Pathophysiology and Risk Factors in Peptic Ulcer Disease

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Abbreviations

EGFR	Epidermal growth factor receptor
H. pylori	*Helicobacter pylori*
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
PG	Prostaglandins
PUD	Peptic ulcer disease
TGF-α	Transforming growth factor-α

2.1 Introduction

The stomach plays a pivotal role in the digestion of foods that we consume. This organ can resist to a great variety of detrimental factors, including hydrochloric acid, alcohol, refluxed bile salts, and other irritating agents. Maintaining this high resistance to damage is possible because of the presence of a number of physiological defensive mechanisms as well as the ability of rapid repair of injured mucosa when such occurs. Nonetheless, when these protective mechanisms are overwhelmed by irritating factors, a gastric mucosal lesion such as gastric erosion and ulcer may develop (Fig. 2.1). Aggressive factors are responsible for alterations in the mucosal barrier and subsequently cause epithelial cell injury in the stomach. The role of several factors including *Helicobacter pylori* (*H. pylori*), gastric acid,

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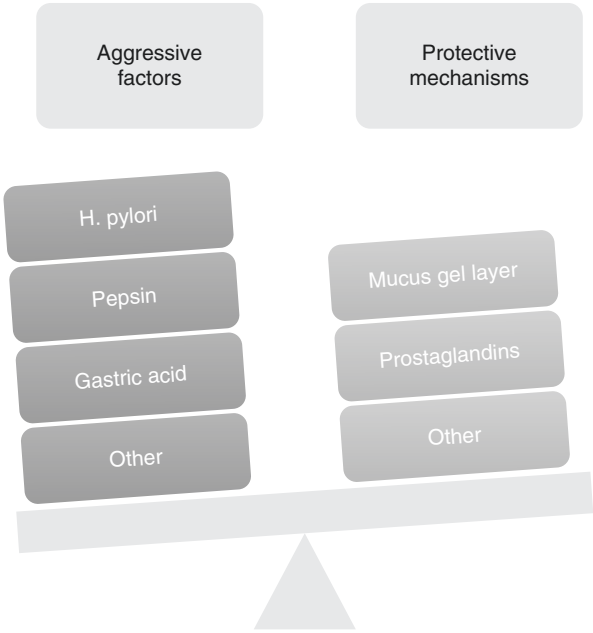

Fig. 2.1 Factors playing a pivotal role in peptic ulcer disease pathogenesis. Imbalance between aggressive factors and the defensive mechanism are responsible for mucosal damage and, thus, peptic ulcers. Recent research emphasizes the role of *H. pylori infection* in pathogenesis of peptic ulcer disease. *H. pylori* colonization has a detrimental effect on the mucus gel layer integrity and prostaglandin production and allows irritating agents, such as pepsin or gastric acid, to enter and damage the deeper layers of stomach wall

and pepsin in pathogenesis of peptic ulcer disease is now well established in the literature. It is well known that the major role in the development of peptic ulcer disease is played by *H. pylori* infection, gastric acid, and pepsin. Nevertheless, recent research suggests that other factors, for instance, smoking and obesity, may contribute to the development of peptic ulcer disease and constitute potential risk factors for development and a more severe course of this disease in individuals.

In the first part of this chapter, characterization of noxious factors responsible for mucosal damage and defensive mechanism in the stomach is described. Moreover, the molecular mechanisms underlying the pathophysiology of mucosal injury development is briefly presented. In turn, second part of this chapter is focused on the available evidence on the risk factors contributing to the development of peptic ulcer disease.

2.2 Pathophysiology

Under normal conditions, a physiologic balance exists between gastric acid secretion and gastric and duodenal mucosal defense systems. Mucosal injury occurs when the balance between aggressive and protective factors is disrupted. Thus, peptic ulcers are defined as defects in the gastric or duodenal mucosa and submucosa, which extend through the muscularis mucosa.

The epithelial cells of the stomach and duodenum secrete mucus under the influence of cholinergic stimulation or in response to irritation of the epithelial lining. The foveolar cells produce mucus and bicarbonate, which form a gel layer

impermeable to aggressive factors such as acid and pepsin. This layer is extremely important, as it prevents the stomach from digesting itself. In the event of injury, additional mechanisms help to prevent acid and pepsin from entering the epithelial cells. For example, increased blood flow removes acid that diffuses through the damaged mucosa and provides adequate bicarbonate level in the gel layer superficially to epithelial cells. Additionally, epithelial cells regulate intracellular pH by removing excess of hydrogen ions through the ion pumps in the basolateral cell membrane.

