Gastric acid secretion and peptic ulcer due to *H. pylori.*

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DEDICATED TO:-

My Sister

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Objective:

My objective is to know about gastric acid, secretion of gastric acid, regulation of gastric acid, function of gastric acid. The main cause of peptic ulcer and other disease that are related to gastric acid. Different part of stomach which helps to gastric acid secretion. The impact of *H. pylori* in gastric acid secretion also in peptic ulcers. Different types of drug needed to treat peptic ulcers.

Abstract

Ulceration is a process of the formation of an ulcer in the body. Gastric acid mediating ulcer is called peptic ulcer. This acid is generating by a physiological pathway with the help of different secretogauges and secretomotors. When ulceration is complete in the GIT, a pathological condition is creating. This condition called peptic ulcer. Gastric acid normally secreted according to the need of the body. The help of H^+/K^+ ATPase or proton pump secretes the acid. The source of the gastric acid (H^+) is the dissociation of the carbonic acid. Carbonic acid is produce by the hydration of the carbon dioxide with the help of the enzyme carbonic anhydrase. Our body needs gastric acid for many purposes. Gastric acid helps to transfer drugs and nutrition from GIT to blood. It also kills unwanted microorganism in the GIT. Normal gastric acid secretion is always helpful for the body. If the amount of gastric acid in the body becomes more than the normal, the condition turns to the ulceration. The concentration of H^+ in the gastric juice can be as high as 0.15 M. This gives gastric juice a pH somewhat less than 1. Peptic ulcer is the most common disease in the world. Many people in every year are getting involved with this disease. The percentage is relatively low due to the discovery of different drugs to treat this ulcer. There are a number of peptic ulcers depending on their harmful action in the different parts of GIT. Among all peptic ulcers, duodenal ulcer is the most serious one and this can lead to death of the gastric patient. As many as 80% of ulcers are associated with *Helicobacter pylori* which is a spiral-shaped bacterium living in the acidic environment of the stomach. Ulcers can also be cause or worsened by drugs such as aspirin and other NSAIDs. Improper diet taking is another reason for the ulceration. There are many causes, which help induce ulcer like smoking, alcohol, poor food habit, not properly maintain mealtime. Irregular treatment of peptic ulcer may lead to death of a human. So proper treatment must be received patient after he or she has been exposing to ulcer. The main target for inhibiting acid secretion is the inactivation of activities of secretgauges and secretomotor and in the end inhibition of the proton pump.

Method

There are different types of methods used for this study. Information collects from website through Google. I used many books, journals, articles to collect information. I also collect information form official journals. I use official website to collects information. I also collected information form my friends.

Chapter-1-Peptic Ulcer

1. Peptic Ulcer:

It is the erosion of the stomach caused by the gastric acid. A peptic ulcer is an ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. The 80% of ulcers are associated with *Helicobacter pylori* that are a spiral-shaped bacterium that lives in the acidic environment of the stomach. Ulcers can also caused by drug such as aspirin and other NSAID (Marshall BJ, Warren JR-1984).

According to common belief, more peptic ulcers arise in the duodenum first part of the small intestine, just after the stomach. About 4% of stomach ulcers caused by a malignant tumor, so multiple biopsies needs to exclude cancer.

1.1 Types of Peptic Ulcer:

Peptic ulcer can be classified in the following groups:

- Stomach (called gastric ulcer)
- Duodenum (called duodenal ulcer)
- Oesophagus (called Oesophageal ulcer)
- Meckel's Diverticulum (called Meckel's Diverticulum ulcer)

1.2 Symptoms of Peptic Ulcer:

Symptoms of ulcer disease are variable. Many ulcer patients experience minimal indigestion or no discomfort. Some report upper abdominal burning or hunger pain one to three hours after meals and in the middle of the night. The pain of ulcer disease correlates poorly with the presence or severity of active ulceration (Bortoli M, Leonardi G, Ciancia E- 2007).

Gastric ulcer symptoms are not in consistent pattern like eating sometimes exacerbates rather than relieves pain. This is true for *H. pyloric* channel ulcers. Which are often associated with symptoms of obstruction like bloating, nausea, vomiting (Bertram G. Katzung -8th Ed; David E. G -2004).

Duodenal ulcers are more pain that is consistent. Pain is absent when the patient awakens but appears in mid-morning is relieved by food but recurs 2 to 3 h after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer.

1.3 Complications of Peptic Ulcer:

Gastrointestinal bleeding is the most common complication. However, large bleeding can be life threatening. It occurs when the ulcer erodes one of the blood vessels (Cullen DJ, Hawkey GM, Greenwood DC-1997).

Perforation is a hole in the wall of stomach some time leads to catastrophic consequences. Erosion of the gastrointestinal wall by ulcer leads to spillage of stomach. Perforation at the anterior surface of the stomach leads to acute peritonitis, initially chemical and later bacterial peritonitis. The first symptom is sudden intense abdominal pain. Posterior wall perforation leads to pancreatitis pain in this situation often radiates to the back. Penetration the ulcer continues into adjacent organs such as the liver and pancreas (Cheney GR-1949). Scarring and swelling due to ulcers because narrowing in the duodenum and gastric outlet obstruction. Patient often presents with severe vomiting.

