Review Article

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Risk factors leading to peptic ulcer disease: systematic review in literature

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ABSTRACT

This review is aiming to discuss the risk factors which lead to the occurrence of PUD during the period from July 2018 to August 2018. The present review was conducted by searching in Medline, Embase, Web of Science, Science Direct, BMJ journal and Google Scholar for, researches, review articles and reports, published over the past years. Books published on peptic ulcers and on the pathogenesis of human disease were also included., were searched up to August 2018 for published and unpublished studies and without language restrictions, the selected studies were summarized and un reproducible studies were excluded. If several studies had similar findings, we randomly selected one or two to avoid repetitive results. On the basis of findings and results this review found the H. Pylori and the use of NSAIDs are the most common risk factors for developing PUD, and also the genetic, stress and comorbidity increase the risk of PUD occurrence so successful eradication and prevention of the risk factors should be conducted to prevent the presence of PUD and is complication.

Keywords: Peptic ulcer disease, Risk factors, *Helicobacter pylori*, Non-steroidal anti-inflammatory drugs

INTRODUCTION

Peptic ulcer disease (PUD) is a common disease worldwide also known as peptic ulcer or stomach ulcers, PUD occurs as a defect in the mucosa of the stomach or duodenum that exceeds the muscularis mucosa. PUD follows gastric mucosal injuries as a result of imbalance between the defensive and the aggressive factors affecting the mucos. Many factors contribute to the development of PUD, of which environmental factors such as psychosocial conditions and stress are the most

outstanding.⁵ Stress is an acute hazard/risk to homeostasis that excites an allostatic or adaptive response. Stress affects the function of the gastrointestinal tract either in short or long-term impacts.⁵ Studies revealed that stress contributes to the formation of PUD and is frequently used to produce PUD in experimental animal models.⁶ The life time for developing a peptic ulcer is approximately 10%.⁷ They resulted in 301,000 deaths in 2013 down from 327,000.⁸ In western countries the percentage of people with *Helicobacter pylori* infections roughly matches age (i.e., 20% at age 20, 30% at age

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30,80% at age 80).prevalence is higher in developing countries where it is estimated at about 70% of the population, whereas developed countries show a maximum of 40% ratio.9 In developing countries, where most children become infected by the age 10 of gastric cancer rates are very high. 10 Researchers in Sabah, Malaysia confirmed a prevalence of 32.26% Helicobacter pylori infection in 1156 subjects, in age groups 12 to 80 years. 11 In the past duodenal ulcer was 10 times as common in men as in women and gastric ulcer had a male preponderance of 3:2, now the frequency is much less, largely because of H. pylori eradication incidence being more even. 12 The sale of antacid drugs worldwide exceeds \$5 billion, making ulcer disease major burden to the public healthcare system.⁶ In the UK as example mean initial in-hospital costs were £2458(SE=£216)per patient. Annual initial in-hospital costs of for all acute upper gastrointestinal bleeding (AUGIB) cases in the UK was estimated to be £155.5 million. 13 Etiology of PUD include H. pylori infection, NSAIDS, pepsin, smoking, alcohol, bile-acids, steroids, stress, and changes in gastric mucin consistency (may be genetically determined). 14,15 Other causes include Behcet disease, Zollinger Ellison syndrome, Crohn disease and liver cirrhosis, and similar symptoms stomach cancer, coronary heart disease, and inflammation of the stomach lining or gallbladder. 16 Symptoms of PUD are nonspecific and diagnosis unreliable on history, frequent symptoms include, epigastric pain, nausea, flatulence and bloating, heartburn, a posterior ulcer may cause pain radiating to the back, and symptoms are relieved by antacid. 17 Diagnosis is mainly established based on the characteristic symptoms, endoscopies or barium contrast and tests for *H. pylori* infection. ¹⁸ Prognosis of PUD is excellent if the underlying cause such as H. pylori infection or drugs can be addressed. 19

