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Helicobacter pylori Infection and Gastric Cancer

Research presented

By

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

{ يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَ الَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ}

صدق الله العظيم

المجادلة : [11]

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Contents

Helicobacter pylori Infection and Gastric Cancer

Abstract:

Helicobacter pylori is a most common causes of gastric cancers worldwide, and only a minority of patients will be survived from this disease. Most often people get infected with the bacterium during childhood. *Helicobacter pylori* is transmitted by people, probably partly due to sharing food and unhealthy living conditions. *Helicobacter pylori* can also cause stomach ulcers. The clinical symptoms from ulcers lead to treat of the bacterium. Treatment is given using a medicine that decreases acid production in the stomach (proton pump inhibitor) in combination with at least two antibiotics. Treatment can be an important approach to prevent stomach cancer. Therefore, it was important to do a review study based on published studies of *Helicobacter pylori* infection and the risk of stomach cancer. These studies were designed in a systematic way that all relevant studies were found.

Objective of this study: To determine the treatment of *Helicobacter pylori* and its role in gastric cancer.

Key words: *Helicobacter pylori*, Gastric cancer, Diagnosis, Treatment.

1. Introduction

Gastric cancer is the fifth most common cancer worldwide. The strongest risk factor for developing gastric cancer is infection with the bacterium *Helicobacter pylori* (1). However, *Helicobacter pylori* has been associated with a decreased risk of oesophageal adenocarcinoma, which is a highly lethal cancer with an increasing incidence in these days. This can probably be explained by a decrease in gastrooesophageal reflux as a result of gastric atrophy caused by *Helicobacter pylori*, decreasing gastric acid production. It was demonstrated that the incidence of oesophageal adenocarcinoma is

currently higher than that of oesophageal squamous cell carcinoma (2). *Helicobacter pylori* is estimated to be present in the gastric tissue of around half of the human population. The largest part of individuals with *Helicobacter pylori* will not show any symptoms from the infection. The recommended treatment for *Helicobacter pylori* is a 7-14 day treatment, most often consisting of a proton pump inhibitor and two or more antibiotics. Some data indicate that eradication treatment may decrease the risk of gastric cancer by 30-50 % (3, 4) but this needs to be evaluated in further research. The aims of this review were to clarify the risk of gastric cancer after treatment for *Helicobacter pylori*.

2. Literature review:

2.1 *Helicobacter Pylori*:

Helicobacter pylori was discovered in 1982 by Barry Marshall and Robin Warren, when they were the first to link its presence in the gastric tissue of patients with gastritis and peptic ulcers to these conditions.(5) At the time of discovery, the bacterium was first named *Campylobacter pyloridis*. In 1987, the name became *Campylobacter pylori*, until in 1989 it was discovered by genome sequencing that the bacterium was not supposed to be a part of the *Campylobacter* genus and it finally was named *Helicobacter pylori* (6,7).

Helicobacter pylori is estimated to be present in the stomach of more than 50% of the human population (8). Aetiology *Helicobacter pylori* is usually acquired early in life, before the age of 10, by person-to-person transmission.(9) It is believed that transmission occurs orally via saliva, for example by using the same kitchen utensils or eating from the same pot, or via faeces or vomit, for example from a faeces contaminated water source. Transmission is more likely to occur in

individuals that grow up in an environment with low socioeconomic status,(10) crowded 3 living conditions and lack of access to running water.(11)

Helicobacter pylori is a gram-negative, spiral shaped bacterium with flagella (Figure 1). It is able to survive in the stomach due to the bacterial enzyme urease that breaks down urea in the stomach into ammonia and carbon dioxide. These basic substances neutralise gastric acid and form a protection around the bacterium.

