Review Article

Pathophysiology and Clinical Applications of Gastro-Esophageal Reflux Disease

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Abstract

Gastro-esophageal reflux disease is a persistent affliction of gastrointestinal tract upper part with the growing prevalence throughout the world. By the time there has been an increase in the cognizance of its pathophysiology, clinical presentation and management. The disease could be identified easily by the symptoms. Many of the risk components are involved in the occurrence of disease including medications, obesity, pregnancy and asthma. It can be diagnosed by a number of procedures like manometry, ambulatory pH monitoring , endoscopy and radiology. Although different drugs are being utilized to treat GERD but PPIs (Proton pump inhibitors) have shown remarkable achievement in the curing the disease. When proton pump inhibitors are utilized for the extended period several of the safety ways are being explored to avoid any side effect. There has been a debate over the use of long term medications and surgery for quite a long time. Although both surgery and long term usage of PPI's have proven effective in managing the disease.

Keywords: GERD; Pathophysiology; Diagnosis and Treatment

1. Introduction

GERD is an incessant digestive disease. It occurs when acid or stomach content circulates backward into the esophagus. The typical symptoms include heartburn, regurgitation, disturbances in sleep, pain in chest, hoarseness, cough, asthma, and dental erosions. The incompetence of the anti- reflux barrier at the esophago-gastric junction is

the principal reason of GERD. Salivary production and peristalsis promote esophageal clearance. GERD may result in esophagitis, barrette's esophagus, esophageal cancer and adenocarcinoma. Gastro-esophageal reflux disease effect 3-7% of U.S population each year [1]. About 2-3 times it is more pervasive in men than women [2]. It is considered clinically significant if the manifestations arise twice weekly. 10-30% of the population in North America and Europe suffers from the symptoms at least once weekly [3, 4]. 34-89% of asthmatic patients irrespective of the bronchodilators use have gastro-esophageal disease [5]. Occurrence of disease is related to the changes in sleep pattern, diet and physical activity [6]. It is scarcely found in Africa [7]. Gastro-esophageal disease has been divided into two groups upon endoscopy findings with the mucosal damage of the esophagus (erosive esophagitis, and Barrett's esophagus) and in the absence of damage in the mucosa (non- erosive reflux disease termed as NERD). Upon 24 hour evaluation of pH, NERD is subdivided into three types as in type 1, an abnormal time for acid exposure in patients is recorded similar to the patients of erosive esophagitis [8]. Type 2 is referred as hypertensive esophagus as there is repeated reflux along with normal time of acid exposure [9, 10]. In type 3, patients have symptoms of reflux with balanced pH studies [11]. The occurrence of symptoms does not vary between Caucasians and African Americans in U.S [12]. Increased prevalence of esophagitis is related to the age and sex [13-15]. As compared to normal BMI, obese individuals are 2.5 times more susceptible to it [16]. The risk of GERD becomes greater due to presence of plethora belly fat creating pressure on the stomach, the build-out of hiatal hernia causing the flow of acid in backward direction or hormonal changes (increase in estrogen exposure). Risk factors for GERD and esophagitis are alcohol use and hiatus hernia [17-19]. The size and presence of hiatus hernia are related with grievous damage of mucosa, increased acid exposure, defective peristalsis and incompetence of inferior esophageal sphincter [20]. In accordance with the studies in Japan, alcohol use and cigarette smoking were the chief causes of gastro-esophageal reflux disease [21]. Whereas in Nigeria, use of cola and coffee by the medical student for the purpose of staying awake during examinations resulted in GERD. By the use of medications (calcium channel blockers, anti-cholinergic, theophylline, benzodiazepines, dopamine, nicotine, nitrates, progesterone, estrogen, glucagon and prostaglandins) and food (coffee, alcohol, chocolate, fatty meals), it is reported as it result in the transient lower esophageal sphincter relaxation. Mostly patients with connective tissue disease (scleroderma) and chronic obstructive airway disease developed it [22]. The hormonal variations during the period of pregnancy cause the lower esophageal muscles to relax more frequently causing acid reflux particularly while lying down. During second and third trimester while the fetus is growing, the uterus expands and stomach is under more pressure, which causes food contents and acid to flush back towards esophagus [23].