As it was mentioned earlier, the mucosal damage and, thus, peptic ulcer occur when the balance between aggressive factors and the defensive mechanism is disrupted. Aggressive factors include *H. pylori* infection, NSAIDs, alcohol, bile salts, acid, and pepsin. The defensive mechanism includes mucous, bicarbonate, prostaglandins, adequate mucosal blood flow, and ability to epithelial renewal.

2.2.1 Defense Mechanisms: Role in Prevention of Mucosal Injury

2.2.1.1 Superficial Gel Layer

The first line of gastric mucosal defense consists of mucus and bicarbonate barrier. The surface of gastric mucosa is covered by a layer formed by mucus gel and bicarbonate anions. The layer has the ability to retain the bicarbonate ions secreted by surface epithelial cells and to maintain pH near 7 in proximity to mucosa. The mucous layer is also able to protect from proteolytic actions of pepsin on epithelium. The mucus gel secreted by foveolar cells is formed in nearly 95% of water and various kinds of mucin glycoproteins, such as MUC2, MUC5AC, MUC6, and others [1]. Gel formation is possible due to the ability of mucin units to polymerize into large mucin multimers. Moreover, various GI hormones, such as gastrin, secretin, and prostaglandins, play a role in regulation of gastric mucus secretion. The secretion of bicarbonate into the mucus gel layer is essential to maintain a pH gradient at the epithelial surface, which represents a first line of defense against gastric acid. Bicarbonate anions are secreted from the apical membrane of surface epithelial cells. The Cl^{-}/HCO^{3-} exchanger, which is responsible for regulation of bicarbonate secretion, can be stimulated by various factors such as prostaglandins, luminal acid, melatonin, and orexin-A [1].

Importantly, the mucus-bicarbonate barrier is the only system which separates the epithelium from the gastric lumen. Therefore, when the protective barrier breaks down during pathological events or under influence of injuring agents, other protective mechanisms are activated. They include intracellular acid neutralization, rapid epithelium renewal, and maintenance of mucosal blood flow.

2.2.1.2 Prostaglandins

The gastric mucosa is characterized by constant production of prostaglandins, especially PGE_2 and PGI_2, which play a crucial role in the maintenance of mucosal integrity and protection against damaging factors [2]. It has been proved that prostaglandins interact with almost all the mucosal defense mechanisms. Notably, they have potential to reduce acid output, stimulate mucus and bicarbonate production,

as well as increase mucosal blood flow. Moreover, prostaglandins are responsible for acceleration of epithelial restitution and mucosal healing. Furthermore, prostaglandins have the ability to inhibit mast cell activation and leukocyte adhesion to vascular endothelium [2].

2.2.1.3 Epithelial Cells

The continuous layer of surface epithelial cells, which are closely interconnected by tight junctions, represents the next line of mucosal defense. Due to the presence of tight junctions, epithelial cells form an impermeable barrier, which prevents back infusion of gastric acid as well as pepsin and the damage on deeper layers of the gastric lining [1]. Epithelial cells—owing to the presence of phospholipids on the surface—are hydrophobic and can repulse acid- and water-soluble agents responsible for mucosal damage. Furthermore, epithelial cells produce cathelicidins and beta defensins, which are cationic peptides with antimicrobial prosperities. Those cationic peptides play an important role in the innate defensive system at the mucosal surface and prevent stomach mucosa from bacterial colonization [3].

2.2.1.4 Mucosal Cell Renewal

The integrity of the continuous layer of surface epithelial cells in the stomach is maintained by a constant process of cell renewal by mucosal progenitor cells. The process of complete epithelial renewal takes about 3–7 days, while the restitution of epithelium after exposure to injuring agents occurs within minutes and depends on migration of preserved cells from the neck area of gastric glands [4].

Progenitor cell proliferation is controlled by growth factors, such as transforming growth factor-α (TGF-α) and insulin-like growth factor 1 (IGF-1). These growth factors activate the epidermal growth factor receptor (EGFR), which is the major growth factor receptor expressed in gastric progenitor cells [4]. Furthermore, prostaglandins (PGE_2) and gastrin interact with EGFR and stimulate cell proliferation and renewal of gastric mucosa [5]. Of note, the presence of EGF alone has not been detected in the gastric mucosa. Nevertheless, it can be found in the gastric lumen, derived from salivary and esophageal glands, and can stimulate progenitor cell proliferation in case of injury [4].

