REVIEW ARTICLE

CONTENTS

Innovative therapeutic strategies in the treatment of gastroesophageal reflux disease (GERD): A review of progress and perspectives

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ABSTRACT

Gastroesophageal Reflux Disease (GERD) is a commonly occurring condition that can significantly impact quality of life. Often considered a lifestyle disease. Traditional treatment methods focus on pharmacotherapy, lifestyle modifications, and in extreme cases, surgical interventions. This article discusses current and novel approaches to managing gastroesophageal reflux disease. The foundation of this work was medical articles and research gathered from the PubMed database. Keywords such as "esophageal reflux treatment", "new technologies in GERD treatment", "innovative reflux treatment methods", were used to facilitate the literature search. In managing gastroesophageal reflux disease, the application of appropriate pharmacological therapy and lifestyle changes for the patient remains key. However, new technologies and treatment methods, such as advanced endoscopic repair procedures, innovative medications, and personalized approaches, are gaining importance. These new strategies can significantly improve patients' quality of life, reduce symptoms, and minimize the need for surgical interventions.

KEY WORDS: GERD, diagnostics, treatment, new technologies

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INTRODUCTION

Gastroesophageal reflux disease, or GERD for short, is a disease of civilization dimensions and affects people of all ages. Although its main symptom is the backflow of food content from the stomach into the esophagus, the above health problem manifests itself not only with the popular heartburn – that is, burning chest pain behind the sternum radiating to the neck or throat, but also manifests itself with extraesophageal ailments. These include asthma, laryngitis, dry cough, esophagitis and esophageal stricture, Barrett's esophagus [1]. In addition to the aforementioned, cardiac, neurological and dental disorders occurring without specific reasons may find their cause in asymptomatic reflux. Incorrectly diagnosed patients usually neglect morning hoarseness, idiopathic sore throat and empty belching [2].

AIM

This paper aims to review and present the current state of knowledge on new therapies used to treat reflux esophageal disease.

MATERIALS AND METHODS

The foundation of this work was medical articles and research gathered from the PubMed database. Keywords such as "esophageal reflux treatment", "new technologies in GERD treatment", "innovative reflux treatment methods", were used to facilitate the literature search. In managing gastroesophageal reflux disease, the application of appropriate pharmacological therapy and lifestyle changes for the patient remains key.

REVIEW AND DISCUSSION

PATHOPHYSIOLOGY OF GERD

Gastroesophageal reflux (GER) does not always represent a pathology of the digestive system. It occurs naturally when the esophagus, with the help of peristaltic movements, effectively eliminates retreating acid. A key element in preventing pathological reflux is the lower esophageal sphincter (LES), which acts as a protective barrier against retreating acidic gastric contents. In order for the LES to work effectively, the gastroesoph-

ageal junction must be located in the abdominal cavity, allowing the diaphragm to further enhance its action. An anomaly in the position of the lower esophageal sphincter is a sliding or periaesophageal hernia.

Factors contributing to the development of GERD are primarily abnormalities in the function of the LES. They are caused by the presence of an esophageal hiatus hernia, inefficient esophageal clearance, the presence of an acid pocket and delayed gastric emptying. The use of gravity, which in the standing position helps to remove acid faster, peristalsis, which mechanically removes food contents, and the buffering effect of saliva, whose slightly alkaline pH, close to 6.0, assists in neutralizing acid in the final stage of esophageal cleansing account for a properly functioning esophageal barrier [3].

MAJOR RISK FACTORS FOR ESOPHAGEAL REFLUX

LES DYSFUNCTION

The lower esophageal sphincter (LES) forms a protection that prevents gastric contents from backing up into the esophagus. In gastroesophageal reflux disease (GERD), there is excessive breaking of this barrier and consequent movement of gastric contents into the esophagus. The disease results from weakness of the sphincter, abnormalities in its anatomical structure or impaired esophageal motility [4].

Excessive transient relaxation of the LES along with defective background pressure have been classified as its two main causes of dysfunction. The prevalence of transient increases in abdominal pressures, present, for example, during pushing or blowing the nose, defective neural control, and impaired sphincter muscle have a significant impact on this [5].

