The Pathogenesis and Diagnosis of Bile Reflux Gastropathy

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ABSTRACT

Bile reflux gastropathy is a disease caused by reflux of duodenal fluid to the gaster. This fluid contains pancreatic juices and duodenal secretion. The manifestations that occur depend on the frequency, amount, and duration of reflux. This disorder is quite rarely recognized in daily clinical practice. Endoscopy of the upper gastrointestinal tract is required to establish the diagnosis of this disorder. This paper will give a brief view of the pathogenesis and diagnostic method for this disorder.

***Key words**: Gastropathy, bile reflux, motility.*

INTRODUCTION

Bile reflux gastropathy (BRG) is a clinical condition that is relatively unrecognized in daily practices. This is because there is no accurate yet simple, affordable, and practical method to diagnose this condition. Diagnosis of BRG requires endoscopy of the upper gastrointestinal tract, and its clinical complaint is hard to identify.

In daily practice, many patients come with a chief complaint of nausea, gas in the stomach, and epigastric discomfort. Coming up with a diagnosis is sometimes very difficult without the aid of endoscopic examination.

Duodenogastric reflux is a pathologic condition in the form of backward flow of duodenal fluid that consists of bile, pancreatic juices and secretions of the intestinal mucous.[1] Such a condition can occur asymptomatically in normal subjects, but can often manifest as serious clinical conditions.[2]

In Indonesia, cases of BRG are rarely reported. In Padang, 11.53% (46/399) of endoscopic examinations from the year 1981 to 1983 turned out to be BRG cases.[6] In Medan, from January 1985 to 1988, out of 127 patients with gastritis of the antrum, 25 patients suffered from BRG.[7] At the Persahabatan Hospital, Jakarta, in a two-year research period from October 19th 1987 to October 19th 1989, there were 44 patients with BRG out of all patients who underwent endoscopy.[8] Daldijono reported a prevalence rate of 4.5% out of 600 patients with dyspepsia who underwent endoscopy of the upper gastrointestinal tract.[9] We reported a prevalence rate of 6.02% (KOPAPDI 1999) out of all patients with dyspepsia who underwent endoscopy of the upper gastrointestinal tract at the Tebet Hospital for 7 years from the year 1992 to 1999.

PHYSIOLOGY OF THE BILE AND PANCREATIC JUICES

The pancreas secretes approximately 1500-3000 cc of juices daily. This fluid is alkaline with a pH above 8, amilolytic, lypolytic, and contains abundant electrolytes, especially sodium bicarbonate.

The amilolytic enzyme of the pancreas is amylase which hydrolyses starch into oligosaccharides and disaccharides, while the proteolytic enzyme is endopeptidase (tripsin and chemotripsin) which breaks apart protein peptide chains.

Lypolytic enzymes include lipase, phosphorilase A, and cholesterolesterase which hydrolyse fat into glycerol and fatty acid.

Secretin stimulates secretion of pancreatic juices, containing especially water and electrolytes, while cholecystokinin – pancreosimin stimulates secretions rich in digestive enzymes.

Gastrin also stimulates pancreatic secretion, but not as much as the two hormones mentioned above. The

parasympathetic branch of the vagal nerve also stimulates pancreatic secretion, directly and with the aid of gastrin.

The liver secretes approximately 200-1000 cc of bile daily, containing water, electrolyte, mucous, bile salts, bile pigments, and the lipid lesithin, phospholipid and cholesterol. These substances are secreted from the hepatic lobules into the bile vessel, then to the duodenum.

In the intestines, bile acts as a vital detergent for the absorption of fat. During fasting, the Oddi sphincter contracts, thus blocking bile flow into the duodenum. This bile then flows back into the bile duct to be stored and becomes highly concentrated.

The hormone cholecystokinin is secreted by the duodenal mucous membrane as a result of stimulation by fatty and protein rich foods, which contract the bile duct and relax the Oddi sphincter, thus letting bile flow out of the duodenum.

The vagal nerve, secretin hormone, atropine and pilocarpine stimulate bile secretion, while the sympathetic nerve, adrenaline, morphine and fasting prevents bile secretion.

MOTORIC PHYSIOLOGY OF THE GASTER

Based on its motoric function, the gaster is divided into two parts

1. The proximal portion
2. The distal portion

The location of the boundaries between the two portions differs from its division based on the physiology of acid secretion, where it is divided into the secretoric and non-secretoric portions.

