INTRODUCTION

Helicobacter pylori (Hp) is a gram-negative bacillus responsible for one of the most common infection found in humans worldwide ***(Warren and Marshall, 1984)*** first cultured and identified the organism as Campylobacter Pylori in 1982. By 1989, it was renamed and recognized to be associated closely with antral gastritis (gastric and duodenal ulcers in adults and children) ***(Holton et al., 1994).***

A high prevalence of upper gastrointestinal symptom is described is diabetic patients and at least in part, this has been attributed to abnormal emptying of the stomach ***(Gulcelik et al., 2005)***.

There is a high prevalence of Helicobacter pylori infection in Diabetic patients and it is correlated with dyspeptic symptoms. Diabetic subjects complicated with autonomic neuropathy and dyspepsia are at high risk of Helicobacter pylori infection and should be carefully investigated and considered for eradication therapy ***(Gulcelik et al., 2005)***.

Delay gastric emptying and antral dysmotility are important causes of dyspepsia in diabetes. The role of helicobacter pylori infection in diabetic dyspepsia is mainly related to blood glucose concentration. Hyperglycemia may induce the infection of H. pylori or silent infection may get reactivated and produce symptoms of dyspepsia in diabetes ***(Gentile et al., 2008).***

AIM OF THE WORK

A high prevalence of Helicobacter pylori (Hp) infection in diabetic patients has been described in recent years. The aim of the work is to investigate the prevalence of H. pylori and if the glycemic control affects its incidence.

H. PYLORI

The observations of Warren and Marshall between 1979 and 1984 allowed investigators to tie together the various threads that had been constructed in the medical literature in the preceding 100 years. Warren had observed patients with spiral organisms on their gastric mucosa since 1979 and had documented the inflammation associated with the bacteria/by the time he and Marshall began a concerted attempt to study the organisms in patients with various upper gastrointestinal symptoms ***(Warren and Marshall, 1984).***

It was observed that H. pylori is a helix-shaped Gram-negative bacterium, about 3 micrometres long with a diameter of about 0.5 micrometres. It is microaerophilic; it requires oxygen although at lower concentration than is found in the atmosphere. It contains a hydrogenase which can be used to obtain energy by oxidizing molecular hydrogen (H2) that is produced by intestinal bacteria ***(Olson and Maier, 2002).***

It produces oxidase, catalase, and urease. It is capable of forming and can convert from spiral to a possibly viable but nonculturable coccoid form, both likely to favor its survival and be factors in the epidemiology of the bacterium. The coccoid form can adhere to gastric epithelial cells in vitro ***(Liu et al., 2006).***

H. pylori possesses five major outer membrane protein (OMP) families. The largest family includes known and putative adhesins. The other four families include porins, iron transporters, flagellum-associated proteins, and proteins of unknown function. Like other typical Gram-negative bacteria, the outer membrane of H. pylori consists of phospholipids and lipopolysaccharide (LPS). The O antigen of LPS may be fucosylated and mimic Lewis blood group antigens found on the gastric epithelium. The outer membrane alsoxontains cholesterol glucosides, which is found in few other bacteria ***(Kusters et al., 2006).*** H. pylori has 4-6 flagellae, all gastric and enterohepatic Helicobacter species are highly motile due to flagellae ***(Josenhans et al., 2000)***. The characteristic sheathed flagellar filaments of helicobacters are composed of two copolymerized flagellins, FlaA and FlaB ***(Chan et al., 1994).***

Epidemiology

The prevalence of H. pylori infection varies widely by geographic area, age, race, ethnicity.