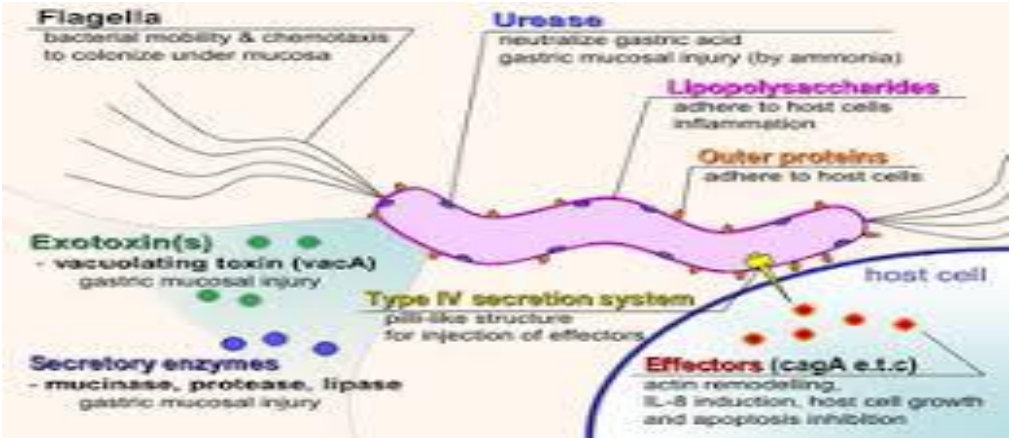

Figure 1: *Helicobacter pylori* structure.

It can then enter the gastric mucosa and move through this layer with the help of its flagella. There the bacterium is able to attach to the gastric epithelium (Figure 2) (12). Strains with different levels of virulence have been found, depending on the expression of proteins like vacuolating cytotoxin (VacA) and the oncoprotein cytotoxin-associated gene A (CagA). These highly virulent strains have been associated with an increased risk of gastric cancer and peptic ulcer disease (13,14).

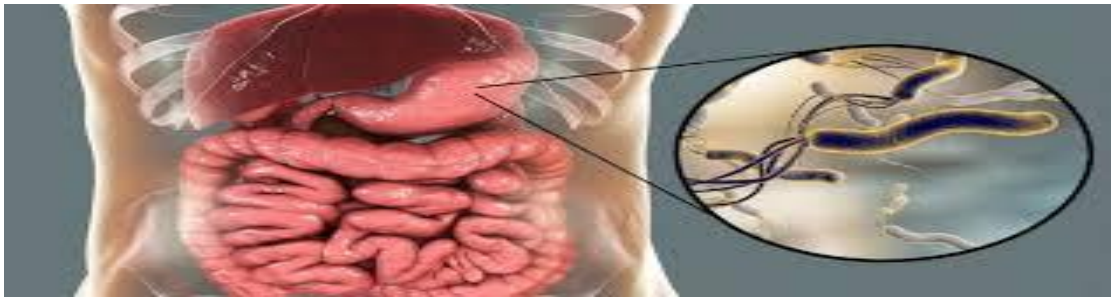

Figure 2: *Helicobacter pylori* attach to the gastric epithelium.

The incidence of these bacteria is due to the virulence genes that are carried by particular genetic patterns of this bacteria it is the most important virulence genes accompanying stomach and bowel disease are (cag A *and* vac A) (15). To avoid the harsh condition in the gastric lumen, this bacteria have developed an antibiotic resistant to the stomach acid of the microbial through colonization in a very narrow place of gastric lactation and secretion of the urease which analyses urea located in the medium to ammonia which have the effect of the acidic acid around in the stomach lining which enables them to stay in the human stomach lifelong if not treated with antibiotics (16).

2.2 Diagnosis:

Diagnosis of *Helicobacter pylori* are early gastric cancer or mucosa-associated lymphoid tissue (MALT) lymphoma, some guidelines also advise testing in dyspeptic individuals less than 60 years old without symptoms like weight loss. Testing with non-invasive methods may be initiated immediately in individuals below 50 years of age without symptoms who present with dyspepsia. This strategy is recommended over prescribing a proton pump inhibitor (PPI) or endoscopy in this patient group (17, 18). Both invasive and non-invasive methods can be used to detect the presence of *Helicobacter pylori*. The non-invasive test that has the highest sensitivity and specificity is the urea breath test (19). This test is based on the knowledge that *Helicobacter pylori* possesses the enzyme urease, which allows it to break down urea into ammonia and carbon dioxide. During the test, a patient is given urea orally, after which the amount of labelled carbon dioxide is measured in the exhaled breath. Another non-invasive test with high sensitivity and specificity when using ELISA, is the monoclonal stool antigen test. Serology is an often used method to detect *Helicobacter pylori* because it is readily available and in contrast to most other test, the results remain reliable in patients with atrophic gastritis, gastrointestinal bleeding, gastric

MALT lymphoma and gastric cancer. Endoscopy with biopsies is an invasive method to detect *Helicobacter pylori*. The biopsies can also be used for culture and the rapid urease test. This test can be performed during the endoscopy, giving immediate results. It is based on the same concept as the urea breath test, where the breakdown of urea by *Helicobacter pylori* will increase the pH of the test medium.