Studies indicate that weakness of the LES, occurs in 80% of affected individuals and significantly contributes to the severity of GERD, as manifested by excessive contact between the esophageal mucosa and acid. On endoscopic examination, the condition is visualized as its damage caused by the irritant.

ESOPHAGEAL HERNIA

Esophageal hiatal hernia is the insertion of part of the stomach above the diaphragm through the esophageal hiatus. This situation reshapes the LES, weakening its ability to maintain tightness. Such esophageal threading can lead to inefficiencies in the cooperation of the diaphragm and the LES, which together protect the esophagus from the excessive dumping of gastric contents [6].

ACID POCKET

This is a phenomenon in which hydrochloric acid, proteolytic enzymes, lipases and pepsin accumulate in the lower part of the esophagus. The condition is often seen in patients with gastroesophageal reflux disease (GERD) and those suffering from a hiatal hernia. The presence of an acid pocket is thought to contribute to lower esophageal sphincter (LES) dysfunction and irritation of the mucosal epithelium. Chronic exposure of the esophageal walls to accumulated acidic substances can lead to inflammation, epithelial damage, and more serious consequences such as esophageal stenosis, ulceration, and even precancerous conditions such as Barrett's esophagus [7].

CURRENT TREATMENTS FOR GASTROESOPHAGEAL REFLUX DISEASE

A variety of approaches are used to treat different types of gastroesophageal reflux disease (GERD), tailored to the severity of symptoms and patient response to treatment[8]. Primary approaches include:

GENERAL RECOMMENDATIONS

Lifestyle modifications: Weight reduction in overweight patients, elevation of the bed headboard during sleep, and avoiding eating at least 3 hours before bedtime are recommended [9].

PHARMACOLOGICAL TREATMENT

Proton pump inhibitors (PPIs): Considered most effective in the treatment of GERD, especially in healing mucosal damage and esophagitis [10].

H2 blockers: May be used, but their role is limited.

Topical preparations: Such as Esoxx® (available in Poland), alkaloids and alginates [11] are used to treat episodes and recurrences of reflux for better symptom control.

Prokinetics: These are not recommended because of their lack of efficacy in GERD. In the overlap syndrome of GERD and dyspepsia, the addition of a prokinetic to improve gastric contractility (e.g., itopride) may be considered [12].

SURGICAL TREATMENT – LAPAROSCOPIC FUNDOPLICATION

Laparoscopic fundoplication, a procedure known as Nissen surgery, is recommended as a therapeutic option for selected cases of refractory gastroesophageal reflux disease (GERD) where conventional treatments

are unsuccessful. Qualification for this surgical intervention requires meeting certain clinical criteria, which include persistent reflux symptoms despite pharmacotherapy, the presence of Barrett's esophagus, vitamin B12 deficiency and multiple erosions and chronic gastrointestinal bleeding. The fundoplication procedure involves laparoscopically wrapping the upper part of the stomach around the lower esophagus, which increases pressure on the lower esophageal sphincter and significantly reduces the frequency of reflux episodes. Evaluating the effectiveness of this method requires preoperative testing, including esophageal manometry and pH-metry, to confirm the diagnosis of GERD and assess the functionality of the lower esophageal sphincter.

EPISODIC REFLUX TREATMENT

For episodic reflux that occurs less than twice a week and does not reduce the patient's quality of life, outpatient treatment is recommended. A number of preparations can be used to relieve reflux symptoms. Esoxx® One, which contains hyaluronic acid and chondroitin sulfate, forms a protective barrier on the esophageal mucosa, which contributes to the relief of symptoms associated with reflux esophagitis. It is recommended to be taken once a day, optimally before the main meal, to maximize protection of the esophageal wall from the aggressive effects of gastric acid.

Histamine H2 receptor antagonists, such as ranitidine or famotidine, effectively reduce gastric acid synthesis by inhibiting the action of histamine. They are recommended to be taken twice daily, before breakfast or dinner, for optimal control of reflux symptomatology and prevention of complications.

Innovative therapies emerging in the treatment of gastroesophageal reflux disease

Current research into improving the treatment of gastroesophageal reflux disease focuses on, among other things: the use of P-CABs – potassium-dependent proton pump blockers, the development of endoscopic techniques, lower esophageal sphincter electrostimulation, TRPV1 receptor inhibition, inhibition of nuclear factor NF-κB activation, and the use of bile acid-binding agents in a new formulation.

