Pathogenesis in Portal Hypertensive Gastropathy Due to Liver Cirrhosis

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ABSTRACT

The recent advances of endoscopic examination had proven that source of upper gastrointestinal bleeding in liver cirrhosis is not always caused by esophageal varices rupture but also gastric mucosal lesion. The prevalence of gastric ulcer in patients with liver cirrhosis is higher than healthy individuals. Imbalance of defensive and aggressive factors of gastric mucosa may involve in development of portal hypertensive gastropathy (PHG). Several studies reported hemodynamic changes associated wuth portal hypertension causing decreased mucus layer thickness as one of mechanism of PHG. Other etiologic factors of PHG were hypoacidity, hypergastrinemia, reduced hexosamin concentration, mucus metabolic function associated with decreased prostaglandin E2, and increased nitric oxyde which had caused mucus wall thickness changes. Gastric mucus damage induced by portal hypertension has important role in the pathogenesis of gastric ulcer in liver cirrhosis.

Keywords: *Pathogenesis, PHG, liver cirrhosis*

INTRODUCTION

The development of fiber optic technology in the 70's had helped to identify the source of upper gastrointestinal bleeding which was not always caused by rupture of esophageal varices but also gastric mucosal lesion.[1,2] In 1985, Mc Cormack et al., had mentioned that morphologic study described vascular dilatation in mucosa and submucosa without inflammation. Thus, the gastric lesion was more likely due to congestion than gastritis.[3]

Gastric mucosal lesion in patients with portal hypertension had been identified on agreement in the Baveno II Consensus in Italy (1996) with the term portal hypertensive gastropathy. Diagnosis of portal hypertensive gastropathy (PHG) is based on combination of endoscopic and histopathologic findings indicates changes in gastric mucosal conditions associated with the presence of dilatation and vascular ectasia of mucosal and submucosal microvascular structure without significant evidence of inflammation.[3-6]

Endoscopic description of gastric mucosa in PHG according to OMED may be classified into mild and severe grade. Scarlatinna rash, snake skin appearance or mosaic pattern appearance indicate mild grade, while cherry red spot and black brown spot of diffuse mucous bleeding are sign of more severe grade.[7]

The prevalence of PHG is increased in accordance with severity of liver disease.[8] Mortality rate depends on Child Pugh classification. Almost 90% patients with of Child Pugh C liver cirrhosis will die in 12 months.[7]

Initial bleeding had high mortality rate of 50%, while recurrent bleeding had 70% in one year period.[9] Sarin et al., reported the incidence of PHG was varied from 4% to 98% with prevalence of 53% portal hypertension due to liver cirrhosis.[5] Incidence of PHG had been reported to worsen after variceal eradication by sclerotheraphy with higher risk of bleeding. Variceal ligation had lower

risk of bleeding possibly because ligation does not cause total variceal obliteration and allow redistribution of blood in gastric and esophageal mucosa.[5,8] On the other hand, Viegeneri reported no correlation between endoscopic findings, Child-Pugh score and esophageal varices grading (Beppu score).[10] Cales et al., also found no significant correlation between the incidence of gastropathy and Child-Pugh score.[11]

The exact mechanism and pathogenesis of PHG remains unclear, but portal hypertension might be caused by vascular resistance, increased pressure in portal system and many humoral factors involved.[1,12] How the blood flows in the mucosa of PHG is still controversial. Several researcher found association between size of varices with hepatic portal venous pressure gradient and the incidence of PHG.[11] Most of studies had reported decreased blood flow gastric mucosa due to congestion, while Iwao et al stated that PHG was caused by increased portal pressure and reduced hepatic blood flow.[11] Study by Linn et al., indicated that portal pressure was the only cause of PHG. The controversies continued on blood flow in gastric mucosa. Some reported it was increased in PHG while the others reported the other way around. Experimental study by Imanishi using rat as animal model showed that hemodynamic changes due to PHG may cause thinning of mucus layer in gastric mucosa.[6]