2.2.1.5 Mucosal Blood Flow

Maintaining adequate mucosal blood flow is crucial to deliver indispensable substances, such as nutrients and oxygen and to remove toxic metabolites from gastric mucosa. Endothelial cells located in small vessels in the stomach produce potent vasodilators such as nitric oxide (NO) and prostacyclin, which protect the gastric mucosa against a detrimental effect of restricted blood flow.

After the exposure to irritating agents, a massive and rapid increase in mucosal blood flow occurs in the stomach. This process allows removal of damaging agents and dilution of gastric acid. The proper blood flow is pivotal for prevention of gastric mucosal damage and a decrease results in the development of tissue necrosis. Experimental evidence clearly shows that the increase in mucosal blood flow is mediated by NO, and inhibition of NO synthase exacerbates mucosal injury [6].

2.2.2 Selected Aggressive Agents: Mechanisms of Action

2.2.2.1 *Helicobacter pylori*

Since the discovery of a possible link between *H. pylori* and gastritis in 1983, there has been a great interest in the contribution of *H. pylori* to the mechanism of gastric mucosal injury. The unique adaptation features of the gram-negative *H. pylori*, such as urease production, allow it to survive in the acidic, unfavorable environment of the stomach, where it causes inflammation and triggers peptic ulcer disease. Noteworthy, *H. pylori* initially colonize the antrum, where parietal cells, which produce gastric acid, are absent from, and thus acid secretion is not directly affected. Generally, the mechanism by which these bacteria cause disease can be described as a multistage process. In the first step, the bacteria disrupt the antimicrobial activity of gastric acid barrier, enter the mucous layer, and adapt to environmental conditions of gastric mucus. In the next step, *H. pylori* adhere to the host gastric mucosa, and this event triggers the expression of several bacterial genes, which allows the pathogen to persist in this environment and avoid clearance caused by peristaltic movements or shedding of the mucous layer. One of the important factors in *H. pylori* colonization is enzyme urease, which is able to convert urea into ammonia and carbon dioxide in order to elevate the pH to neutral by forming an acid-neutralizing cloud of ammonia near bacterium and thus protecting the bacterial cell from gastric acid.

H. pylori colonization is characterized by an abundant inflammatory response and gastric epithelial cell injury. *H. pylori* gastritis is characterized by infiltration of the gastric mucosa with inflammatory cells, such as polymorphonuclear leucocytes, lymphocytes, plasma cells, and macrophages. Protease and lipase produced by *H. pylori* is responsible for degradation of gastric mucus and cell injury from back infusion of gastric acid. Moreover, ammonia produced through urease activity may be toxic to gastric epithelial cells. Of note, it is well known that *H. pylori* infection induces chronic oxidative stress on gastric mucosa, thereby causing mucosal damage and retardation in mucosal repair.

2.2.2.2 Gastric Acid and Pepsin

Gastric acid is a fluid formed in the stomach, which plays an important role in digestion of proteins by activating digestive enzymes. The main constituent of gastric acid is hydrochloric acid, which is produced by parietal cells in the gastric gland in the stomach. The pH of gastric acid is 1.5–3.5 in the stomach lumen. Four types of cells are involved in the process of regulation of gastric acid secretion: G cells, D cells, parietal cells, and enterochromaffin-like cells. Gastric acid production is also regulated by the autonomic nervous system and several hormones, such as histamine, vasoactive intestinal peptide, cholecystokinin, and others.

Of note, *H. pylori* infection has also a great impact on gastric acid secretion. Patients infected with *H. pylori* produce a lower than normal amount of acid probably due to apoptosis induced by pro-inflammatory mediators. This state may occur during acute infection. On the other hand, *H. pylori* infection may cause an increase in gastric acid secretion. *H. pylori* infection leads to increased release of the

acid-stimulating hormone, gastrin. Persistent hypergastrinemia causes proliferation of parietal cells and further production of gastric acid which causes ulcer formation especially in duodenum. Elevated gastric acid secretion increases the duodenal acid load, which damages the mucosa, causing ulceration.

