIs would be the first

choice of treatment.[75] PPIs can also be used as maintenance therapy in patients with proven mucosal damage or previously recurrent symptoms. Regarding treating patients with reflux disease without erosive esophagitis or patients with reflux-related conditions (extra-esophageal symptoms), outcomes will vary, so individualized treatment plans are often done; treatment may include continuous therapy, step-down therapy, or on-demand therapy.[76] The goal of any treatment plan is to administer the least amount needed for sufficient relief from your symptoms.[77]

5.4 Management of Refractory Symptoms

Some individuals will continue to demonstrate refractory symptoms even after having their acid suppression therapy optimally treated. The management plan will include: 1) reviewing the patient's compliance with the prescribed therapy and reviewing the maximum daily dose of their current medication;[78] 2) considering the possibility of another or concurrent diagnosis; and 3) optimizing the patient's lifestyle measures. Adjunctive medications can be used in select patients; however, they have variable efficacy and their AE's should be considered. Once the types of patients with the diagnosis of reflux hypersensitivity or functional heartburn have been identified, these patients may not respond to any significant benefit to further suppression of acid and may require other therapeutic modalities.[79]

5.5 Endoscopic Treatments

Endoscopic treatment options are an option for patients with GERD who have been carefully selected and have had objective testing of their GERD. Patients who have a partial response to pharmacologic therapy, who are intolerant to long-term use of medications, and/or wish to avoid chronic pharmacologic therapy are considered good candidates for endoscopic treatment options.[80] The goal of all procedures is to provide an anti-reflux barrier at the level of the lower esophageal sphincter. Endoscopic treatment options appear to be most successfully used for patients with early stage disease and those with optimal anatomy. Patient selection criteria and long-term follow-up are essential for providing lasting symptom relief and limiting patients' exposure to adverse outcomes.[81]

5.6 Surgical Management

In cases of GERD where there have been documented cases in addition to suffering from the problem despite treatment with oral medications, there is a possibility that you may be given the option of undergoing surgery.[82] Surgical procedures will re-establish the barrier between the stomach and esophagus by correcting the anatomical defect at the junction of the

esophagus and the stomach and then providing a new supplemental barrier to maintain that barrier.[83] It is important to have a good evaluation prior to surgery; confirm that reflux is the root of your symptoms, and check for proper movement of the esophageal muscles in order to provide you with the best chance at a successful outcome and to reduce the chance of complications after the surgical procedure.[84]

5.7 Long-Term Management and Follow-Up

To properly manage GERD in the long run, it is necessary to periodically evaluate how well symptoms are being controlled, what medications are required, as well as how many side effects may occur as a result of taking the medication on a long-term basis.[85] With regards to specific complications such as Barrett's esophagus, erosive esophagitis, long-term medical management is necessary in addition to ongoing monitoring and surveillance as a means of preventing recurrence and/or monitoring changes associated with progression of the disease.[86] The most effective approach to comprehensive long-term management of GERD consists of implementing an individualized, stepwise plan combining lifestyle modifications, pharmacologic therapy, and any necessary procedural interventions.[87]

6. Complications and Outcomes of Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease (GERD), if left unchecked or persistent, can create a lot of complications for those who suffer from it in terms of their health care, prognostic impact and other complications that develop as a result of having GERD.[88] The majority of individuals who have GERD report experiencing signs and symptoms of GERD without having any visible inflammation on an endoscopy or any mucosal integrity changes. With time, the exposure of the esophagus to refluxed material (stomach contents) increases a patient’s chance of developing structural (anatomical) and functional (physiological) changes such as esophageal stricture, Barrett Esophagus, etc.[89] Whether or not an individual has complications due to GERS is dependent upon a variety of factors such as length and severity of timeframe of reflux events from a standard point of view, nocturnal acid exposure events, clearance from the esophagus as well as conditions (e.g. a hiatal hernia).[90] Despite the different factors that determine if someone will develop complications due to GERD, there may be little correlation between the severity of symptoms reported by patients with GERD versus the degree of mucosal injury seen at the time of their endoscopy, which can present a challenge to health care practitioners when identifying a patient with GERD who is at risk for developing complications secondary to GERD.[91]