Gastric acid secretion activity decreased because gastric mucosal barrier is damaged, thus it causes local hemodynamic changes resulting active and passive congestion and hyperemic gastric mucosa.[13] Humoral factors have role in PHG by decreasing mucosa metabolic function, decreased response to pentagastrin, decreased mucosa glycoprotein, decreased prostaglandin E2 (PGE2) level and increased nitrite oxide (NO) synthesis. All these will make the luminal gastric acid decreased and cause reduced response of defensive factors to intraluminal stimulation of inciting factors such as H^+ back-diffusion, bile acid and non steroidal anti-inflammatory drug (NSAID). All may cause electrical potential changes in the mucosa and increased fragility of gastric mucosa to injury.[14-17]

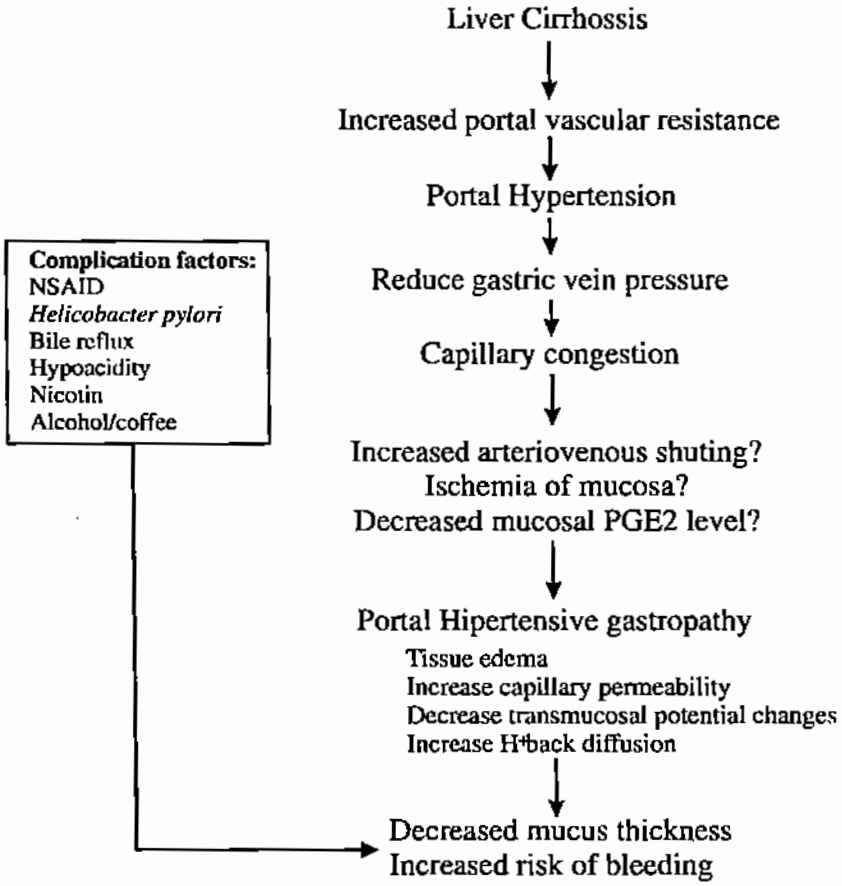

Figure 1. Pathogenesis of PHG Theory [1,6,11,15,17]

Defense mecanism of gastroduodenal mucosa

In normal condition, there is balance between aggressive and defensive factors. When the aggressive factors reach beyond the defensive factors, disease will occur.[18] The well-known theory called balance theory refers to balancing between aggressive and defensive factors. The aggressive factors are gastric acid, pepsin, bile reflux, drugs (corticosteroid; NSAID), food and drinks (acid; alcohol), smoke (nicotine) and infection (*Helicobacter pylori*). The defensive factors mucus, bicarbonate, prostaglandin, surface epithelial layer, mucus blood circulation (micro circulation and motility) and hexoxamin.[18,19] The defensive factors have role in defense mechanism or cytoprotection. It refers to the ability of epithelial mucosal cells to defense from any insult that can damage the integrity of mucosa. Mucosal integrity consists of 3 components; pre-epithel, epithel and subepithel.[18-20] The pre-epithelial component has the protective role. The mucus functions as barrier to support the neutralization of hydrogen ion by bicarbonate secretion to maintain normal pH gradient on mucosal epithelial layer in order to prevent injury from insulting agents.[18-21]

