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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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MODERN MANAGEMENT OF GERD: INTEGRATING ADVANCED DIAGNOSTICS AND INTERVENTIONAL THERAPIES

Michał Drabik *(Corresponding Author, Email: michaldr2551@gmail.com)*
5th Military Clinical Hospital with Polyclinic SPZOZ, Kraków, Poland
ORCID ID: 0009-0004-0198-4926

Maksym Sikora
The Hospital of the Brothers of St. John of God, Kraków, Poland
ORCID ID: 0009-0008-4495-7732

Jakub Nowak
Independent Public Healthcare Institution of the Ministry of the Interior and Administration in Kraków, Kraków, Poland
ORCID ID: 0009-0003-7097-0635

Michael Platschek
Blessed Marta Wiecka Hospital in Bochnia, Bochnia, Poland
ORCID ID: 0009-0008-9085-4531

Klaudia Dybalska
Brzeziny Specialist Hospital, Brzeziny, Poland
ORCID ID: 0009-0006-9900-0167

Julia Kosmulska
University Hospital in Wrocław, Wrocław, Poland
ORCID ID: 0009-0000-8770-3793

Mateusz Kęska
5th Military Clinical Hospital with Polyclinic SPZOZ, Kraków, Poland
ORCID ID: 0000-0003-0712-7613

Anna Barbara Tuleja
University Hospital in Wrocław, Wrocław, Poland
ORCID ID: 0009-0003-9185-9493

Sylwia Kolano
Independent Public Healthcare Institution of the Ministry of the Interior and Administration in Kraków, Kraków, Poland
ORCID ID: 0009-0000-1180-1135

Karol Józef Szkarłat
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0004-2889-8382

ABSTRACT

Gastroesophageal reflux disease (GERD) is a widespread gastrointestinal disorder with a significant global burden. Its multifactorial etiology is influenced by unmodifiable risk factors such as sex-based differences; men, for instance, show a higher predisposition for more severe complications like esophageal adenocarcinoma. GERDs pathophysiology is heavily connected with mechanical failure of the anti-reflux barrier, a two-component system that consists of the intrinsic lower esophageal sphincter (LES) and the extrinsic crural diaphragm. Interference in the form of hiatal hernia, hypotensive LES pressure or transient LES relaxations leads to reflux. Modern approach highlights the critical role of microscopic mucosal damage, which causes visceral hypersensitivity and allows the distinction of various phenotypes like non-erosive reflux disease and reflux hipersensitivity. Diagnosis is guided by the Lyon Consensus 2.0 using endoscopy, manometry, and impedance-pH monitoring. Treatment is a multi-step process – it includes lifestyle modification, numerous pharmacological agents such as proton pump inhibitors or newer potassium-competitive acid blockers, and, for refractory cases, interventional treatment via laparoscopic Nissen fundoplication, transoral incisionless fundoplication or magnetic sphincter augmentation.

KEYWORDS

GERD, Esophagus, Reflux, Acid, Health

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Introduction

Gastroesophageal reflux disease (GERD) is a chronic disorder with the presence of troublesome symptoms due to the reflux of gastric contents and erosive complications in the esophagus [2]. The most common symptoms of GERD include heartburn and acid regurgitation, though atypical symptoms like cough, hoarseness and chest pain can be present as well [45]. Variance of symptom presentation and response to treatment methods might be determined by the composition of refluxate and the esophageal differences – structural, mechanical, biochemical and physiological [25,36]. GERD belongs to the most common gastrointestinal disorders, with an estimated overall prevalence of up to 20% of the global population, making it a major contributor to global healthcare costs [1].

Patients with GERD require chronic medical care which generates both direct and indirect cost on individuals and healthcare systems [3]. Moreover, if the condition stays untreated or poorly managed, it can lead to various complications such as erosive esophagitis (EE), peptic strictures, the precancerous condition of Barrett's esophagus and esophageal adenocarcinoma (EAC) [5,6]. The disease predisposition is complex – starting with sex-based differences, women more frequently report non-erosive reflux disease (NERD) or hypersensitive phenotypes, whereas men tend to develop severe complications, such as Barret's esophagus or EAC [2,5,13]. Furthermore, studies show that GERD is heritable, with a genetic contrubtion of 31-40% [2,13]. It indicates that the disease is not only associated with one's lifestyle, but is also rooted in an individual's susceptibility.

Typically, GERD arises from anatomical and functional failure of the anti-reflux barrier (ARB) at the esophagogastric junction (EGJ) [23]. This barrier consists of two synergistic components: the intrinsic lower espohageal sphincter (LES) and extrinsic crural diaphragm. The presence of a hiatal hernia (HH) leads to separation of these two components, which causes pathological acid exposure [21, 23].

