

REVIEW ARTICLE

IDIOPATHIC PEPTIC ULCER DISEASE

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Peptic ulcer disease is a problem of the gastrointestinal tract characterized by mucosal damage secondary to pepsin and gastric acid secretion. Typical symptoms of peptic ulcer disease include history of episodic or epigastric pain, relief of pain after food intake, and night-time awakening because of pain with relief following food intake. Until relatively recently, most ulcers were considered 'idiopathic'. However, in 1983, association between peptic ulcers and *Helicobacter pylori* (*H. pylori*) infection was demonstrated. The complex and multifactorial pathogenesis of peptic ulcer has been studied over several decades, and results from an imbalance of aggressive gastric luminal factors acid and pepsin and defensive mucosal barrier function. Among environmental factors, smoking, excessive alcohol use, and drug use are most often quoted but none of them, apart from NSAID use, were identified as an individual ulcerogenic agent. There appear to be a true subset of patients who do not have *H. pylori* infection, have not been exposed to NSAIDs, and after appropriate testing have unexplained peptic ulceration. These patients can be referred to as having idiopathic ulcer disease. The prevalence of idiopathic ulcers appears to be increasing, and in some studies, it accounts for up to 50% of peptic ulcers. There is some evidence to suggest that genetic factors play an important role in the aetiology of peptic ulcer disease. Blood group O and non-secretor status are genetic traits associated with duodenal ulcer disease, and when both are present, they increase the risk of the disease by 150%. The long-term management of unexplained chronic duodenal and gastric ulcer disease remains ill defined. Antisecretory drugs remain the mainstay of treatment for promoting healing of idiopathic peptic ulceration. *H. pylori* and NSAIDs remain important causes of peptic ulcer, but the epidemiology is changing. It is unclear whether there is, in fact, a real increase in non-*H. pylori*/NSAID-negative ulcers occurring, or whether this is just a change in proportion caused by the disappearance of the infection because of a cohort effect.

Keywords: Idiopathic peptic ulcer disease, *H. pylori*, NSAID,

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INTRODUCTION

Peptic ulcer disease is a problem of the gastrointestinal tract characterized by mucosal damage secondary to pepsin and gastric acid secretion. It usually occurs in the stomach and proximal duodenum; less commonly, it occurs in the lower oesophagus, the distal duodenum, or the jejunum, as in unopposed hypersecretory states such as Zollinger-Ellison syndrome, in hiatal hernias (Cameron ulcers), or in ectopic gastric mucosa (e.g., in Meckel's diverticulum).¹ Typical symptoms of peptic ulcer disease include history of episodic or epigastric pain, relief of pain after food intake, and night-time awakening because of pain with relief following food intake are the most specific findings for peptic ulcer and help rule in the diagnosis.

Peptic ulcer disease and specifically duodenal ulcer (DU) disease had long been thought to have a multifactorial pathogenesis without a common denominator. Historically, our understanding of the pathophysiology of peptic ulcer disease focused on abnormalities in the secretion of gastric acid and pepsin and on the suppression of acid as a treatment strategy.

Until relatively recently, most ulcers were considered 'idiopathic'. However, in 1983, Warren and Marshall demonstrated the association between peptic ulcers and *Helicobacter pylori* (*H. pylori*) infection.¹ The discovery of *H. pylori* was one of the most exciting advances in the history of peptic ulcer disease and it has dramatically changed the management of this clinical entity.² Eradication of *H. pylori* infection is now the mainstay of treatment for peptic ulcer disease and has resulted in very high ulcer healing rates and a dramatic reduction in recurrence rates.³

Table-1 shows an aetiological classification of peptic ulcers. The complex and multifactorial pathogenesis of peptic ulcer has been studied over several decades, and results from an imbalance of aggressive gastric luminal factors acid and pepsin and defensive mucosal barrier function. Several environmental and host factors contribute to ulcer formation by increasing gastric acid secretion or weakening the mucosal barrier.⁴ Among environmental factors, smoking, excessive alcohol use, and drug use are most often quoted but none of them, apart from NSAID use, were identified as an

individual ulcerogenic agent. Emotional stress and psychosocial factors are frequently identified as important contributors to ulcer pathogenesis.⁵ Although stress cannot be neglected as a contributing factor, convincing evidence for it being the sole cause of duodenal ulcer is scarce.⁶