Gastric mucosa and duodenum are layered by mucus barrier of pH and bicarbonate, while it also covered by thick mucus gel, connected by gelatinous layer. Cecillia et al., found that mucus thickness was ranging from 50 mm to 450 mm,[21] while others found it thinner between 73 mm and 145 mm. Mucus contains 95% of water and 5% of glycoprotein which keeps on secreted dynamically by mucous glands. It consists of several layers and can protect from acid and pepsin. Mucus function not only to protect before the lesion is formed but it can help healing process and work as lubricants to prevent mechanical damage during digestive process.[18-21]

Gastric glands have several layers. The upper layer called submucosa layer, muscularis layer, mucus secreting cells and mucus layer and finally the lumen.[20-22] About 75% gastric glands found in corpus in parietal mucosa (oxyntic) and are in charge in acid secretions. Parietal mucosa consists of parietal lining cells, chief cell (zymogen), mucus neck cell and endocrine cell.[22] Lining epithel in gastric lumen are thick folds called rugae. The thickness of the epithelial layer and rugae are different for each part of gaster. Gastric surface epithelial cells which invaginated microscopically are called gastric pit. Each epithelial cell contains mucus cell and endocrine cell. Every 1-3 days the epithelial cells migrate to upper part of folveulus to prevent injury induced by acid, pepsin, food and other pathogenic agents through mucus and bicarbonate secretion forming protective secretion layer.[21,22]

About 50% of endocrine cells are G-cells which placed in antrum, other 30% secrete serotonin and 15% produce somatostatin which are distributed in the antral mucosa and oxyntic. G-cells not only produce gastrin but also contain adrenocorticotropic hormone (ACTH). Gastrin is main growth factor for oxyntic mucosa and directly stimulates cell proliferation. In continuous hypergastrinemia, both parietal cells and mucus cells increase the number of G-cell associated to increased acid secretion.[21]

Gaster in liver cirrhosis

Sergio Vigneri et al., studied three subject groups of patients with cirrhosis and portal hypertension, cirrhosis without portal hypertension and control group.[10] It was found that the most frequent endoscopic findings were snake skin (75%), scarlattina rash (70%) and petechiae (60%) in patients with cirrhosis and portal hypertension and no characteristic of inflammation in gastric mucosa. Gastric mucosa in patients with cirrhosis indicated the association with portal hypertension.[13] Reference data showed that vasculopathy is characteristic for congestive gastropathy in patients with portal hypertension. Quintero et al., found that ectasia description in capillary area in antral mucosa with red spot in cirrhotic patients is associated with hypergastrinemic condition.[14] A study by Lam was supported this finding. Gastrin level was signicant higher than in control subjects. The presence of mucosal abnormalities can be observed by endoscopy had showed that there were 2 conditions of portal hypertension: gastropathy and varices. PHG criteria had been used according to Mc Cormack et al., also NIEC and OMED, while the severity of varices is determined by the level of variceal protrusion into lumen of esophagus.[3,7,23]

The evaluation of gastric mucosa by endoscopy includes that PHG must be seen in proximal of gaster (fundus/corpus) with or without disorders in the antrum. If the abnormalities were only found in the antrum, it is not considered PHG.

Gastric mucosa is constantly exposed to dangerous substances such as hydrochloric acid, pepsin, lysolecithin, bile acid and exogenous factors like alcohol, NSAID, etc. To protect against all those agents, gastric mucosa has defense mechanism. Tanoe et al., found that defense mechanism in patients with portal hypertension was reduced compare to control.[12] On the

Table 1. Mucosal Appearance of PHG[2,3,6]

Mild PHG	Severe PHG
Scarlatina type rash	Red spots
Mosaic pattern, snake skin	Diffuse hemorrhagic gastritis
Superficial reddening	

other hand, Kitano et al., found the imbalance of aggressive and defensive factors in patients with cirrhosis compare to non cirrhotic patients.[15] Aggressive factors e.g. *Helicobacter pylori* infection, acid and pepsin only had little influence in the pathogenesis of gastric ulcers in cirrhosis. Portal hypertension tended to decrease incidence of *Helicobacter pylori* infection and reduced gastric acid secretion but the prevalence of gastric ulcers was increased. Toyonaga et al., reported prevalence of gastric ulcer (20%), gastric erosion (44%), while Chen et al., reported gastric ulcers (20.8%) in liver cirrhosis.[4] Based on these findings, it was assumed that portal hypertension as one etiologic cause of increased prevalence of gastric lesion in patients with cirrhosis.