Despite the use of eradication therapy for the *H. pylori* infection and proton-pump inhibitors (PPIs), and advanced endoscopic therapy possibilities available during recent decades, mortality associated with PUD has not decreased concurrently with the incidence.²⁰ So we aim to enforce the prevention of the PUD through known the risk factors. This article reviews the current literature regarding the risk factors of PUD.²⁰

METHODS

The present review was conducted July 2018 to August 2018 in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) declaration standards for systematic reviews. We reviewed all the topics on peptic ulcers, such as genetics, etiology, epidemiology, psychology, anatomy, neurology, bacteriology, pathology, and clinical statistics. To achieve this goal, we searched Medline, Embase, Web of Science, Science Direct, and Google Scholar for, researches, review articles and reports, published over the past 15 years. Books published on peptic ulcers and on the pathogenesis of human disease were also included.

Our search was completed without language restrictions. Then we extracted data on study year, study design, and key outcome on peptic ulcers. The selected studies were summarized and unreproducible studies were excluded. Selected data is shown in the Table 1.

Inclusion criteria

Inclusion criteria were peptic ulcer disease; age 15 to 70 years; males and females' patients, healthy or asymptomatic.

Exclusion criteria

Exclusion criteria were other condition involving stomach or duodenal such as Gastroenteritis, Gastritis, Gastroparesis, and malignancies.

Data extraction and analysis

Information relating to each of the systematic review question elements was extracted from the studies and collated in qualitative tables. Direct analysis of the studies of PUD is made with extreme caution, as different sampling techniques can provide bias as overview of the assemblage.

RESULTS

Common risk factors— causes for PUD and gastritis include infection with H.pylori, and NSAIDs. Less common risk factors include alcohol, smoking, cocaine, severe illness, autoimmune problems, radiation therapy and Crohn disease among others.²¹

H. pylori major causative factor 60% of gastritis and up to 50-75% duodenal ulcers) is chronic inflammation due to H.pylori that colonizes the antralmucosa.²²

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.²²

H. pylori is able to survive and multiply in gastric environment, which is hostile to the growth of other bacteria. ²³

Numerous adaptations permit survival of *H. pylori* in the acidic milieu of the stomach.²⁴ Although most organisms appear to be adherent to the mucosal epithelial cells and form adherence pedestal resembling those produced by enteropathogenic *Escherichia coli*, several important adhesions have been identified.^{25,26} Bacterial lipopolysaccharide usually has proinflammatory activities, but *H. pylori* lipopolysaccharide has remarkable little.²⁷ *H. pylori* polysaccharide may express

the type 11 Lewisx, Lewisy) neither, or both of these antigens as well as type 1 antigens (Lea, Leb).²⁸ This observation is significant because these antigens are present on gastric epithelial cells, and there is evidence that host Lewis phenotype selects for the particular Lewis expression of the *H. pylori* population.²⁹

H. pylori is highly associated with gastric ulcer disease. The pathogenic role of *H. pylori* in chronic active gastritis and its association between H. pylori and duodenal ulcer in 95 to 99% of patients is well established.³⁰ All *H. pylori* spp. causes some degree of persistent inflammation in the mammalian stomach. Gastritis is found in virtually all infected humans, although the majority has no symptoms; only one in 10 develop ulcer disease. Gastric adenocarcinoma is 3 to 12 times more likely to develop in individuals infected with H.pylori.³¹ There a number of postulated mechanisms whereby H. pylori can cause injury to mucosa, urease can result in ammonia production and hemostatic factors and cytotoxins (e.g., protease, lipases and phospholipase A and vacuolating cytotoxin) can cause injury. H. pylori is more likely to associated with the early or initial states of primary gastric lymphoma than advanced tumors; H. pylori can disappear during progression of gastric lymphoma.³² pylori-specific Н. IgG antibody concentrations can be expected to fall significantly after successful antibacterial therapy.³³ A symptomatic and untreated patients continue to test IgG seropositive as long as H. pylori is present, even after histological resolution.³⁴ Eradication of H. pylori is associated with significant reduction in duodenal ulcer recurrence and is also useful in differentiating between H. pylori gastritis and gastric MALT lymphoma (mucosa-associated lymphoid tissue). 35,36 In *H. pylori* infected patients who develop gastric cancer, serum IgG against CagA is 94% sensitive and 93% specific; indicating that detection of antibodies to CagA is useful marker for diagnosis of duodenal and gastric cancer.37