1.4 Pathophysiology of Peptic Ulcer:

Tobacco smoking, not eating properly, blood group, spices and other factors cause ulcers. A major factor 60% of gastric and up to 90% of duodenal ulcers is chronic inflammation due to *Helicobacter pylori*. The immune system is unable to clear this infection. The bacterium can cause a chronic active gastritis. The regulation of gastrin production is a part of the stomach. Gastrin stimulates the production of gastric acid by parietal cells and *H. pylori* colonization responses that increase gastrin. The increase amount of acid can cause erosion of the mucosa and ulcer formation (Med NZJ-. 2006).

Another major cause is NSAIDs. The gastric mucosa protects itself from gastric acid with a layer of mucus. NSAIDs block the function of cyclooxygenase 1 (cox-1). This is essential for production of prostaglandins. NSAIDs like celecoxib, rofecoxib only

inhibit cox-2 and it is less essential for gastric mucosa. Ulcers will increase due to increasing NSAIDuse (MartinJP, Connor PD, Charles K -2000).Glucocorticoid lead to atrophy of all epithelial tissues. Their role in ulcerogenesis is relatively small. Smoking leads to atherosclerosis and vascular spasms, causing vascular insufficiency and promoting the development of ulcers through schemia. Nicotine in cigarettes can increase parasympathetic nerve activity of GI tract. It has action on nicotinic receptors synapses increased stimulation to the enterochromaffin-like cells. G cells increases the amount of histamine and gastrin secreted. Increases amount the acidity of the gastric juice. A family history is often present in duodenal ulcers, especially when blood group O is also present. Inheritance appears to be unimportant in gastric ulcers. Gastrinomas (Zollinger Ellison syndrome) rare gastrin-secreting tumors, cause multiple and difficult to heal ulcers (Martin JP, Connor PD, Charles K- 2000).

1.5 Risk Factors of Peptic Ulcers:

1.5.1 *Helicobacter pylori*:

Helicobacter pylori are small microaerophilic, spiral-shaped, gram-negative bacteria that cause duodenal ulcer, a type of peptic ulcer (Bortoli M, Leonardi G, Ciancia E- 2007).Oral proton pump inhibitors are effective as endoscopic treatment for bleeding peptic ulcer. The bacteria are protective by mucous coating layer of the stomach. Allowing the acid and bacteria to irritate the lining duodenum and cause a sore or ulcer. *Helicobacter pylori* exist in the strong stomach acid secreting enzymes that neutralize the acid (Bortoli M, Leonardi G, Ciancia E- 2007). Research studies shown that most ulcers are cause by an infection of bacteria called *Helicobacter pylori*. *H. pylori* are now considere the cause of most ulcers. The *H. pylori* bacterium found in the stomach and along with acid secretion, can damage the tissue of the stomach and duodenum causing inflammation and ulcers.

1.5.2 Smoking:

Cigarette smoking causes ulcers and increases the risk of ulcer bleeding, stomach obstruction and perforation. Smoking also leads to failure in ulcers medication treatment. (Yuhong Y, Ireneusz TP, Richard HH- 2006). Research Studies have been show that cigarette smoking can increase chance of getting of ulcer. Smoking also cause slows healing of existing ulcers and contributes to ulcer recurrence.

1.5.3 Alcohol:

Consumption of alcohol irritates and erodes the mucous lining of stomach cause increase productions of acid, which cause ulcerations (David E. Golan -2004; Bortoli M, Leonardi G, Ciancia E- 2007;Kim JI, Cheung DY, Cho SH -2007). *H. pylori* cause ulcers and elimination of these bacteria by antibiotics to heal ulcers and prevent ulcer recurrence (Kim JI, Cheung DY, Cho SH -2007). There is link has been found between alcohol consumption and peptic ulcers. Most common in people got ulcer that have liver cirrhosis. Ulcer often linke to heavy alcohol consumption of a person.

1.5.4 Acid and pepsin:

Acid and pepsin powerful digestive fluids that help formation of ulcer. The stomach produces lubricant-like mucus that coats the stomach and shields stomach tissues. The stomach produce chemical called bicarbonate that neutralizes digestive fluids. Blood circulation in the lining of the stomach also cell renewal and repair to protect the stomach. However, when any hyper or hypo acid and pepsin secretion in stomach which cause imbalance of those mechanism. The neutralization digestive fluid are not occurs it may lead ulcer (Correa P-1992).

1.5.5 NSAIDs:

Non-steroidal anti-inflammatory drugs (NSAIDs). The most commonly known NSAIDs are aspirin, ibuprofen and naproxen sodium. NSAIDs can fail stomach defense mechanisms. They can make the stomach very harmful effects of acid and pepsin by interfering with the stomach's ability to produce mucus and bicarbonate. They can affect

cell repair and blood flow to the stomach. NSAID also involve for ulcer formation by interfering with prostaglandin. Prostaglandins help the gut linings from resisting corrosive acid damage (Kim JI, Cheung DY, Cho SH- 2007).

1.5.6 Caffeine:

Beverages and foods that contain caffeine can stimulate acid secretion in the stomach. This can aggravate ulcer. The stimulation of stomach acid cannot be attributing solely to caffeine (Sharon G- 2008).

1.5.7 Stress:

Emotional stress is not main cause of ulcers. However, people who are experiencing emotional stress often report increased pain of existing ulcers. Physical stress is different (Sharon G- 2008). It can increase the risk of developing ulcers in the stomach. In emotional stress acid secretion may increased. Physical stresses that can lead to ulcers are that suffered by people with injuries such as severe burns, and people undergoing major surgery (William DC, Benjamin CY, Wong- 2007).