6.1 Esophageal Complications

Long-term acid reflux can lead to esophagitis, an inflammatory condition resulting in the distal esophagus' mucosa becoming eroded or ulcerated. When these areas continue to be affected by inflammation and epithelial damage, there is an increased risk in developing upper gastrointestinal bleeding (either as severe hematemesis or melena, or as more subtle and chronic iron-deficiency anemia due to occult blood loss).[92] When there are repeated cycles of tissue damage and repair within the esophagus, fibrous tissue will replace areas of normal or damaged tissue leading to the formation of peptic strictures, which will narrow the esophageal lumen and result in progressive dysphagia, odynophagia, and food impaction.[93] Peptic strictures are common in older adults and in those with a history of recurrent nighttime reflux. These patients will often require multiple endoscopically dilations, along with long-term acid suppression, to keep the narrow lumen of esophagus open.[94] In cases of severe injury or a result of deep ulceration, and the esophagus outgrowing its space, the esophagus can perforate (tear) or erode (to adjacent structures), which can lead to serious complications such as mediastinitis or the formation of fistulas (abnormal openings) between the esophagus and adjacent structures.[95]

An important long-term complication of GERD is Barrett's esophagus, which will result from chronic damage to the distal esophagus' squamous (skin) lining resulting in it being replaced with an altered type of columnar skin lining through metaplasia (the development of one type of cell type into another). Barrett's esophagus is a significant health concern, as it can lead to increased risk of developing esophageal adenocarcinoma, which has a very poor prognosis.[96] Patients that present with long term GERD symptoms, particularly if they have frequent or severe night symptoms, central obesity, or a hiatal hernia, are also at an increased risk of developing Barrett's esophagus.[97] Although the annual rate of malignant progression in Barrett's esophagus is low (i.e., about 0.5% per year), Barrett's esophagus will have a very poor prognosis once maligant (i.e. esophageal adenocarcinoma). Therefore, timely diagnosis and proper surveillance of Barrett's esophagus is a very important aspect of managing GERD over the long term.[98]

6.2 Extra-Esophageal Complications and Broader Outcomes

Esophageal reflux is also commonly associated with various extra-esophageal manifestations that increase the overall burden of the disease. Chronic reflux may create or worsen laryngopharyngeal inflammation, resulting in symptoms such as hoarseness, chronic throat

clearing, sore throat, and laryngitis.[99] Respiratory symptoms may include chronic coughing, wheezing, or asthma-like symptoms and may occur through microaspiration of gastrointestinal contents, or reflexively, via a vagus nerve-mediated response to stimuli that originate in the gastrointestinal tract. Chronic microaspiration in some susceptible individuals may predispose them to pulmonary infections and chronic airway inflammation.[100] Individuals may also develop dental erosions and ulcers of the oral mucosa from repeated exposure to acidic refluxate in the oral cavity. Although the relationship between gastroesophageal reflux disease and some of the extra-esophageal manifestations is thought to be multifactorial, the presence of reflux increases the complexity of diagnosis, utilization of multispecialty health care, and ultimately the overall morbidity experienced by patients.[101]

6.3 Impact on Quality of Life, Healthcare Utilization, and Long-Term Prognosis

In addition to structural consequences of GERD, the condition leads to poor quality of life and poor functional outcomes for the patient in the long run. Patients with chronic symptoms and fear of recurrence will have issues with disrupted sleep, limited diet and lifestyle choices, decreased productivity at work, and overall psychological stress.[102] Patients with complicated GERD will often require long-term pharmacologic therapy, multiple endoscopic procedures, and ongoing monitoring for pre-malignant changes which leads to higher rates of healthcare costs and financial burden on society.[103] Although with the increased use of strong acid-suppression medications there have been fewer occurences of some serious complications related to GERD (especially peptic strictures and bleeding) the overall rate of morbidity associated with GERD continues to be high since it is a chronic-and-relapsing disease and because obesity is becoming a larger factor and the population continues to age.[104]

6.4 Long-Term Outcomes and Disease Course

GERD has a natural history characterized by episodes of remission and relapse, resulting in most patients needing either continuous or occasional maintenance therapies to continue symptom control and promote mucosal healing.[105] Patients with erosive gastroesophageal reflux disease (GERD), Barrett's Esophagus, or anatomically predisposed to developing these conditions are at a greater risk for recurrence and progression and benefit from guided continued follow-up and maintenance strategies. Long-term clinical outcomes for GERD are

most positive when diagnosis occurs early, treatment is appropriate, and at-risk patients receive ongoing monitoring.[106]