Non-steroidal anti-inflammatory drugs (NSAIDs)

Worldwide studies have confirmed that H. pylori infection was present in more than 90% of patients with duodenal ulcers and about 85% of those with gastric ulcers, and they suggested that majority of the remaining ulcers were related to the use of NSAIDS. 23,38 The use of NSAIDS is the major cause of peptic ulcers, although the pathophysiological interaction between *H. pylori* NSAIDS is still controversial.³⁹ infection and Surprisingly, a number of recent reports from around the world, especially from the United States and Australia suggest a relatively low prevalence of infection of H. pylori in duodenal and gastric ulcers, even when the users of NSAIDS are excluded. 40 In the greater Rochester area, New York, only 61% of patients with non-NSAIDS induced duodenal as well as gastric ulcer showed the presence of H. pylori, but the situation is not the same outside the USA.⁴¹ In Europe, three studies from Scotland, Denmark, and Italy show a prevalence of H.

pylori-negative ulcer 10-15% which is lower than that observed in the US, but still higher than expected. 42,43 NSAIDs interfere with mucosal defense in the stomach via direct toxic effects in addition to cyclooxygenase inhibition and depletion of endogenous prostaglandins.⁴ Among drugs diclofenac and aspirin are the most common commonly associated drugs. 45 Aspirin increases the risk for gastric ulcer in patients of all ages, whereas non aspirin, non-steroidal use increases the gastric ulcers to varying degrees in patients over 55, depending on race and history of ulcer. 46 The use of NSAIDs increases the risk of peptic ulcer 3-anf 5 fold in H. pylori positive and H. pylori negative patients, respectively. 47 The success of eradication therapy should always be confirmed, because of the risk of ulcer recurrence and bleeding in H. pylori infected patients who require anti-inflammatory treatments. 48

Past gastric ulcer and family history of ulcer disease is an increased risk of recurrence with *H. pylori* infection. Family history of gastric ulcer disease is a risk factor, as there is some genetic predisposing to develop the disease, but there is no genetic relationship in developing *H. pylori* infection. Some research results suggest that there is a significant association between genetic polymorphism at the PGR-RFLP gene locus and gastric body ulcer. Genetic play an important role in ulcer pathogenesis. The concordance for peptic ulcer in identical twins is approximately 50%, and the lifetime prevalence of developing ulcer in first degree relatives of ulcer patients is about three-fold greater than in the general population. The inheritance of blood group 0 is associated with modest (1.3 fold) increase in duodenal ulcer. So

Stress and diet

Stress due to serious health problems such as those requiring treatment in an intensive care unit is well described as a cause of peptic ulcers, which are termed stress ulcers.⁵³ While chronic life stress was once believed to be the main cause of ulcers this is no longer the case. It is, however, still occasionally believed to play a role.⁵⁴ 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.⁵⁵ Caffeine and coffee, and also commonly thought to cause or exacerbate ulcers, appear to have little effect.⁵⁶ Skipping of meals allows gastric acid to directly act on surface mucosa of the stomach causing irritation which ultimately leads to gastric ulcers. Gastric ulcers cause abdominal pain which aggravate with meals.⁵⁷