2. Pathophysiology

Lower sphincter of the esophagus is 3-4 cm long and composed of smooth muscles present at the distal portion of esophagus [24]. Reflux is prevented by this sphincter that generates a high pressure in between stomach and esophagus. Reflux is produced normally by the relaxation of lower sphincter. Transient relaxation occurs more frequently in GERD patients. High calcium influx mediated by the cholinergic neuron helps the sphincter to maintain higher tone than other structures. Resting sphincter has high intracellular calcium levels as compared to non-sphincteric esophageal muscles. Due to hiatus hernia, there is decreased pressure in the lower sphincter as well as decreased peristalsis in distal esophagus resulting in reduced clearance of refluxed acid. Delayed gastric emptying

is also a cause as it increases the time of the gastric contents that stay there for a long time, thus increasing transient relaxations of lower sphincter muscles along with the gastric acid secretions. During sleep the reflux episodes increases because of reduced swallowing of saliva, which neutralizes the gastric acid [25].

3. Signs and symptoms

A common symptom is heartburn, which is a sensation of burning in the middle of the abdomen, middle of chest and behind breastbone and. Other common symptoms in adults include bad breath, nausea, pain in stomach, respiratory problems, painful swallowing, wearing away of teeth and vomiting [26]. In case of pediatric patients crying, loss of appetite, bradycardia, vomiting, wheezing, stridor, recurrent pneumonitis, chest pain or abdominal pain, hoarseness, sore throat, chronic cough, water bash, Sandifer syndrome, bloating and hiccups can be observed [27].

4. Diagnosis

In Accordance with The Society of American Gastrointestinal Endoscopic Surgeon, GERD can be confirmed by the existence of mucosal break in endoscopy, peptic strictures and Barrett's esophagus [28]. Reflux syndrome includes heartburn and regurgitation that are diagnosed easily due to these characteristic symptoms [29, 30]. Diagnosis of erosive esophagitis by radiology has low specificity and sensitivity therefore, the choice of investigation is endoscopy. The most frequent Savary-Miller grading system is used having various grades [31]. Grade 1 is characterized by one or multiple erosions on a single fold with exudative or non- exudative erosions. Grade 2 consists of multiple erosions affecting many folds with confluent erosions. Grade 3 comprises of multiple circumferential erosions. Grade 4 consists of ulcer, stenosis and esophageal shortening and Grade 5 with Barrett's epithelium (columnar metaplasia in circular or non- circular extensions). A to D classification of Los Angeles grades is more recent where grade A has single or multiple breaks in mucosa none of them longer than 5mm and not a single one extending between the top of mucosal folds. Grade B with one or many mucosal breaks longer than 5mm, not extending between the top of two mucosal folds. In Grade C, mucosal breaks extend in between 2 or more folds of mucosa. Grade D has mucosal breaks which involves more than or equal to 75 percent of the mucosal circumference [32]. In NERD different histological lesions have been discussed that differentiated it from GERD like dilation of intercellular spaces (DIS) [33], basal cell hyperplasia [34], papilla elongation [35], intraepithelial eosinophils [36] and neutrophils [37]. GERD is diagnosed by biopsy. During a biopsy, a tiny apparatus is passed that removes a small piece of esophageal lining which is further analyzed in pathology lab in order to confirm the underlying cause as cancer of esophagus. Barium swallow radiograph is a painless procedure that is useful for evaluating patients with dysphagia where a patient swallows a barium solution and then X-rays of esophagus are taken. It is not a useful test in those patients who had GERD because the patients had little or no damage to the esophageal lining and not used in routine diagnosis. The X-rays show ulcers and strictures. Only 1 out of every 3 patients with GERD have changes in esophagus being visible on X-rays. According to the American Gastroenterological Association short term PPIs treatment is carried out to check out the symptomatic relief in patients. GERD is suggested by the significant improvement of the symptoms. The test may have either false positive or false negative results [38]. Motor esophageal abnormalities are identified by manometry. The function and peristaltic activitiy of the lower sphincter of esophagus and esophagus are analyzed by manometry before the