Motility of The Proximal Portion of The Gaster

The proximal portion of the gaster (the fundus and 1/3 of the upper corpus) is marked with tonic contraction and slow relaxation. In this portion, there is no peristaltic contraction of the gaster. When a person swallows, this portion loosens together with the relaxation of the lower esophageal sphincter (LES). Such loosening occurs for 10 seconds and is called receptive relaxation. As more food enters the proximal portion of the gaster, relaxation time lengthens, allowing the gaster to fill up with more food without increasing intraluminal pressure. This phase is called adaptive relaxation.

Motility of The Proximal Portion of The Gaster

Motility of the lower portion of the gaster consists of systematic peristaltic contractions towards the pylorus. The contraction of the pylorus itself is tightly connected to the contraction of the antrum and the proximal portion of the duodenum. The peristaltic wave of the lower portion of the gaster spreads in a circular manner towards the distal with a cycle of 3 times every minute, seen as a ring contraction on the gastric wall.

The main function of the distal gaster is to grind solid foods. This grinding process is assisted by gastric acid by changing the solid foods into small particles in fluid, or so called chyme, which is then passed to the duodenum. Peristaltic contraction from the antrum towards the pylorus forces the gastric contents downwards. Just before the peristaltic wave reaches the distal portion of the antrum, the pylorus closes. This array of events is what is called the terminal antrum contraction sequence, which allows the antropyloric segment to act as a sorter, where particles less than 1 mm will pass into the duodenum, while larger particles are returned into the upper portion of the gaster for further grinding.

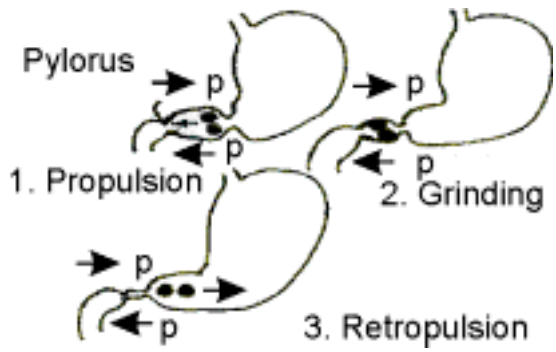

Figure 1. Cinefluoroscopy examination demonstrating the unique movement pattern when the distal portion of the gaster and the pylorus contract, capturing, blending and expulsing solid foods back in to the proximal portion of the gaster due to closure of the pylorus

The Process of Gastric Emptying

Food components have different consistencies. Fluid foods pass through the gaster most rapidly. The process of emptying fluid foods occurs due to a pressure gradient between the gaster and the duodenum, while this gradation is determined by the tonus of the proximal portion of the gaster.

The time needed by the gaster to empty itself depends on the composition of the chyme inside the gaster, while fat is the last to be evacuated.

Interdigestive Motility and Gastric Emptying

The process of gastric emptying usually occurs several hours after meals, and continues until the gaster is empty. Once empty, the gaster moves in a manner particular to fasting. This systematic and repetitive movement begins at the proximal portion and LES, slowly moving towards the small intestines. This phenomena is called the interdigestive motor complex (IMC) or the migrating motor complex (MMC), consisting of 3 sequential phases.

- Phase 1: There is no movement for 15 minutes.
- Phase 2: Intermittent contractions similar to what occurs during digestive status, occuring for 40 minutes.
- Phase 3: A period of strong rhythmical peristaltic contractions for approximately 5 minutes.

During phase 3, the gastric antrum contracts with a maximum frequency of 3 times per minute. During this phase, indigestible foods are expulsed from the gaster.

GASTRIC BALANCE

The gastric mucous membrane secretes hydrochloric acid (HCl) and the proteolytic enzyme pepsin. These two substances, besides being necessary for the physiologic process, are also a combination that could potentially destroy its own gastric mucous membrane (autodigestion).

