

The Pathophysiology of Gastroesophageal Reflux Disease

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ABSTRACT

The incidence of Gastroesophageal Reflux Disease (GERD), especially in Indonesia, is increasing with the change of community life-style. Also, the doctors' perception in understanding clinical manifestation of GERD is alike in addition to the development of diagnostic facilities such as endoscopy in Indonesia. The GERD incidence in Indonesia is as high as the incidence in developed countries.

Esophageal reflux develops in physiological condition, which may be found in normal individual. GERD development is caused by anatomical and physiological disorders such as hereditary or acquired factor; and other factors that may be categorized into offensive factors such as gastric acid, pepsin, bile acid, trypsin and disturbance in defensive factors such as hypotensive Lower Esophageal Sphincter (LES), Transient Lower Esophageal Sphincter Relaxations (TLESR), hiatal hernia, disrupted saliva production, esophageal peristaltic disorder; as well as other factors such as genetic, diet, or certain drugs. Imbalance of such factors may cause pathological repeated esophageal reflux which may damage esophageal mucosa and lead to GERD development including all of complications.

Keywords: *esophageal reflux, GERD, LES*

INTRODUCTION

Gastroesophageal Reflux Disease (GERD) is a condition of gastric content reflux into the esophagus and causes clinical manifestations.¹ This disease is a consequence of various physiological and anatomical disorders which may have important role of anti-reflux mechanism in the stomach and esophagus. Basically, gastrointestinal reflux is a physiological process which normally occurs for approximately one hour daily in normal individual. Such reflux may not occur continuously due to anatomical barriers, i.e. lower esophageal sphincter (LES), diaphragm crural and phrenoesophageal ligament.²

The incidence of GERD is high in Western countries and recently, the experts are getting more curious about GERD. It is reported that there are

13.4-16.3% patients with GERD in Taiwan, Malaysia and Japan. At the Faculty of Medicine, Cipto Mangunkusumo hospital, Syam AF et al, reported that there was increased GERD prevalence from 5.7% in 1997 into 25.18% in 2002 (approximately 13.13%).^{3,4}

Heartburn and acid regurgitation are reported once weekly by 20% of Americans, and the annual prevalence is more than 59%. Traditionally, reflux treatment is aimed to deal with aggressive substance of gastric acid. However, we found other factors which have important roles in GERD development and esophageal mucosa damage.⁵

Noxious substances that may damage esophageal mucosa include gastric-derived substances, i.e. gastric acid and pepsin and duodenal-derived substances, i.e. conjugated and unconjugated bile acid as well as trypsin. Injury induced by such substances may cross esophagogastric junction and moisten esophageal mucosa. To prevent such condition, LES together with diaphragm crural have a major role in protecting structures from noxious substances of gastroduodenal reflux. Gastroesophageal junction may

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be pass due to transient lower esophageal relaxations (TLESR), hypotensive LES (HLES), or by other cause associated with hiatal hernia.⁵ The mucosa is exposed to noxious gastroduodenal substance, therefore esophagus lumen is protected by esophageal clearance mechanism through peristaltic and acid neutralization process which is also part of defense mechanism and epithelial cell recovery. Hence, it is important in preventing mucosa damage.⁵ Normally, there is a balance between aggressive factors and defense mechanism.^{5,6} When the protection mechanism fails, it may cause GERD complication including esophagitis, stricture, or Barrett's esophagus,^{5,7} or even esophageal carcinoma.⁷ In some individuals, genetic factor may also have a role as predisposition factor of GERD.⁵

PATHOPHYSIOLOGY

Gastroduodenal Factors

Gastric substances that most frequently cause injury are gastric acid produced by parietal cells and pepsin produced by gastric chief cells. In endoscopy, usually gastric substances may be mixed with duodenal substances which contain bile acid and trypsin. Therefore, when there is a reflux of gastric content into esophagus, it is a combination of gastric and duodenal substances which contribute to pathogenesis of GERD.⁵ Other gastric factor contributes to such pathogenesis is *Helicobacter pylori*, which has a role in acid secretion.⁵