At least half the world's population are infected by the bacterium, making it the most widespread infection in the world. Actual infection rates vary from nation to nation; the Third World has much higher infection rates than the West (Western Europe, North America, Australasia), where rates are estimated to be around 25% ***(Pounder and Ng, 1995).***

The reason for that racial difference in incidence is uncertain. Suggested explanations for this finding include genetic differences, and transmission and perpetuation of infection within the same ethnic group resulting from varied habits and socio-cultural practices ***(Li et al., 2009).***

Many studies aimed to identify the relation between H. pylori and age, one study showed a definite trend in age distribution, as it is proved that infections were usually acquired in early childhood in all countries. However, the infection rate of children in developing nations, was higher than in industrialized nations, probably due to poor sanitary conditions. Another study showed that the incidence was higher in unskilled lower income earners and it is related to socioeconomic status and education level, in developed nations it was currently uncommon to find infected children, but the percentage of infected people increases with age, as 10% between 18 and 30 years and 84% of the index patients over the age of 40 yrs. The higher prevalence among the elderly reflects higher infection rates when they were children rather than infection at later ages ***(Kusters et al., 2006).***

This age group (over 40 years) was more susceptible to gastric malignancies and as such the identification of these patients and eradication of H. pylori might be very important. This is because of the fact that the World Health Organization has already recognized and classified H.

pylori as a class 1 carcinogen. Sixty percent of the asymptomatic family relatives were under the age of 40. The main pathology noted in the index group was gastric in nature and was found in 80%. The main pathology in them was antral gastritis, while the rest had gastric ulcers. Amongst the family relatives 37% had asymptomatic antral gastritis ***(Quigley, 1998).***

The majority of studies have not found tobacco use or alcohol consumption to be risk factors for H. pylori infection. Knowledge of the epidemiology and mode of transmission of H. pylori is important to prevent its spread and may be useful in identifying high-risk populations, especially in areas that have high rates of gastric lymphoma, gastric cancer, and gastric ulcer ***(Brown et al., 2002).***

Mode of transmission

Understanding the route of H. pylori transmission is important. But the mode of transmission of H. pylori remained poorly understood; No single pathway has been clearly identified. Studies, proved that 3 ways of transmission of H. pylori infection:

Iatrogenic

The first, and most frequent, mode of transmission is iatrogenic, in which tubes or endoscopes that have been in contact with the gastric mucosa of one individual were used for another patient ***(Akamatsu, 1996).*** Occupationally

acquired infections — usually in which infection is transmitted from a patient to staff member — have also been reported, especially among endoscopists and gastroenterologists.

Faecal-oral

The second possible route is faecal-oral. H. pylori has been isolated from the faeces of infected young children, but isolation from adults[1] faeces has been rare ***(Namavar, 1995)***. Failure to recover the bacterium from faeces might be due to the toxic effect of faeces or the methods used may not have been suitable.

Faeces – contaminated water may be a source of infection; an association between H. pylori and the absence of hot running water was found in some studies ***(Neale and Logan, 1995)***. In addition, an increased risk of infection was observed in children who swam in rivers, streams, or swimming pools ***(Friis et al., 1996).***

Oral-oral

The third possible route of transmission is oral-oral. Few reliable studies have cultured H. pylori from the oral cavity; only sporadic isolates from dental plaque and saliva have been recorded ***(Lin, 1998)***. There have been problems with the specificity of bacterial cultures and the polymerase chain reaction from samples from the oral cavity. The use of the same spoon by both mother and child, intimate oral-oral contact and aspiration from vomit ***(Megraud, 1995).***

A significant association was found between positive test results for H. pylori and increased number of tooth surfaces with plaque ***(Peach et al., 1997).***

Interfamilial clustering of infections and the higher prevalence found in institutionalized populations might indicate that person-to-person contact was a route of transmission, but this could also indicate that there had been a common source of transmission, such as contaminated drinking water or food.

The use of molecular typing on bacterial strains isolated from infected members of a family might indicate whether there had been a common source. In a small study of six families, in only two families did two members harbour the same strain ***(Chalkauskas, 1998).*** In the other four families, each member carried a different strain. Outbreaks of H. pylori have not been described, except for the few observed following infection after endoscopy ***(Megraud, 1995).***

Clinical Picture

Most of the people who are infected with H pylori do not develop significant clinical complications, and they remain carriers with asymptomatic chronic gastritis. Some individuals who carry additional risk factors may develop peptic ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphomas, or gastric adenocarcinomas.