Under physiologic conditions, the gastric mucous membrane remains resistant to this process of autodigestion due to protection from external forces.[10] In other words, there is a balance between aggressive and protective forces that maintains the integrity of the gastric mucous membrane (cytoprotection). Under certain conditions, this cytoprotective mechanism could be reduced, while aggressive forces increase, thus creating a lesion in the gastric mucous that results in pathologic conditions.[11,12]

A general theory on the pathophysiology of acute upper gastrointestinal tract mucous disorder including bile

Defensive factors:	**Aggressive factors:**
Mucous	Gastric acid
Bicarbonate	Pepsin
Prostaglandin	Bile reflux
Phospholipid/surfactant	OAINS
Surface epithelial cell	Corticosteroid
Mucous blood flow (micro-circulation)	Alcohol
Motility	Nicotine
	Helicobacter pylori

Figure 2. The balance theory of the gastrointestinal tract mucous integrity, especially of the gaster and duodenum.[12]

reflux gastropathy is known as the balance theory of the defensive and aggressive factors, as summarized below:

Defensive Factors

1. Mucous

   Mucous is a gel secreted by the cells of the gastric mucous membrane of the fundus, corpus and antrum. This mucous consists of glycoproteins and glycosaminoglycans. It does not dissolve in water and it covers the inner lining of the whole gaster. The mucous layer acts as a lubricant that disturbs re-diffusion of H^+ ions, maintains pH balance between the lumen and the surface of the mucous membrane, and may also act as a bacteriocide.[13]
2. Bicarbonate

   Bicarbonate is produced by the epithelial cells of the gastric mucous membrane. Some of it enters the lumen, while a larger portion remains under or inside the mucous layer, so that the gastric mucous membrane remains in a neutral pH condition, even though the lumen is acidic. Re-diffusion of H ions is blocked by the mucous layer, neutralized with HCO_3^- to maintain a pH of 7.4 on the surface of the mucous membrane. Thus, the mucous-bicarbonate are essential barriers for the protection of the mucous membrane from aggressive factors such as HCl, pepsin, and other substances.[14]
3. Cell regeneration

   The surface epithelial cells are generated from gland cells near the surface of the gastric lumen. Thus, a destruction of the mucous-bicarbonate barrier would cause the gastric conditions to highly influence such regeneration. [14]
4. Mucous blood circulation

   Adequate blood supply is vital for the maintenance and functioning of the epithelium, both for aerobic metabolism, mucous-bicarbonate production, as well as cell regeneration, to maintain the barrier of the mucous membrane. [14]
5. Prostaglandin

   Prostaglandin is produced and secreted by the epithel of the gastric mucous membrane. Prostaglandin is a saturated long-chain fatty acid made up of twenty carbon atoms formed from the metabolism of arachidonic acid.[15,16] To date, 20 prostaglandins have been discovered in the body tissue and fluids, and more have been synthesized as analogs of natural prostaglandins.[15]

Aggressive Factors

1. Hydrochloric acid

   Secreted by parietal mucous stomach cells, with approximately 1 million times the concentration of H^+ ions found in blood. Its secretion is mainly stimulated by the hormone gastrin as well as the vagus nerve, histamine and food. Once the pH of the stomach is low (pH=3) secretin, cholesistocinin, somatotostatin and glucagon inhibit HCl secretion.
2. Pepsin

   The precursor of pepsin, pepsinogen is secreted by the chief cells. Once secreted into the gastric lumen it is converted by HCl into active pepsin. This conversion is optimal at a pH of 1.8-3.5. Pepsin cleans the mucous in phases. The proteolitic action of pepsin and the corrosive effect of HCl form a combination which can cause gastric lesions.

PATHOGENESIS OF BILE REFLUX GASTROPATHY

Aside from internal factors mentioned above, there are still external factors that could potentially destroy the gaster, such as physical and chemical forces, radiation, medicine, alcoholic beverages, and psychologic stress. Physical stress includes severe illness and duodenogastric reflux. Duodenogastric reflux occurs in normal subjects during fasting or after overeating. In gastric conditions such as peptic ulcer, cholelithiasis or after gastric operations, there is continuous reflux at a greater rate than in normal subjects.[17]

The mechanism of duodenogastric reflux is still unclear. Some researchers proved that in patients with peptic ulcer, the motility of the antrum is greatly reduced, and in most of them, a high concentration of bile is found in the gastric fluid, both during fasting and after meals.[18,19] Weak motility of the antrum, even in cases were the duodenum is normal, would result in duodenogastric reflux.[17] Many patients with chronic gastritis of the antrum demonstrate normal antrum motility, and yet many of them have high concentrations of bile in their gastric fluid. This is associated with pyloric sphincter incontinence.[19]