Gastric Substances

Experimental findings and clinical evidences support the important role of gastric acid and pepsin in GERD. An experimental animal study demonstrates that the gastric acid itself may cause esophageal mucosa injury in a very low pH (pH 1-2).⁵ Acid reflux may become pathological when the esophagus is exposed to acid condition (pH < 4) for more than 5.8% of 24 hours pH-metry.⁷ Combination of acid and slight concentrated pepsin will cause esophageal injury, either macroscopic or microscopic.^{5,8,9} At pH 2, pepsin disrupts the histological integrity of mucosa barriers which increases the permeability of hydrogen ion and produces bleeding. In contrast, esophageal contact with pepsin at pH 7.5 followed by solution contact at pH 2 without any pepsin demonstrate minimal mucosa disruption or permeability change. Hence, pepsin may produce mucosa injury depend on pH with maximal enzyme activity at pH 3.⁶ In acid condition (pH < 4), pepsin may produce esophageal damage due to proteolytic characteristic and it is inactive at pH > 4.^{5,8} Several studies that measure distal esophageal to acid exposure demonstrate that there is a correlation between heartburn symptom and exposure of reflux substance at pH < 4. It is also found

that esophagitis, including the Barrett's esophagus, increases with frequency and contact duration of esophagus and the refluxate at pH < 4.^{5,8,9} It is interesting that GERD may occur even when the patient's gastric acid production does not increase. This is found by Hirschowitz et al, who reveal that stimulation of basal pentagastrin gastric acid secretion and pepsin is similar in GERD patients and normal control subjects. Therefore, esophageal disturbance due to acid exposure in GERD case may be identified by ambulatory pH monitoring, which shows that the most frequent cause is esophageal barrier failure and poor esophageal clearance.⁵ A small number of patients with Zollinger-Ellison syndrome and acid hypersecretion that cause increased gastroesophageal reflux.⁵ Frequency and duration of acid exposure on esophageal are not always reliable in predicting the severity of esophageal mucosa injury. Other factors may also play a role including duodenogastroesophageal reflux, mechanism of esophageal lumen clearance and epithelial recovery and protection.⁵ Pepsin, bile acid, trypsin and hyperosmolar diet increase the sensitivity of esophageal mucosa to acid-induced injury.⁶ Locke et al, found that 72% of 2,118 participants who had body mass index of > 30 kg/m², family history of heartburn, or symptoms of esophageal or gastric disorder, smoking history, alcohol consumption more than 7 times weekly and obvious psychosomatic symptoms are associated with frequent heartburn.⁹

Duodenal Substances

Duodenogastric reflux is a condition with regurgitation of duodenal content (bile acid and pancreas secretion) into the stomach. This condition normally occurs especially after meal (post prandial) and at night.⁸ If the duodenogastric reflux reach esophagus, it is referred as duodenal gastroesophageal reflux or it may be mentioned as bile reflux or alkaline reflux (because of esophageal pH that > 7). The high esophageal pH is also influenced by saliva bicarbonate.⁸ Bile acid and pancreatic enzymes may migrate from duodenum to gastric pylorus and cause a mixture with gastric secretion. The role of duodenal content, especially bile acid and trypsin the pancreatic enzyme in the development of esophageal mucosa injury is still controversial.⁵ Some studies propose that the esophageal mucosa damage is depend on conjugation state of bile acid. Conjugated bile acid may bring damage at acid pH, while unconjugated form may cause damage at alkaline pH. Little has been known of how bile acid may cause esophageal mucosa injury. The proposed mechanism is cell damage due to dissolved lipid membrane of the mucosa and intra mucosa damage after bile acid influx into the cells.^{5,8} Trypsin, akin to pepsin, bring damage through proteolysis mechanism and it frequently causes damage at

