# A REVIEW STUDY ON RISK FACTORS, PATHOPHYSIOLOGY, MANAGEMENT OF GASTRO ESOPHAGEAL REFLUX DISEASE

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## ABSTRACT
GERD is the most common disorder of GIT. Characterized with troublesome symptoms (Including heartburn, acid regurgitation, and epigastric pain) and some complications that are due to reflux of stomach content into esophagus. Its long-term complication is esophageal ulcer, Barrett's esophagus, stricture, and adenocarcinoma of Gastroesophageal region lower esophagus sphincter play a vital role in this disease .its prolonged relaxation cause the disease. The prevalence of the disease varies for different nations, diverse epidemiology area. Many factors responsible for disease there are two types: non-modifiable and modifiable factors. Non-modifiable factors are age, gender, and some genetic factors, modifiable factors like body weight, obesity, eating habits, lifestyle, smoking, alcohol consumption, physical activity, eating habits (irregular timing of food, overeating), many diseases change the normal physiology of GIT motility and alter the phenomena of sphincter relaxation .some drugs also directly or indirectly contribute to disease. It is a worldwide common disease with an increasing prevalence rate. Management of gastrointestinal reflux disease involves modification of lifestyle, habits; avoid triggers, medical management, and surgical intervention. To properly diagnose and management of GERD, it is important to recognize the epidemiologic various risk factors for disease. Aluminum containing antacid are not used because aluminium plasma level in infants lifestyle involved reduce the volume of feed.
**Keywords:** GERD, symptoms, risk factors, lifestyle modification , management ,infants

## INTRODUCTION:
Across the globe, millions of people are suffering from digestive disorders and disease. As per the American Nutrition in the globe, 70 million individuals experience some form of digestive problems on every day basis. [1] Gastroesophageal reflux disorder is one of the most common chronic disorders of the gastrointestinal system. It is a relapsing disorder characterized by the retrograde movement of reflux ate into the Esophagus.[2]According to the Montreal definition, GERD is defined as troublesome symptoms. (Including heartburn, acid regurgitation, and epigastric pain) and some complications that are due to reflux of stomach content into the esophagus.[3] GERD is one of the foremost gastrointestinal problems around the globe and its effects greatly on individual health, quality of life, social life, and economy [4].
To properly diagnose and management of GERD, it is important to recognize the epidemiologic various risk factors for disease [5]. To prevent its adverse consequences its early detection on basis of earlier symptoms and proper management is necessary.

**RISK FACTORS FOR DISEASE**

**Age**: Various studies show that GERD is increasing with increasing age [9,10,13]. Puspita et al. describe age>50 as significant with the disease. Fakhre Yaseri et al. also reveal a similar result. A study by Rai, S et al describes GERD is more prevalent in age (35-59) in western countries. Eusebiet al show advancing age is a significant risk factor for disease.[14] Spantideas, N et al. reported in the study that the prevalence of GERD about64% in the age group is 65-79 years and 56.4 % in age group (50-64)year.[6] Wang H et al. Also show an association between age above 50 years and GERD with the 4.3 odds ratio. Increasing age is significant factor for GERD

**Gender:** The studies show male gender is more associated with the prevalence of gastroesophageal disease [1, 7] Alrashed, A *et al* reveals in the study for disease male is higher significant factor .a study consist of 56.8% male population and 43.3% female population showing GERD in 30.8% in males and 14.7% in females show GERD. Awadalla, N *et al*.the similar result in Saudi Arabia shows that in multivariable analysis GERD is significantly higher in males with OR[ (1.44 ) CI;117-1.65],[7]

**Obesity and BMI: studies** shows that increasing weight is significant factor.(Body Mass Index): a study by Arivan, R *et al*. present in a study that BMI more than 25kg/m [8]. Alrashed, A *et al* also shows a similar result.[1] Esubi*et al* shows in their study prevalence rate were higher in individuals having obesity with OR:1.73(95% CI 1.46-2.06). [14] A study by Singh, S *et al.* show that obesity is not only associated with an increased rate of GERD but also responsible for GERD complication. It associated with erosive esophagitis with an odds ratio1.59, Barrett s esophagus with an odds ratio of 1.98, and carcinoma of the esophagus with an odds ratio of 2.51.[15] Ness-Jensen *et al*.confirmed in a study that decreasing the weight reduces the chances of GERD or decrease the symptoms of the disease.[16]