Smoking and alcohol

Consumption of alcohol and smoking are risk factors. Chronic alcohol disturbs gastric mucosal barrier by inhibiting COX 1 receptor enzymes which reduce the production of cytoprotective prostaglandin. Cigarette smoking causes reduction of circulating epidermal

growth factor and increase free radical production in gastric mucosa. $^{58,59}\,$

Although some studies have found correlations between smoking and ulcer formation. Others have been more specific in exploring the risks involved and have found that smoking by itself may not be much of a risk factor unless associated with *H. pylori* infection. Researchers in Denmark in a series of 2416 subjects found that tobacco smoking and *H. pylori* infection are the main risk factors for PUD in Danish adults. 62

Studies have found that alcohol consumption increases risk when associated with *H. pylori* infection, it does not

seem to independently increase risk. Even coupled with *H. pylori* infection, the increase is modest in comparison to the primary risk factor. ⁶¹ Satarasinghe and colleagues in a series of 1500 patients found alcohol was a contributory factor in one third of gastrointestinal bleeding (IGIB) patients. ⁶³

Elderly patient

Study show a 7-year follow-up, aging hemodialysis patients had significantly higher incidences of PUB than the matched controls.⁶

Table 1: Risk factors of peptic ulcers.

Risk factor	Sample	Author and year	Key points
Genetic ⁶⁵	3159 cases and 2816 controls	Ma, Wu, Hu, Li, Cao, Dong, 2017	IL-1B-31C/T gene polymorphisms might increase H. pylori infection risk. IL-1B-511-C/T and IL-8-251T/A gene polymorphisms might -related diseases including GC or PUD
Obesity ⁶⁶	47,120 men	Boylan, Khalili, Huang, and Chan, 2014	In a large prospective cohort of male health professionals, central and total obesity wereassociated with increased risk of peptic ulcer—particularly gastric and H pylori–negative ulcers.
Inflammatory ⁶⁷	120	Tourani, Habibzadeh 2018	Increased level of TNF-α could probably play pivotal role in pathogenesis of peptic ulcer in the presence of H. pylori
Psychosomatics ⁶⁸	166	Levenstein, Jacobsen, Rosenstock & Jørgensen (2017)	A vulnerable personality raises risk for hospital-diagnosed peptic ulcer, in part because of an association with health risk behaviors.
H. pylori ⁷⁴	2416 Danish	Rosenstock, Jørgensen, Bonnevie, Andersen, 2003	Tobacco smoking and H pylori infection are the main risk factors for PUD in Danish adults
Hostility ⁶⁹	13,539	By Lemogne, Cédric, Schuster, 2015	Hostility might be associated with an increased risk of peptic ulcer.
NSAIDs ⁷⁰		Tomizawa, Shinozaki, 2017	Immunosuppressive agents were correlated with peptic ulcer
Hypoalbuminemia ⁷¹	18435	Hu, Huang and Chang, 2016	Patients diagnosed with hypoalbuminemia have a significantly elevated risk of developing PUB
Epstein-Barr virus ⁷²	Healthy individuals, n=129, and PUD patients (n=78, 58 duodenal and 20 gastric ulcers).	Cárdenas-Mondragón, Torres, 2015	Study suggests that EBV reactivation in gastric and duodenal epithelium increases the risk to develop PUD.
Tobacco smoking ⁷³	2416 Danish	Rosenstock, Jørgensen, Bonnevie, Andersen, 2003	Tobacco smoking and H pylori infection are the main risk factors for PUD in Danish adults
Healthcare workers ⁷⁴	50,226 physicians, 122,357 nurses, 20,677 pharmacists, and 25,059 other HCWs	Lin, Weng, Lin, Hsu, Wang, Su, et al. (2015)	Nurses and other HCWs had a significantly higher PUD risk than did the general population

DISCUSSION

The main purpose of this article was to determine the risk factors which lead to the occurrence of PUD, in which there are common risk factors – causes for PUD include infection with *H. pylori*, and NSAIDs. Less common risk factors include alcohol, smoking, cocaine, severe illness, autoimmune problems, radiation therapy and Crohn disease among others.²¹