pH 5-8.^{5,8} It seems that gastric acid itself only cause least mucosa damage. However, when it is combined with pepsin or conjugated bile acid, it will cause a significant mucosa damage.⁸ Clinical evidences on noxious effect of duodenogastroesophageal reflux on esophageal mucosa is still controversial. Nevertheless, Vaezi and Richter study⁵ that utilized a monitor of bilirubin ambulatory instrument (bilitec) suggest that duodenogastroesophageal reflux is parallel to acid reflux in clinical spectrum of GERD with the highest spectrum in patients with Barrett's esophagus. Moreover, it is found that esophageal exposure acid and duodenogastroesophageal reflux are the most common reflux and it occurs in 95% patients with Barrett's esophagus, 79% patients with GERD.⁵ Hence, the study supports the possibility of a synergy between gastric acid and bile acid in the development of esophagitis and Barrett's esophagus.^{5,8} The role of duodenogastroesophageal reflux in bringing damage to esophageal mucosa without any of acid reflux has not been known. A study by Marshall et al, utilizing extended pH and bilirubin monitoring in 38 patients with GERD found that duodenogastroesophageal reflux without acid reflux is rarely occur (7%) in patients without previous gastric operation.⁵ Sears et al, who studied partial gastrectomy in 13 patients with reflux symptoms found that there was an increase of duodenogastroesophageal reflux by bilitec monitoring in 77% patients. Endoscopic esophagitis was only found in patients who had concomitant acid reflux.^{5,8} Furthermore, Vaezi et al, observed and found that there was only 24% patients with upper gastrointestinal tract symptoms who had partial gastrectomy due to duodenogastroesophageal reflux without any acid reflux. The study demonstrates that duodenogastroesophageal reflux without any excessive acid reflux may cause reflux symptom without producing esophagitis.⁵ Thus, so far it is suggested that acid and pepsin are the main etiologies of mucosa injury.⁵ Duodenal content may exaggerate mucosa damage due to acid and pepsin and without acid and pepsin it will not cause mucosa injury.^{5,8} In non-acidic reflux, gastroduodenal content may be taken into account in persistent symptoms of some patients treated with acid-blocking agents. Using pH and bilirubin monitoring, Koek et al, demonstrated that in 15 symptomatic patients treated with proton pump inhibitor (PPI), bile acid reflux will cause GERD symptoms. Vela et al, reported that in a group with frequent heartburn symptom after meal, omeprazole significantly decrease the number of acid reflux episode, but the non-acid reflux may persist and responsible for symptoms.⁵ Esophagitis reflux is rarely found in achlorhydria patients such as secondary gastric atrophy due to anemia pernicioosa or post gastrectomy.⁸

Gastric Emptying

The loose of gastric cardia is a main factor in GERD development. Prolonged distention of proximal gastric part increases the number of post-prandial TLESR and reflux episode. Sustained diet accumulation in stomach body is found in GERD patients. It is assumed that prolonged diet accumulation at the stomach body (fundus) will induce increased TLESR.⁵ In spite of contradictory result in a study evaluating the correlation of gastric emptying and reflux, it is suggested that gastric emptying rate of upper stomach has more significant effect compared to the reflux. Stracher et al, measured gastric emptying of semi-solid diet and conducted 24 hours pH monitoring in 71 patients with slow gastric emptying symptoms and reflux. It was found that gastric emptying is slow at the proximal and not at the distal part and gastric emptying is correlated to increased acid exposure to esophagus, either in 24 hour or after meal.⁵

Helicobacter pylori Microorganism

Helicobacter pylori, known as a risk factor of peptic ulcer in stomach and duodenum, may prevent GERD because corpus gastritis caused by such microorganism may decrease the production of gastric acid.^{5,9} On the contrary, *H. pylori* eradication shows increased basal gastric acidity.^{5,9} A large epidemiological study found that between 1975 and 1995, the number of patients hospitalized due to GERD and esophageal adenocarcinoma increased significantly in the United States; while patients hospitalized due to peptic ulcer and gastric cancer decrease. Such tendency occurs because of reduced infection rate of *H. pylori* in Western population. In another study Labenz et al, explained that in 450 patients with duodenal ulcer and treated with *H. pylori* treatment and 3 years following the therapy, the incidence of esophagitis reflux was found 2 times higher in the subject group that had successful eradication treatment (26%) compared to the group with persistent infection (13%). Moreover, they suggested that *H. pylori* has protecting effect against reflux.^{5,9}

Another study gives different result about the correlation between *H. pylori* and GERD. Vakil et al, studied 242 patients with duodenal ulcer who received treatment for *H. pylori* infection in four randomized control studies and they found no increased incidence of GERD in patients who had successful *H. pylori* eradication treatment. Eight double-blinded prospective study of *H. pylori* treatment in 1.165 patients with duodenal ulcer found that eradication of such microorganism may not increase the development of esophagitis or exacerbate symptoms in patients who previously had GERD.⁵ However, the clinical significance of *H. pylori* role

on GERD is still being disputed. In some patients who had corpus gastritis due to *H. pylori* strain cytotoxin associated gen A (cagA), it may have protecting effect against reflux through reduced gastric acid production.⁵