1.6 Treatments of peptic ulcer:

Many ulcers due to *H pylori* bacteria infection. In this reason main approach to peptic ulcer treatment

- Kill the bacteria.
- Reduce acid level in digestive system to relieve pain and encourage healing.

In this case, we use triple therapy. This triple therapy about combination drugs includes two antibiotics together with an acid suppressor or cytoprotective agents.

A-Antibiotic medications.

Combination of antibiotics to treat *H. pylori* because one antibiotic alone isn't always sufficient to kill the organisms. Antibiotics prescribed for treatment of H. pylori include amoxicillin, clarithromycin and metronidazole. Combination drugs that include two antibiotics together with an acid suppressor specifically for the treatment of *H. pylori* infection. Antibiotics take two weeks depending on their type (Soll AH-2008).

B-Acid suppressor or cytoprotective agents.

Acid blockers.

Acid blockers also called histamine H-2 blockers reduce the amount of hydrochloric acid released digestive tract. It relieves ulcer pain and encourages healing. Acid blockers work keeping histamine from reaching histamine receptors acid blockers include ranitidine,famotidine, imetidine and nizatidine.

Antacids.

May antacid in drug regimen is used. An antacid may be taken in addition to an acid blocker or in place of one. Instead of reducing acid secretion, antacids neutralize existing stomach acid and can provide rapid pain relief (Lau JY- 2007).

Proton pump inhibitors.

Another way to reduce stomach acid is pumps within acid-secreting cells. Proton pump inhibitors reduce acid by blocking the action of these tiny pumps. Proton pumps inhibitors omeprazole, lansoprazole, rabeprazole and Esomeprazole (Lau JY- 2007).

Cytoprotective agents.

In some cases, Cytoprotective agents may prescribe in medications that help protect the tissues stomach and small intestine. That agent's are sucralfate and misoprostol.

Chapter-2 -Gastric Acid

2. Gastric Acid:

H+ ion produced by the H^+/K^+ ATPase of proton pump. It has both physiological and pathological role in the body to maintain gastric acid secretion. It also kills bacteria in the stomach and plays an important role in the immunity system of our body. It helps to transport essential metabolite also nutrient from GIT to blood. It also helps our digestion system. The higher rate secretion of gastric acid in stomach causes peptic ulcer. Gastric acid is produce by parietal cells, which also called oxyntic cells in the stomach. The secretion of gastric acid is a complex process. Parietal cells contain an extensive secretory network called canaliculi (Guillaume J- 2009). The gastric acid is secreting into the lumen of the stomach help of parietal cell. These cells are part of epithelial fluidic glands in the gastric mucosa. The pH of gastric acid is 2 to 3 in the human stomach lumen. The acidity is maintained by the proton pump H^+/K^+ ATPase. The parietal cell releases bicarbonate into the blood stream. This bicarbonate causes the temporary rise of pH in the blood that known as alkaline tide (Van der WJ, Vulpe- 2002).This may cause highly acidic environment in the stomach lumen causes denature of the protein's structure from the food. This exposes the protein's peptide bonds. The chief cells of the stomach secrete inactive enzymes pepsinogen and rennin for protein breakdown (Hersey SJ, Sachs G -1995). Gastric acid activated by pepsinogen into pepsin–this enzyme helps digestion by breaking the bonds linking amino acids, a process known as proteolysis. Many microorganisms present in the stomach, which may cause many infection in the stomach. This acidic condition inhibits their growth. Acidic environment helps to prevent many infection of stomach (Van der WJ, Vulpe -2002).

2.1 Stimuli Responsible for gastric acid Secretion:

2.1.1 Histamine:

Parietal cells produce gastric acid (HCl) in response to histamine via H_2 receptors. The histamine receptors act by increasing intracellular cAMP, whereas the muscarinic and gastrin receptors increase intracellular Ca^{2+} levels. Both cAMP and Ca^{2+} act via protein kinases to increase the transport of acid into the stomach.

Parietal cells contain an extensive secretory network called canaliculi. The HCl is secreting by active transport into the stomach. The enzyme hydrogen potassium ATPase (H^+/K^+ ATPase) is unique to the parietal cells and transports the H^+ against a concentration gradient (Epple HJ, Amasheh S, Mankertz J, et al. -2000).

2.1.2 Gastrin:

The presence of gastrin stimulates parietal cells of the stomach to secrete gastric acid. This is indirectly via binding onto CCK2/gastrin receptors on ECL cells in the stomach. It then responds by releasing histamine, which in turn acts in a paracrine manner on parietal cells stimulating them to secrete H^+ ions. This is the major stimulus for acid secretion by parietal cells. Gastrin is a hormone that stimulates secretion of gastric acid by the parietal cells of the stomach and helps in gastric motility. It is release by G cells in the stomach, duodenum, and the pancreas (Nagata A, Ito M, Iwata N, Kuno J, Takano H, et al. -1996). In Zollinger-Ellison, syndrome gastrin is produce at excessive levels often by a gastrinoma of the duodenum or the pancreas. To investigate for hypergastrinemia a pentagastrin test can be perform. In autoimmune gastritis, the immune system attacks the parietal cells leading to hypochlorhydria. This results in an elevated gastrin level in an attempt to compensate for low acidity. The parietal cells are lost and achlorhydria results leading to a loss of negative feedback on gastrin secretion (Lee MG, Choi JY, Luo X, Strickland E, Thomas PJ, Muallem S-1999).

2.2 Secretion of Gastric Acid:

Gastric acid secretion in the stomach flow several steps. Chloride and hydrogen ions are secreting from cytoplasm of parietal cells and mix in the canaliculi. Gastric acid is then secrete into the lumen of the oxyntic gland and gradually reaches the main stomach lumen.

