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COMPLICATION, PATHOGENESIS AND MEDICATION OF PERFORATED PEPTIC ULCER: A PARADIGM SHIFT IN TODAY'S TREATMENT

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ABSTRACT

A peptic ulcer is an erosion in a segment of the gastrointestinal mucosa, typically in the stomach (gastric ulcer) or the first few centimeters of the duodenum (duodenal ulcer), that penetrates through the muscularis mucosa. The peptic ulcers usually occur as a result of various factors such as imbalance of acid secretion, pepsin, refluxed bile, reactive oxygen species (ROS) and functional mucosal defences that resist the acid digestion. Upper gastrointestinal (UGI) bleeding is the most frequently encountered complication of peptic ulcer disease (PUD). Most typical way for ulcer to be diagnosed is by the procedure called EsophagoGastroDuodenoscopy(EGD). PUD is most commonly associated with Helicobacter pylori infection and the use of acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs). H pylori is said to account for 80% of all gastric or stomach ulcers and more than 90% of all duodenal ulcers. Treatment requires a combination of several antibiotics, sometimes in combination with a proton-pump inhibitor(PPIs), H2 blockers. The persisting high incidence of peptic ulcer disease is a superimposing of two trends: a higher incidence in the growing population of elderly patient with a higher intake of NSAIDs and a lower incidence among younger patients due to a decrease in incidence and improved medical treatment. The main aim of this review article has summarise the ulcerogenic mechanism of various mediator involved in PUD.

KEYWORDS: Peptic ulcer disease (PUD), Upper gastrointestinal (UGI), Proton Pump Inhibitor(PPI), Nonsteroidal anti-inflammatory drugs(NSAIDs), EsophagoGastro-Duodenoscopy(EGD), H pylori.

INTRODUCTION

Peptic ulcer (stomach or duodenal) is a break in the inner lining of the esophagus, stomach, or duodenum. A peptic ulcer of the stomach is called a gastric ulcer; of the duodenum, a duodenal ulcer; and of the oesophagus, an oesophageal ulcer. Peptic ulcers occur when the lining these organs is eroded by the acidic digestive (peptic) juices that the cells of the lining secrete of the stomach secrete.

Ulcers average between one-quarter and one-half inch in diameter. They develop when digestive juices produced in the stomach, intestines, and digestive glands damage the lining of the stomach or duodenum. The two important components of digestive juices are hydrochloric acid and the enzyme pepsin. Both substances are critical in the breakdown and digestion of starches, fats, and proteins in food.

They play different roles in ulcers

Hydrochloric acid: A common misperception is that excess hydrochloric acid, which is secreted in the stomach, is solely responsible for producing ulcers. Patients with duodenal ulcers do tend to have higher than normal levels of hydrochloric acid, but most patients with gastric ulcers have normal or lower than normal acid levels. Some stomach acid is actually important for protecting against H. pylori, the bacteria that cause most peptic ulcers.

Pepsin: Pepsin, an enzyme that breaks down proteins in food, is also an important factor in the formation of ulcers. Because the stomach and duodenum are composed of protein, they are susceptible to the actions of pepsin. Fortunately, the body has a defines system to protect the stomach and intestines against these two powerful substances:

1. The mucus layer, which coats the stomach and duodenum, forms the first line of defense.
2. Bicarbonate, which the mucus layer secretes, neutralizes digestive acids.
3. Hormone-like substances called prostaglandins help widen the blood vessels in the stomach, to ensure good blood flow and protect against injury. Prostaglandins are also believed to stimulate bicarbonate and mucus production.

Thus, disrupting any of these defense mechanisms makes the lining of the stomach and intestine susceptible to the actions of acid and pepsin, increasing the risk for ulcers.

Symptoms

The main symptoms of the disease are;

- Burning pain in the upper abdominal wall lining.
- Acid reflux or heart burn.
- Feeling of satiatment while eating.
- Weight Loss.
- Bloating or burping.
- Nausea and vomiting.

In severe cases, symptoms can include

- Dark or black stool (due to bleeding).
- Vomiting blood (that can look like "coffee-grounds").
- Weight loss.
- Severe pain in the mid to upper abdomen.

Though ulcers often heal on their own, you shouldn't ignore their warning signs. If not properly treated, ulcers can lead to serious health problems, including:

- Bleeding.
- Perforation (a hole through the wall of the stomach).
- Gastric outlet obstruction from swelling or scarring that blocks the passageway leading from the stomach to the small intestine.

Gastric ulcer symptoms do not follow a consistent pattern (For example, eating sometimes exacerbates rather than relive pain). In general, gastric ulcer pain typically starts whenever the stomach is empty (usually approximately an hour after eating) and is generally relieved byantacids or food but aggravated by alcohol and caffeine.

