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Alginate as an Efficacious Treatment for GERD Patients: A Literature Review

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Abstract

Gastroesophageal reflux disease (GERD) is a medical condition defined by the retrograde flow of gastric contents into the esophagus, leading to various symptoms. The principal therapy for GERD consists of proton pump inhibitors (PPIs). Nevertheless, PPIs demonstrate reduced effectiveness in patients with non-erosive GERD or unusual symptoms. Alginates operate by forming a gel "raft" that floats on the gastric contents, serving as a physical barrier against reflux. Multiple studies demonstrate that alginate is more effective than antacids in alleviating GERD symptoms and has a longer duration of action.

Keywords: Alginate, GERD, reflux

Abstrak

Penyakit refluks gastroesofagus (GERD) adalah kondisi medis yang didefinisikan oleh aliran balik isi lambung ke kerongkongan, yang menyebabkan berbagai gejala. Terapi utama untuk GERD terdiri dari inhibitor pompa proton (PPI). Namun demikian, PPI menunjukkan efektivitas yang berkurang pada pasien dengan GERD non-erosif atau gejala yang tidak biasa. Alginat bekerja dengan membentuk "rakit" gel yang mengapung di atas isi lambung, berfungsi sebagai penghalang fisik terhadap refluks.Beberapa studi menunjukkan bahwa alginat lebih efektif daripada antasida dalam meredakan gejala GERD dan memiliki durasi aksi yang lebih lama.

Keywords*: Alginat, GERD, refluks*

I. INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common digestive disorders worldwide, with a rising prevalence. Gastroesophageal reflux disease (GERD) results from the reflux of stomach acid into the esophagus, leading to a range of symptoms from mild to severe. This condition can diminish patients' quality of life, obstruct daily activities, and increase the risk of serious outcomes, such as esophagitis, esophageal stricture, and esophageal cancer. The principal risk factors for GERD include obesity, tobacco consumption, alcohol intake, and inadequate dietary practices.[1–3]

As GERD prevalence increases, many diagnostic and therapeutic strategies have been developed to effectively manage this condition. The diagnosis of GERD often depends on clinical history, response to empirical treatment, and further assessments including endoscopy and esophageal pH monitoring when necessary. The two principal forms of GERD frequently encountered are erosive GERD and non-erosive reflux disease (NERD). In patients with erosive gastroesophageal reflux disease (GERD), proton pump inhibitors (PPIs) are often quite effective as a treatment. In patients with NERD, PPI therapy often fails to yield satisfactory results.[2,4]

The therapy options for GERD include lifestyle modifications, pharmacological interventions, and surgical procedures for more severe cases. Alterations in lifestyle, such as weight loss, avoidance of trigger foods, and adjustment of sleep habits, might mitigate GERD symptoms. The conventional pharmaceutical interventions generally utilized comprise antacids, histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs). Although PPIs serve as the principal intervention for suppressing gastric acid secretion, some patients continue to encounter recurring symptoms after discontinuing medication.[4,5]

II. GASTROESOPHAGEAL REFLUX DISEASE (GERD)

PATHOPHYSIOLOGY OF GERD

Gastroesophageal reflux disease (GERD) is one of the most common digestive disorders worldwide, with a rising prevalence. Gastroesophageal reflux disease (GERD) occurs due to the reflux of stomach acid into the esophagus, leading to a range of symptoms from mild to severe. This condition can diminish patients' quality of life, obstruct daily activities, and increase the likelihood of serious complications, such as esophagitis, esophageal stricture, and esophageal cancer. The principal risk factors for GERD include obesity, smoking, alcohol consumption, and poor dietary practices.[6,7]

GERD arises from a disparity between protective mechanisms and harmful agents, between valve functions and the transdiaphragmatic pressure gradient, and is also associated with the impacts of pepsin and bile. Mucosal inflammation arises from the impairment of tight junction proteins in the esophageal epithelium, resulting in increased paracellular permeability and expanded intercellular spaces. The widening of intercellular spaces permits stomach acid, bile, and pepsin to penetrate the deeper basal layer of the esophagus mucosa, leading to esophageal damage through inflammatory mediators. This inflammation may impact nociceptors, provoking symptoms and dysmotility. This clarifies the manifestations of GERD without mucosal damage (non-erosive variety).[8–10]