Aetiological classification of peptic ulcers⁴

- Positive for *Helicobacter pylori* infection
- Drug (i.e., non-steroidal anti-inflammatory drug [NSAID])- induced
- *H pylori* and NSAIDs positive
- *H pylori* and NSAIDs negative
- Acid hypersecretory state (i.e., Zollinger-Ellison syndrome)
- Anastomosis ulcer after subtotal gastric resection
- Tumours (i.e., cancer, lymphoma)
- Rare specific causes
- Crohn's disease of the stomach or duodenum
- Eosinophilic gastroduodenitis
- Systemic mastocytosis
- Radiation damage
- Viral infections (e.g, cytomegalovirus or herpes simplex infection, in particular in immunocompromised patients)
- Colonization of stomach with *H. heilmannii*
- Severe systemic disease
- Cameron ulcer (gastric ulcer where a hiatus hernia passes through the diaphragmatic hiatus)
- Idiopathic Peptic Ulcer Disease

Diagnosis

A peptic ulcer is diagnosed at endoscopy when there is a mucosal break of diameter 5 mm or larger, covered with fibrin; a mucosal break smaller than 5 mm is called an erosion. The 5 mm criterion is arbitrary, but is used in clinical trials. The extent to which this criterion relates to the pathological criterion of penetration of the muscularis mucosa is unclear. Peptic ulcers can be single or many. The typical location of the duodenal ulcer is in the bulb, where gastric contents enter the small intestine. The site of predilection for gastric ulcers is the angulus of the lesser curvature; however, they can occur at any location from the pylorus to the cardia. Occasionally, kissing ulcers are seen located face to face on the anterior and posterior walls of the duodenal bulb. If ulceration is seen in the more distal duodenum, then underlying Crohn's disease, ischaemia, or the rare Zollinger-Ellison syndrome should be considered. On endoscopic diagnosis of peptic ulcer, biopsy samples of the antral and body or fundus mucosa should be taken for detection of *H pylori* infection by rapid urease and histological tests. In many developed

countries, ulcer-like symptoms in patients aged up to 55 years are generally not investigated by endoscopic examination but by testing non-invasively for *H pylori* (13C-urea breath test [UBT], stool antigen test) and treated with *H pylori* eradication if positive.⁷

Idiopathic Peptic Ulcer Disease

There does appear to be a true subset of patients who do not have *H. pylori* infection, have not been exposed to NSAIDs, and after appropriate testing have unexplained peptic ulceration. These patients can be referred to as having idiopathic ulcer disease. The prevalence of idiopathic ulcers appears to be increasing, and in some studies, it accounts for up to 50% of peptic ulcers.⁸ Harris *et al.* demonstrated that patients with recurrent idiopathic duodenal ulcers have significantly higher pentagastrin-stimulated peak acid output suggesting that acid hypersecretion may be a special feature in idiopathic ulcer disease.⁹ McColl *et al.* suggested that patients with idiopathic duodenal ulcer disease develop ulceration because of increased acid exposure in the duodenum, caused by rapid gastric emptying into the duodenal cap in the setting of a high acid secretory background rate.⁸

Pathogenesis

There is some evidence to suggest that genetic factors play an important role in the aetiology of peptic ulcer disease. Blood group O and non-secretor status are genetic traits associated with duodenal ulcer disease, and when both are present, they increase the risk of the disease by 150%.¹⁰ McColl *et al.* showed that the presence of blood group O and the total absence of A1 antigen and gene were associated with idiopathic ulcers.¹⁰ Importantly, the genetic effects linked to the development of peptic ulcer appear to be independent of the genetic influences for acquiring *H. pylori* infection.¹¹ An association between cigarette smoking and peptic ulcer disease has been observed for many years. Friedman *et al.* showed that the prevalence rates of peptic ulcers in current smokers as compared with those who had never smoked was increased 2-fold in men and slightly less in women.¹² Although conflicting data exist in regards to the mechanism by which cigarette smoking could adversely affect the gastric mucosa, the bulk of the evidence supports the hypothesis that nicotine is harmful to the gastric mucosa.¹³ The development of a peptic ulcer is presumably determined by the balance of defensive and aggressive forces acting on the gastric mucosa.¹⁴ It remains controversial whether psychological stress