As indicated above, the efficient treatment of GERD is not always obvious. Even though it is classically considered a disease of excess acid, up to 50% of patients with GERD experience little to no relief with pharmacologic acid suppression [45]. The means of this article is to summarize the most recent knowledge about GERD and its treatment. The authors of this article aim to present up to date information about GERD, especially about the risk factors, pathophysiology, diagnostic guidelines and available treatment methods.

Anatomy

GERD is rooted in failure of the ARB which can be not only functional but also related to one's anatomy [2, 23] The integrity of the ARB relies on several anatomical structures that function to prevent the retrograde flow of gastric contents [22, 24].

The ARB can be described by the "two-sphincter hypothesis" which includes intrinsic and extrinsic component. The LES – an intrinsic component – is a zone of circular smooth muscle at the distal end of the esophagus, up to 5 cm in length [20]. The main role of the LES is to maintain tonic resting pressure high enough (10-30 mm Hg above gastric pressure) that it prevents reflux at rest[20]. The crural diaphragm – an extrinsic component – consists of muscular bundles of the diaphragm that surround the esophageal hiatus. Its role is to provide the support to the LES, particularly during periods of incresead intra-abdominal pressure (e.g. coughing) [23, 22]. The most frequent anatomical abnormality that contribute to GERD incidence is the presence of the hiatal hernia (HH). It causes a sliding-related migration of the LES into the chest cavity, which prevents the crural diaphragm from supporting the LES, impairing their crucial synergistic function [23].

Risk Factors

The etiology of GERD is influenced by risk factors that could be divided into unmodifiable and modifiable which compromise the ARB and increase intra-abdominal pressure [2,13]. Among the unmodifiable risk factors are: anatomical defects mentioned in the paragraph above, age – the prevalence of GERD symptoms increase with advancing age [13]. Sex and genetics also do play a role [15]. Modifiable risk factors mainly relate to lifestyle and are targets for prevention and management of GERD. Obesity is one of the strongest among them – it has been determined that Body Mass Index is in positive correlation with the incidence of GERD symptoms and its complications like EE. [14,15]. The excessive weight, particularly located in abdominal area, increases the pressure on the stomach, further compromising the function of the LES [14]. Secondly, diet and eating habits strongly influence the prevalence of GERD symptoms. Eating fatty, fried or acidic foods, meals of large volumes and short interval between dinner and bedtime all increase the likelihood of acquiring GERD [16,17]. Use of specific substances is another risk factor – smoking being the major one [13, 18], but consumption of alcohol, caffeine and carbonated beverages is also said to increase the symptoms of GERD because of their effect on the LES function [16]. On the other hand, physical activity has protective effect against GERD, especially in older adults and smokers. Meeting the recommended level of physical activity (150 min per week) may significantly reduce the prevalence of GERD [19].

Pathophysiology

Understanding of multifactorial patophysiology of GERD is crucial to choosing proper treatment. In general, there is an impairment in balance between aggressive gastric contents and compromised defensive mechanisms [26, 25]. Traditional understanding was mainly focused on the mechanical failure of the ARB, but now, the researchers highlight complex interactions between neurophysiological, anatomical and mucosal factors which all result in the vast clinical heterogeneity of GERD manifestations [2, 26].

Defects of the ARB

As stated in the Anatomy paragraph, the disfunction of the "two-component sphincter" is often the main culprit of GERD. There are two major forms of its mechanical defect:

- Hypotensive LES and the presence of the HH:

Patients with erosive reflux disease (ERD) are often found to have the LES with a baseline low resting pressure [7]. This could be exacerbated by the presence of the HH, which causes anatomical disruption of the ARB. The HH eliminates synergistic reinforcement of intrinsic LES and extrinsic crural diaphragm, creating a reservoir for gastric contents, which aggravates reflux [23, 35].

- Transient LES Relaxations (TLESRs):

TLESRs are spontaneous relaxations of the LES that account for majority of reflux episodes not only in GERD patients but also in healthy individuals [9, 27]. In GERD, TLESRs generally result in more severe acid reflux because of allowing a greater quantity of refluxate into the esophagus [27, 28]. Neurophysiological research shows that TLESRs are vagally-mediated reflexes, triggered by the stomach expansion after a meal [28].

Refluxate

- The "acid pocket":

Immediately after a meal, a layer of gastric acid forms in the stomach, proximally to the meal itself [8, 28]. This acidic, highly corrosive content is the most likely to be refluxed during TLESRs, which make its specific location critical in postprandial GERD [25].