Reflux commonly occurs through four mechanisms: transient lower esophageal sphincter relaxations (tLESR), reduced pressure of the lower esophageal sphincter (LES), LES relaxation after swallowing, and

straining during periods of decreased LES pressure. The processes that prevent reflux vary according to the physiological and anatomical state of the esophagogastric junction. The crural diaphragm may play a crucial role in increased intra-abdominal pressure and tension. In contrast, basal lower esophageal sphincter (LES) pressure may be vital in the supine position and postprandial state, as a hypotensive LES could result in heightened reflux in patients during overnight and post-meal intervals. Disruption of any of these protective mechanisms may result in an elevated incidence of reflux episodes and improper esophageal reflux exposure.[7,11,12]

Compelling data demonstrates that tLESR is the primary reflux mechanism during periods of normal LES pressure (>10 mmHg). Transient lower esophageal sphincter (LES) relaxation occurs independently during swallowing, is not associated with peristalsis, requires diaphragm inhibition, and lasts longer than the LES relaxation generated by swallowing (exceeding 10 seconds). Twenty-four The principal catalyst for tLESR is the distension of the proximal stomach, which stimulates the intraganglionic lamellar endings situated at the vagal afferent receptor terminals. These fibers project to the nucleus tractus solitarii in the brainstem and later to the dorsal motor nuclei of the vagus nerve. The neurons of the dorsal motor nucleus innervate inhibitory neurons in the myenteric plexus of the distal esophagus, resulting in a coordinated motor response that includes lower esophageal sphincter (LES) relaxation through a reflex inhibition mechanism, longitudinal muscle contractions that relieve obstruction at the esophagogastric junction via LES relaxation enabled by tension and repositioning of the LES above the crura, inhibition of the crural diaphragm, and contraction of the costal diaphragm as the final components of the tLESR reflex. A diverse array of neurotransmitters and receptors participates in the regulation and modulation of tLESR, including gamma-aminobutyric acid, which activates gamma-aminobutyric acid-B receptors in the brainstem and vagal afferents; glutamate, which interacts with metabotropic glutamate-5 receptors in the brainstem; and endocannabinoids, which engage type 1 cannabinoid receptors in the brain.[13–15]

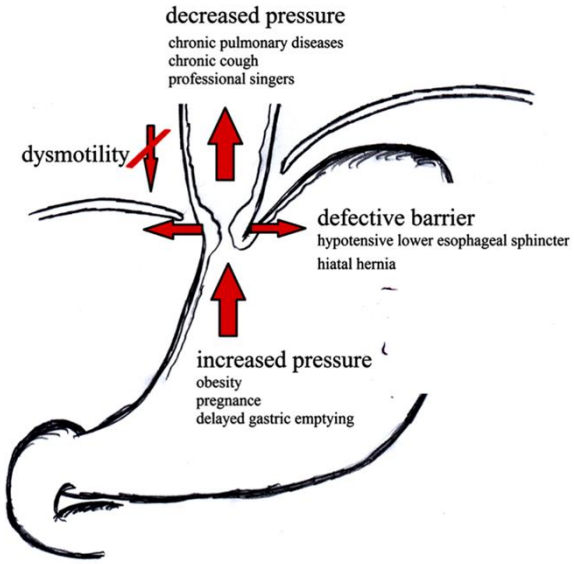

FIGURE 1. PHATOPHYSIOLOGY OF GERD[11]

CLINICAL SYMPTOMS OF GERD

Gastroesophageal reflux disease (GERD) is frequently diagnosed through classic symptoms and the efficacy of acid suppression therapy. Heartburn, with or without regurgitation, generally raises suspicion of GERD, especially if symptoms worsen after meals or when lying down. Commencing treatment with H2 receptor antagonists or proton pump inhibitors (PPIs) that subsequently alleviates symptoms is considered a diagnostic criterion for GERD. In patients who demonstrate a favorable response to empirical treatment and do not present alarm features or symptoms, further investigation is unwarranted.

In certain patients, reflux symptoms may persist after high-dose proton pump inhibitor medication. Additional evaluations may be necessary to investigate alternate causes and to screen for possible GERD issues. The severity of reflux symptoms does not

necessarily correlate with the degree of mucosal damage. The principal diagnostic method utilized for evaluating GERD and its potential complications is upper gastrointestinal endoscopy, commonly referred to as esophagogastroduodenoscopy (EGD). The principal benefit of endoscopy is the direct visualization of the esophageal mucosa. This evaluation assists in recognizing complications of GERD, such as esophagitis, strictures, and Barrett's esophagus. The Los Angeles classification is an endoscopic evaluation system for the severity of GERD, categorized from A to D, with D indicating the most severe illness.[2,16,17]