Aggressive factors in liver cirrhosis

1. *Helicobacter pylori* infection
   Mc Cormack et al., found the prevalence of *Helicobacter pylori* colonization was 26% compare to 38% in control group.[3] In addition, *Helicobacter pylori* was found to decrease the severity of PHG. It was assumed that gastric mucosa in patient with PHG did not provide suitable environment for *Helicobacter pylori* colonization.[16] On the other hand, Kitano et al., did not found correlation between *Helicobacter pylori* prevalence and severity of PHG or esophageal varices.[15]
2. Gastric acid secretion
   Gastric acid secretion in liver cirrhosis is generally less than usual or normal at least.[24] Most studies only measured basal or stimulated acid secretion. Only one study had evaluated gastric acidity for 24 hours in liver cirrhosis.[25] Hypoacidity was found more in patients with liver cirrhosis than in control group. The mechanism of reduced acid secretion in liver cirrhosis remains unclear. Gaur et al., did not find correlation between acid secretion and hepatocelullar dysfunction severity in liver cirrhosis. Conversely, Ferraz & Wallace found epithelial acidification rate in response to acid load correlated with mucus gel thickness in tetrachloride induced liver cirrhotic mice.[17] Pentagastrin stimulated gastric acid secretion less in PHG than in control group. These finding indicated that portal hypertension might be responsible in reducing acid secretion in PHG.[15]

Defensive factor in liver cirrhosis

1. Gastric mucosal modulator
   The main modulators of gastric mucosa are prostaglandin and NO. The gastric mucosa might be susceptible to injury caused by suppressed endogenous prostaglandin (PGE) production. Gastric PGE2 is reduced in cirrhosis, thus decreased prostaglandin level on gastric mucosa is associated with portal hypertension. Research data showed suppressed generation of gastric prostaglandin was one of mucosal defense mechanism in portal hypertension.[15] However, little known about NO production in portal hypertension. This might be due to difficulties in measuring NO concentration directly. Gastric constitutive NO mRNA was found increased in mice with portal hypertension. Ohta et al., found that normalization of NO synthesis activity was associated with less mucosal injury. It was assumed that excessive inducible NO might be cytotoxic and had role in increasing gastric mucosa susceptibility in portal hypertension.[15]
2. Gastric mucosal blood flow
   Gastric mucosal blood flow has important role in defense mechanism because it is responsible to allow back diffusion in order to eliminate toxin and inciting agent of injury.[12,17] About 90% gastric blood in human flows through the mucosa. Hemodynamic changes in animal model may induce portal hypertension.[6] hemodynamic and morphologic studies had showed ischemic condition in gastric mucosa was in accordance with increased submucosal blood flow. Soto found congestion and blood stasis in mucosa had reduced oxygen perfusion. Gastric mucosal congestion and hypoxia had caused the mucosa susceptible to aggressive factors.[17] Change in mucosal blood flow in patients with PHG is still controversial. Iwao et al., reported decreased perfusion. These controversies emerged caused by lack of adequate methods for measuring blood flow in human. Any changes occur in gastric mucosal blood flow in portal hypertension, the presence of hyperemic mucosal appearance indicates damaged mucosal resistance caused by dangerous agents.[28]

3. Gastric mucus in portal hypertension

There has not been study to evaluate the role of mucus in PHG and its association with mucus thickness in human. Imanishi et al., had done the study on mice and concluded that pathogenesis of bleeding in PHG might be associated with decreased mucus thickness and condition.[6] Gastric mucus thickness was also found to be reduced in cirrhotic mice like shown by in vivo study microscopically. It was assumed to be related with potential differences in cellular homeostasis.[17] Defensive factors capacity in response to intra luminal stimulation is decreased due to induction by aggressive factors make the mucosa more susceptible and prone to bleeding.[1] Mucus layer which covers gastric mucosa is secreted by mucus secreting cells induced by acid, pepsin and luminal fluid flow. Thickness of mucus layer is dynamic and depends on balance of mucin production by mucus secreting cell in the apical part of the surface. In PHG there are hemodynamic changes in gaster that can reduce mucus production and alter the mucus structure.[26-28]