Chloride and sodium ions are secrete actively from the cytoplasm of the parietal cell into the lumen of the canaliculi. This creates a negative potential of -40 mV to -70 mV across the parietal cell membrane. Then Potassium ions and small number of sodium ions diffuse from cytoplasm into the parietal cell canaliculi (JiangS. Meadows, J, Anderson S. A. Mukkada, A. J- 2002; Tripartite KD-2004).

The carbonic anhydrase is an enzyme. Carbonic anhydrase catalyze reaction between carbon dioxide and water to form carbonic acid in the stomach. This carbonic acid immediately dissociates into hydrogen and bicarbonate ions. The hydrogen ions leave the cell through H^+/K^+ ATPase antiproton pumps (Richter JE, Peura D, Benjamin SB, Joelsson B, Whipple J-2000).

At the same time, sodium ion actively reabsorbed. The majority of secreted K^+ and Na^+ ions return to the cytoplasm. The canaliculi secreted hydrogen and chloride ions mix and secreted into the lumen of the oxyntic gland (Jiang SJ, Anderson SA, Mukkada AJ-2002).

The highest concentration that gastric acid reaches in the stomach is 160 mM in the canaliculi. This is about 3 million times that of arterial blood. Which exactly isotonic with other bodily fluid. The lowest pH of the secreted acid is 0.8 but the acid is diluted in the stomach lumen to a pH between 1 and 3.

There are three phases in the secretion of gastric acid

a. The cephalic phase: 30% of the total gastric acid is produce by anticipation of eating and the smell or taste of food.

b. The gastric phase: 60% of the acid secrete is stimulate by distention of in stomach with food. Digestion of protein causes even more gastrin production.

c. The intestinal phase: the remaining 10% of acid is secrete when chyme enters the small intestine and stimulated by small intestine distention.

2.3 Physiology of Gastric Acid Secretion:

Gastric acid secretion is not a very simple process. It is a continuous process controlled by multiple central and peripheral factors. The gastric parietal cells are located in the body and fundu of the stomach produce H^+. Neural, paracrine and endocrine all factors play important roles in the regulation of acid secretion. Neural is acetylcholine, where paracrine and endocrine are histamine and gastrin respectively. There are two major pathways that are present within the gastric parietal cells are the cyclic AMP-depended pathway and the $ca2^+$- depended pathway. Histamine use first pathway, gastrin, and Ach exert their activity via another pathway. The cyclic AMP-depended pathways causes

phosphorylation of parietal- cells effedctor proteins and the $Ca2^+$ dependent pathway leads to an increase in cytosolic $Ca2^+$.Both pathways activate the H^+ K^+ ATPase. The H^+K^+ATPase consist of a large α-subunit and smaller β-subunit. This pump generates the largest ion gradient known in vertebrates, with an intercellular PH of about 7.3 and an intracellular PH of about 0.8.Histamine is release from ECL cells through multifactor pathways. It is a critical regulator of acid production through the H_2 subtype of receptor. Histamine activates the parietal cell in a paracrine fashion. It diffuses from its release site to the parietal cell. Its involvement in the gastric acid secretion has been convincingly demonstration by the inhibition of acid secretion with the use of H_2-receptor antagonists. The ECL cell is the sole source of histamine involved in acid secretion. (Goodman_& Gillman's- 10^{th} Ed).Gastrin primarily is present in the antral G cells. Histamine release of gastrin is regulating through multifactorial pathways involving other factors.

2.4 Mechanism of Action of Acid Secretion:

The hydrogen ion accumulation in parietal cell secretions is roughly 3 million fold higher than in blood, and chloride is secrete against both a concentration and electric gradient. The ability of the parietal cell to secrete acid is largely dependent on active transport.

The acid secretion is an H^+/K^+ ATPase or "proton pump" which is present in the cannalicular membrane. This ATPase is magnesium-dependent. The enzyme not inhibited by ouabain. The current model for explaining acid secretion is as follows:

- Hydrogen ions generate within the parietal cell from dissociation of water. The hydroxyl ions resulted by this process rapidly combines with carbon dioxide to form bicarbonate ion. This reaction catalyzed by carbonic anhydrase (Samuelson LC, Hinkle KL- 2003).
- Bicarbonate is move out of the basolateral membrane in exchange for chloride. The outflow of bicarbonate into blood results in a slight elevation of blood pH recognized as the "alkaline tide". This process act for maintain intracellular pH in the parietal cell (Samuelson LC, Hinkle KL- 2003).
- Chloride and potassium ions are move into the lumen of the canaliculi by conductance channels. It is necessary for secretion of acid.

- Hydrogen ion is pumpe out of the cell into the lumen in exchange for potassium through the action of the proton pump. Potassium is thus effectively recycled.
- Accumulation of osmotically-active hydrogen ion in the cannaliculus causes an osmotic gradient across the membrane those results in outward diffusion of water(Yao X, Forte JG- 2003).

2.5 Regulation of secretion of Gastric Acid:

Gastric acid production is regulating by both the autonomic nervous system and some hormones. The parasympathetic nervous system via the vagus nerve and the hormone gastrin stimulate the parietal cell to produce gastric acid. Parietal cells indirectly cause stimulation of the secretion of the hormone histamine from enterochromaffine-like cells.Vasoactive intestinal peptide, cholecystokinin, and secretin all inhibit production of gastric acid.