MANAGEMENT OF GERD

With the rising incidence of GERD, numerous diagnostic and therapeutic approaches have been established to manage this condition efficiently. The diagnosis of GERD often relies on clinical history, response to empirical treatment, and further evaluations such as endoscopy and esophageal pH monitoring when warranted. The two primary types of GERD commonly observed are erosive GERD and non-erosive reflux disease (NERD). Proton pump inhibitors (PPIs) are typically highly successful in people with erosive gastroesophageal reflux disease (GERD). In patients with NERD, PPI medication frequently fails to produce desirable outcomes.[18,19]

Therapeutic choices for GERD encompass lifestyle adjustments, pharmacotherapy, and surgical procedures for more severe instances. Lifestyle adjustments, including weight loss, avoidance of trigger foods, and regulation of sleep patterns, can alleviate GERD symptoms. The standard pharmacological treatments typically employed include antacids, histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs). Despite PPIs being the primary treatment successful in suppressing stomach acid secretion, certain individuals persist in experiencing recurrent symptoms following the cessation of therapy.[19]

TABLE 1. MANAGEMENT OF GERD[19]

Lifestyle modification · Tobacco cessation · Limiting alcohol · Weight loss · Raising the head of the bed while sleeping · Avoid eating late at night · Reduce acidic or refluxogenic foods (chocolate; fatty foods; mint; citrus; spicy foods) and drinks (coffee; caffeine; carbonation).
Pharmacological Therapy · Antacids (calcium, aluminum, magnesium, sodium salts) · Alginato · Histamine-2 receptor antagonist · Proton pump inhibitor · Prokinetic agent inhibitor TLSRsc

III. ALGINATE AS TREATMENT FOR GERD

SOURCE OF ALGINIC ACID

Alginate is a natural polymer extracted from the cell walls of brown algae (Phaeophyceae), especially from species such as Laminaria, Macrocystis, and Ascophyllum. These brown algae are generally found in frigid maritime habitats and are harvested for many industrial applications, including pharmaceuticals, food, and textiles. The alginate extraction method is dissolving algae in an alkaline solution, like sodium hydroxide, to produce water-soluble alginate salts.[20]

Upon extraction, alginate is frequently purified and converted into various salt forms, such as sodium alginate, calcium alginate, or potassium alginate, depending on its intended application. Sodium alginate is the primary kind employed in pharmaceutical formulations due to its superior solubility in water and its ability to produce stable gels when interacting with calcium ions or gastric acid. Concerns

regarding the sustainability of alginate sources have emerged within the pharmaceutical industry, as production reliant on the harvesting of wild algae may negatively impact marine ecosystems. Recent studies, therefore, focus on more sustainable and efficient methods for cultivating brown algae to meet industrial requirements while reducing environmental impact.[20,21]

CHEMICAL COMPOUND ALGINATE

Alginates are linear polymers composed of mannuronic acid (M) and guluronic acid (G), arranged in various configurations, yielding M blocks, G blocks, or mixed MG blocks. The content and ratio of these two types of acids determine the physical and chemical properties of alginate, including gelation capacity, viscosity, and interaction with calcium ions. Sodium alginate is commonly employed in pharmaceutical formulations owing to its water-solubility and ability to build a protective barrier on the gastric lining. Sodium alginate interacts with hydrogen ions in stomach acid, leading to the production of a gel that can float over the stomach contents, so creating a mechanical barrier against acid reflux. Besides its application in the pharmaceutical industry, alginate is widely employed in the food sector as a thickening and stabilizing ingredient, as well as in biomedical technology for pharmaceutical gel formulations and tissue engineering. Its biocompatibility and non-toxicity make it an ideal material for various therapeutic applications. [21]

HOW ALGINATES WORK IN GERD THERAPY

Alginat is a medicine that functions by modifying the postprandial gastric acid pocket. The acid pocket is a transient area of very acidic gastric fluid lacking buffering capacity that forms underneath the esophagogastric junction after eating. Conventional factors, such as transient lower esophageal sphincter relaxation (TLSR) and hiatal hernia, may exacerbate GERD by increasing the acid pocket. Alginates form a frothy gel like a raft that floats over the stomach contents, and this gel-like barrier prevents acid reflux in GERD.[21,22]