Gastroesophageal Junction Factor

Increased abdominal and gastric pressure is normally occur in some of physiologic condition.¹⁰ Discrepancy between abdominal and thoracic pressure push the gastric content continuously into esophagus,^{5,7} and the pressure increase during inspiration and strained abdominal muscle. Hence, the pressure at boundary which is able to compensate intragastric pressure is important to prevent esophageal reflux. The border of such dynamic pressure is gastroesophageal junction.^{5,7,10} Lower esophageal sphincter and crural diaphragm are part of sphincter complex which provide protection against gastroesophageal reflux.⁷ LES is an internal sphincter, which is part of circular smooth muscle at distal esophagus. The healthy volunteers have sphincter complex with tonus pressure 15-30 mmHg above the intragastric pressure. Reflux is mainly occur when the LES pressure below 5 mmHg.⁷ Crural diaphragm prevents stress reflux and it may also prevent reflux when the LES pressure ceased. This indicates the significance of external sphincter complex in maintaining effective anti-reflux barrier.⁷ GERD develops as a consequence of the incompetence of gastroesophageal junction against gastric secretion reflux. It may be overstated by some of anatomical and physiological disorder of gastroesophageal junction.¹¹

Transient Lower Esophageal Sphincter Relaxation (TLESR)

The TLESR is a physiologic response of stomach distention due to food or gas and it is a mechanism that responsible in stomach gas expulsion. Some studies reported that it was found in all of reflux state in individual with normal LES pressure during the reflux occur.^{6,7,10,12} TLESR occurs spontaneously, prolonged relaxation is not depend on the swallowing process.^{5,7,10} During TLESR, the activity of crural diaphragm is also inhibited,^{5,7} in the presence of crural diaphragm relaxation, this condition may be induced by stomach distention through the pathways mediated by the vagal nerve that integrate stimulation and inhibition of such factors. When excitation threshold is reached, it will give signal to LES and crural diaphragm to be relaxed.⁵ Relaxation of transient LES is the most common mechanism of reflux in healthy subjects and patients with GERD. It is reported that there is more than 90% reflux episodes in a healthy individual.⁵ In patients with reflux, the progression of lower esophageal contraction is frequently disrupted

during spontaneous TLESR associated with acid gastroesophageal reflux.¹²

A study evaluated mechanisms responsible for reflux episode of more than 24 hours duration in patients with and without hiatal hernia. It demonstrated that in patients with moderate to severe hiatal hernia, the contribution of TLESR against reflux is relatively small. However, there was significant number of reflux caused by hypotensive LES.⁵ Pharmacological inhibition of TLESR provides new alternative for GERD treatment through acid inhibition.⁵ Experimental studies in animal and human reported that it found reduced bile acid reflux and symptoms following treatment with GABA-B agonist, i.e. baclofen, which may reduce gastroesophageal reflux through TLESR inhibition, and it was suggested as a novel treatment for GERD patients.^{6,7} A study of postprandial reflux in patients with heartburn demonstrated that baclofen may reduce acid and non-acid reflux associated with symptoms in postprandial period.⁵

Hypotensive Lower Esophageal Sphincters (HLES)

The length of LES segment is 3-4 cm. It has smooth muscles with tonic contraction at distal part of esophageal end. The tonic contraction of LES has two characteristics, i.e. from the muscle itself and extrinsic innervations. Normal LES tonus at rest is varried, i.e. 10 -30 mmHg.⁶ There is only a small number of GERD patients who have a very low LES pressure (< 10 mmHg). Some factors may reduce LES pressure: stomach distension, cholecystokinin, some diet (fat, chocolate, caffeine, alcohol), smoking and some drugs.^{5,6} Gastroesophageal reflux occurs due to low basal LES pressure which is incompetent to maintain the effective anti-reflux barrier.¹⁰ However, relaxation of transient LES is a main mechanism of reflux development, low LES pressure is also an important mechanism of reflux in patients with severe GERD. HLES (basal pressure < 10 mmHg) facilitates the gastric content to freely enter the esophagus which lead to esophagitis or GERD symptoms. Mechanism causing low LES pressure in reflux has not been known yet. The possible combination of hypotensive LES and hiatal hernia is necessary in development of erosive esophagitis. The degree of hernia severity, the width of esophagus hiatus, and the incompetent crural diaphragm component of sphincter affect GERD development.⁵ The severity of injury, which can be observed through endoscopy, is correlated to LES pressure. For example, patients with scleroderma who frequently have severe esophagitis may also have a very low LES pressure. Myogenic and neurogenic failure, either primary or secondary due to acid injury are suggested to explain the low LES pressure, but the mechanism which responsible for such condition