anti-reflux surgery. Dysphagia is diagnosed by manometry when no mechanical obstruction is determined. Abnormal exposure of the esophagus to acid by manometry localizes LES for subsequencial monitoring of pH and indicated for the preoperative assessment of anti-reflux surgery to exclude achalasia [39]. Ambulatory pH monitoring is the best way by which patients of NERD not responding to medications are evaluated. Ambulatory esophageal pH monitoring monitors the duration when the intra-esophageal pH stays less than 4 [40]. All types of reflux (weakly acidic, acidic and weakly basic) can be detected by multichannel intraluminal impedance monitoring with a pH sensor (MII-pH). Resistance in electrical conductivity of esophageal content is measured that detects any change in esophageal pH because of liquid presence or gas reflux [41, 42]. Ambulatory testing could be carried out by radiotelemetry capsule monitoring to measure acid and non- acid reflux by attaching to esophageal mucosa a capsule [43]. Esophageal impedance monitoring is performed mostly in combination with manometry to obtain complete information of esophagus functions using a manometry tubes along with electrodes that are placed at distinct points along the length measuring the rate at which gases and liquids pass through the esophagus. When such outcomes are compared with manometry findings, it is effectively known that how esophageal contractions move substances through the esophagus into stomach [44].

5. Treatment

Treatment includes prevention of complications, healing of esophagus, mitigation of the symptoms and prevention from recurrence. Treatment includes lifestyle modification, pharmacological treatment and surgery.

6. Lifestyle modification / dietary modifications

Lifestyle modification includes upraising the head of bed, cessation of smoking, reducing the intake of fats, avoiding lying horizontally for 3 hours postprandial avoiding coffee, alcohol, citrus juices, tomato products, chocolate, peppermint, avoiding drugs that affect esophageal motility (nitrates, tricyclic antidepressants, anti-cholinergics) or damage lining of mucosa (potassium salts, NSAIDs, alendronate) [45]. Lifestyle modifications are referred as first line therapy to pregnant women with GERD. Along with these modifications, educating the patient about various behaviors that could result in reflux is necessary.

7. Pharmacological therapy

Symptoms are relieved in patients with mild form of GERD by utilization of over the counter medications such as anti- refluxants and antacids. This combination of two therapies is more effective. The treatment plan of GERD has been illustrated in Table 1 and Table 2 respectively.

Drugs	Doses	Age (FDA indicated)
Histamine 2 receptor antagonists		
Cimetidine	20-40mg/kg/day	≥ 16 years
Ranitidine	5-10mg/kg/day	1 month-16 years
Nizatidine	50mg twice daily for up to 8 weeks	≥12 years

Famotidine	<3months to 16 years (0.5-1mg/kg/day)	<3months- 16years
Proton pump inhibitors		
Omeprazole	5 to <10kg (5mg O.D) 10 to <20kg (10mg O.D) ≥ 20kg (20mg O.D)	1-16 years
Lansoprazole	Short term treatment of GERD/EE: ≤30kg (15mg O.D for 12 weeks) >30kg (30mg O.D for 12 weeks)	1-11 years
	Short term treatment of non-erosive GERD: 15mg O.D for 8 weeks EE: 30mg O.D for 8 weeks	12-17 years
Esomeprazole	EE due to acid-mediated GERD: 3-5kg (2.5mg O.D for 6 weeks) >5-7kg (5mg O.D for 6 weeks >7.5-12kg (10mg O.D for 6 weeks)	1 month to < 1 year
	Short term treatment of symptomatic GERD: 10mg O.D for 8 weeks Healing of EE: <20kg (10mg O.D for 8 weeks) ≥20kg (10-20mg O.D for 8 weeks)	1-11 years
	Healing of EE: 20-40mg O.D for 4-8 weeks Symptomatic GERD: 20mg O.D for 4 weeks	12-17 years
Rabeprazole	20mg daily for 8 weeks	12-17 years
	<15kg (5-10mg O.D for 12 weeks) ≥15kg (10mg O.D for 12 weeks)	1-11 years
Pantoprazole	≥15 to <40kg (20mg daily) ≥40kg (40mg daily)	≥5 years

Table 1: Pediatric doses of medication for GERD

Drugs	Doses	Mechanism of action
Surface barrier		
Sodium alginate	10-20mL Q.I.D	Floats on the gastric contents
Mucosal protectant		