Duodenal ulcers tend to produce more consistent pain. Pain is absent when the patient awakens but appears midmorning, is relieved by food, but recurs two to three hours after a meal. Pain that awakens a person at night, a few hours after falling asleep, is also common and is highly suggestive of duodenal ulcer. The pain then usually subsides by morning and is often relieved after eating. This is not commonly noticed in gastric ulceration.

Differences between gastric and duodenal ulcers		
PROPERTY	**GASTRIC ULCER**	**DUODENAL ULCER**
Pain: Localisation	Epigastric	Epigastric or umbilical
Spreading Nature Frequency	Substernal Sharp, Stabbing Every day pain more severe or seldom	Back Dull Periodic, Sometimes persistence
Response to ingestion of food Night time pain Antacid	Seldom Often Relives pain	Pain improves Often Relives pain
Age	Older than 40 years	Between 30 to 40 years
Eating after vomiting	Always	Often

Complications

Generally, when the ulcerative condition is left untreated then it may result in further complications like:

- Internal bleeding: Bleeding can occur as slow blood loss that leads to anaemia or as severe blood loss that may require hospitalization or a blood transfusion. Severe blood loss may cause black or bloody vomit or black or bloody stools.
- Infection: Peptic ulcers can eat a hole through (perforate) the wall of your stomach or small intestine, putting you at risk of serious infection of your abdominal cavity (peritonitis).
- Obstruction: Peptic ulcers can lead to swelling, inflammation or scarring that may block passage of food through the digestive tract. A blockage may make you become full easily, vomit and lose weight.

Incidence

Peptic ulcers are more frequent in middle age adults. The peak incidence for duodenal ulcer is 5th decade, while for gastric ulcers it is a decade later (6th decade). Duodenal as well as gastric ulcers are more common in males than in females. Duodenal ulcer is almost four times more common than gastric ulcer; the overall incidence of gastroduodenal ulcers being approximately 10 percentage of the male population.

Incidence of peptic ulcer in 3,400 autopsies.

Location	Cases	Incidence in percentage	Multiple ulcer (%)	Combination of location (%)
Duodenum	122	3.6	34	11
Stomach	105	3.1	35	12

Aetiology

The immediate cause of peptic ulcer disease is disturbance in normal protective mucosal barrier by acid -pepsin, resulting in digestion of the mucosa. However, in contrast to duodenal ulcers, the patients of gastric ulcer have low to normal gastric acid secretions, though true achlorhydria in response to stimulants never occurs in benign gastric ulcer. These factors discussed below but the first two H-pylori gastritis and NSAIDS induced injury are considered most important:

1. Helicobacter pylori gastritis

About 15-20% cases infected with H pylori in the antrum develop duodenal ulcer in their life time gastric colonisation by H pylori never develops ulceration and remains asymptomatic. A major causative factor (60% of gastric and up to 50–75% of duodenal ulcers) is chronic inflammation due to Helicobacter pylori that colonizes the antral mucosa. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis). Gastrin stimulates the production of gastric acid by parietal cells. In H. pylori colonization responses to increased gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation. People with ulcers who are infected with H. pylori. should have their infection treated. Treatment usually consists of taking either three or four drugs. The drug therapy will use acid suppression therapy with a proton pump inhibitor (PPI) along with antibiotic therapy and perhaps a bismuth containing agent such as Pepto-Bismol.

2. NSAIDs induced mucosal injury

On steroidal anti- inflammatory drugs are most commonly used medications in the developed countries and are responsible for direct toxicity, endothelial damage and epithelial injury to both gastric as well as duodenal ulcer. NSAIDs cause ulcers by interrupting the natural ability of the stomach and the duodenum to protect themselves from stomach acid. NSAIDs also can interfere with blood clotting, which has obvious importance when ulcers bleed. People who take NSAIDs for a long time and/or at high doses, have a higher risk of developing ulcers. These medications include ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve, Anaprox, others), but not acetaminophen (Tylenol).

3. Acid-pepsin secretions

There is conclusive evidence that some level of acid-pepsin secretions is essential for the development of duodenal as well as gastric ulcer. Gastric acid secretions are established as

one of the major ulcerogenic factor for induction of gastric ulcer. It has been reported that about 50% of gastric ulcer patients are acid and pepsin hyperscecretors.

4. Gastritis

Gastritis indicates inflammation of gastric mucosa without ulceration. Gastritis is usually a precursor of ulceration, but either condition can occur in isolation. Some degree of gastritis is always present in the region of gastric ulcer, though it is not clear whether it is the cause or the effect of ulcer.

5. Other local irritant

Pyloric antrum and lesser curvature of the stomach are the sites most exposed for longer periods to local irritants and thus are the common sites for occurrence of gastric ulcers. Some of the local irritating substances implicated in the aetiology of peptic ulcers are heavily spiced food, alcohol, cigarette smoking, unbuffered aspirin.