Alginates exhibit a unique, nonsystemic, physical, non-pharmacological mechanism of action, necessitating the careful selection of the appropriate alginate to ensure efficacy in various critical areas, including the prevention of gastric reflux, postprandial reflux, inhibition of pepsin and bile acids, and topical protection. The G-block configuration of alginate improves gel strength, promoting a reaction between sodium alginate and gastric acid, resulting in a low-density viscous gel that floats in the stomach, thereby forming a physical barrier that protects the delicate esophageal mucosa and airways from gastric reflux. The physical barrier formed by alginate is essential for removing or replacing the acid pockets observed in GERD patients. Acid pockets form at the gastroesophageal junction after meals that are too acidic and lacking in buffers, and they possess pathophysiological relevance in GERD. An effective alginate raft can enclose the acid pouch, reducing or possibly eradicating postprandial acid reflux.[20,22,23]

Moreover, alginate can neutralize pepsin and bile acids from gastric reflux, thereby limiting their diffusion and particularly affecting the enzymatic activity of pepsin. Alginates are crucial for the topical protection of the sensitive esophageal mucosa, reducing the risk of irritation caused by gastric reflux components, such as acid, pepsin, and bile acids. A well formulated sodium alginate suspension can produce a viscous coating that adheres to the esophageal mucosa, exhibiting bioadhesive characteristics in this area, which is more susceptible to damage from gastric reflux components.[21,24,25]

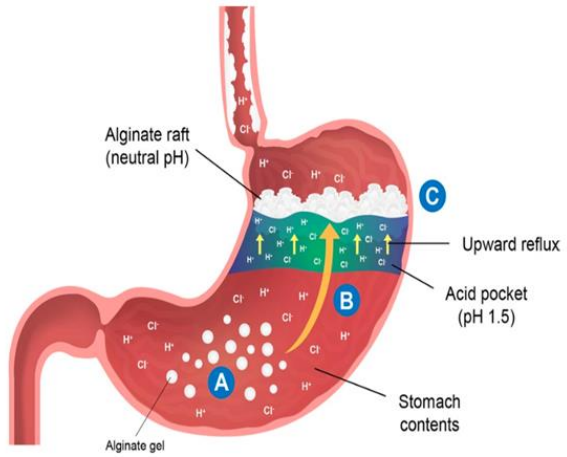

FIGURE 2. HOW ALGINATES WORK IN GERD THERAPY[21]

In vitro and in vivo studies demonstrate that the therapeutic effects of alginate occur more swiftly (within 1 hour of therapy) compared to proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RAs). Alginate-based formulations are more effective than antacids in regulating postprandial esophageal acid exposure and alleviating reflux symptoms, including heartburn, regurgitation, vomiting, and belching, with sustained efficacy. Sixty-five alginate-based formulations are equivalent to omeprazole in delivering heartburn-free durations for patients experiencing moderate episodic heartburn.[22,26]

The action mechanism of alginate commences with its interaction with stomach acid, producing a gel-like substance with a neutral pH (A); subsequently, the sodium bicarbonate in the formulation releases carbon dioxide gas, which is contained within the gel. The encapsulated carbon dioxide gas allows the gel to rise to the surface of the gastric contents, forming a raft structure that acts as a barrier above the gastric pouch, preventing upward reflux.(Figure 2).[21]

THE EFFICACY OF ALGINATES IN GERD TREATMENT

Multiple clinical research demonstrate that alginate is more effective in alleviating GERD symptoms than antacids and exhibits a more advantageous safety profile compared to PPIs. Leiman et al. (2017) found that individuals using alginate saw a more expedited alleviation of symptoms compared to those just using antacids. The amalgamation of alginate with PPI has exhibited enhanced effectiveness relative to PPI monotherapy in mitigating postprandial acid reflux symptoms. Rohof et al. (2013) conducted a study indicating that alginate is superior to traditional antacids in mitigating esophageal acid exposure, especially in patients with non-erosive GERD. Alginates also alleviate nocturnal GERD symptoms, which are often insufficiently managed by PPIs. Alginate forms a protective barrier over gastric contents, reducing the risk of reflux in supine patients, so improving the sleep quality of those with GERD.[4,23]

Multiple studies have evaluated the efficacy of alginate therapy for GERD relative to antacids, proton pump inhibitors, histamine receptor antagonists, or placebo. Alginate medicine shown superior efficacy in symptom management compared to placebo or antacid treatment. Leiman et al.'s 2017 systematic review and meta-analysis demonstrated that findings from current clinical research validate the effectiveness of alginate in alleviating GERD symptoms. Alginates are more effective than placebo or antacids in mitigating GERD symptoms. The 2020 experiment conducted by Zhao et al. similarly demonstrated that alginate is more efficacious than placebo or antacids in improving GERD outcomes. However, existing data regarding the efficacy of alginate-based formulations in comparison to PPIs, or the effects of combining alginate with PPIs, remains disputed, suggesting no substantial difference between the two therapies. The likelihood of side effects linked to alginate is comparable to that of a placebo or proton pump inhibitor (PPI).[4,27]