contributes to the pathogenesis of peptic ulcer disease. It has been suggested that between 30–65% of peptic ulcers may be influenced by psychosocial factors such as objective life stresses, personality patterns, anxiety, and depression.¹⁵ It has been postulated that stress affects the stimulation of gastric acid secretion, alters gastric motility, modifies gastric blood flow, or affects cytokines interfering with the gastric mucosal barrier.¹⁶ Although psychological stress may contribute to the pathogenesis of peptic ulcer disease, multiple confounding variables exist making it difficult to clarify the relevance of this factor. Another possible explanation for idiopathic ulcer disease is relapse of previous ulcer disease initially caused by *H. pylori*, where there has been disappearance of the organism. There is good evidence that a subset of patients with *H. pylori* ulcer disease still relapse after successful *H. pylori* eradication.¹⁷ An explanation for this remains unclear, but it may be that once there is a mucosal defect through the muscularis layer, patients are more prone to recurrence of ulceration at the same site because an inherent weakness is retained. In Hawkey *et al.*'s study when NSAID-induced peptic ulcers relapsed after treatment with omeprazole or misoprostol, the nature and site of the lesions at relapse tended to be the same as the initial ulcer, supporting the theory that local mucosal factors play a significant role.¹⁸ This might explain why patients already exposed to traditional NSAIDs may not receive additional protection from eradication of *H. pylori*, but those never exposed may be partially protected.

Management

The long-term management of unexplained chronic duodenal and gastric ulcer disease remains ill defined. As a first step, it is important to ensure that misdiagnosis of *H. pylori* infection has not occurred. Testing for *H. pylori* should be delayed for 4 week after antibiotic use or for 1–2 week after PPI use.¹⁹ Secondly, surreptitious or unrecognized NSAID use must be excluded as accurately as possible. Serum salicylate levels especially in the context of intractable peptic ulcer disease should be considered. Thirdly, it is reasonable to measure serum gastrin as a screening test in these patients. Although the Zollinger-Ellison syndrome is rare, it is certainly a diagnosis that should not be missed. Fourthly, it is essential to obtain biopsies from idiopathic ulcers to exclude other rare diseases that may mimic peptic ulceration. This applies not only to gastric ulcers, which are routinely biopsied to rule

out malignancy, but also any unexplained duodenal ulcer, which reflects a change in management strategy. A repeat endoscopy is necessary only in those patients who have symptom recurrence, to determine if their symptoms are linked to persistent ulceration and to exclude secondary causes. However, it is essential that all gastric ulcers are re-endoscoped to exclude refractory ulceration associated with malignancy. Antisecretory drugs remain the mainstay of treatment for promoting healing of idiopathic peptic ulceration. However, in the absence of *H. pylori* infection, antisecretory drugs are less effective in inhibiting gastric acidity.²⁰ Several key issues in terms of long-term management remain. For example, should maintenance therapy be considered for these patients? In practice, the main group where this requires serious consideration is those patients who have presented with ulcer complications. In this group, lifelong maintenance appears to be a reasonable therapeutic strategy until clinical studies define optimal management. Smoking cessation appears sensible but is an unproven intervention, and it has been suggested that the unfavourable effects of smoking on ulcer relapse may be overcome by low-dose, long-term, antisecretory treatment.

CONCLUSIONS

H. pylori and NSAIDs remain important causes of peptic ulcer, but the epidemiology is changing. It is unclear whether there is, in fact, a real increase in non-*H. pylori*/ NSAID-negative ulcers occurring, or whether this is just a change in proportion caused by the disappearance of the infection because of a cohort effect. The introduction of the Cox-2 inhibitors (which do not cause peptic ulceration) will presumably further accelerate the recognition of idiopathic peptic ulcers. Management needs to be further defined and will require new clinical studies

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