Sucralfate	1 g Q.I.D	Binds to damaged tissues
Histamine 2 receptor antagonists		
Cimetidine	200-400mg B.I.D	Competitively inhibit histamine receptors on gastric parietal cells
Famotidine	10-20mg B.I.D	
Nizatidine	150mg B.I.D	
Ranitidine	75-150mg B.I.D	
Proton pump inhibitors		
Esomeprazole	20-40mg O.D	Irreversible deactivation of H+/K+ proton pump on parietal cell
Lansoprazole	15-30mg O.D	
Omeprazole	20-40mg O.D	
Omeprazole-IR	20-40mg O.D	
Pantoprazole	40mg O.D	
Rabeprazole	20mg O.D	
Prokinetics		
Metoclopramide	5-10mg every 6-8 hours	Promotes gastric emptying
tLSER inhibitors		
Baclofen	10-20 mg 3 times daily	Increases lower esophageal tone

Table 2: Doses of medication for GERD

8. Antacids/Alginates

They are effective in relieving of symptoms by neutralizing the gastric acid as they contain alkali ions, thus reducing the damage of esophagus and suppressing pain. They should always be taken after meal or at bedtime [46-48]. These include aluminium hydroxide, magnesium hydroxide and simethicone. Antacids help in the healing of erosive esophagitis while offering symptomatic relief [49].

9. Acid Suppressive Therapy

Acid suppressive therapy is the centerpiece for the treatment of GERD currently [50].

10. Histamine 2 receptor antagonists

Famotidine, ranitidine, cimetidine and nizatidine decrease the secretion of gastric acid after a meal but are not efficacious in the healing of esophagitis [51]. Now- a -days these have been used for the relief of nocturnal symptoms and for the milder stage of the disease [52]. In US for the short-term (14 days) treatment of heartburn, omeprazole is available over-the-counter. Because of the development of tolerance within 1-2 weeks, this class is not recommended for long term use.

11. Proton pump inhibitors

Acid suppression can be effectively achieved by the use of proton pump inhibitors (pantoprazole, lansoprazole, esomeprazole, omeprazole, rabeprazole). They are the benzimidazoles which are substituted that works by irreversibly binding to the H^+K^+ATPase, the last step in gastric acid secretion [53]. Resolution of heartburn is achieved in 61% of the NERD patients having erosive esophagitis by the use of PPIs as compared to 40% relief by histamine 2 receptor antagonists in similar patients [54, 55]. PPI treatment failure occurs because of delayed gastric emptying, residual acid reflux, improper dosing time, weakly acidic reflux, deuodeno-gastroesophageal reflux, esophageal hypersensitivity, nocturnal reflux, eosinophilic esophagitis, residual acid reflux, reducing PPI bioavailability and psychological comorbidity. In chronic or complicated type of GERD, long term PPI therapy has been proven beneficial [56, 57]. In the Netherlands, 21% of the PPIs prescriptions are prescribed for the gastro protection of patient taking non-steroidal anti- inflammatory drugs or aspirin. The PPIs should be taken before meals (before breakfast or evening meal).

12. Prokinetics

GERD is caused by the esophago-gastric motility problems such as incompetence of lower esophageal sphincter and delay in gastric emptying time. Among the promotility agents (baclofen) may be useful in suppressing acid. Prokinetic medicines (cisapride, metoclopramide) stimulate serotoninergic or dopaminergic receptors in order to increase esophageal and gastric peristalsis resulting in the delayed esophageal clearance [58].

13. Treatment of GERD in pregnancy

Heartburn is reported in 45–80% of pregnant patients and although it is self-limited. Typically, GERD arises in a first trimester of pregnancy, worsens during latter period of pregnancy and resolves after the delivery. GERD occurs during pregnancy due to the increase levels of hormones (progesterone) and growth of the uterus. Owing to the side effects on the growing fetus, pregnant patients are often unwilling to use any medications during pregnancy.

Treatment in pregnancy should begin with lifestyle modifications. According to the Canadian Dyspepsia working group, if lifestyle modifications don't work, then antacids are recommended as the first line of treatment. Products containing Ca are preferred. Antacids, which contain Na CO_3 should not be used leading to metabolic alkalosis and fluid accumulation in both mother and fetus.

Alginates such as Gaviscon TM, is considered safe during this period. Absorption of aluminum could affect developing organs in the fetus such as the brain and kidneys. Magnesium in larger quantity and ingested over prolonged periods of time could result in nephrolithiasis and respiratory distress. A systematic review by the Motherisk Program (Hospital for Sick Children, Toronto, ON) showed no risk for fetal malformations , teratogenicity, increased risk of low birth weight or miscarriage when H2RAs especially ranitidine was used during the period of pregnancy. In case of failure of therapy, including H2RAs and persistence of symptoms patient should refer physician possibly for the use of a proton pump inhibitor. Omeprazole has been assigned to "category C" by U.S. FDA and lansoprazole to "category B" [59] .