- Cigarette smoking: It is a risk factor for the development of ulcers and their complications. In addition, smoking impairs ulcer healing and increases the incidence of recurrence. Risk correlates with the number of cigarettes smoked per day.
- Alcohol: Chronic drinkers of alcohol develop ulceration, while the occasional drinker normally only develops gastritis.
- Medicine: Medicine such as aspirin, NSAIDs and corticosteroids can cause peptic ulceration.

6. Other medications

Taking certain other medications along with NSAIDs, such as steroids, anticoagulants, low-dose aspirin, selective serotonin reuptake inhibitors (SSRIs), alendronate (Fosamax) and risedronate (Actonel), can greatly increase the chance of developing ulcers.

7. Dietary factor

Dietary factors such as spice consumption, were hypothesized to cause ulcers until late in the 20th century but have been shown to be of relatively minor importance. Caffeine and coffee, also commonly thought to cause or exacerbate ulcers, appear to have little effect. Similarly, while studies have found that alcohol consumption increases risk when associated with H-pylori infection, it does not seem to independently increase risk. Even when coupled with H-pylori infection, the increase is modest in comparison to the primary risk factor.

8. Stress

Psychological stress, anxiety, fatigue and ulcer type personality may exacerbate as well as predispose to peptic ulcer. Severe physiologic stress can cause peptic ulcer disease, for example burns, central nervous system trauma, surgery and severe medical illness.

9. Hypersecretory states

This is an uncommon cause. Examples include gastrinoma (Zollinger Ellison syndrome), multiple endocrine neoplasia (MEN-I), antral G cell hyperplasia, systemic mastocytosis and basophilic leukaemia's. Very few patients have hypersecretion of gastrin (Zollinger-Ellison syndrome is a condition in which a gastrin-secreting tumour or hyperplasia of the islets cells in the pancreases causes overproduction of gastric acid). Zollinger-Ellison syndrome (ZES) is caused by a non–beta islet cell, gastrin-secreting tumour of the pancreas that stimulates the acid-secreting cells of the stomach to maximal activity, with consequent gastrointestinal mucosal ulceration.

10. Chronic conditions

Diseases associated with an increased risk of peptic ulcer disease include cirrhosis, chronic obstructive pulmonary disease, renal failure and organ transplantation.

Pathogenesis

Although the role of various etiologic factors just described is well known in ulcerogenesis, two most important factors in peptic ulcer are as under:

- Exposure of mucosa to gastric acid and pepsin secretion.
- Strong etiological association with H pylori infection.

Duodenal ulcer

There is conclusive evidence to support the role of high acid-pepsin secretions in the causation of duodenal ulcers. Besides this, a few others noteworthy features in pathogenesis of duodenal ulcer are;

- There is generally hypersecretion of gastric acid into the fasting stomach at night which takes place under the influence of vagal stimulation.
- Patients of duodenal ulcer have rapid emptying of stomach so that the food which normally buffers and neutralises the gastric acid, passes down into the small intestine, leaving the duodenal mucosa exposed to the aggressive action of gastric acid.

- Helicobacter gastritis caused by H pylori is seen in 95-00% cases of duodenal ulcers. The underlying mechanism are as under:
- Gastric mucosal defense is broken by bacterial elaboration of urease, protease, catalase and phospholipase.
- Host factor:H pylori infected mucosal epithelium release proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumour necrosis factor -α, all of which incite inflammatory reaction.
- Bacterial factors: Epithelial injury is also induced by cytotoxin associated gene protein (CagA), while vacuolating cytotoxin (VacA) induces elaboration of cytokines.

Gastric ulcer

The pathogenesis of gastric ulcer is mainly explained on the basis of impaired gastric mucosal defenses against acid-pepsin secretions. Some other features in pathogenesis of gastric ulcer are:

1. Hyperacidity may occur in gastric ulcer due to increased serum gastrin levels in response to ingested food in an atonic stomach.
2. Ulcerogenesis in such patients is explained on the basis of damaging influence of other factors such as gastritis, bile refluxe, cigarette smoking etc.
3. The normally protective gastritis mucus barrier against acid-pepsin is deranged in gastric ulcer. There is depletion in the quantity as well as quality of gastric mucus. One of the mechanisms for its depletion is colonisation of the gastric mucosa by H pylori seen in 75-80% patients of gastric ulcer.

Diagnosis

Diagnosis of peptic ulcer is by patient history and confirmed by endoscopy and testing for H-pylori.

- Carbon-13 urea breath tests detect active H pylori infection by testing for the enzymatic activity of bacterial urease. In the presence of urease produced by H pylori, labelled carbon dioxide is produced in the stomach, absorbed into the bloodstream, diffused into the lungs and exhaled.
- Stool or faecal antigen testing identifies active H pylori infection by detecting the presence of H pylori antigens in stools.