Other researchers associate duodenogastric reflux with abnormalities in pressure changes during peristalsis, thus resulting in incoordinated antroduodenal motility. That creates a chance for reflux of the duodenal contents into the gaster.[3,4] This could also occur in patients who underwent partial gastrectomy, where absence of the pyloric sphincter facilitates duodenogastric reflux.[20]

Other than food, the duodenum also contains bile salts and pancreatic juices in high concentrations. If reflux occurs, all of these contents enter the gaster, creating a

pathologic condition in the form of gastritis and all its clinical manifestations. This condition is known as bile reflux gastropathy.[3] However, this reflux condition does not always manifest clinically. The clinical condition depends on the amount of fluid, constituent concentration in the reflux fluid, the length of contact time with the gastric mucous membrane, and the degree of sensitivity of the gastric mucous membrane.[3,2,1]

Of all of the contents of the duodenum, the bile and pancreatic juices are most potentially destructive to the gastric mucous membrane.[4] The concentration of these two fluids also determines the extent of the symptoms. Chenodeosycholic acid is more toxic than trihydroxicholic acid. This is probably due to its more lypophillic characteristics, abling it to penetrate deeper into the lipid structure of the cell membrane.[1]

A study demonstrated that both bile and pancreatic juices could result in chronic gastritis if one of them flows into the gaster over a long period of time (200 days), while gastritis worsens if both are present at once. The mechanism is still unclear.[22] Another researcher stated that bile and pancreatic juice break down the barrier of the mucous on the mucous membrane, which then destroys the underlying layers to induce inflammation.[11,12,13]

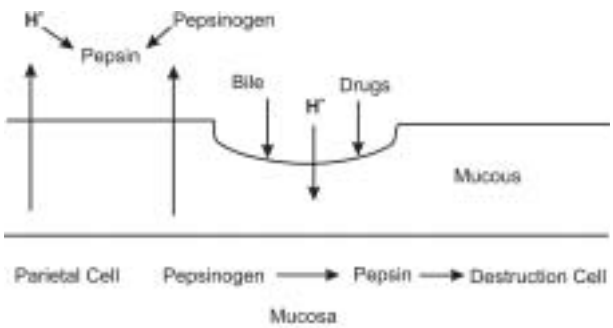

Figure 3. Destruction of the mucous barrier, re-diffusion of H^+ ion and conversion of pepsinogen into pepsin[11]

In an experiment, rats that were given bile meals for 3 months suffered from erosive gastritis, while in another experiment, rats that were given bile meals for 200 days suffered from atrophic gastritis. The two groups suffered from lesions especially in the pyloric region.[22]

It has also been proven that bile causes a reduction in the transmembrane potential of the gastric mucous, increasing H^+ ion re-diffusion, and increasing sodium ion concentration in the gastric lumen.[23] These effects increase with high concentrations of bile (20 mM) and low pH (pH=2).

There is another opinion that bile causes destruction of the gastric mucous through degeneration of mast cells and the subsequent release of large amounts of histamine into the lumen.[24,25]

Another study found that bile causes instability of the lysozome of the mucous cell.[5] This lysozom disturbance results in the outflow of proteolytic lysozome enzymes into the cytoplasm of the cell, consequently causing degeneration and disturbance of cellular metabolism. Aside from that, the pores of the mucous membrane also become dilated. These two events affect the permeability of the mucous membrane.

With the destruction of the mucous, the permeability of the membrane against H^+ ion increases, facilitating H^+ ions movement into the mucous membrane. In the mucous membrane, the H^+ ions activate the pepsinogens, which then turn into pepsin that destroys the mucous membrane further. The H^+ ions that enter the mucous membrane would also cause degranulation of mast cells,[25] which then release histamine into surrounding tissues. Histamine causes vasodilation of the capillaries of the mucous membrane, increasing their permemability and causing edema of the mucous membrane.[24]

The histamine released would also stimulate parietal cells to secrete more HCl into the lumen of the gaster, further increasing the concentration of the H^+ ions that undergo re-diffusion, thus creating an endless chain of reactions.