The production of gastric acid in the stomach is regulating by positive regulators and negative feedback mechanisms. Four types of cells are involved in this process: parietal cells, G cells, D cells and enterochromaffine-like cells. The endings of the vagus nerve and the intramural nervous plexus in the digestive tract influence the secretion gastric acid significantly (Loughlin MF, Ala Aldeen DA, Jenks PJ -2003).

Nerve endings in the stomach secrete two stimulatory neurotransmitters acetylcholine and gastrin-releasing peptide. Their action both direct on parietal cells and mediated through the secretion of gastrin from G cells and histamine from enterochromaffine like cells. Gastrin acts on parietal cells directly and indirectly by stimulating the release of histamine (Tipnis NA, Rhee, PL, Mittal, RK- 2007).

The release of histamine is the most important positive regulation mechanism of the secretion of gastric acid in the stomach. Its release is stimulate by gastrin and acetylcholine and inhibited by somatostatin.

are taken orally and act locally in the stomach (Rang HP, Dale MM, Ritter JM, Moore PK- 2003).

2.8.3 Proton pumps inhibitors:

These drugs suppress the secretion of hydrochloric acid into the lumen of the stomach.The PPI use for ulcer treatmen, Omeprazole, Lanisoprazole, Esomeprazole, Pantoprazole Rabeprazol (Tripathhi KD -2004).They act secretory surface receptors to prevent the final step of acid production and decrease the level of acid in the stomach. The pump in the parietal cell is the H^+/K^+ ATPase enzyme system on the secretory surface of the gastric parietal cells (Rang HP, Dale MM, Ritter JM, Moore PK- 2003).

2.8.4 Mucosal protectants:

Any injure these agents's coat in the stomach. It prevents further injury from acid. This is given to protect the eroded ulcer sites in the GIT from further damage by acid and digestive enzymes (Tripathhi 2004 -KD).

Chaptr-3-Anatomy of stomach and acid secretion

3. The Stomach as a host of gastric acid:

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. The shape of stomach indicates major acid secretion area. The right side of the stomach called the greater curvature and left side lesser curvature. The most distal and narrow section of the stomach is called the pylorus. Food is liquefying in the stomach. Then food passes through the pyloric canal into the small intestine. The wall of the stomach is structurally similar to other parts of the digestive tube. The stomach has an oblique layer of smooth muscle inside the circular layer. It helps complex grinding motion of gastric secration (Bertram G.katzung 8thed; RangHP, DaleMM, Ritter JM, Moore PK- 2003).

. Number of cells presents in the stomach. Mucous cells secrete alkaline mucus that protects the epithelium against shear stress and acid. The mucosa goes to longitudinal folds gastric folds or rugae**.** Which disappear when the stomach is fully distended (Rang HP, Dale MM, Ritter JM, Moore PK- 2003). The shallow groove divides the mucosa into gastric areas. The surface mucosal is small and funnel-shaped depressions gastric pits. Mucosa is occupied by very simple and tubular gastric is a glands which open into the bottom of the gastric pits. Parietal cells secrete hydrochloric acid most frequently in the neck of the glands of the stomach. They reach the lumen of the gland. They are situating deeper between and below chief cells in lower parts of the gland. Parietal cells is responsible for secrete the hydrochloric acid in stomach. Chief cells secrete pepsin. Pepsin is a proteolytic enzyme (Tipnis NA, Rhee PL, Mittal RK-2007). It is the most numerous of the four types. They occur primarily in the body of the glands. They produce pepsinogen. This is the precursor of proteolytic enzyme pepsin. The optimum pH of pepsin is about 2. This enzyme is able to break down collagen cells. Chief cells secrete the gastrin. Gastrin releasing peptide by the post-ganglionic fibers of the vagus nerve onto G cells during parasympathetic stimulation. Gastrin released peptide. Amino acids also present in the stomach. Stimulate the cell of gastrin G cells. Gastrin stimulates enterochromaffin cells to release histamine. Histamine is responsible for secretion gastric acid in stomach. Gastrin also targets parietal cells which increased the amount of

histamine and the direct stimulation by gastrin, causing the parietal cells to increase secretion in the stomach (Guyton AC, John EH- 2006).

3.1 Important parts of the stomach:

3.1.1 Duodenum:

Duodenum is one of most important part of stomach. This gut restores isotonicity through water and solute absorption, and the pH rises about 7.0. Acid is neutralizing by HCO_3^- in pancreatic and biliary secretions. They also secreted direct secretion in Brunner's glands along the duodenum (Charney AN, Donowitz M -2005). The specific ion transporters involved in duodenal HCO_3^- secretion.

3.1.2 Pancreas:

The gastric acid secretions into the duodenum signal the pancreas to secrete its highly alkaline solution of HCO_3^- into the gut. The transportation of primary anion responsible for this process. The apical membrane is a Cl^-/HCO_3^- exchanger. The main activity of this ion exchanger is to regulate the Cl^- channel. This recycles Cl– channel across the apical membrane (Lee MG, Choi JY, Luo X, Strickland E, Thomas PJ, Muallem S-1999).