**SMOKING**: A study by Alrashed, A *et al*. suggest that smoking is a significant factor for disease.. This study shows the correlation between current smokers and GERD with a p-value < 0.05. [1] A Study by Awadalla, N et al shows that ex-smoker and current smoker both are significant with disease, ex-smoker significant with an odds ratio 1.84 confidence interval 95% and current smoker are significant with an odds ratio of 1.71, .95% confidence interval [7]. A study by Spantideas *et al.* also shows that smoker is significantly related to GERD with p-value <0.05. Smoking is directly or indirectly associated with the relaxation of the esophagus [6].

**LIFESTYLE FACTORS*:*** Arivan, R *et al*. represent lifestyle factors related to GERD. Consumption of carbonated drinks is significant with the disease with an odds ratio of 3.63, $p$=0.008, and tea, coffee consumption significantly associated with an odds ratio of 4.65; $p$=0.026. some lifestyles are not associated like vegetarian, non-vegetarian diet, exercise, skipping breakfast not associated.[8] Alrashed, A *et al*. show that fast food intake, consumption daily of tea, carbonated drinks are significantly associated with the disease with a p-value <0.05 .the factors that are not significantly associated are coffee, skipping breakfast, and exercise.[1] A meta-analysis study by Rai, S., *et al*. represents that non-vegetarian diet, tea coffee intake are significantly associated with the disease. Tea /coffee and carbonated drinks direct linked with the relaxation of the sphincter [13]. Puspita*et al*. show that coffee consumption is not associated with the disease [10].

**DISEASE*:*** Awadalla, N *et al*. represent that **Stress** is significant with the disease with odds ratio 1.30; CI :1.01-1.44),[7],. In the study by Akyuz, F *et al.* reveal various diseases related to GERD. **Systemic sclerosis:** the prevalence rate of gastro diseases in sclerosis patients is 60-80%.It leads to motor abnormalities, abnormalities in peristalsis movement which reduced sphincter pressure. **Diabetes mellitus:** the prevalence of GERD in diabetic patients is from 30-50%. It alters delayed gastric emptying, decreased acid clearance, frequent relaxation of lower esophageal sphincter [12]. A study by Kung, Y. *et al*. represent **Allergic Rhinitis** is a significant risk factor for newly diagnosed with GERD with adjusted HR 1.94; CI :95%'[11].

**DRUGS:**A study by Alrashed, A *et al*. shows that NSAID consumption is not associated with GERD[1], a similar result was found by Rai, S., et al in India. [13] A study by Mungan, Z *et al*. show that NSAIDS, Oral

contraceptive, estrogen, calcium channel blocker, nitrate, benzodiazepine, anticholinergic, theophylline, and albuterol increasing the prevalence of GERD [17].

## PATHOPHYSIOLOGY OF GERD

- Barrier related function:Lower esophageal sphincter (LES),Basal lower esophageal sphincter pressure (LESP) ,Crural diaphragm ,Hiatal hernia
- Clearance of Acid ;Peristaltic action of tubular esophagus ,Saliva production
- Mucosaldefense mechanism :Pre Epithelial (mucus, bicarbonate),Epithelial (tight cell contacts, ion exchanger) ,Post Epithelial (blood supply)
- Gastric emptying
- Abdominal pressure
- Genetic predisposition [18]

**Lower esophagus sphincter**

The esophagus at its lower ends has two layers of smooth muscles one is longitudinal and the other is circular. Some anatomy studies show that lower esophagus sphincter muscles are not properly circular; they are shown as rings of incomplete C. These fibers are arranged with left side clasp fibers and right side gastric sling fibers. The gastric sling fibers act as the oblique layer of muscles of the stomach and help in the formation and alteration of the angle of HIS. clasp fiber maintains more basal tone than the oblique fibers

The lower esophagus zone is categorized as the high-pressure zone in humans it is about 2-4 cm in length. The tone of the lower esophagus sphincter depends upon 3 factors[19]

- **Myogenic factor**
- **Neural factor**
- **Neurohumoral**

**Myogenic factors basal** tone of the sphincter is due to differential protein.LES has more alpha-actin and light chains LC17b than the esophageal body circular muscles.