has not been clear.¹⁰

Hiatal hernia

Hiatal hernia derived from herniation of abdominal organ at the abdominal cavity through esophagus hiatus of the diaphragm. There are 4 types of hiatal hernia, the most common type is sliding hernia (type I) with prevalence of 10-80%. Type II, III, and IV are variations of hernia paraesophageal which are rarely found.⁵ Patients with hiatal hernia will have reflux only when the basal LES pressure is low. In severe GERD, basal LES pressure is frequently found low.^{10,11} In patients with severe GERD such as erosive esophagitis and Barrett's metaplasia, hiatal hernia is common because it is exposed to higher degree of esophageal acid.¹¹ It has been known that all patients with severe GERD (erosive esophagitis, Barrett's esophagus, or esophageal stricture) have basal hypotensive LES of 0 – 5 mmHg. Nevertheless, not all of patients with reflux have hypotensive LES which suggests there is another factor that may affect the pathogenesis of GERD.¹⁰ LES pressure recording usually increase during inspiration due to contraction crus of diaphragm surrounding the LES. Observation on anti-reflux mechanism during certain maneuver such as raising leg and compressing abdomen may bring on crural contraction which will enhance the anti-reflux barrier. Crural diaphragm is a component of pressure at the gastroesophageal and it is very relevant in patients with hiatal hernia, who may have disturbance of such component.⁶ Patients with hernial hiatal may have progressive sphincter diaphragm disorder which depend on the extent of herniation. A lot of patients with moderate to severe gastroesophageal reflux may also have type I hiatal hernia. Furthermore, in a study of 66 GERD patients and 16 controlled subjects who had experienced endoscopy, manometry and pH monitoring, we found that the size of hiatal hernia correlated to the severity of esophagitis.^{5,6} Hiatal hernia is correlated to decreased LES pressure which lead to accumulation of gastric contents at the hiatal sac which facilitates the development of reflux during swallowing process and induces LES relaxation. Hiatal hernia may also disturb the esophageal peristaltic and consequently it will reduce esophageal clearance.⁷ Regarding the correlation between the function and anatomy associated with reflux, i.e. TLESR and hiatal hernia, Kharilas et al, demonstrated that in patients with hiatal hernia had more significant TLESR compared to the patients without hiatal hernia.⁷ Moreover, they indicated a positive correlation between the distance of intra-squamocollumnar junction and the centre of hiatus and TLESR rate which are induced by stomach distention. Hence, in a the condition of big-size hernia, loss of basal LES pressure, diminished compensation function of the crural diaphragm, and disrupted

clearance, the rate of TLESR increase. Combination of such factors may explain the increased incidence in patients with reflux.⁵

Phrenoesophageal Ligament

It is a component of anatomical barrier which separates the abdomen from the thorax. Hence, it is a border between intra abdominal part and the esophagus. Integrity of phrenoesophageal ligament and its insertion into distal esophagus is an important factor in controlling reflux. Disruption of caudal insertion of such ligament into esophagus wall is likely to cause shortening and straightening of intraabdominal esophageal segment. Therefore, it will increase the possibility of reflux.¹⁰

Esophageal Factor

Anti-reflux mechanism is the first-line defense mechanism against reflux which may cause injury due to gastroduodenal content. Such mechanism appears to restrict refluxate frequency and volume. Once the first mechanism is retrieved, there is a second-line defense mechanism which includes esophageal clearance, esophageal protection by gastric emptying through peristaltic process and neutralization of acid residue in the lumen by saliva bicarbonate and other secretion. Each factor may start performing clearance to prevent mucosa damage.⁵