In their 2006 study, Giannini et al. investigated the effects of sodium alginate

and anhydrous magaldrate antacids in individuals with GERD, revealing that the onset of action within < 30 minutes was significantly more prevalent in the alginate group (49.4% vs. 40.4%; P = 0.0074). The sodium alginate group exhibited a tendency for extended action duration (median: 16.5 vs. 12.7 hours) and a more significant difference in symptom intensity (median: 40.0 vs. 31.0). A total remission of symptoms was noted in 81.6% of the sodium alginate cohort and 73.9% of the magaldrate cohort. Thus, sodium alginate is found to be more beneficial than magaldrate in alleviating GERD symptoms, demonstrating a tendency for sustained action and improved efficacy.[28]

The 2012 study by Pouchain et al. compared Gaviscon® (containing sodium alginate and sodium bicarbonate) with omeprazole, indicating that the average onset time for a heartburn-free period within the first 24 hours post-initial dose was 2.0 (± 2.2) days for Gaviscon® and 2.0 (± 2.3) days for omeprazole (p = 0.93); however, the average number of heartburn-free days by the 7th day was significantly higher in the omeprazole group (p = 0.02). The total effectiveness of pain relief with Gaviscon® was slightly greater than that of omeprazole (p = 0.049). Tolerance and safety were adequate and equivalent in both groups. Therefore, it can be concluded that Gaviscon® is equally effective as omeprazole in delivering 24-hour relief from heartburn in instances of moderate episodic heartburn and functions as a viable alternative treatment for moderate GERD in primary care environments.[29]

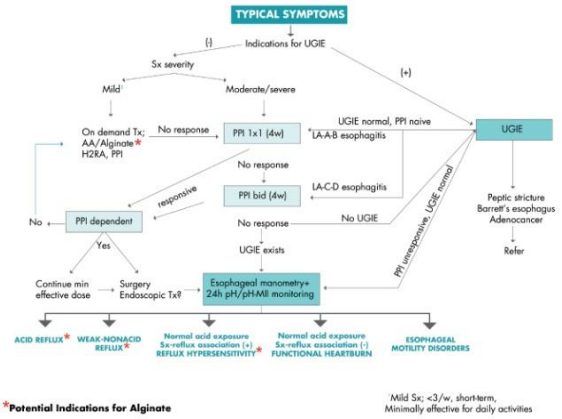

FIGURE 3. ALGORITHM AND INDICATIONS FOR ALGINATES IN GERD TREATMENT[21]

ADVERSE EFFECTS OF ALGINATES

Alginate often demonstrates a positive safety profile with minimal side effects. The most commonly reported adverse effects encompass severe gastrointestinal disturbances, including bloating and a feeling of fullness in the stomach. These effects are generally temporary and can be alleviated with suitable adjustments in dosage or consumption practices. Patients may occasionally demonstrate allergic reactions to alginate components; however, such occurrences are highly rare. Hypersensitivity reactions may present as skin rashes, itching, or breathing difficulties, requiring discontinuation of use and subsequent medical assessment.[21,29]
Moreover, the extended use of alginate requires assessment, especially in patients with renal disorders who may demonstrate sensitivity to the sodium or calcium ion levels found in specific alginate formulations. Therefore, medical oversight is recommended for patients with particular health issues using alginate as a prolonged therapy for GERD. Alginate, noted for its favorable safety profile and unique mode of action, is an effective therapeutic choice for GERD, usable as both monotherapy and adjuvant therapy for patients with chronic symptoms.[30]

IV. CONCLUSION

Alginat is a medicine that functions by modifying the postprandial gastric acid pocket. The acid pocket is a transient area of highly acidic gastric fluid lacking a buffer, situated underneath the esophagogastric junction following eating. Alginates are crucial for the topical safeguarding of the sensitive esophageal mucosa, reducing the danger of irritation caused by gastric reflux components, such as acid, pepsin, and bile acids. Alginate-based formulations surpass antacids and omeprazole in controlling postprandial esophageal acid exposure and alleviating reflux symptoms, including heartburn, regurgitation, vomiting, and belching, providing extended efficacy and promoting heartburn-free intervals in patients with moderate episodic heartburn.

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