The chief cells synthesize and release the proenzyme pepsinogen, the precursor of pepsin. They are the most abundant cells in the gastric mucosa and can be found in the body, fundus, and antrum of the stomach. Pepsin, a member of the peptidase A1 family, is a predominant digestive protease in the gastric juice. Pepsin damage is characterized by focal areas of discontinuity in the adherent mucus gel layer, localized hemorrhagic punctuate ulcers with bleeding into the lumen, and no evidence of reepithelialization or mucoid cap formation. Damage by pepsin is markedly different from that caused by ethanol or NaCl; these agents rapidly penetrate the mucus barrier and result in exfoliation of epithelial layer with a dramatic increase in mucosal permeability, followed by reepithelialization under a fibrin-based mucoid cap.

The adherent mucus gel layer is a physical barrier to luminal pepsin accessing the underlying mucosa. Because of its relatively high molecular size, pepsin cannot permeate the continuous adherent mucus layer within a physiologically meaningful time scale. Nevertheless, luminal pepsin at acidic pH slowly hydrolyzes and erodes the mucus layer. At the same time, mucus loss is balanced by a new secretion. Unfortunately, pepsin-induced mucosal damage and its role in PUD are still unclear and merits further studies. Lack of interest in pepsin as a mucosal-damaging agent may be explained by pharmaceutical success of acid-inhibiting drugs in treatment of PUD.

The proteolytic activity of pepsin in gastric juice falls rapidly above pH 3, and it was assumed that above this pH, most of the pepsin activity in vivo is lost.

2.2.2.3 NSAIDs

Prostaglandins are produced from arachidonic acid in the presence of cyclooxygenases (COX-1 and COX-2) and prostaglandin synthases. NSAIDs block the cyclooxygenases; thereby, gastric injury related to their administration is closely associated with inhibition of prostaglandin production. Inhibition of cyclooxygenases results in suppression of a number of prostaglandin-related protective functions. For instance, prostaglandins reduce the activation of mast cells as well as inhibit leukocyte adhesion to vascular endothelium. Furthermore, prostaglandins play a role in maintaining adequate blood flow in mucosal microcirculation. Administration of NSAIDs results in cyclooxygenase-dependent inhibition of bicarbonate secretion, which also inevitably impairs mucosal defense mechanism.

2.3 Risk Factors

2.3.1 *H. pylori* Infection

Impact of *H. pylori* infection on gastric acid and pepsin secretion was described above. A separate chapter is devoted to describing the complex relationship between *H. pylori* and PUD.

2.3.2 NSAIDs Administration

Conventional nonsteroidal anti-inflammatory drugs are known as a common cause of PUD. Up to half of regular NSAID takers report gastrointestinal intolerance, 15–25% of them have an endoscopically confirmed ulcer, and up to 4.5% develop serious gastrointestinal complication [7]. These drugs disrupt the mucosal permeability barrier and damage the mucosa in a cyclooxygenase-dependent and cyclooxygenase-independent way. Noteworthy, selective COX-2 inhibitors reduce, but not eliminate, gastric and duodenal ulcerations and complications among patients chronically using NSAIDs.

Of note, aspirin used in a low dose for prophylaxis of cardiovascular disease was associated with significant increase in the risk of ulcer presence and ulcer complications. For instance, in a multinational study of 189 patients taking low-dose aspirin (75–325 mg daily), the ulcer prevalence defined as presence of a lesion of more than 3 mm deep was 11% [7].

Importantly, NSAIDs and *H. pylori* infection account for approximately 90% of gastric and duodenal ulcers. Thus, knowledge about the relationship between NSAIDs and *H. pylori* infection in pathogenesis of PUD is important, both for treatment and prevention of ulcers. Both, *H. pylori* and NSAIDs may exert detrimental effect on the gastric mucosa, which may be additive or synergistic. However, whereas the interaction between NSAIDs and *H. pylori* infections is biologically plausible, the causative roles of those risk factors combined in ulcer pathogenesis are still controversial. Some studies showed an increase in NSAID-associated damage in the presence of *H. pylori* infection, and others failed to demonstrate this relationship [7]. Nevertheless, recent research conducted by Aalykke et al. showed that risk of bleeding from peptic ulcer in current NSAIDs users in Denmark was almost twofold higher in *H. pylori*-infected patients in comparison to those without infection [8].

Other studies performed by Voutilainen et al. demonstrated that the use of NSAIDs increases the risk of peptic ulcer three- and fivefold in *H. pylori*-positive and *H. pylori*-negative patients, respectively [9].

