INTRODUCTION

Helicobacter pylori (Hp) is a gram-negative bacillus spiral-shaped bacteria that are highly motile because of multiple unipolar flagella. They are microaerophilic and potent producers of the enzyme urease. H pylori inhabits the mucus adjacent to the gastric mucosa. responsible for one of the most common infections found in humans worldwide ***(Blecker, 1997).***

Warren and Marshall 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). By the early-to-mid 1990s, further evidence supported a link between chronic gastritis of H pylori infection in adults and malignancy, specifically gastric lymphoma and adenocarcinoma ***(Blecker, 1997).***

Important adaptive features that enhance survival of the organism in an acidic environment include its shape and motility, its reduced oxygen requirement, its adhesion molecules that are trophic to certain gastric cells, and its urease production. Bacterial urease converts urea to ammonium and bicarbonate, neutralizing gastric acid and providing protection in the hostile, highly acidic gastric environment ***(Appelmelk et al., 1996).***

H pylori produces suspected disease-inducing factors, including urease, vacuolating cytotoxin, catalase, and lipopolysaccharide (LPS). Urease, a potent antigen, induces increased immunoglobulin G and immunoglobulin A production. Expression of vacuolating cytotoxin, which induces inflammatory cytokines, may be associated with more pronounced inflammation and increased propensity to cause disease. Catalase helps H pylori survive in the host by preventing the formation of reactive oxygen metabolites from hydrogen peroxide. The LPS outer membrane of H pylori is a less potent inducer of the host complement cascade.

Cytotoxin-associated antigen (CagA) is probably the most important virulence factor in H pylori. Translocating the CagA protein into the gastric epithelial cells causes rearrangement of the host cytoskeleton and alters cell signaling and perturbs cell cycle control. Furthermore, CagA-positive strains are known to induce the expression of a DNA-editing enzyme, which leads to accumulation of mutations in the tumor suppressor p53 ***(Figueiredo et al., 2005).***

H pylori colonizes the stomach, induces inflammatory cytokines, and causes gastric inflammation. Individuals with H pylori– associated antral-predominant gastritis with increased gastric acid production are prone to peptic ulcer disease (PUD). In contrast, H pylori pan-predominant

gastritis or corpus-predominant gastritis with decreased gastric acid production are

more prone to developing gastric atrophy (intestinal metaplasia and gastric adenocarcinoma).

H pylori has been associated with iron-deficiency anemia. The two main hypotheses that potentially explain this relation are:

(1) Sequestration of iron due to antral H pylori infection and

(2) Decreased non-heme iron absorption caused by hypochlorhydria.

H pylori infection and its association with gastric malignancy have been well described in several epidemiologic studies ***(Williams et al., 1999).***

However, the course of progression from inflammation to cancer remains unclear. One model describes the stepwise progression of H pylori infection to hypochlorhydria, chronic gastritis, atrophic gastritis, intestinal metaplasia, and gastric cancer. Increased production of the cytokine interleukin 1β has been linked to an increased risk of hypochlorhydria and gastric cancer in infected subjects. Duodenal and gastric ulcers may be associated with H pylori gastritis in adults but is uncommon in children. The risk of gastric cancers, including non-Hodgkin lymphoma (eg, mucosa-associated

lymphoid tissue [MALT]) and adenocarcinoma, is increased in adults.

Some studies suggest that H pylori protects human subjects from developing gastroesophageal reflux disease, whereas others postulate a causative association between them. A recent retrospective study revealed a significantly higher prevalence of reflux esophagitis in children with H pylori infection ***(Moon et al., 2009).***

H pylori infection has also been associated with extraintestinal manifestations, such as short stature, immune thrombocytopenic purpura, and migraine with varying level of evidence. ***(Goodman et al. 2006).***

Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes, It affects one in five people, and prevalence increases with age. Metabolic syndrome is also known as metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome, and CHAOS (Australia) CHAOS as an abbreviation for Coronary artery disease, Hypertension, Atherosclerosis, Obesity, and Stroke ***(Ford et al., 2002).***

Symptoms and features are:

- Fasting hyperglycemia - diabetes mellitus type 2 or impaired fasting glucose, impaired glucose tolerance, or insulin resistance;
- High blood pressure;
- Central obesity (also known as visceral, male-pattern or apple-shaped adiposity), overweight with fat deposits mainly around the waist;
- Decreased HDL cholesterol;
- Elevated triglycerides;

Associated diseases and signs are: hyperuricemia, fatty liver (especially in concurrent obesity) progressing to non-alcoholic fatty liver disease, polycystic ovarian syndrome (in women), and acanthosis nigricans.