Esophageal Clearance

In normal condition, gastroesophageal reflux occurs approximately one hour daily in asymptomatic subjects who have 24 hours continuous pH examination. Although reflux phenomenon occurs regularly; but it does not occur in esophagitis. Esophagitis may develop due to some factors including duration of gastric contents which contact to esophageal mucosa, potency of gastric contents and neutralization capacity, and refluxate clearance from the esophagus. Fast clearance of refluxate contents which have a potency to injure esophagus is the main role in preventing mucosa damage. Successful clearance depends on esophageal motoric activity and sufficient saliva drainage.¹⁰ After the reflux occurs, a period when esophageal pH still reach < 4 is known as acid clearance period.⁶ When gastric contents have exceed gastroesophageal junction, exposure period in esophageal epithelial should be limited because the mucosa is not able to bear prolonged exposure of gastric acid, pepsin and bile acid. During the reflux, one or two peristaltic movement will empty the distal esophagus, and only a little part of refluxate will be left. However, the pH remains low following the peristaltic movement. The esophageal pH will be maintained after one has frequent swallowing and due to the buffer ability of saliva.⁷ Prolonged clearance period of esophageal acid is found in 50% patients

with esophagitis. A quite large-scale study report with 24 hour esophageal monitoring suggested that individuals with known hiatal hernia tend to have prolonged acid clearance period when lying down. Two main causes of such problem are disturbance of esophageal emptying and saliva function.⁶ There are two steps of esophageal acid clearance which involve esophageal refluxate emptying through gravitation and peristaltic pressure (primary and secondary) followed by acid neutralization at esophageal lumen by bicarbonate in saliva and secreted by esophageal submucosa gland.⁵

Abnormal Peristaltic Movement

Anterograde peristaltic movement of esophagus drives solid and liquid bolus into the stomach and removes the irritating gastric contents out from esophagus.¹⁰ Although peristaltic movement is usually a primary condition induced by swallowing process, but it may also occur without being induced by swallowing due to secondary peristaltic movement. Esophageal distention due to gastric reflux may also act as a stimulation of secondary peristaltic movement which is an important component of esophageal clearance.^{5,10}

In patients with peristaltic disorder such as Scleroderma, gravitation is very important for esophageal clearance. Loss of esophageal motoric function may because reduced esophageal clearance in lying down position. Contraction force is also important in esophageal clearance. A study on esophageal motility suggested that there is a correlation between the stage of esophagitis and peristaltic dysfunction. An individual with severe esophagitis may have low-amplitude esophageal contraction and primary peristaltic failure. Such alteration is more apparent at the distal esophagus.¹⁰ A defect in primary peristaltic (which is also known as ineffective esophageal motility) characterized by low-amplitude contraction (< 30 mmHg) at distal esophagus may cause esophageal clearance disorder. Moreover, ineffective esophageal motility is a main abnormal motility disorder in patients with GERD. Peristaltic dysfunction more frequently exaggerates esophagitis stage, i.e. it is found in 50% patients with severe esophagitis.^{5,6} Acute dysfunction is correlated to active esophagitis which is partly reversible, while chronic dysfunction is associated with extensive stricture or fibrosis.⁶

Acid Neutralization

Saliva plays an important role in neutralization of gastric content. Recovery of esophageal intraluminal neutralization process requires not only esophageal peristaltic movement but also saliva production. Normal pH saliva varies of 6-7 due to bicarbonate. If saliva is suck from the mouth or it is prevented to

enter the esophagus, administration of acid bolus will induced persistent low pH in the esophagus although the esophageal clearance is effective. This shows that saliva has important function as a buffer in neutralizing acid. Intra-esophageal acid perfusion stimulates saliva secretion.¹⁰ Reduced saliva secretion or reduced neutralization capacity of the saliva may also prolong acid clearance.⁶ Saliva contains growth factor, including skin growth factor which has a potency to increase mucosa repair and acts as cytoprotection against irritant and reduce the esophageal mucosa permeability against hydrogen ion.⁵ In a condition disturbing saliva production, it may cause a defect on esophageal acid neutralization. For example, prolonged acid exposure has been demonstrated in patients with chronic xerostomia.⁵ A study indicated that smoking may exaggerate GERD thorough anticholinergic effect reducing saliva production and cause significant increase of acid clearance period compared to the non-smoker. In contrast, stop smoking may be associated with significant improvement of bicarbonate saliva secretion.^{5,6}