Aside from the events listed, several researchers also found during research on animals that the presence of bile in the gaster could increase the secretion of the hormone gastrin, which stimulates HCl secretion and reduces blood circulation in the mucous membrane thus disturbing tissue regeneration.[26]

An important fact to be noted is that bile in the gastric fluid causes reduction of PGE2 secretion by the epithelium of the gastric mucous membrane, thus reducing its cytoprotective function. Unfortunately, the mechanism for the reduction of PGE2 secretion remains unclear.[11]

In the pancreatic juices, phospholipase A and lysolesithin are known to be able to directly destroy the barrier of the mucous membrane. Phospholipase A is a pancreatic enzyme, while lysolesithin is a product of lesithin after dehydrolysis by phospholipase A. After the mucous barrier is destroyed, consequent events are similar to those that occur with the presence of bile, re-diffusion of H^+ ions and all its consequences which result in lesion of the gastric mucous membrane.

CLINICAL SYMPTOMS

Clinical symptoms of bile reflux gastropathy are unspecific. In general, symptoms resemble gastritis due to other causes. There is often no relationship between the extent of gastropathy and the symptoms.[8]

Patients commonly complain of discomfort in the upper gastrointestinal tract, gas in the stomach, nausea, and heartburn, often related to meals. Patients usually feel pain during meals, feel better soon afterwards and start feeling discomfort again after about 3 hours.[11]

There is often nausea and vomiting with severe even colic-like heartburn. If the patient vomits, the vomit often contains yellowish green bile, and the patient feels relieved afterwards.[11]

DIAGNOSIS

Clinical diagnosis is based on history, physical examination, endoscopic examination, and hystopathology.

The pathogenesis of BRG is defined as a chronic, continuous condition where the contents of the intestines undergo reflow to the gaster, both through an intact pylorus with a dysfunctional sphincter or through a passage created after gastric operation.[21]

The main problems that cause BRG in a patient that has undergone gastric operation are dysfunction of the pyloric sphincter and abnormal motility of the duodenum.[1]

The diagnosis of BRG is based on history, clinical manifestation, measurement of bile fluid in the gastric and proximal intestines, radiologic findings, endoscopic findings, and histologic findings of the gastric mucous.[5]

Reflux that does not manifest clinically differs from the reflux in BRG in its frequency, amount of reflux, and duration of illness.[2]

From endoscopy, BRG is based on the presence of bile in the gaster, with adherence of bile on the gastric mucous membrane in the form of crusts and changes in the mucous membrane. The mucous membrane becomes hyperemic, frail, and erosive. Clinically, the patient complains of a feeling of fat in the throat, intolerance to milk, and vomit containing bile.[27]

Histopathologic examination demonstrates inflammatory reaction, foveolar hyperplasia, edema, increased smooth muscles in the lamina propria, as well as dilation and congestion of the blood vessels. These findings are identical to the findings in gastropathy due to NSAID.[21] There is no specific pathologic or pathognomonic findings to confirm this diagnosis.

CONCLUSION

1. Cases of BRG are rarely reported due to special procedures required to confirm the diagnosis.
2. The pathophysiology of BRG is well known, even though further research is still required to understand this condition further.
3. Diagnosis is based on clinical findings with the aid of endoscopic and pathologic findings.
4. There is no pathognomonic pathologic finding to confirm BRG.