Although symptoms may improve with treatment, failure to achieve sustainable reflux control results in both a substantial symptom burden and an increased likelihood that progression of mucosal injury and malignant transformation will occur among at-risk patients.[107] The above-mentioned complications and anticipated outcomes support the principle that GERD may not simply be a benign symptomatic disorder but rather a chronic condition with long-term serious potential consequences; therefore, comprehensive management strategies should be enacted including treatment of acute symptoms as well as prevention of complications, surveillance for premalignant conditions, and long-term, patient-centered care.[108]

7. Recent Advances and Future Directions

In just ten years, there has been significant refinement of both the conceptual framework and clinical management of GERD due to advances in pharmacotherapy, diagnostic technologies, endoscopic intervention, and phenotyping of the disease. As a result of this growing recognition that GERD is a heterogeneous group of disorders rather than a single disease caused by excess acid reflux, the various phenotypic types of GERD include: erosive esophagitis; non-erosive reflux disease; reflux hypersensitivity; and functional heartburn. This change in thinking about GERD has highlighted the limitations of one-size-fits-all acid suppression strategies and has led to new therapies that are target and mechanism based, as well as patient centered.

7.1 Advances in Acid Suppression and Medical Therapy

While traditional proton pump inhibitors (PPIs) are still the mainstay of GERD management, the limitations of PPIs (e.g., slow onset; incomplete suppression of nocturnal acid production; interindividual variation in metabolism; and partial symptom relief) have led to new developments in acid-suppressing pharmacology. Potassium-competitive acid blockers (PCABs) are a significant therapeutic development as they provide rapid, potent, and long-acting inhibition of gastric acid secretion with better nocturnal symptom control and more consistent results across dosing cycles. PCABs are especially promising for patients with erosive esophagitis or severe disease phenotype or who are refractory to treatment with PPIs and for whom the clinically relevant phenomenon of nocturnal acid breakthrough is present. Also, next-generation formulary PPI products that offer modified-release and/or dual delayed-release properties are designed to provide more even 24 hour acid control and

correspondingly improve symptom control and mucosal healing. Additionally, acid suppression combinations with mucosal protectants and alginate-based barrier treatments have gained interest from patients with persistent symptoms related to postprandial reflux and weakly acidic refluxate. The increase in pharmacological options represents a shift from total reliance upon single-agent acid suppression to more rational combinations of medications and individualized dosing regimens based upon patterns of symptoms, circadian rhythms of acid secretion, and patient phenotypes.

7.2 Targeting Non-Acid Mechanisms and Esophageal Defense

Research has shown that the digestive issues associated with gastroesophageal reflux disease (GERD) are attributable to not only the presence of acid in the esophagus but also the degree of susceptibility of the tissue (the mucosa) to injury by acidic liquid and the way the nervous system processes sensations from the tissue. Therapies are being developed to protect the epithelial barrier (the layer of cells lining the esophagus) to make it more resistant to refluxate getting into the esophagus from the stomach and therefore will lead to fewer symptoms and less inflammatory response (activation of somatic nerves). Additionally, some compounds are being tested in patients whose GERD symptoms persist in spite of adequate gastric acid suppression to target the component of mixed reflux related to bile constituents and mixed reflux. Pharmacalogic modulation of transient lower esophageal sphincter (LES) relaxations to reduce the number of reflux events is also being explored as a possible approach to limit reflux at its point of origin. The therapeutic agents evaluated to date have demonstrated modest clinical efficacy and also resulted in adverse events; however, more recent studies are investigating the use of more highly selective agents for consideration for advancement as a means for addressing the mechanical factors contributing to reflux. Collectively, there is a progressive paradigm shift toward protection of the mucosa from subsequent damage and decreasing the likelihood of a recurrence of reflux, rather than simply neutralizing the acidity of gastric contents.

7.3 Advances in Diagnostics, Phenotyping, and Precision Medicine

The advancements in esophageal physiology testing have completely changed the way GERD is diagnosed. With high-resolution manometry and combined impedance-pH monitoring, we can better characterize reflux patterns and calculate how well the reflux is being cleared and where reflux is related to the symptoms; for example, when an acid reflux occurs, it can be distinguished from weak acid reflux, from an acid sensitivity. New methods for measuring

clarifying reflux time and measuring baseline mucosal impedance are leading us to understand more about mucosal integrity and severity of disease so we are better able to determine the risk of each patient and the best way to treat them.