In case of maximal stimulation, some HCO_3^- secreted to enter into the lumen directly via the CFTR channel. In addition, Cl^-/HCO_3^- exchange is occur (Melvin JE, Yule D, Shuttleworth T, Begenisich T- 2005). Hormone secretin stimulated by Pancreatic HCO_3^- secretion. This is secreting when acidic fluid enters the duodenum. The HCO_3^- secretion occurs only when counterbalance of acid secretion in the stomach and this acidic fluid is passes into the duodenum. The secretion is primarily isotonic NaCl depend on HCO_3^-. Amounts Pancreatic secretion about 1 to 2 L/d (Spirli C, Granato A, Zsembery K, Anglani F, et al. -1998)

3.1.3 Biliary Secretion:

Although the pancreas is by far the major source of the HCO_3^- added to the duodenal contents. Biliary secretion stimulated by the hormones secretin and cholecystokinin. It produces an alkaline solution (HCO_3^-). It concentration higher than plasma concentration.

The amount of secretion is about 1 L/d (Turnberg LA, Fordtran JS, Carter NW, Rector FC Jr -1970).

3.1.4 Jejunum and Ileum:

This two responsible for the bowel both absorbs and secretes fluid in stomach. However, absorption normally predominatesby reducing the total gut fluid content. it enters the colon absorption is driven by sodium and chloride uptake also water uptake and it occurs via two linked transporters Na^+/H^+ exchanger and Cl^-/HCO_3^- exchanger (Charney AN, Donowitz 2005; Lee MG, Choi JY, Luo X, Strickland E, Thomas PJ, Muallem S- 1999) . These two transporters take Na^+ and Cl^- from the gut lumen and secrete H^+ and HCO_3^- into it. These two ions combine to form H_2CO_3. This dehydrates to form CO2 in the intestinal lumen (Turnberg LA, Fordtran JS, Carter NW-1970). The Cl^-/HCO_3^- exchanger in the small intestine is the downregulated in adenoma gene product also called CLD (Spirli C, Granato A, Zsembery K, Anglani F, Okolicsanyi L, LaRusso NF, Crepaldi G, Strazzabosco-1998).

In the end of the ileum Cl^-/HCO_3^- exchange is predominates. In this case alkaline solution secreted Chloride in specialized cells in the intestinal crypts via a series of apical Cl^- ion channels. The CFTR channel recycles Cl^- into the lumen. In colon, the small intestinal secretory cells do not have an apical K^+ channel. Potassium movement across the membrane by passive diffusion and solvent of drag absorption predominated by this channel. These absorptive and secretory processes leave the fluid and enter the colon by hypotonic (Wesson DE, Laski- 2005).

3.1.5 Colon:

In the colon the fluid volume of the stool is normally reduced to <50 ml/d. The concentrations of Na^+ and Cl^- reduce. Sodium chloride absorption is accomplished by the same linked transporters describe for the small intestine. The Na^+ is absorbed via an apical membrane Na^+ channel regulated by aldosterone. The HCO_3^- secreted in the colon by the Cl^-/HCO_3^- exchanger is consumed in buffering organic acids produced by colonic bacteria (Guyton AC, John EH- 2006). Some of the organic anions produced by this reaction are absorbed via a linked HCO_3^- exchange transporter (Wesson DE, Laski-2005). The potential alkali lost in the stool despite the absence of measurable HCO_3^- in

the stool .The colonic absorptive epithelial cells also have a unique apical membrane H^+/K^+-ATPase that absorbs K^+ and secretes H^+ into the gut lumen.

Chapter-4-Hormone that control gastric acid secretion

4. Major hormonal controls over pump activity:

4.1 Thyroid hormones:

Thyroid hormones play major role in maintaining steady state concentrations of pumps in most tissues. This effect appears to result from stimulation of subunit gene transcription (Tripathhi KD- 2004; Bertram G. katzung 8thed).

4.2 Catecholamines:

Catecholamines have varied effects depending on the specific hormone and tissue. Dopamine inhibits Na^+-K^+-ATPase activity in kidney. Epinephrine stimulates pump activity in skeletal muscle. These effects mediated via phosphorylation or dephosphorylation of the pumps(Tripathhi KD- 2004; Bertram G. katzung -8thed).

4.3 Insulin:

Insulin is a major regulator of potassium homeostasis. It has multiple effects on sodium pump activity. Insulin secretion pumps containing alpha-1 and 2 isoforms have increased affinity for sodium and increased turnover (Tripathhi KD -2004; Bertram G. katzung- 8th Ed).

4.4 Aldosterone:

Aldosterone is a steroid hormone it has major effects on sodium homeostasis. It stimulates rapid and sustained increases in pump activity within several tissues. The sustained effect is due to enhanced transcription of the genes for both subunits (Tripathhi KD -2004; Bertram G. katzung -8th Ed).

4.5 Acid is only one of four major secretory products of the gastric epithelium, all of which are important either to the digestive process or to control of gastric function:

4.5.1 Mucus:

The most abundant epithelial cells are mucous cells, which cover the entire luminal surface and extend down into the glands as "mucous neck cells". These cells secrete bicarbonate-rich mucus that coats and lubricates the gastric surface, and serves an important role in protecting the epithelium from acid and other chemical insults (Rang HP, Dale M, Ritter JM, Moore PK -2003).

4.5.2 Acid:

Hydrochloric acid is secreting from parietal cells into the lumen where it establishes an extremely acidic environment. This acid is important for activation of pepsinogen and inactivation of ingested microorganisms such as bacteria (Rang HP, Dale MM, Ritter JM, Moore PK -2003).

4.5.3 Proteases:

Pepsinogen, an inactive zymogen, is secreting into gastric juice from both mucous cells and chief cells. Once secreted, pepsinogen is activating by stomach acid into the active protease pepsin, which is largely responsible for the stomach's ability to initiate digestion of proteins. In young animals, chief cells also secrete chymosin (rennin), a protease that coagulates milk protein allowing it to be retain more than briefly in the stomach (Guyton AC, John EH -2006).