- Gastric contents:

Apart from hydrochloric acid, pepsin and bile acids need to be mentioned. Pepsin is a proteolytic enzyme that has the highest activity in acidic environment (pH < 4). It remains stable at higher pH levels and can be reactivated in result of acid re-exposure, hence it contributes to damage even in weakly acidic reflux [8, 33]. Bile acids are part of the duodenal contents. They act as natural detergents and their cytotoxic effect is synergistically enhanced in an acidic environment which allows them to penetrate the mucosa [33]. These two additional factors explain why GERD symptoms and mucosal damage can still be present in patients on proton pump inhibitors (PPIs) – acid suppression does not remove the other pathophysiological components.

Esophageal Mucosal Integrity and GERD Phenotypes

Latest findings emphasize the critical role of the integrity of esophageal mucosa, which defines the different phenotypes of GERD.

- Impaired mucosal barrier: The most common phenotype – NERD [29], is characterized by the presence of microscopic damage to the mucosa, even though macroscopically it shows no signs of impairment. Said damage consists of the disruption of tight junction proteins and dilated intracellular spaces [11, 29]. It allows noxious agents to penetrate into the deeper layers of the mucosa and stimulate the nerve endings.
- The hypersensitivity spectrum: Consists of reflux hypersensitivity (RH) and functional heartburn (FH). The RH patients experience severe symptoms with physiological levels of reflux which is a result of a visceral hypersensitivity. Diagnosis is based on normal acid exposure time (AET) with positive symptom-reflux association [30, 34]. Patients experiencing FH have neither abnormal AET nor a positive symptom-reflux association [34]. The mucosal integrity is usually intact and the mechanism is believed to be a disorder of a central impulse processing [30].
- Inflammatory and neural modulation: in both NERD and ERD, the damage present triggers an inflammatory response which further modulates nociceptors. This is the mechanism which result in chronic pain or discomfort [11, 26].

The multitude of mechanisms that comprise GERD accentuates the necessity of a complex and thorough approach to diagnostics and treatment, deliberately chosen to each patient [25].

Diagnostic Methods

The diagnostic path in GERD patients starts with the initial diagnosis based on typical symptoms, such as regurgitation and heartburn [2]. PPIs are used there not only as an empirical treatment, but also as a diagnostic tool, even though their specificity is limited [3, 30]. The upper endoscopy remains the gold standard for evaluating the esophageal mucosa [2]. Its diagnostic role in symptomatic GERD is limited, because majority of patients have no visible mucosal changes (NERD) [29]. Instead, the endoscopy is crucial to identifying alterations made in the mucosa and an aftermath of the chronic reflux. These include detecting stenosis in the esophagus, grading the severity of ERD and screening of metaplastic changes of Barrett's esophagus [5]. In accordance with the guidelines, the upper endoscopy remains obligatory in patients presenting with "alarm symptoms" such as dysphagia, odynophagia, weight loss, or anemia, to exclude other, more severe disorders [2].

Lyon Consensus 2.0 introduces the latest guidelines to objectively assess and diagnose GERD [36]. This route relies on quantifying the disease through ambulatory reflux monitoring, being the gold standard [30]. In such task, Multichannel Intraluminal Impedance-pH (MII-pH) monitoring appears to be superior to traditional pH-only monitoring. Its advantages in objective assessment of GERD are:

- Measuring AET – the primary metric for diagnosing abnormal reflux [36].
- Characterizing refluxate based on its acidity, which is critical for understanding PPI-refractory symptoms [10, 30].
- Assessing mucosal integrity – measuring an epithelial integrity is possible by calculation of mean nocturnal baseline impedance (MNBI). A low MNBI value correlates strongly with dillated intracellular spaces seen in pathophysiology, which provides an objective marker of microscopic mucosal damage even in NERD [37].

- Measuring esophageal clearance – allows for the quantification of esophagus's low ability to clear refluxate – a key motor defect in GERD [37].

High-Resolution Manometry (HRM), measuring esophageal muscle pressure, also plays a critical role [31]. Apart from assessing esophageal motor function, it allows evaluating the anatomy of the EGJ. It is compulsory prior to performing any anti-reflux surgery to confirm adequate peristalsis and rule out motility disorders, such as achalasia [2,31]. It also indentifies a hypotensive LES [7] and the HH. Lastly, novel techniques provide a better understanding of the ARB's mechanical properties. Esophageal mucosal impedance, measured with a probe during endoscopy, detects the compromised epithelial integrity, which is an objective marker of microscopic damage [32]. Similarly Endoluminal Functional Lumen Imaging Probe system (EndoFLIP), often used during the ndoscopy, measures the stiffness of the EGJ [38]. In GERD, the EGJ often becomes stretchable, which highly correlates with the barrier impairment. This multifocal approach, which combines the endoscopy with the physiological measurements from MII-pH, HRM and EndoFLIP, allows for an accurate and conclusive assessment and diagnosis, further profiling the disease (ERD, NERD, RH), helping to choose an appropriate therapeutic approach [36].