At cellular level, esophagitis may occur in patients with GERD due to diffusion of hydrogen ion into the mucosa which causes cellular acidity and necrosis. Reflux, esophageal emptying disorder and reduced saliva function may worsen esophageal exposure against hydrogen ion.⁶

Epithelial Defense and Repair

Esophageal mucosa has several morphologic and physiologic defense against cellular acidity.⁶ The surface of esophagus epithelial is a defense structure against acid and pepsin diffusion because there are tight junction and intracellular glycoprotein matrix which mutually produce a high-resistance electric epithelial that prevent acid influx into the tissue.⁵ GERD may develop when the acid reflux of gastroduodenal contents damages intracellular relationship of esophageal mucosa, which finally facilitate hydrogen ion influx and cause afferent nerves contact in the esophagus epithelial and produce heartburn symptom in patients with GERD.^{4,5,6} When hydrogen ions entering cells, phosphate, protein and carbonic anhydrase derived from bicarbonate will react as a buffer system, but if the intracellular buffer is fail and saturated, esophagus epithelial cells may prevent acid by two transmembrane pumps: Na/H exchanger and sodium dependent Cl/HCO₃ exchanger. If the epithelial finally has exceeding acid, the intracellular pH will be reduced, causing cell injury, disturbance in volume control, and defense mechanism disorder resulting increased permeability against acid and lead to cell death and necrosis. Repeated acid exposure will cause continued cell death and subsequently cause mucosa erosion which appears

as erosive GERD by endoscopy examination.⁵ Furthermore, if there is severe and uncontrolled mucosa injury and high acid exposure, epithelial repair will occur through cell replication and subsequently migrates into the injured area. Depending on the maintenance stage of germinativum layer, cell proliferation occur through epithelial repair which is histologically characterized by basal cell hyperplasia that may cause epithelial to re-growth or get back into normal condition and it may also cause pathological condition such as stricture or Barrett's esophagus.⁵

Genetic Factor

It is suggested that genetic factor may have a role in GERD development and some of its complications.^{5,9} Some case reports in families with GERD and Barrett's esophagus by Romero and Lock explained that of 88 siblings, 28% had Barrett's esophagus and 42% had esophagitis or heartburn symptom.⁵

Three case-control studies evaluating reflux symptoms in the families of GERD patients by Romereo et al, found that there was no increase prevalence of reflux symptoms in the families of GERD patients compared to subject control.⁵ In contrast, Trudgill et al, studied on prevalence of reflux symptoms in the first degree family with a variation of GERD severity (positive symptom, abnormal acid exposure in pH assessment, peptic stricture, and Barrett's esophagus) using patients with and without dyspepsia symptoms as the control. It is found that the frequency of reflux symptoms is significantly higher in patient's family with abnormal pH, or Barrett's esofagus.^{5,9} Moreover, Chak et al, found that individuals with Barrett's esophagus and esophagus adenocarcinoma are more likely have positive family history compared to control subjects without Barrett's esophagus or adenocarcinoma. Further study is required to confirm the role of genetic factors in GERD.⁵

Cameron et al, conducted a study in twin siblings evaluating reflux symptoms. They performed telephone interview in 8,401 twin siblings and they found high similarity rate of reflux symptoms for monozygotic twin (31%) compared to dizygotic twin (14%) in equal sexual category. Although it was performed only by telephone interview but this study supported the role genetic factors as etiology of reflux.⁵

A study which is designed to find genetic locus in severe childhood GERD in 5 families found that there are genes maps of chromosome 13q14 in the childhood GERD.⁵

CONCLUSION

Gastroesophageal reflux disorder is a condition with reflux of gastric and duodenal contents into esophagus resulting disruption and varied clinical symptoms that

depend on the severity of disease. The reflux may be found in normal condition. However, if it is prolonged then it may cause pathological condition.

Factors that have a role in GERD development includes aggressive factors such as gastric acid and pepsin derived from the stomach, bile acid and trypsin derived from duodenum which has a potency to cause esophagus mucosa injury and disturbed defensive factor such as TLESR, hypotensive LES, crural diaphragm, weak phrenoesophageal ligaments and other factors i.e. *Helicobacter pylori* and genetic factor. Normally, there is a balance between aggressive and defensive factors. Nevertheless, when there is imbalance of such factors, GERD will be developed.

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