**Neural factor**: Cholinergic-derived neurons are responsible for basal tone. Alpha-adrenergic nerves are responsible for contraction and beta-adrenergic for relaxation.

**Neurohormona**l **factor**: a neurohumoral agent called motilin released into circulation from the wall of intestine from specialized cells, is responsible for phasic LES contraction.[20]

**Alteration in basal tone**

Many neurotransmitters and hormone chemicals can alter the LES pressure. (21)

Table 1

| Reduces LES Pressure | Contraction of lower oesophagus sphincter |
|---|---|
| nicotine | Mascaranic M2,M3 receptor agonist |
| Beta adrenergic agonist | Alpha adrenergic agonist |
| dopamine | Gastrin |
| cholecystokinin | Substance P |
| secretin | Prostaglandin F2 |
| Vasoactive intestinal polypeptide | |
| calcitonin | |
| Nitric oxide | |
| Prostaglandin | |

## LES REFLEXES

LES relaxation associated with swallowing:

.During the swallowing phase Therelaxation of the Lower esophageal sphincter occurs to prevent the LES response to swallowing consisting of relaxation of the LES tone, which is followed sometimes by a rebound contraction. The monitoring of the LES relaxation requires avoidance of the artifacts related to the movement of the abdominal esophagus into the chest. The relaxation starts within seconds of swallowing and lasts 5 to 8

minutes. The relaxation is part of the deglutition inhibition and is mediated by the vagal inhibitory pathway and the postganglionic mesenteric neurons that act by releasing nitric oxide. [22]TLERS transients lower esophageal Relaxation not related to peristalsis movement or swallowing. It occurs for 10-35 seconds. [23]

**Hiatal Hernia:** Hiatal hernia is a condition wherein parts of the stomach substance, mostly the GEJ and the stomach, are proximally dislodged over the stomach through the esophageal rest into the mediastinum. Types sliding hiatal hernia and second form called para esophageal hernia.[24] hiatal hernia disrupts most of the natural anti-reflux mechanisms and is considered an independent factor for GERD[25]

**Diaphragm**

The crural diaphragm has skeletal muscles which create a high-pressure zone at the level of EGJ. Its defective action leads to GERD[26]

**The delayed oesophageal bolus clearance mechanism**

Bolus clearance of acid involves two processes. first is clearance by peristalsis movement and the second process involvesneutralization by saliva. If 15 ml or less bolus of acid is instilled it is cleared by esophagus peristalsis. after 7 – 10 swallows esophageal acidification is restored by saliva to maintain ph 5-7. This delay in acid clearance is one of the reasons for excessiveesophageal acid exposure observed in patients with reflux-esophagitis.[27]

**Delayed stomach emptying**. It is due to gastroparesis, and partial gastric outlet obstructions are seen in 15% patients of with GERD

**Impaired mucosal resistance**. The esophageal epithelium cells produce bicarbonate and mucus. Bicarbonate neutralizes the acid mucusform a protective layer. Pepsin present in the acid refluxate can destroy the esophageal mucosa by digesting protein. Of epithelial cells. Enhanced mucosal sensitivity to acidcan also be associated with chronic heartburn[28]

Genes involvedin GERD

Proinflammatory cytokines interleukins 1 beta and IL – IRN combined with H.Pylori infection are responsible for GERD. Changed expression of cyclooxygenase -2 enzyme, IL-10, Glutathione S transferase, Cyclin D1, and DNA repair genes associated with GERD.FOXF1 genes are also responsible for GERD.[29]

**Symptoms :**

symptoms are categorized as typical symptoms and extraesophageal symptoms. Typical symptoms are heartburn, regurgitation, dysphagia. Other symptoms are chest pain (without any cardiac complaint ) , dyspepsia, Nausea, bloating, sore throat, epigastric pain, and globus sensation.