4.5.4 Hormones:

The principal hormone secreted from the gastric epithelium is gastrin, a peptide that is important in control of acid secretion and gastric motility (Guyton AC, John EH-2006).

Chapter-5-Gastric acid secretion due to *H pylori*

5. Effect of *H pylori* on parietal cells and secretion of gastric acid:

Parietal cells derive form stem cells in the isthmus of the oxyntic pit-gland. They migrates bidirectionally along the pit-gland axis. The outward direction and n inward direction continue until they reach the base of the gland (Karam- 1999). The function hetero genetic parietal cell population along the pit-gland axis that younger cells in the isthmus and neck are more active than older cell in the pit and base regions (Karam -1999).

Preparietal cells develop from tissue-derived stem cells. They increase in the surface area of the apical plasma membrane forming numerous long microvilli. They acquire a few cytoplasmic H^+/K^+-ATPase containing tubules and vesicles. Full maturation of the canaliculi and increase in cell size (Karam, Yao X, Forte JG -1997).

H. pylori can damage the gastric epithelial layer by direct and indirect mechanisms. The organism can directly induce apoptosis of gastric epithelial cells by production of numerous molecules also cytotoxin (VacA), lipopolysaccharide, monochloramine, and nitric oxide (Xia HHTalley NJ-2001). This proapoptotic effect is dependent on activation of nuclear factor (Neu B, Randlkofer P, Neuhofer M- 2002).*H pylori* organisms that capable of attaching to gastric epithelial cells and are responsible for production of proinflammatory cytokines like interleukin (IL)-8, IL-1ß, and tumour necrosis factor). This inflammatory activity can also damage epithelial cells including parietal cells cause acid secretion. IL-1ß is the most powerful acid inhibitor and TNF- has acid inhibitory properties (El Omar EM-2001).

5.1 Effect of *H pylori* on the gastric H^+/K^+-ATPase:

The H^+/K^+-ATPase is an ion motive ATPase. The subfamily P2 of ATPases and it contain of alpha and beta subunits. It forms an integral part of the apical membranes of parietal cells. It transports cations cycle of phosphorylation and dephosphorylation of protein transport. When parietal cells stimulated the pumps translocated from the cytoplasmic tubulovesicles into the membrane of secretory canaliculus. Then microvilli lining the canalicular space also KCl pathway is activating to allow K^+ to carry external surface of the ATPase and secretion of Cl^-(Wallmark B, Stewart HB, Rabon I - 1980).

The H^+/K^+-ATPase actually pumps hydronium ions (H_3O^+) rather than H^+ ions. It able to release H_3O^+. The H^+/K^+-ATPase pump involved with final stage of gastric acid secretion and stimulated to secrete acid by intracellular signals from H_2 receptors, muscarinic M_3 receptors, and gastrin receptors on parietal cells.(Sachs G, Shin JM, Munson K- 2000).

There is evidence that *H pylori* infection exerts inhibitory effects on the human gastric H^+/K^+-ATPase subunit. *H pylori* inhibit subunit gene expression via intracellular pathways involving protein kinases A and C and protein tyrosine kinase (Göõz M, Hammond CE, Larsen K- 2000).

5.2 The effect of eradication of *H pylori* on gastric acid secretion:

The H^+/ K^+-ATPase increases mRNA expression of *H pylori* infection eradication (Osawa H, Kita H, Ohnishi H-2006). It is reasonable for initial recovery in acid secretion is most likely due to release of inhibition on expression of the H^+/K^+-ATPase. *H pylori* plays important role in peptic ulcers disease and cause of major morbidity and mortality (Wallmark B, Stewart HB, Rabon E- 1980). The eradication of *H pylori* infection leads to normalisation of acid secretion and recovery of parietal cell numbers.

6. Other diseases due to gastric acid:

6.1 Zollinger-Ellison syndrome (ZES):

ZES is a rare disorders in stomach it like a tumors in the pancreas, duodenum, or both. The tumors cause the stomach to make too much acidic condition leading to peptic ulcers in the duodenum. The tumors are sometimes cancerous and spread to other areas of the body.

6.2 Causes ZES:

ZES is cause by tumors called Gastrinomas. It releases the hormone gastrin. Cells present in the stomach produce and control gastrin so only the right amount is released. Gastrin travels through the bloodstream to give signal other cells in the stomach to release gastric acid to help break down food. Gastrinomas release abnormal amounts of gastrin, resulting in excess gastric acid in the stomach and duodenum. The excess acid eventually causes sores called peptic ulcers to form in the lining of the duodenum. About 25 percent of gastrinoma are cause by an inherited genetic disorder called multiple endocrine neoplasia type (MEN1).MEN1 release hormone tumors like prolactinomas and insulinomas (Norton JA, Fraker DL, Alexander HR -1999).

6.3 Who gets ZES:

Anyone can get ZES. The disease is more common in men 30 to 50 years old. People with MEN1 have a 20 to 61 percent chance of developing ZES. Children who have a parent with MEN1 have a 50 percent chance of inheriting the MEN1 gene (Jensen RT-1998).