POTASSIUM-COMPETITIVE ACID BLOCKERS (P-CABS)

Effective proton pump inhibition is the cornerstone of GERD therapy. Widely used PPIs reduce the need for surgery, but are not always fully effective. 40-55% of patients taking the drug show partial resistance or intolerance to them. Potassium-competent acid blockers (P-CABs) offer an alternative, bringing rapid and long-lasting control of acid secretion and can protect the esophageal mucosa. As a primary or adjunct treatment, P-CABs can provide significant benefits for patients who do not respond to PPIs, especially in relieving reflux symptoms. The main differences between PPIs and P-CABs stem from their mechanism of action and their effectiveness. PPIs show effect only after repeated use, as they require activation and bind irreversibly to the proton pump showing effect after repeated administration and when taken on an empty stomach. P-CABs act directly and reversibly, providing rapid and sustained efficacy regardless of the time of intake, making them more effective in some aspects, especially in controlling nocturnal acid secretion [13]. Tegoprazan is a P-CAB drug that has been successful in GERD therapies conducted in Japan [14]. This drug is not yet in widespread use, due to concerns about the following ailments: hypergastrinemia and hypochlorhydria. The first refers to elevated gastrin levels in the blood. The second refers to a complete lack of hydrochloric acid in the stomach. Nonetheless, studies are continually being conducted in many Asian countries in patients with erosive reflux disease. In addition, given the high efficacy of vonoprazan in triple therapy against Helicobacter pylori and the disease burden associated with this infection, such as gastric cancer, the indications for this drug are expected to be further expanded [15].

ELECTRICAL STIMULATION IN GASTROESOPHAGEAL REFLUX DISEASE

Electrical stimulation of the lower esophageal sphincter (LES) is a novel method of treating GERD, especially for patients insufficiently responsive to medication. The method involves implanting electrodes that, by emitting low electrical pulses, enhance LES function and prevent reflux. In a two-year randomized trial of patients who did not respond adequately to treatment with proton pump inhibitors (PPIs), promising results were observed. At the end of the study, the median score on the GERD-related quality of life scale (GERD-HRQL) decreased from an initial 23.5 points to 0 points, indicating complete elimination of symptoms in most participants ($p < 0.001$). In addition, the median time that esophageal pH levels remained below 4 decreased from 10% to 4%, indicating a significant improvement in control of gastric acidity ($p < 0.001$). More importantly, 76% of patients (16 out of 21) were able to stop taking PPIs altogether. No serious side effects associated with the therapy were reported [16, 17]. This approach shows

promise in improving GERD symptoms and patients' quality of life, offering an alternative to traditional treatments such as pharmacotherapy or surgery.

WIRELESSLY POWERED DEVICES IMPLANTED ENDOSCOPICALLY INTO THE SUBMUCOSA OF THE LOWER ESOPHAGEAL SPHINCTER

Following the positive results of studies on electrical stimulation of the lower esophageal sphincter, it was decided to develop a new type of therapy for GERD. It focuses on an implantable, miniature, battery-free device that is implanted into the submucosa of the esophagus, providing its electrical stimulation when appropriate. The goal is to reduce the size and weight of the device while providing effective therapy. The device is powered wirelessly, which minimizes risk and increases safety. In studies conducted on animal models using electrical stimulation of the lower esophageal sphincter (LES) at a frequency of 20Hz and a pulse width of 3ms, effective prevention of gastroesophageal reflux was observed. Subsequently, a human study was conducted, which showed that both a high frequency of 20Hz, with a pulse width of 200μs, and a low frequency in the form of 6 cycles per minute, with a pulse width of 375ms lead to an increase in LES pressure without affecting its ability to relax during swallowing. High-frequency stimulation has also been found to be more energy efficient, meaning the device can run longer without needing to be recharged, offering long and uninterrupted therapy. [18]