Most cases of H. pylori infection produce no signs or symptoms.

Signs or symptoms that can occur with H. pylori infection include:

1. An ache or burning pain in abdomen, is comfort, bloating, nausea and perhaps vomiting and weight loss.

2. Chronic gastritis

H. pylori-associated chronic gastritis progresses with the following 2 main topographic patterns that have different clinical consequences.

Antral predominant gastritis is characterized by inflammation and is mostly limited to the antrum. Individuals with peptic ulcers usually demonstrate this pattern of gastritis.

Multifocal atrophic gastritis characterized by involvement of the corpus and gastric antrum with progressive development of gastric atrophy (loss of the gastric glands) and partial replacement of gastric glands by an intestinal-type epithelium (intestinal metaplasia). Individuals who develop gastric carcinoma and gastric ulcers usually demonstrate this pattern of gastritis.

3. Ulcers

Symptoms that suggest ulcers:

1- Burning pain in the upper abdomen, usually occurring about an hour or so after meals or even during the night. The symptoms are often relieved temporarily by antacids, milk, or medications that reduce stomach acidity.
2- Water brash (rush of saliva after an episode of regurgitation to dilute the acid in esophagus).
3- Nausea, and copious vomiting; loss of appetite and weight loss.
4- Hematemesis: this can occur due to bleeding directly from a gastric ulcer, or from damage to the oesophagus from severe/continuing vomiting, melena (tarry, foul-smelling feces due to oxidized iron from hemoglobin).

Types of ulcers:

- ***Stomach Ulcers:*** With stomach ulcers H. pylori infection is found in 60 to 80 percent of the cases. Again, it is still uncertain how the infection acts to cause the ulcer. It probably weakens the protective mucous layer of the stomach. This allows acid to seep in and injure the underlying stomach cells. However, there is still a great deal of research to be done to unravel this relationship.

- ***Duodenal Ulcers:*** In times past, physicmns were taught "no acid, no ulcer. The medical profession felt the single most important factor causing duodenal ulcers to form was strong stomach acid. Research has now shown that over 90% of all patients who develop duodenal ulcers have H. pylori infection in the stomach as well. Medical studies are under way to determine the relationship between the two and how an infection in the stomach can be related to a\duodenal ulcer. Acid is still important; patients without acid in the stomach never get duodenal ulcers. However, physicians now accept the fact that the infection is diirectly related to the development of duodenal ulcers. It is now rather easy to clear duodenal ulcers with the strong acid-reducing medicines available. But, the ulcers will usually recur unless the H. pylori infection is also cleared from the stomach ***(Kim et al., 2002).***

4. Stomach Cancer and Lymphoma

These two types of cancer are now known to be related to H. pylori bacteria. This does not mean that all people with H. pylori infection will develop cancer; in fact, very few do. However, it is likely that if the infection is present for a long time, perhaps from childhood, these cancers may then develop. This is another reason why it is important to treat H. pylori infection, as it was found that H. pylori infection is associated with a 1-2% lifetime risk of

stomach cancer and a less than 1% risk of gastric MALT lymphoma ***(Starpoli, 2005).***

In uncomplicated H pylori -associated atrophic gastritis, clinical findings are few and nonspecific, epigastric tenderness may exist, if gastric ulcers coexist, guaiac-positive stool may result from occult blood loss ***(Antonia et al., 2007).***

Pathophysiology

Researches proved to colonize the stomach, H. pylori must survive the acidic pH of the lumen and burrow into the mucus to reach its niche, close to the stomach's epithelial cell layer. The bacterium has flagellae and moves through the stomach lumen and drills into the mucoid lining of the stomach. Many bacteria can be found deep in the mucus, which is continuously secreted by mucous cells and removed on the luminal side. To avoid being carried into the lumen, H. pylori senses the pH gradient within the mucus layer by chemotaxis and swims away from the acidic contents of the lumen towards the more neutral pH environment of the epithelial cell surface ***(Schreiber et al., 2004).***