H. pylori is considered to be major causative factor 60% of gastritis and up to 50-75% duodenal ulcers.²² The large sample of the Danish study indicate the huge contribution of the *Helicobacter pylorus* as the number one risk factor in PUD, And the use of NSAIDs and immunosuppressive agents were correlated with peptic ulcer. Genetic factor as people have IL-1B-31C/T gene polymorphisms might increase H. pylori infection risk, and also IL-1B-511-C/T and IL-8-251T/A gene polymorphism might act as a risk factor to H. pylori-related diseases including GC or PUD.

In a large prospective cohort of male health professionals, central and total obesity were associated with increased risk of peptic ulcer particularly gastric and *H. pylori*negative ulcers, which may indicate the higher incidence in general population or it may be cofactor with the higher stress and work pressure which found in heath field.⁶⁶

There is also an inflammatory predisposing factor in which increased level of TNF- α could probably play pivotal role in pathogenesis of peptic ulcer in the presence of *H. pylori*.

On the other hand, the personality and the psychological aspect of the person have great association with the occurrence of the PUD through the life time as result of stress or the vulnerability of the person. Vulnerable personality raises risk for hospital-diagnosed peptic ulcer, in part because of an association with health risk behaviors. Its impact is seen in 'idiopathic' and H. pylori -associated ulcers, and in acute surgical cases.⁶⁸ Hostile behavior is also might be associated with an increased risk of peptic ulcer. In a prospective study of a population-based Danish cohort, psychological stress increased the incidence of peptic ulcer, in part by influencing health risk behaviors. Stress had similar effects on ulcers associated with H. pylori infection and those unrelated to either H. pylori or use of non-steroidal anti-inflammatory drugs.⁷⁵

Severely ill and people with chronic illness, whereas aging hemodialysis patients had significantly higher incidences of PUB than the matched controls. ⁶⁴ And also co morbidity in patients diagnosed with hypoalbuminemia has a significantly elevated risk of developing PUB.

EBV play a significant role as risk factor for PUU, in which Duodenal PUD was significantly associated with

high anti-EBV IgG titers (p=0.022, OR=2.5), while anti-EBV IgA was positively associated with gastric PUD (p=0.002, OR=10.1), which indicate the EBV reactivation in gastric and duodenal epithelium increases the risk to develop PUD.

Health care workers (HCWs) in Taiwan have heavy, stressful workloads, are on-call, and have rotating nightshifts, all of which might contribute to peptic ulcer disease (PUD). Subgroup analysis for physician specialties was also done. Nurses and other HCWs had a significantly higher PUD risk than did the general population (odds ratio [OR]: 1.477; 95% confidence interval [CI]: 1.433-1.521 and OR: 1.328; 95% CI: 1.245-1.418, respectively); pharmacists had a lower risk (OR: 0.884; 95% CI: 0.828-0.945); physicians had a nonsignificantly different risk (OR: 1.029; 95% CI: 0.987-1.072). In the physician specialty subgroup analysis, internal medicine, surgery, Ob/Gyn, and family medicine specialists had a higher PUD risk than other physicians (OR: 1.579; 95% CI: 1.441 1.731, OR: 1.734; 95% CI: 1.565–1.922, OR: 1.336; 95% CI: 1.151–1.550, and OR: 1.615; 95% CI: 1.425–1.831, respectively). In contrast, emergency physicians had a lower risk (OR: 0.544; 95% CI: 0.359–0.822).⁷⁴

CONCLUSION

H. pylori and the use of NSAIDs are the most common risk factors for developing PUD, and also the genetic, stress and comorbidity increase the risk of PUD occurrence, as also the work stress in the medical field play significant role as risk for developing PUD so successful eradication and prevention of the risk factors should be conducted to prevent the presence of PUD and is complication.

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