2.3.3 Genetic Factors

Studies investigating genetic background as a risk factor of PUD come from the time where *H. pylori* was not identified and associated with peptic ulcers. Those studies suggested that polygenic inheritance pattern may be responsible for familiar aggregation of PUD. Interestingly, a familiar aggregation pattern differs between gastric and duodenal ulcers. First-degree relatives of patients with gastric ulcers have a threefold increase in the prevalence of gastric ulcers but no duodenal ulcers. On the other hand, first-degree relatives of patients with duodenal ulcers have a threefold increase in the prevalence of duodenal ulcers but no gastric ulcers [10].

Nowadays, an important question should be answered: Are there any genetic factors that operate independently of *H. pylori* or are all genetic factors associated with greater predisposition to *H. pylori* infection?

For instance, host polymorphism involving the cytokine IL-1β is linked to duodenal ulcers. In their meta-analysis of 3793 subjects, Zhang et al. found by subgroup analyses that IL-1β–31 C/C genotype has protective effect against duodenal ulcer risk. On the other hand, in the same study, Zhang et al. showed that there is no evidence of significant association between IL-1β–31 C/T polymorphism and duodenal ulcers with or without *H. pylori* infection [11]. In another Chinese study, the association between IL-8 gene –251T/A polymorphism and the risk of PUD was investigated. Whereas the overall result of this study indicated that IL-8 gene –251T/A polymorphism is not associated with the development of PUD in the general population, subgroup analysis showed increased risk of PUD among Asians, especially for the subgroup with *H. pylori*-positive duodenal or gastric ulcers diagnosed [12]. In turn, in a Japanese study, host polymorphism in TNFα rather than IL-1β were associated with increased risk of gastric ulcers but not duodenal ulcers [13]. Furthermore, other inflammatory cytokine genes polymorphisms such as IL-2, IL-4, IL-6, and IL-8 were investigated in relation to PUD development, yet this association remains controversial and requires further research [14].

Of note, twin studies provide evidence for a clear genetic predisposition to PUD, which is independent of any predisposition to *H. pylori* infection. For instance, Malaty et al. in a cross-sectional study examined 258 twin pairs, both monozygotic and dizygotic, and have found by interclass correlations for PUD that genetic effect is important for liability to peptic ulcer [15].

Interestingly, some indirect genetic factors were proposed to be associated with increased risk of PUD development. For instance, blood groups O and A, as well as nonsecretors of ABH, have been associated for increased risk of peptic ulcers [16, 17]. Since other studies failed to find any association between blood groups with *H. pylori* infection or PUD, this relation remains unclear and needs further research [18, 19].

Summarizing, existing studies clearly indicate that genetic background influences the risk of PUD development in genetically susceptible individuals. The major question to answer is whether genetic factors are associated with greater predisposition to *H. pylori* infection or those factors act independently. Second question to answer is whether some individuals have increased risk of both gastric ulcer or duodenal ulcer development or both. Nevertheless, this problem merits further research with a proper, repetitive study design and sample size.

2.3.4 Obesity

The prevalence of obesity in the worldwide population is dramatically increasing in recent years. It becomes a major public health concern in developed countries, because it increases the risk of cardiovascular disease, diabetes, and dyslipidemia. Obesity is associated with gastrointestinal diseases such as gastroesophageal reflux disease, gallstone disease, and colon, esophagus, and pancreas tumors. Excessive amount of visceral adipose tissue can be found in obese patients. Visceral adipose

tissue is recognized to be metabolically active and has been associated with increased levels of pro-inflammatory cytokines that may contribute to the development of inflammation in the GI tract. Thus, obesity has been proposed to have potential effect on PUD. Aro et al. in a random population-based study have found that obesity is an independent risk factor for gastric ulcer but not duodenal ulcer [20]. On the other hand, in a study performed by Fujimoto et al., no difference in gastric ulcer and duodenal ulcer has been found between obese patients versus nonobese [21]. Thus, possible connection between obesity and PUD remains controversial.