Diagnosis:

According to American Heart Association/Updated NCEP(National Cholesterol Education Program)

- Elevated waist circumference:

- Men — Equal to or greater than 40 inches (102 cm)
- Women — Equal to or greater than 35 inches (88 cm)

 Elevated triglycerides: Equal to or greater than 150 mg/dL

 Reduced HDL (―good‖) cholesterol:

- Men — Less than 40 mg/dL
- Women — Less than 50 mg/dL

Elevated blood pressure: Equal to or greater than 130/85 mm Hg or use of medication for hypertension Elevated fasting glucose:

Equal to or greater than 100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia ***(Grundy et al., 2004).***

THE AIM OF THIS STUDY

We aim in this study to asses the correlation between helicobacter pylori infection and metabolic syndrome.

Chapter (1)

HELICOBACTER PYLORI HISTORY

Robin Warren and Barry Marshall reminds us of similar efforts by Frank Gorham, a Missouri physician, in trying to understand peptic ulcer disease. Gorham ***(Freeberg et al., 1940)***

Began using bismuth in 1930 to treat peptic ulcers in patients whose disease would not heal under normal ulcer management. In these patients, he noted encouraging results. Since bismuth had known antisyphilitic properties, he postulated that an organism thriving in an acid medium was ―a possible factor of chronicity, if not an etiological factor, in peptic ulcer ***(Freeberg et al., 1940).***

At the same time, E V Cowdry and colleagues at the Washington University School of Medicine, USA, were studying an unidentified so-called spirochete in the stomachs of rhesus monkeys. ***(Cowdry et al., 1936)***

Being familiar with Cowdry‘s research, Gorham forwarded stomach samples to Cowdry for analysis. In turn, Cowdry‘s preliminary findings led a colleague, James Doenges, to undertake a more comprehensive study. Through examination of 242 human stomachs removed at necropsy, Doenges reported 43% to be positive for the spirochete. ***(Doenges et al., 1939)***

In a later study by Freeberg and Barron, they noted that in the absence of ulceration, spirochetes were rarely found; yet, overall they concluded that any evidence of pathogenic significance was lacking, Although so close to an understanding of the cause and treatment of this disease, these inconclusive results thwarted further progress.. ***(Freeberg et al., 1940)***

Conclusive proof of an association was not identified until the revitalisation of this research by Warren and Marshall. After more than a century since the first observation of H pylori in the human stomach by Salomon, and although many clinical applications of this discovery have been developed, we believe that this story is far from over. ***(Salomon et al., 1896)***

Gastric organisms were first observed more than 100 years ago and their association with gastritis has been recognized since the 1970s ***(Marshall et al., 1989).***

The true implication of these microbes was not fully realized, however, until 1982 when Marshall and Warren identified and subsequently cultured the gastric bacterium, Campylobacter pyloridis, later reclassified as Helicobacter pylori (H. pylori) ***(Marshall et al., 1984).***

Epidemiology of Helicobacter pylori infection:

Helicobacter *pylori* infection is now recognized as a worldwide problem. *H. pylori* infection is the most common cause of chronic gastritis, and has been strongly linked to peptic ulcer disease and gastric cancer. *H. pylori* is estimated to infect one-half of the world‘s population. The epidemiology of infection reveals that given the right circumstances it is readily transmissible. Infection is generally acquired in childhood, but disease manifestations typically do not appear until adulthood and often only after long periods of latency. The infection has a high morbidity rate, but a low mortality rate, and is curable with antibiotic therapy. The prevalence of *H. pylori* infection varies from country to country, with the largest differences being observed between developed and developing countries ***(Megraud et al., 1989; Graham et al., 1991; Taylor and Blaser, 1991; Bardhan et al., 1998; Redlinger et al., 1999)***

The epidemiology of H.pylori infection in developing countries such as India, Saudi Arabia, Egypt and Vietnam is characterized by a rapid rate of acquisition of infection such that approximately 80% of the population is infected with the bacterium by the age of 20 ***(Megraud et al., 1989; Al-Moagel et al., 1990; Graham et al., 1991a).***

Current data suggest that the increase with age is actually related to different birth cohorts, and reflects that each successively younger cohort has had a lower rate of acquisition of infection than those born earlier ***(Parsonnet et al., 1992; Banatvala et al., 1993).***

H. pylori infection has been shown to follow the routes of human migration by their geographical origin, and several studies have examined the effect of immigration on the prevalence of the infection. One recent study examined *H. pylori* strains among three major ethnic groups in Malaysia (namely the Malay, Chinese and Indian populations), reporting that while the majority of the Malay and Indian *H. pylori* isolates share the same origin, the origin of the Malaysian Chinese *H. pylori* is distinctive, The study concluded that the Malay population was likely to have been initially H. pylori-free and gained the pathogen recently from cross infection from other populations. ***(Tay et al., 2009).***

It has been also established that the prevalence of *H. pylori* is inversely related to socio-economic status, with the major variable being the status during childhood, the period of highest risk of acquisition.***(Graham et al., 1991b; Malaty et al., 1996a, b, 2001).***