Extra esophageal symptoms are Asthma ,laryngitis ,chronic cough, pharyngitis,sinusitis,dental erosion ,recurrent otitis media ,idiopathic pulmonary fibrosis.[30]

**Diagnosis**

diagnosis of the disease is clinically based on symptoms. Two major symptoms involved are heartburn and regurgitation. Chest pain is also indicated without heart disease. Sometimes epigastric pain, dyspepsia, bloating which are reduced by a proton pump inhibitor are also indicated diseases. Endoscopy is used when the symptoms are worse, Dysphagia, weight loss, and symptoms are not modified by drugs. Esophageal biopsy, esophagealmanometry, barium swallow studies are used to evaluate complications such as Barrett's esophagus, esophageal stricture .[31]For the extraesophageal symptoms like asthma, sinusitis, dental erosion PPI given then check for responses. The ambulatory reflux monitoring technique is used to evaluate esophageal acid exposer and reflux frequency. The diagnosis of GERD in adults can usually be made in patients which are not a response to proton pump inhibitor and without GERD diagnosis based on endoscopy reconfirmed by ambulatory test, the positive test shows pathologic gastric acid reflux.[32]

- **Diagnosed** in the children are based on symptoms, such as regurgitation, abdominal pain, cough, refusal of fees associated with vomiting. anorexia is associated with erosive esophagitis In infants, spitting up to 4 times or more indicates gastroesophageal reflux disease. Some other symptoms areback-arching, vomiting. [31]

**MANAGEMENT:**

**lifestyle modification**: it acts as the stone of GERD management. Many studies show that altering lifestyle, modifying some food habits which are responsible for GERD such as carbonated beverages, onion, chocolate, spicy food, fatty meals. the main approaches are the elevated head end of the bed ,avoid the right lying down position ,loss of weightwithin 3 hours of bedtime avoid meals. [33]

**Therapy**; the patient with continued symptoms are required medical therapy.it includes

Antacid, Gaviscon, Proton pump inhibitor , H2 Receptor antagonist , Prokinetic, Baclofen

**PPI**: it acts as by suppression of stomach acid production by acting on H2/K2+ATPase pump are the most common effective medication for the treatment of GERD [34].drugs under PPI are mentioned in table 2. Except for dexlansoprazole, all other proton pumps are taken at least 60 minutes before a meal for proper PH control It is used as first-line treatment for GERD. if the GERD symptoms are only day times then taken once a day if symptoms occur night time then taken in the evening. its long-time use causes side effects diarrhea, osteoporosis, bone fracture, microscopic colitis, acute intestinal nephritis, increased risk of hip fracture, vitamin B12 deficiency. [35,36,37]

Table 2

| | |
|---|---|
| Proton pump inhibitor | Rabeprazole,Omeprazole, lansoprazole,dexlansoprazol, Pantoprazole, Omeprazole with sodium bicarbonate |
| H2 RA | Famotidine, Cimetidine, Ranitidine, Nizatidine |

**H2RA:** The most potent drug in this category is famotidine FDA setup warning for this drug in patients suffering from kidney disease it is majorly eliminated by kidney cimetidine is the eldest drug with fewer side effects common side effect is headache.[33]

**Surgical intervention**; `

The surgical intervention involved in case of erosive esophagitis endoscopy is used .laparoscopy, fundoplication, anterior or Nissen fundoplication[30]

**GERD in paediatrics**

Regurgitation us common in infants with vomiting when the episodes of regurgitation is repetitive occur mostly after 6 months to 12 months is showed as GER, and GERD.

**Symptoms** : symptoms in infants involved regurgitation,vomiting related to irritability,anorexia,refusal of feeding, dysphagia, difficulty weight gain ,back arching during the feedback .some extraesophageal symptoms are choking weezing,coughing,uper respiratory symptoms .symptoms in age 1-5 year are vomiting, abdominal pain, anorexia without interfering with growth older children age above 5 year having symptoms similar to adults. (38]

**Pharmacotherapy for GERD in paediatrics**: Antacid that are acted by neutralizing acid are used limited in infants. Aluminium Containing antacid are not used because aluminium plasma level in infants are 9 times more . Aluminium toxicity arise in infants which linked to microcytic anaemia and[39osteomalacia. According to the guidelines of national institute for health and care excellence : alginates is act as feed thickening agents are used as alternative treatment for the prevention of reflux in breastfeeding .one of the main pharmacologic agents used to manage GERD in paediatric are the acid suppressants.histamine-2 receptor antagonists and proton pump inhibitors are the foremast therapy.