H. pylori was also found on the inner surface of the stomach epithelial cells and occasionally inside epithelial cells. It produces adhesins which bind to membrane-associated lipids and carbohydrates and help it adhere to

epithelial cells. For example, the adhesin BabA binds to the Lewis b antigen displayed on the surface of stomach epithelial cells ***(Ilver et al., 1998).***

H. pylori produces large amounts of the enzyme urease, molecules of which are localized inside and outside of the bacterium. Urease breaks down urea (which is normally secreted into the stomach) to carbon dioxide and ammonia (which neutralizes gastric acid). The survival of H. pylori in the acidic stomach is dependent on urease, and it would eventually die without the enzyme. The ammonia that is produced is toxic to the epithelial cells, and, along with the other products of H. pylori—including protease, vacuolating cytotoxin A (VacA), and certain phospholipases—damages those cells ***(Smoot, 1997).***

Colonization of the stomach by H. pylori results in chronic gastritis, an inflammation of the stomach lining. The severity of the inflammation is likely to underlie H. pylori-related diseases. Duodenal and stomach ulcers result when the consequences of inflammation allow the acid and pepsin in the stomach lumen to overwhelm the mechanisms that protect the stomach and duodenal mucosa from these caustic substances. The type of ulcer that develops depends on the location of chronic gastritis, which occurs at the site of H. pylori colonization ***(Dixon, 2000).***

The acidity within the stomach lumen affects the colonization pattern of H. pylori and therefore ultimately determines whether a duodenal or gastric ulcer will form:

In people producing large amounts of acid, H. pylori colonizes the antrum of the stomach to avoid the acid-secreting parietal cells located in the corpus (main body) of the stomach. The inflammatory response to the bacteria induces G cells in the antrum to secrete the hormone gastrin, which travels through the bloodstream to the corpus ***(Blaser and Atherton, 2004).***

Gastrin stimulates the parietal cells in the corpus to secrete even more acid into the stomach lumen. Chronically increased gastrin levels eventually cause the number of parietal cells to also increase, further escalating the amount of acid secreted. The increased acid load damages the duodenum, and ulceration may eventually result. In contrast, gastric ulcers are often associated with normal or reduced gastric acid production, suggesting that the mechanisms that protect the gastric mucosa are defective ***(Schuber and Peura, 2008).***

H. pylori can also colonize me corpus of the stomach, where the acid-secreting parietal cells are located. However chronic inflammation induced by the bacteria causes further reduction of acid production and, eventually, atrophy of the stomach lining, which may lead to gastric ulcer and increases the risk for stomach cancer.

Response to H. pylori infection:

The host response to H pylori and bacterial products is composed of T- and B-cell lymphocytes, denoting chronic gastritis, followed by infiltration of the lamina propria and gastric epithelium by polymorphonucle leukocytes that eventually phagocytize the bacteria. The presence of polymorphonuclear leukocytes in the gastric mucosa is diagnostic of active gastritis ***(Viala et al., 2004).***

The interaction of H pylori with the surface mucosa results in the release of proinflammatory cytokine interleukin (IL)-8, which leads to recruitment of polymorphonuclear cells and may begin the entire inflammatory process. Gastric epithelial cells express class II molecules, which may increase the inflammatory response by presenting H pylori antigens, leading to further cytokine release and more inflammation. High levels of cytokines, particularly tumor necrosis factor-a (TNF-a) and multiple ILs (eg, IL-6, IL-8, IL-10), are detected in the gastric mucosa of patients with H pylori gastritis.

Leukotriene levels are also quite elevated, especially leukotriene B4, which is synthesized by host neutrophils and is cytotoxic to gastric epithelium. This inflammatory response leads to functional changes in the stomach, depending on the areas of the stomach involved. When inflammation affects the gastric corpus, parietal cells are inhibited, leading to reduced acid secretion. Continued