14. Surgical interventions of GERD

Two options of treatment are available to cure the chronic and relapsing nature of GERD such as long term medication and anti-reflux surgery or repair of LES (lower esophageal sphincter). Surgery is indicated when medical treatment plan is failed (severe regurgitation, inadequate or side effects of medication), complications (peptic stricture, Barrett's esophagus) [60, 61], extra esophageal manifestations (hoarseness, asthma, chest pain, cough, and aspiration) [62-65]. Patients are not subjected to surgical therapy if he is unresponsive to PPIs.

15. Nissen fundoplication

Surgical procedure have been advanced from an open to a laparoscopic method and then in to transoral incisionless fundoplication during 50 years. Nissen fundoplication is the vastly used procedure. Stomach fundus is wrapped around the esophagus to create a new cardiac valve-equivalent at the gastro-esophageal junction in Laparoscopic fundoplication and is suggested in patients with Barrett's esophagus, postmenopausal women with osteoporosis, erosive GERD, poor compliance of medicine and serious respiratory manifestations. The advantages of laparoscopic fundoplication involve shorter duration of hospital stay, fewer incisional hernias and reduced pain [66]. Complications of this technique are impotence to belch, persistent dysphagia, vomiting, epi-gastric fullness, postprandial pain, temporary swallowing, bloating, and intense flatus [67].

16. Laparoscopy

Laparoscopy is performed by passing a small viewing device and surgical instruments through several small puncture sites in the abdomen avoiding the need for major abdominal incisions.

17. Endoscopic procedures

Endoscopic methods of treating GERD have been currently developed in which sutures near the gastro-esophageal junction are placed using a device connected to the endoscope. This technique improves GERD symptoms, pH probe results and decrease PPIs use in the short term, but it does not reduce total costs because many patients subsequently return to the long term use of PPIs.

18. Radiofrequency ablation (Stretta procedure)

Endoscopically-controlled radiofrequency ablation (Stretta procedure) of the LES has shown to improve typical GERD symptoms thus, decreasing acid exposure to esophagus and medication use in an unrestrained trial with short-term follow-up. High-energy waves are targeted on wall lower esophagus wall which in return produce a less number of scar tissues reducing heartburn and other symptoms in most people. More than one radiofrequency treatment may be required to achieve good results.

19. Long term complication of GERD

If left uncontrolled, persistent heartburn and other serious problems are observed [68]. Esophagitis may cause chest pain, heartburn, swallowing difficulty or bleeding [69]. Barrett's esophagus leads to the cancer of esophagus. Acid

reflux causes abnormal changes esophagus lining. Normal cells are replaced with the abnormal ones in lining of esophagus. These abnormal cells are indistinguishable with those found normally in lining of the small intestine. Roughly 1 in 300 people with Barrett's esophagus develops esophageal cancer each year [70]. The damaged lining of the esophagus becomes blemished, narrowing the esophagus resulting in strictures and preventing food and liquid passing in to the stomach. Squamous cell carcinoma is the development of squamous cells lining esophagus usually affecting the upper and middle esophageal area whereas, adenocarcinoma in lower part of the esophagus due to Barrett's esophagus. Hemorrhage occurs by the widespread gastric mucosal irritation or ulceration with acute bleeding resulting in tarry or bloody stools, syncope, diaphoresis, hypovolemic shock.

20. Conclusion

GERD is one of the aspects of gastroenterology which has encountered stupendous renovations in the last 30–40 years. Multiple factors are involved in the pathophysiology of the GERD. As GERD is a chronic as well as a relapsing disease so, patients should be managed with either long-term medical treatment or surgery after a thorough analysis of the pros and cons of each modality. Where medical therapy affects production of gastric acid only, fundoplication refurbishes the activity of LES and improves peristalsis of esophagus. Fundoplication cannot regress Barrett's esophagus and prevent adenocarcinoma development. PPIs are being extensively used currently for the treatment. According to my opinion, there is an intense need to develop a combinational therapy to mask the aftereffects of PPIs or a new safer therapeutic agent should be discovered to resolve the underlying issues of treatment that have been remained unresolved after the surgery or by the use of different therapies.

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