2.3 Treatment:

Treatment for *Helicobacter pylori*, called eradication, is initiated after a positive test result. Therefore it is important that the indications for testing are followed. Standard eradication treatment is triple therapy using a PPI in combination with two antibiotics; clarithromycin, and amoxicillin or metronidazole in case of penicillin allergy.(20) However, this treatment has become less effective in most parts of the world because of the increasing clarithromycin resistance, except for in Northern Europe (including Sweden) where clarithromycin resistance is still low.(20, 21) Global resistance rates for *Helicobacter pylori* are 1-25% for clarithromycin, 10-80% for metronidazole and less than 1% for amoxicillin.(22) In case of high clarithromycin resistance, the first step is to consider the metronidazole resistance in the area. If this is low, triple therapy can be given using the antibiotics amoxicillin and metronidazole.(20) In case of high antibiotic resistance for both clarithromycin and metronidazole, eradication treatment can be given as quadruple five therapy with a PPI, two antibiotics and bismuth, or without bismuth using a PPI and three antibiotics.(20, 23) Another recommended second line option is levofloxacin-based treatment.(23) Sometimes sequential therapy is given, where the antibiotics are administered one after the other, but superior efficacy has not been shown.(20) Recommended antibiotics in case of high resistance are tetracycline, levofloxacin, rifabutin, and furazolidone.(20) If eradication fails with standard triple therapy, one of the above-mentioned treatments can be prescribed. Repeating the same regimen is not meaningful (24)

If the second line treatment also fails, resistance testing should be performed to guide further treatment.(20)

2.4 Treatment association with gastric cancer:

In all individuals infected with *Helicobacter pylori*, the bacterium will cause chronic gastritis, which can later develop into associated conditions like atrophic gastritis, peptic ulcer disease, gastric cancer and MALT lymphoma.(20) Since the majority of individuals with *Helicobacter pylori* will not develop any symptoms, the bacterium is sometimes considered to be non-pathogenic, and thus not considered an infection. It was found that *Helicobacter pylori* was a causal factor for the development of peptic ulcer disease (25). *Helicobacter pylori* is associated with approximately 95% of duodenal ulcers and 70% of gastric ulcers.(26) *Helicobacter pylori* infection has been shown to be a risk factor for gastric cancer in a number of studies.(27, 28) It was shown that for developing gastric cancer in individuals with *Helicobacter pylori*.(29, 30) The mechanism by which the bacterium causes cancer is not completely clear. Most likely there are different factors that play a role, for example bacterial characteristics like the virulence of the strain (31) genetic factors of the infected individual that determine immune responses, and environmental factors like dietary differences (32-33).

2.5 Gastric Cancer:

Gastric cancer is the fifth most common cancer and the third most common cause of cancer death globally. There were 1,000,000 new cases and nearly 800,000 deaths in 2018 (34). The highest incidence rates are found in Eastern Asia, while the incidence is lower in Northern America, Northern Europe and Africa (34). The incidence is about two times higher in men, compared to women.(34).It was

found that there are more than 95% of gastric cancer are histologically classified as adenocarcinoma, which is further divided into intestinal or diffuse type carcinoma, both of which are associated with *Helicobacter pylori* infection (34). The development of the diffuse type is not clear, but the intestinal type has been shown to develop according to a specific pathway, the Correa pathway; from chronic gastritis, gastric atrophy, intestinal metaplasia, and dysplasia to invasive adenocarcinoma (36). *Helicobacter pylori* is the strongest risk factor for gastric cancer. Among other risk factors it has been found that a diet high in fruits and vegetables protects against gastric cancer, while a diet high in salt can increase the risk (37-38). Tobacco smoking has also been found to be a moderately strong risk factor for gastric cancer (39). There is a possible acceleration of the cancer risk in individuals who smoke and also have a more virulent strain of *Helicobacter pylori* (40). Low socioeconomic status is also associated with an increased risk of gastric cancer (39.41).

3. Conclusions

Helicobacter pylori is the most important causes of gastric cancer that can be developed after the infection with this bacterium. In a diagnosis, endoscopy with biopsies is an invasive method to detect *Helicobacter pylori.* The treatment of this bacterium may be prevent the development of gastric cancer, based on low prevalence of *Helicobacter pylori* and low incidence of gastric cancer.

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