Visualization of mucus gel layer histologically is difficult, that is why preservation technique and analysis were developed by various methods. Mucus thickness of gastric mucosa layer in mice was varied from 73 mm to 145 mm, but other study using frozen section found the mucus thickness between 23.9 mm and 53.7 mm. This difference might be due to different study methods and technical procedure.[6,21,22]

Gastric mucus is important component of gastric defense mechanism. Basic components of gastric mucus are mucus gel layer and mucinous contain. Mucus production has important role in coping with mild irritation which can damage sitoprotective adaptation of gastric mucosa in PHG such as reduced concentration of hexosamin[14] and decreased mucus production.[28] Iwao et al., found that PHG had reduced production of antral gastric mucus. Gastric mucosal hexosamin level may be used as quantitative parameter of mucus generation. Hexosamin is known to be gastric mucosal defensive factor.[28] Kaynema et al., reported that portal hypertension affect mucus thickness layer.[19] Reduced hexosamin concentration in gastric mucus in constrictive portal vein indicated increasing ulcer index. The antral mucus thickness was shown to decrease in early phase compare to those in corpus.[19] Tanoe et al., found significant lower concentration of hexosamin in mice with portal hypertension than by pass surgery control group.[12] The administration of teprenone had significantly increased hexosamin concentration of gastric mucus in by pass surgery and portal hypertensive mice.

Imanishi et al., pressumed that portal hypertension affect the mucus surface thickness. The study methods included make portal hypertension condition by portal vein ligation to obtain pre hepatic portal hypertension and cirrhotic condition in mice.[16] It was found that gastric corpus and antral mucus was significantly reduced in both groups of cirrhotic and pre hepatic portal hypertensive mice compare to control group. This finding indicated that antrum was susceptible to change during acute phase and corpus was affected by chronic phase.

In gastric ulcer, there are changes in structural formation of gel polymeric of mucus glycoprotein that made it fragile to cover the mucosa. On the other hand, the changes in portal hypertension include hemodynamic changes might be responsible in decreased production and structural changes of mucus.[6,15]

Erosion in gastric mucosal lesion in patients with portal hypertension makes the gastric mucosa more susceptible to injury. The gastric acid secretion and aggressive factors do not have important role in this condition. On the other hand, gastric mucosal circulation associated with reduced oxygenation and perfusion which are essential in defense mechanism is decreased in PHG.[6,28,29] Study of gastric mucus weakness in mice measured by potential changes revealed that gastric mucus showed decreased potential changes during rest condition and more reduced in ethanol and aspirin exposure[1,6] In addition, gastric mucosa in cirrhotic mice cannot maintain neutral intracellular pH during acid administration and viability of gastric mucosal epithelial decrease significantly.

Finally, reduced mucus layer is caused by various factors such as changes in mucosal blood flow, oxygenation, cholinergic control or PG level. All these factors make high portal pressure and alter the mucosal hemodynamic and affect the mucus secretion by mucus secreting cells or changes in mucus viscosity.[6,28] Aside from that, It had been reported that there were decreased in mucosal metabolism in PHG which manifested in decreased response to pentagastrin, decreased mucus glycoprotein, decreased PGE2 and increased nitrite oxide synthesis. These factors had caused gastric mucosal acid reduced, induced potential changes in mucosa electrically and finally, increased susceptibility of gastric mucosa

Table 2. Mechanism of Gastric Mucosal Defense Alteration in Portal Hypertensive Mice and Patients with Liver Cirrhosis

Factors	Portal Hypertensive mice	Liver Cirrhotic Patients
Hyperemic response	Decreased	No data
Mucin	Decreased	Decreased
Potential difference	Decreased	Decreased
Epithelial proliferation	Decreased	No data
Defense factor modulator		
Nitrite Oxyde	Excess production	Excess production
Prostaglandin	Decreased	Decreased/increased

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CONCLUSION

Imbalance of defensive and aggressive factors of gastric mucosa may involve in development of PHG. Hemodynamic changes, hypoacidity, decreased mucosal metabolic function and decreased hexosamin concentration known to be associated with portal hypertensions wich result in decreased mucus thickness as one of the mechanism of PHG. Gastric mucus damage induced by portal hypertension has important role in the pathogenesis of gastric ulcer in liver cirrhosis.

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