The new methods of diagnosis will help us to manage patients based on their physiology instead of just their symptoms. The goal is to determine which patients will have the greatest benefit from more aggressive acid suppression, from a treatment to the esophagus, or from another type of treatment aimed at modulating the nervous system, in order to prevent overtreatment and produce better outcomes in patients. The new directions in the development of a non-invasive biomarker, better ways of imaging mucosal change at earlier stages, and more digital ways to track symptoms and reflux allow for more real-time, adaptive management.

7.4 Endoscopic and Minimally Invasive Therapeutic Innovations

Endoscopic therapies, also known as minimally invasive procedures, allow more options for treating GERD without using long-term medication; this can include patients who were previously unwilling or unable to undergo surgery. Several advances made recently with these endoscopic devices and techniques allow us to improve upon the anti-reflux barrier at the gastroesophageal junction, reduce the amount of acid in the esophagus and improve the patient's symptoms while protecting the integrity of the gastrointestinal tract. The standardization of procedures, the development of appropriate patient populations for endoscopic therapy, and the implementation of post-procedure evaluation methods have contributed to the increased safety and effectiveness of endoscopic therapies for controlling GERD symptoms.At the same time, improvements made to endoscopic imaging and endoscopic tissue characterization now allow us to detect Barrett's esophagus earlier and better identify dysplastic changes in Barrett's esophagus, thereby allowing for earlier intervention and more reliable follow-up care. Future research should focus on combining therapeutic endoscopy with physiological feedback in real time and the use of biomarkers to help determine which patients will achieve the best long-term outcomes and what can be done to minimize any negative consequences associated with performing unwanted or inappropriate surgical procedures.

7.5 Digital Health, Longitudinal Monitoring, and Patient-Centered Care

Mobile applications for tracking symptoms and tracking sleep and posture through wearable devices, along with a telemedicine system, are examples of the types of digital devices

available. These technologies also allow continuous monitoring of symptom patterns, adherence to treatment, and lifestyle variables for each patient. This allows for real-time changes made to a patient's treatment plan as needed as well as the ability to identify unsuccessful treatments early on. Patient education and engagement are key components in the success of managing a long-term condition like GERD; therefore, digital devices facilitate these two areas.Using digital biometrics along with other physiological measurements and electronic health records can potentially develop predictive models that could create a more personalized treatment plan for the patient and improve the quality of the treatment guidelines used in the management of GERD.

7.6 Future Directions and Unmet Needs

Long-term comparative effectiveness and safety studies of PCABs and PPIs (along with other commonly used medications) among patients with various GERD phenotypes will continue to be a focus of future research. Additionally, there is a need for further studies of the optimization of combination therapies targeting both acid-mediated and non-acid-mediated mechanisms. Rigorous evaluations of the durability and cost-effectiveness of endoscopic interventions will also be an important area of future research.The identification of patients at high risk for Barrett's esophagus and esophageal adenocarcinoma is an important area of future research. More emphasis is expected to be placed on the development of biomarkers that can predict malignant progression as well as on the development of novel therapeutic targets including the use of agents that modulate mucosal inflammation, facilitate epithelial repair, and modulate sensory nerve signaling. The recent advances in the field of GERD coupled with anticipated future developments will result in a transition from an empirical/symptomatic treatment model to a precision-based, phenotype-based, and technology-enhanced model of care in the treatment of GERD. This new approach to the treatment of GERD offers an opportunity for improved control of GERD symptoms, decreased complication rates, and optimized long-term outcomes for individuals living with this common and burdensome chronic disease.

CONCLUSION

GERD is a multifactorial and chronic condition with significant clinical, economic, and quality-of-life implications. Its pathophysiology reflects a complex interplay between mechanical dysfunction, mucosal vulnerability, and sensory alterations. Early diagnosis and individualized treatment strategies are essential to prevent complications such as esophagitis,

strictures, and Barrett's esophagus. While conventional therapies like proton pump inhibitors remain the cornerstone of treatment, emerging approaches focusing on non-acid mechanisms, precision diagnostics, and minimally invasive interventions are reshaping management paradigms. A comprehensive, patient-centered, and stepwise approach integrating lifestyle, pharmacological, and procedural strategies is crucial for effective long-term disease control and improved outcomes.

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