Variation in acquisition of infection among ethnic and racial groups appears to be primarily related to differential exposure (e.g. cultural background; social, dietary and

environmental factors) ***(Graham et al., 1991b; Mitchell et al., 1992; Malaty et al., 1998)*** and not to possible differences in genetic predisposition ***(Malaty et al., 1992).***

The finding regarding socioeconomic status during childhood holds true for all subgroups in the USA. For instance, in a paediatric study conducted in Arkansas, children (aged 11–20 years) from families with an income of <US$5000/year had prevalence rates of up to 60%, whereas those with a family income of >US$25, 000/year had only a 15% rate of infection ***(Fiedorek et al., 1991).***

This phenomenon has also been observed in other countries. In recently developed countries such as Korea, although approximately 80% of individuals more than 20 years of age are infected (reflecting the fact that Korea has become a developed country only within the past 20 years) the prevalence of infection in young children is inversely related to the socioeconomic class of their family. Those aged 10–19 years who were from a high socioeconomic class had a 20% frequency of *H. pylori* infection, while those of the same age who were from a low socioeconomic class had a 60% frequency ***(Malaty et al., 1996a).***

Although *H. pylori* infection is chronic, and possibly lifelong, spontaneous elimination of the infection was reported as early as 1992 using serological tests and was confirmed using breath tests ***(Klein et al., 1994)*** and

histology ***(Guelrud et al., 1994)*** in both developed and underdeveloped countries.

These observations have subsequently been confirmed in a number of populations ***(Matysiak-Budnik et al., 1996; Cranstrom et al., 1997; Roosendaal et al., 1997).*** A longitudinal study, conducted over a 12-year period in 212 black and white children living in the same community and attending the same schools, has provided additional insights into the changing pattern of infection ***(Malaty et al., 1999).*** The study showed differences to exist between the two races. At ages 7–9 years, 19% of children had *H. pylori* infection (40% of blacks versus 11% of whites; P = 0.001).

After a 12-year period of observation, more black children remained infected (or were more likely to become re-infected) compared with white children, in whom the infection was lost in 50% during the observation period. This suggested that the higher rate of acquisition and the lower rate of loss of infection among black children might be due to differences in access to healthcare facilities or more intense exposure, for whatever reason. The high rate of loss of *H. pylori* infection among white children was not related to *H. pylori* ‗eradication therapy‘ as the infection had not yet been diagnosed ***(Malaty et al., 1999).***

The continuing change in the epidemiology of *H. pylori* infection complicates our understanding of the actual

prevalence of H. pylori. The higher rate of loss of infection as compared with acquisition may be related to changes in standards of living in successive generations, or to changes in medical practices leading to increased use of antimicrobials for other common infections. It is impossible to entirely separate environmental factors from genetic influences. ***(Malaty et al., 1999).***

An early twin study in the Swedish population suggested a genetic component for acquiring *H. pylori* infection ***(Malaty et al., 1994)*** and a follow-up study in the same twin population has questioned if there are genetic influences for peptic ulcer disease in common with genetic influences for *H. pylori* infection ***(Malaty et al., 2000b).***

A comparison of monozygotic and dizygotic cross-twin and cross-trait correlations in this Swedish population demonstrated that, despite the similarity in heritability for the two traits (peptic ulcer disease and *H. pylori* infection), the genetic influences for susceptibility to peptic ulcer disease were independent of the genetic effects for acquiring *H. pylori* infection. It is feasible that the relationship between *H. pylori* and peptic ulcer disease could be mediated by familial environmental factors, such as environmental experiences or situations that are shared by family members. infection ***(Malaty et al., 1994).***

Examples of familial environmental factors that may mediate the association between *H. pylori* and peptic ulcer disease are diet, smoking and drug consumption (e.g. alcohol, caffeine and/ or NSAID consumption). Since the early 1980s, the occurrence of peptic ulcer disease has declined remarkably in the USA, Europe, Australia and Japan ***(Vogt and Johnson, 1980; Wylie, 1981; Smith, 1997).***

The risk of peptic ulcers was highest among those born at the beginning of the 20th century and has decreased in all subsequent generations ***(Susser, 1982; Sonnenberg et al., 1985).***

Due to the rapidity of this change in the pattern of peptic ulcer disease in successive generations (birth cohort phenomenon), it is far more likely to be due to changes in environmental factors rather than to changes in the genes of the affected patients ***(Sonnenberg et al., 1985).***

Another possibility is that a change has occurred in the prevalence of particularly virulent *H. pylori* strains ***(e.g. cag pathogenicity island-positive. (Backert et al., 2009).***

However, serological studies have shown that the prevalence of identified *H. pylori* putative virulence factors has not changed in any population over time, which can be interpreted in two ways. Either we have not examined the critical factors, or this is not the correct explanation. The latter appears most likely ***(Backert et al., 2009).***