IW-3718

IW-3718 is a formulation with a novel therapeutic approach belonging to the group of bile acid sequestrants, such as colesewelam. Its primary action is to bind bile acids in the stomach, helping to reduce their irritating effect on the esophageal mucosa. The drug has been on the market for many years, but the current innovation concerns a new method of releasing the active substance. Its gastric retention technology, known as Acuform, which is also used in other drugs such as gabapentin, allows the drug to be retained in the stomach for an extended period of release and action. This is particularly beneficial for bile acid sequestrants like IW-3718, allowing continuous binding of bile acids for hours, reducing their potentially harmful effects on the esophagus and other parts of the gastrointestinal tract. The results of the IW-3718 study showed a significant improvement in the quality of life of patients with GERD, as measured by the GERD-HRQL scale, with a median reduction in symptoms of 50% from baseline, which was significantly better compared to the placebo group. In addition, more than 60% of patients treated with IW-3718 experienced at least a 50% reduction in heartburn frequency and severity, compared to about 30% in the placebo group. Particularly impressive were the results regarding the reduction of nocturnal reflux episodes, with about 70% of patients reporting less than one episode per week, a significant improvement over placebo. The highest doses of the drug tested significantly reduced GERD symptoms in study patients. The therapy was not associated with significant side effects, except for occasional cases of constipation, justifying its use as an additional option to PPI therapy. [19]

INHIBITION OF NUCLEAR FACTOR NF-κB ACTIVATION

According to recent studies, inhibiting NF-κB activation may block GERD damage to the esophageal mucosal barrier. Gastroesophageal reflux disease is complex and may be associated with NF-κB activation, which contributes to inflammation and epithelial barrier damage. Inhibiting nuclear factor kappa b (NF-κB) activation in the treatment of gastroesophageal reflux disease (GERD) is a promising approach that may reduce inflammation and protect the esophageal mucosal barrier from further damage. Preclinical studies have shown that NF-κB inhibitors can effectively reduce the expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and IL-8, which are released in response to gastroesophageal reflux. These inflammatory factors are known to contribute to damage to the esophageal epithelial barrier and exacerbate GERD symptoms. For example, in one study conducted on animal models with gastroesophageal reflux disease, the use of specific NF-κB inhibitors significantly reduced esophageal mucosal barrier damage and reduced inflammation. In this study, after the application of NF-κB inhibitors, a significant increase in transepithelial electrical resistance was observed, implying an improvement in epithelial barrier integrity. In addition, the use of NF-κB inhibitors resulted in a decrease in intercellular spaces and an increase in desmosome density, further confirming their potential in restoring damaged barrier function. However, further research is still needed to fully understand the role of NF-κB in GERD and to develop safe treatments based on this knowledge [20].

TRPV1 RECEPTOR REGULATION

Studies have shown that Esophageal Epithelial Cells (EECs), responsible for directly confronting refluxed acid, show increased expression of TRPV1 (Transient Receptor Potential Vanilloid 1), a receptor sensitive to pain and heat. Increased expression of this receptor exacerbates esoph-

ageal discomfort, which is crucial in the development of esophagitis. An interesting finding is that menthol, the main active ingredient in peppermint, shows the ability to alleviate this discomfort by interacting with TRPV1. In studies conducted on a mouse model of gastric reflux, it was observed that acid stimulation leads to increased expression of TRPV1 in the EEC, as well as increased activity of this channel. Application of menthol significantly reduces acid-induced calcium ion influx, leading to decreased TRPV1 expression and inhibition of hyperplasia in these cells. These effects suggest the potential use of menthol in the treatment of gastric reflux by modulating the activity of TRPV1 in the EEC, which may represent a new strategy for alleviating gastroesophageal reflux symptoms [21].

CONCLUSIONS

Much remains to be done and researched in the treatment of GERD despite significant progress over the past few years. Proton pump inhibitors so invaluable in the treatment of reflux and GERD are not without their drawbacks. Already used on a large scale in Japan, P-CABs are beginning to have their first positive effects as replacements for PPIs. Advances in the technology of miniaturized electrostimulating devices are significant and may offer a revolution comparable to the development of cardiac pacemakers. Bile acid sequestrants such as IW-3718, and drugs that regulate the corresponding mucosal receptors may prove to be a new mainstay of GERD treatment in the near future.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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