6.4 Gastroesophageal reflux:

When we take food, it carried from mouth to the stomach through the esophagus. There is a tube-like structure 10 inches long and 1 inch wide in adults. Tissue and muscle layers make the esophagus. The lower end of the esophagus it joins the stomach. There is a circular ring muscle called the lower esophageal sphincter (LES).the LES allow to food

enter the stomach and then contracts to prevent the back-up of food and acid into the esophagus .The LES Sometimes weak because the stomach is distended allowing liquids in the stomach to wash back into the esophagus. Most of these episodes occur after meals. Normally reflux occur only rarely during sleep (Norton JA, Fraker DL, Alexander HR, -1999).

Chapter-7-Ulcer in Bangladesh due to Helicobacter pylori

Helicobacter pylori are one of the commonest bacterial pathogens in human. The organism is associated with development of peptic ulcer diseases, lymphoproliferative disorders and gastric cancer. In a developing country, poor socio-economic conditions and genetic predisposition regarded as risk factors. Prevalence of infection is higher in developing countries and re-infection is higher. It transmitted mainly through feco-oral route and gastro-oral route in developed nations. Transmission of 'close-contact infection' depends on the degree of mixing and age-distribution between susceptible and infected individuals. Host and bacterial factors with interaction of environment contribute pathogenicity. *H. pylori* cytotoxin-associated geneA (cagA), vacuolating toxinA (vacA) and adherence factors to gastric epithelium have been linked to enhanced pathogenicity of the bacterium. Host genetic polymorphism of cytokines receptor and enzyme influence H. pylori infection.

Studies in the West have showed that strains expressing certain virulence factors (vacAs1, vacAm1, and cagA) are associated with duodenal ulcer disease. The *H. pylori* genotype is vary with geographic region. In the present study, we compared several virulence markers (cagA, vacA, and iceA) and neutral markers (IS605, IS606, and IS608) in H. pylori strains isolated from 65 adult patients with peptic ulcer (PU) and 50 patients with nonulcer dyspepsia (NUD). PCR tests indicated that cagA is present in 75% of the strains from patients with PU compared to 55% in patients with NUD, and 80% of the isolates from patients with PU carried potentially toxigenic vacAs1 alleles of the vacuolating cytotoxin gene (vacA) compared to 60% in isolates from patients with NUD. Phylogenetic analysis of the vacA middle region and the 5′ end of the cagA gene indicates that Bangladeshi isolates more closely related to *H. pylori* isolates from India and are different from isolates from East Asia.

Helicobacter pylori are a spiral gram-negative microaerophilic bacterium that chronically infects the gastric mucosa of more than half of all people worldwide. It is a major cause of gastritis and peptic ulcer (PU) disease and a risk factor for gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. Infection by *H. pylori* usually starts early in life and, unless eradicated by specific antibiotic treatment, persists for the rest of life.

H. pylorus produces a number virulence factors that are essential for colonization of the stomach and survival in the hostile gastric environment. Well-known virulence factor plays an important role in the neutralization of gastric acid secretion flagella, which are essential for swimming through the mucous layer. Together with this are indications of differences at certain loci between strains from different parts of the world or human ethnic groups. However, most of our present understanding of H. pylori genome organization and bacterial traits are base on studies of strains from the West, and it believe that further studies of *H. pylori* genotypes from different well-separated human populations may help to increase our understanding of bacterium-host interactions in colonization and disease.

Prevalence studies have indicated that *H. pylori* infection is extremely common in Bangladesh and in other developing countries. H. pylori strains isolated from Dhaka, the capital of Bangladesh, in order to gain new insights into the population genetic structure of this important human pathogen and to learn if genotypes implicated in the disease in the West are similarly disease associated in Bangladesh (Motiur R, Asish K, Mukhopadhyay, Shamsun N, et al. 2003).

Conclusion:

Many factors in our country induce gastric acid production in the stomach. Bangladesh is one of the highly susceptible countries to the gastric diseases. Geographical location, ecological system, living system, food habit and many other factors negatively affect the Bangladeshi people. Abnormal food habit system is the main reason for the peptic ulcer in the Bangladesh. People especially of rural area seriously neglect food habit system. Irregular diet taking of these people send them to experience peptic diseases. Poor sanitation problem is another main weapon to generate peptic diseases in the country. Absence of cleaning environment also causes the production of peptic ulcer diseases. Gastric acid is both essential and pathogenic for the human body. Secretion under control is beneficial for the body and beyond control pathogenic for the body. Secretion of acid beyond control allows the *Helicobacter pylori* (*H. pylori*) to survive in the acidic environment. The bacterium can exist in the stomach for a prolonged period in many people. Most of the individuals infected by *H. pylori* do not get clinical symptoms despite having chronic gastritis. The bacterium colonizes the stomach and induces chronic gastritis. This pathogenic bacterium mainly causes peptic ulcer. In addition to peptic ulcer, a good number of diseases are also cause by this bacterium. It generates a chronic low-level inflammation of the GIT. The bacterium is strongly involved in the development of duodenal and gastric ulcer. Another devastating action of this bacterium is production of stomach cancer. The inflammation by the bacterium causes peptic diseases by allowing acid and pepsin to overwhelm the mechanism that protects the stomach. It is widely believed that if the infection by this bacterium not treated early, the *H. pylori* established in the stomach and persists for life. However, peptic ulcer caused by this bacterium can be treating. A triple therapy prepared from two different types of antibiotic and PPIs are prescribed.

Limitation of this study

There are some limitations of this study, which was not possible to overcome due to lack of time. Information on the ulcer condition in Bangladesh due to *H .pylori* was not available. Due to lack of time, I was not able to collect more information. I took help from many books but did not get sufficient information.

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