Nevertheless, recently obesity has been linked with gastritis as a term used to refer to symptoms, endoscopic findings, and histologic findings. Csendes et al. [22] investigated the stomachs of 426 morbidly obese patients and reported that 27.5% of these patients showed erosions in stomach. Moreover, 62% of 232 patients, from whom biopsies were obtained, had histological chronic superficial gastritis. In another study, Dutta et al. [23] investigated 101 preoperative morbidly obese patients and demonstrated that these patients had significantly increased prevalence of histologically confirmed gastritis compared to age- and sex-matched control individuals with a normal BMI. Of note, the prevalence of *H. pylori* infection in the morbidly obese patients did not differ from that in the nonobese individuals, suggesting that obesity rather than *H. pylori* accounts for an increased prevalence of gastritis [24]. These findings suggest that obesity may play a role in the development of gastritis.

2.3.5 Smoking

Smoking is the most preventable risk factor of human disease. To date, cigarette smoking is known to be associated with cardiovascular diseases, cancers, and lung diseases [25]. Smoking induces serious problems in humans, and it becomes a major concern in public health.

Over 5000 ingredients are found in a cigarette smoke and among them, at least 150 compounds are known to possess toxic and carcinogenic activities. These ingredients include alkaloids, phenolic compounds, polycyclic aromatic hydrocarbons, nitrosamines, and heavy metals [26]. All these compounds have the ability to induce oxidative stress in smokers and exacerbate the lipid peroxidation which leads to atherosclerosis. Importantly, smoking is responsible for approximately 90% of small cell lung cancer cases and 70% of non-small cell lung cancer cases worldwide [27].

Nowadays, there is a strong evidence that cigarette smoking is a major cause of gastrointestinal disorders in which a major role is played by chronic inflammation. These include inflammatory bowel disease, cancers of the GI tract, and, noteworthy, peptic ulcers [25].

A large US population-based study conducted between 1997 and 2003 demonstrated that the prevalence of ulcers in current and former smokers is almost double of that of nonsmokers (11.43% and 11.52% vs. 6.00%, respectively) [28]. Another

research showed that the risk of peptic ulcer diseases is associated with the quantity of cigarette smoking. Precisely, the risk of peptic ulcer increases in smokers who have a high daily intake of tobacco [28, 29]. Of note, cigarette smoking is not an independent ulcerogenic agent, but it affects the gastric mucosal protective mechanism increasing the risk of *H. pylori* infection.

This increased risk of infection may be related to adverse effects of cigarette smoking on the reduction of gastric mucosa protective mechanisms. Smoking:

- Inhibits epithelial cell renewal in the GI tract
- Reduces level of epithelial growth factor (EGF) and thus inhibits mucosal cell proliferation
- Increases production of gastric acid and decreases bicarbonate anions production
- Induces pyloric incompetence and increases biliary reflux, thereby allowing the bile salts damage gastric mucosa
- May lead to alterations in the immune system

Summarizing, the appropriate advice to smoking patients with PUD should be to stop smoking.

2.3.6 Alcohol Consumption

The association between ulcers and alcohol is complex. Both acute and chronic alcohol consumption can interfere with stomach functioning in several ways. For instance, alcohol can alter gastric acid secretion as well as induce acute gastric mucosal injury. Alcoholic beverages with a low alcoholic content strongly increase gastric acid secretion and the release of gastrin, while beverages with higher alcohol content stimulate neither gastric acid secretion nor gastric release. Moreover, several studies have suggested that alcohol-induced mucosal injury is associated with the decreased formation of prostaglandins.

It is a well-known fact that alcohol consumption can cause mucosal inflammation, which may lead to mucosal damage. Alcohol disrupts the gastric mucosal barrier and increases the mucosal permeability. Of note, changes induced by short-term exposure to alcoholic beverages are rapidly reversible, while prolonged alcohol drinking may lead to disruption in microcirculation and progression in structural mucosal injury.

Garrow et al. investigated the role of alcohol consumption in the development of PUD. Researchers analyzed data from the 1997 to 2003 National Health Interview Survey and reported that an increased probability of ulcer history was associated with former alcohol use (OR 1.29) [28]. On the other hand, cohort studies of general population and case control as well cross-sectional studies did not provide any evidence for a relation between alcohol drinking and peptic ulcer risk [30]. Thus, further research is needed to elucidate the impact of alcohol consumption on PUD development and progression.

2.3.7 Coffee Consumption

Coffee is one of the most widely consumed beverages in the world. Coffee drinking has been reported to be associated with peptic ulcer disease and gastroesophageal reflux disease (GERD). Although caffeine has never been clearly implicated in the pathogenesis of peptic ulcer disease, it is generally recommended that coffee drinks should be avoided.