The Therapeutic Strategy for GERD

The management of GERD follows a progressive approach, beginning with the least invasive interventions [2]. Initial recommendations focus on the modifiable risk factors previously discussed. This includes weight loss for overweight or obese patients, which has been shown to be one of the most effective interventions for reducing esophageal acid exposure, thus allieviating symptoms [14, 15]. Dietary modifications, such as avoiding high-fat meals, caffeine, chocolate or alcohol, which are known for triggering the symptoms, are commonly advised [16], alongside the avoidance of late-night meals [17] and smoking cessation [18]. When lifestyle changes are insufficient, pharmacological treatment is in order. For intermittent symptoms, on-demand therapy with antacids or alginate-based formulations shows to be effective. Alginates offer a unique mechanism by forming a neutral, viscous layer that floats atop the stomach contents, physically dislocating the postprandial acid pocket [8, 28] and protecting the distal esophagus during reflux events [39]. If the symptoms are more frequent and severe, the primary goal is to suppress the acid secretion. H_2-receptor antagonists (H2RAs) are effective for such GERD cases but are prone to tachyphylaxis and appear to be less potent than PPIs [2]. PPIs (e.g. esomeprazole, lansoprazole) remain the gold standard for pharmacological therapy, providing efficient acid suppression and high rates of healing for EE. Nonetheless, their use is limited in patients including those with PPI-refractory GERD [3], non-acid reflux [10] or RH [34]. In this group of patients, another approach is needed to be considered, such as treatment with baclofen, a $GABA_B$ -agonist that reduces the frequency of TLESRs [41]. Lately, a new group of pharmaceuticals have emerged – Potassium-Competitive Acid Blockers (P-CABs), such as vonoprazan. They offer a more rapid and sustained acid supression independent of meal timing. Recent meta-analyses show their superior efficiency over PPIs, especially in healing severe EE [40]. However, for patients with a confirmed refractory GERD, persistent regurgitation despite PPIs therapy, a large HH or a desire to cease long-term medical therapy, an anti-reflux surgery is the definitive treatment [4]. The long-standing gold standard is the laparoscopic Nissen fundoplication (LNF), which is a way to mechanically reconstruct the ARB by wrapping the gastric fundus around the distal esophagus. Even though it is highly effective, it is often associated with postoperative side effects, such as dysphagia [42]. Transoral incisionless fundoplication (TIF) is a less invasive endoscopic procedure which aim is to reconstruct the gastroesophageal valve from within, creating a partial 270-degree wrap without any external incisions. TIF offers a faster recovery and is fairly safe, although its long-term correction may be less resilient than that of LNF [43]. Last but not least, magnetic sphincter augmentation (LINX) is a novel laparoscopic approach that places a flexible ring of magnetic beads around the LES. It augments the sphincter's resting pressure to prevent reflux but still opens to allow for swallowing, emesis or eructation, offering a similar reflux control to LNF with a more physiological side-effect profile [44]. A recent systematic review and network meta-analysis confirmed the efficacy of these modern endoscopic and surgical treatments, providing a comparative framework for this new spectrum of care [12].

Conclusions

GERD is a complex clinical problem, evolving from a simple "acid disease" into a spectrum of disorders. Its etiology is a junction of unmodifiable and modifiable risk factors, and the failure of the ARB [35]. The disease is characterized by its multifactorial pathophysiology, starting from the anatomical failure – specifically the separation of the LES from the crural diaphragm [23], continuing with the refluxate toxicity [33] and the successive breakdown of the epithelial integrity [29]. The latter is critical for understanding the cause of neurosensory visceral hypersensitivity which leads to the most challenging phenotypes like NERD and RH [34]. This article has highlighted the shift from symptom-based management of GERD to a more modern, physiology-based approach. Effective long-term treatment is often connected with moving beyond the empirical PPI intake and focusing on the objective diagnostics, which is possible thanks to the Lyon Consensus 2.0 framework [36], which integrates endoscopy, manometry, and advanced MII-PH monitoring [31, 37], providing the tools needed to accurately assess the disease. This facilitates the differentiation between true acid-refractory GERD from FH or hypersensitivity. Alongside the diagnostic precision, the therapeutic options are also expanding. Even though PPIs remain the pillar of GERD therapy, P-CABs offer a more effective and reliable option for medical acid suppression [40]. For patients with confirmed refractory disease, there are invasive ways of treatment. TIF provide a good safety profile for select patients [43], while LINX and LNF offer the definitive restoration of the ARB [42,44]. The future of GERD management is heavily reliant on this personalized strategy, moving beyond a simple acid neutralization to correcting the underlying cause.

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