PPI are the first choice lansoprazole twice for two weeks improved some reflux symptoms. Studies reveal that PPI are not improved symptoms such as crying,cough,arching back ,rregurgitation,vomiting . It leads to many adverse effect intestinal bowel bacteria overgrowth, increase upper and lower respiratory tract infection.

Mostly prokinetic used to reduce loweresophageal sphincter relaxation the mostly used is baclofen. According to ESPGHAN baclofen is only used when other pharmacological treatment is failure.it help in gastric emptying but is not used as first line of drug. Because it produce side effects drowsiness,fatigue,seizure [40]

Table 3 : dosing of PPI and H2RA in Paediatrics(41)

| Drugs | Population | Dose |
|---|---|---|
| Omeprazole | Infants 3-5Kg<br>5 to <10 kg<br>_> 10 kg<br>Children | 2.5 mg per day<br>5 mg/ day<br>10 mg/ Day<br>1 mg/ kg/ day maximum 20 mg |
| Esomeprazole | Infants 3-5Kg<br>5 to <10 kg<br>_> 10 kg<br>Children <20 kg | 2.5 mg per day<br>5 mg/ day<br>10 mg/ Day<br>10 mg/day |

| | | |
|---|---|---|
| | Children >20 kg | 10-20 mg/ day |
| Lansoprazole | Infants and children | 1 mg/ kg/ day maximum 15 mg/ day |
| Pantoprazole | Children 15 <40 kg<br>Children >_40 Kg | 20 mg/day<br>40 mg/ day |
| Rabeprazole | Children >_ 12 years | 20 mg/day |
| Dexlansoprazole | Children >_ 12 years | 30 mg/ day |
| H2 RA | | |
| Cimetidine | Children | 30mg-40mg/kg / day divided into 4 doses |
| Ranitidine | Children | 5-10 mg/ kg/ day divided into 2-3 dose |
| Famotidine | Children | 1 mg/ kg / day divided into 2 dose |
| Nizatidine | Children | 10-20 mg/ kg/ day Divided in 2 dose |

**Lifestyle changes in infants : life** style are the first line treatment of GERD. In infants it is based on feeding change ( reduce the volume of feed, increase the frequency of feed) positioning therapy. [30]Postural therapy after feeding an infant should be kept in upright position for 30 minutes it include elevation of head, lateral and prone position to decrease the regurgitation. This postural is not recommending if the infants are sleeping it may cause sudden death of infants.(42)

Lifestyle changes : the chances of Gastroesophagus reflux are less in breast feeding infants than formula fed infants so more promoting the breast feeding. Some infants have allergy from cow milk. So breast feeding mother should avoid cow milk, and some allergic substances such as chocolate,nuts,eggs, avoidance of over feed.(43)

**DISCUSSION**

GERD is one of the most prevalent disorders in the world .the research conducted for the risk factors of GERD are contradictory, prevalence of disease changed with variation in geographic area and according to population. Most studies confirm that advancing age is responsible for the disease BMI is significantly linked to GERD. Increasing body weight increases the chances of GERD . studies show smoking is a positive factor. it again depends upon population, duration, and frequency of smoking .therefore further more research in this area is required.Unnecessary use of NSAIDs and other drugs also leads to contributing factors for disease in the upcoming years. The part of the way of life, diet and dietary patterns, and their role in GERD is not clear. Many examinations giving result opposing each other .this may due to the change in geographical area, differential culture system and populations. Beyond therapy, non-pharmacological activities are best for properly managing GERD in the early stages. people are advised to normal their body weight, as the overweight is the major cause of disease shown by numerous research. cessation of alcohol, smoking also decreases the chances of GERD.it is also necessary to decrease or avoid the utilization of some reflexogenic products such as tomato, oranges, spicy, fatty food, grapefruit juices, tea coffee. A heavy meal is consumed with a proper time gap to reduce the chances of disease. Exercise and physical activities reduce the chances of many diseases which are alternatively responsible for GERD. GERD is more common in infants age 6-12 month Widespread researches on modifiable factors are necessary to properly manage the disease. its early prevention is necessary to reduce the chances of severe complications and maintain quality of life.

**Abbreviation**: GERD : ( Gastroesophageal reflux disease) ,LES ( Loweresophageal reflux sphincter) ,ESPGHAN :European Society for Paediatric Gastroenterology, Hepatology, and Nutrition

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