Caffeine is believed to stimulate gastric acid secretion by its action as a phosphodiesterase inhibitor and its effect in increasing cyclic AMP. Interestingly, some studies demonstrated that decaffeinated coffee also produces increase in gastric acid output. Regrettably, the mechanism of its action was not further evaluated.

The study performed by Cohen et al. [31] suggests that regular coffee and decaffeinated coffee are more potent stimulants of gastric acid secretion than caffeine alone. Interestingly, the same study showed that decaffeination only minimally diminishes the acid secretory potency. In another study, Eisig et al. [32] demonstrated that patients with duodenal ulcers reduced the volume of ingested coffee or even stopped drinking coffee once the symptoms of peptic ulcer disease occurred. Thereby, this study suggests a close correlation between the ulcer-like symptoms and the amount of coffee ingested by patients with duodenal ulcers. In contrast, several other studies suggest that coffee drinking seems to be of no importance in relationship with peptic ulcer disease. For instance, the meta-analysis performed by Shimamoto et al. [33] could not detect any significant association between coffee intake and peptic ulcer disease. Thus, the possible connection between coffee drinking and peptic ulcer disease remains controversial.

Conclusion

Despite continuous exposure to several harmful factors, the gastric mucosa in healthy individuals is able to maintain structural integrity and function. Protective factors such as the mucus gel layer and prostaglandins are the first defense line against irritating factors. However, when these protective mechanisms are overwhelmed by irritating factors, a gastric mucosal damage may develop. Thus, recent research, focused on associations between damaging factors and protective mechanisms in the stomach, led to the development of effective therapies based on inhibition of gastric acid production and eradication of *H. pylori*. Hence, prevalence of PUD complication is decreasing worldwide.

Multiple factors are considered as risk factors in pathogenesis of PUD (Fig. 2.2). Role of *H. pylori* infection or NSAIDs intake is well established in literature, whereas the effect of obesity, smoking, and alcohol intake still needs further studies. Nevertheless, a possible impact of all factors on PUD course should be considered during therapy. Thus, the doctor should bear in mind that PUD is a multifactorial disease, and its management should not be based on a simple cause-effect relationship but be adjusted for an individual patient and cover all possible personal factors influencing the disease development and course.

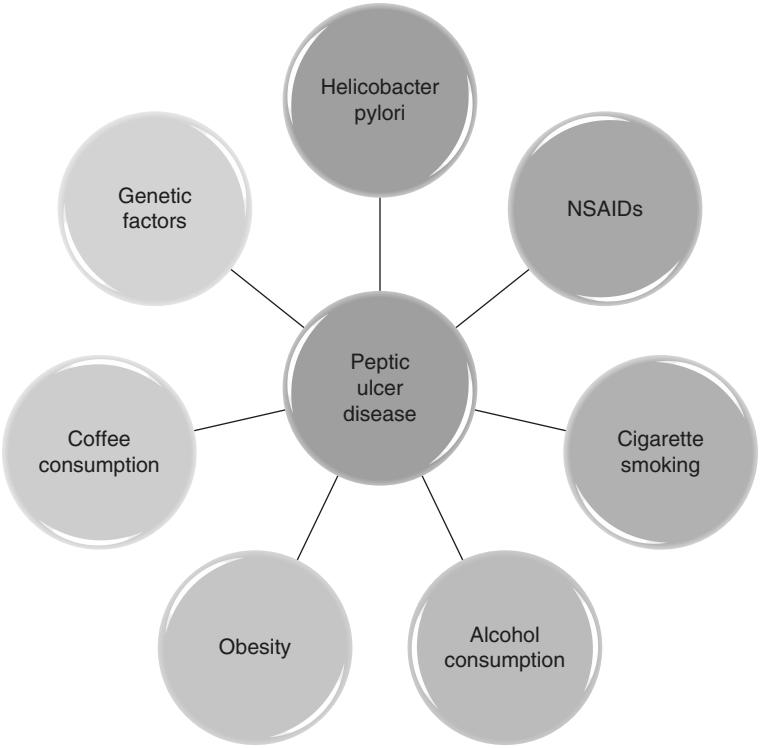

Fig. 2.2 Risk factors for peptic ulcer disease. Nowadays, the role of *H. pylori* infection and NSAIDs is development and progression of peptic ulcer diseases and is established in literature. Of note, studies from last decade suggest that other factors may be relevant in peptic ulcer pathogenesis, such as obesity or cigarette smoking

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