The most typical way for ulcers to be diagnosed is by a procedure called an EGD. EGD stands for Esophago Gastro Duodenoscopy. An EGD (also called "upper endoscopy") is performed by inserting a special lighted camera on a flexible tube into the person's mouth to look directly into the stomach and the beginning of the small bowel. This flexible camera carefully inspects the most likely areas for ulcers to be located. Ulcers identified during an EGD may be photographed, biopsied and even treated, if bleeding is present.

Evidence based pharmacy practice

• Serology, which is immunoglobulin G (IgG) based, can be measured in serum, plasma or whole blood. It will, however, not distinguish between a previous or a current infection.

• Biopsy-based urease tests, which are invasive and can only be done at gastroscopy or in the acute hospital setting. There are two methods for this test. In the CLO test ("Campylobacter-like organisms" test, the rapid urease test) a fragment of mucosal membrane is placed into a special jelly which undergoes a colour change in 10 to 20 minutes, or the specimen is sent for histology which may take up to 24 hours to obtain the result.

Endoscopy allows for biopsy or cytologic brushing of gastric and oesophageal lesions to distinguish between simple ulceration and ulcerating stomach cancer.

Treatment: The treatment for the disease is dependent on the cause of the ulcer. Generally, majority of the ulcerative conditions are treated with in the initial stages but sometimes surgery may be required. The treatment is usually classified into two types i.e.;

Non-surgical Treatment: This sort of treatment is preferred in case of the ulcers caused by the H.pylori. Generally, antibiotics are used to treat this condition. The drug regimen usually includes:

• H2 blockers which are used to decrease the acid production in the stomach

H2-receptor antagonists

The H2-receptor antagonists reduce gastric secretion by blocking the action of histamine at the H2-receptors in the parietal cells of the stomach.2 Gastric acid secretion in response to other secretagogues (for example, acetylcholine and gastrin) is also reduced. Examples include cimetidine, ranitidine and nizatidine. H2-blockers are well absorbed from the gastrointestinal tract, and duration of action is proportional to the dose (ranging from 6 to 20 hours).

• Proton pump inhibitors that block the cells that produce gastric acid.

Proton pump inhibitors

The proton pump inhibitors (PPIs) are the most potent suppressors of gastric acid secretion. Examples include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. They act by irreversibly binding to and inhibiting the H+/K+-ATPase enzyme of the gastric parietal cell. These drugs can completely inhibit acid secretion and have a long duration of action. They promote ulcer healing and are key components of H-pylori eradication regimens. PPIs have replaced H2-blockers in most clinical situations because of greater rapidity of action and efficacy.

• Antacids which act by neutralising stomach acid

Antacids neutralise gastric acid and pepsin activity. Antacids relives symptoms, promote ulcer healing and reduce recurrence. The efficacy of antacids compares well with some of the other ulcer-healing drugs. Antacids remain safe, simple and effective agents for the symptomatic treatment of gastric related symptoms. In practice, antacids have been superseded by H pylori eradication strategies in peptic ulcer disease and are used only for short-term symptom relief.

There are two types of antacids

1. Absorbable

Absorbable antacids (for example, sodium bicarbonate and calcium carbonate) provide rapid, complete neutralisation but may cause alkalosis and should only be used for one to two days.

2. Non-absorbable

Non-absorbable antacids (for example, aluminium or magnesium hydroxide) cause fewer systemic side effects and are preferred.

• Cytoprotective agents which are used to protect the lining of the stomach and small intestine.

Surgical Treatment

In some rare cases such as recurrence of ulcers, internal bleeding, ulcers which tear the stomach lining only surgery may be suggested. The surgery may include complete removal of ulcer, grafting a tissue from other body part and sewing it over the affected area, tying off a

bleeding artery, cutting off the nerve supply to stomach to reduce the production of stomach acid.

Prevention

- **Protect yourself from infections.** It's not clear just how H-pylori spreads, but there's some evidence that it could be transmitted from person to person or through food and water. You can take steps to protect yourself from infections, such as H-pylori, by frequently washing your hands with soap and water and by eating foods that have been cooked completely.
- **Use caution with pain relievers.** If you regularly use pain relievers that increase your risk of peptic ulcer, take steps to reduce your risk of stomach problems. For instance, take your medication with meals. Work with your doctor to find the lowest dose possible that still gives you pain relief. Avoid drinking alcohol when taking your medication, since the two can combine to increase your risk of stomach upset.

CONCLUSION

Although there are significant advances in sciences, this disease remains an important medical problem, because the large use of non-steroidal anti-inflammatory drugs (NSAIDs), excessive smoking, increase alcohol consumption, and life style increase the risk of the disease. Therefore, this explains the reason for choosing this topic in order to promote healthy behaviour and improve health outcomes throughout lifespan by giving attention to the preventive measures.

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