REFERENCES

1. Niemela S. Duodenogastric reflux in patients with upper abdominal complaints or gastric ulcer with particular reference to reflux-associated gastritis. Scand J. Gastroenterol 1985:20 Suppl 115:1-56.
2. Mackie C, Hulks G, Cuschieri A. Enterogastric reflux and gastric clearance of refluxate in normal subjects and in patients with and without bile vomiting following peptic ulcer surgery. Ann Surg 1986;204(5):537-42.
3. Janowitz HD. Bile in the stomach. Gastroenterol 1969;57:356-357.
4. Duane WC, Weigand DM, Gilebertstadt ML. Intragastric duodenal lipids in the absence of Pyloric sphincter. Quantitation, physical state and injurious potential in the fasting and postprandial states. Gastroenterol 1980;78:1480-1487.
5. Meshkinpour H, Mark JW, Schoenfield LJ, Bonoris GG, Carter S. Reflux gastritis syndrome. Mechanism of symptoms. Gastroenterol 1980;79:1283-1287.
6. Yulius. Gastritis. Dalam: Naskah lengkap simposium dispepsia gastrointestinal. Panitia konas IV PGI-PEGI, pertemuan ilmiah V PPHI. Padang;1986:77-82.
7. Marpaung B. Refluks gastritis. Naskah lengkap simposium dispepsia gastrointestinal. Panitia konas IV PGI-PEGI, pertemuan ilmiah V PPHI. Padang;1986:22-26.
8. Simadibrata M, Daldiyono H, Simadibrata R, Zulkarnain I, Ali I, Rani AA, Manan C. Gastritis refluks empedu ("Bile reflux gastritis"). Acta Medica Indonesiana 1990;22(2):65-69.
9. Daldiyono H. Aplikasi ilmu dan teknologi endoskopi dalam bidang gastroenterologi ilmu penyakit dalam. Pidato pada acara pengukuhan sebagai guru besar tetap dalam ilmu penyakit dalam pada fakultas kedokteran universitas indonesia. Jakarta 1997.
10. Kelly KA. Motility of the stomach and gastroduodenal junction. In: Johnson LR,ed. Physiology of the gastrointestinal tract. New York:Raven,1983:393.
11. Amiruddin R. Gastritis refluks Empedu. Naskah lengkap kongres nasional IV PGI,PEGI. Pertemuan ilmiah V PPHI. Jakarta;1990:45-59.
12. Talley NJ, Mc Neil D, Piper DW. Discriminant value of dyspeptic symptoms: a study of the clinical presentation of 221 patients with dyspepsia of unknown cause, peptic ulceration and cholelithiasis. Gut 1987;28:40-46.
13. Jones Ct. Gastric mucus, physycal propertiein cytoprotection. Med. J. Australia,1985;142 (Supp):S5-S7.
14. Valle JD, Lucey MR, Yamada T. Gastric secretion. In: Textbook of Gastroenterology, 3th edition. Lippincott Williams and Wilkins. 1999.
15. Russel RT. Prospective effects of the prostaglandins on the

gastric mucosa. Am J. Med.1986;81(2A):2-4.
16. Sewel RB. Prostaglandins, role in the gastric mucosal cytoprotection.Med.J. of Australia.1985;142:S10-S12.
17. Tollin RD,Malmud LS,Stelzer F, Menin R, Makler PT,Applegate G,et al. Enterogastric reflux in normal subjects and patients with Billroth II gastrenterostomy. Measurement of enterogastric reflux. Gastroenterol 1979;77:1027-33.
18. Fisher R,Cohen S. Physiological characteristic of the human pyloric spinchter. Gastroenterol 1973;64:67-74.
19. Rhodes J, Bernando DE, Phillips SF, Revalstad A, Hoffman AF. Increased reflux of bile into the stomach in patients with gastric ulcer. Gastroenterol 1969;57:241-51.
20. Toye DKM, Williams JA. Postgastrectomy bile vomiting. Lancet,1965;11:524-26.
21. Yamada T. Chronic chemical gastropathy, common forms of gastritis and gastropathy. In: Textbook of gastroenterology,3th ed. Lippincott Williams and Wilkins,1999.
22. Lawson HH. Effect of duodenal content on the gastric mucosa under experimental condition. Lancet 1964;I:469-73.
23. Black RB, Hole D, Rhodes J. Bile damage to the gastric mucosa barrier. The influence of pH and bile acid concentration. Gastrenterol 1971;61:678-83.
24. Rees WDW, Rhodes J. Wheeler MH,Meck EM,Newcomb RG. The role of histamine receptor in the patophysiology of gastric mucosal damage. Gastroenterol 1977;72:67-61.
25. Rees WDW, Rhodes J, William BC, Owen E, Newcomb RG. Effect of mast cell degranulation on gastric mucosal damage produced by sodium taurocholate in rats. Gastrenterol 1978;74:492-95.
26. Levine JS, Coonan JE, Kern F. Effect of antaral instillation of bile salt on fasting serum gastrin level. Dig Dis.Sci1980;25:449-452.
27. Kim BJ, Kleba T. Gastroscopic criteria and most frequent pain in bile reflux gastritis. Pol Merkuriusz Lek, 1998;4(22):190-2.