PERIOD PREVALENCE RATE OF HELICOBACTER PYLORI INFECTION IN EGYPTIAN CHILDREN WITH TYPE 1 DIABETES

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Dedication

With all my love,

To my mother, father, husband

And my beloved son
And all my Colleagues.
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List of Abbreviations

H. Pylori ------------------------------- Helicobacter Pylori
DEMPU----------------------------- Diabetic endocrine metabolic pediatrics unit
CagA----------------------------- cytotoxin associated gene antigen
VacA:----------------- vacuolating cytotoxin associated gene antigen
Cag-PAI ----------------------------- cag pathogenicity island
OIP ----------------------------- outer inflammatory proteins
DUP-------------------------- Duodenal ulcer promoting gene
ROS----------------------------- Reactive oxygen species
PUD---------------------------- Peptic Ulcer Disease
NSAD ----------------- non-steroidal anti-inflammatory drugs
NUD---------------------------- Non-ulcer dyspepsi
PPI---------------------------- Proton Pump Inhibitor
GERD--------------------------- Gastro oesophageal reflux disease
RAB------------------- recurrent abdominal pain
STFR------------------- soluble transferrin receptor
IDA-------------------------- Iron deficiency anemia
ITP------------------- Idiopathic thrombocytopenic purpura
PCR--------------------------- polymerase chain reaction
EGD---------------------------- Esophagogastroduodenoscopy
HPSA---------------- Meridian Diagnostics Inc., Cincinnati, Ohio
UBT---------------------------- urea breath test
ELISA---------------- enzyme linked immunosorbent assay
PCR-------------------------- Polymerase chain reaction
IgG-------------------------- Immunoglobulin G
DM---------------------------- Diabetes mellitus
ICA------------------------- islet cell cytoplasm
IDDM---------------- insulin dependent diabetes mellitus
NIDDM---------------- non insulin dependent diabetes mellitus
GDM -----------------------------Gestational diabetes mellitus
IAA---------------------------------autoantibodies to insulin
GAD----------------------------------glutamic acid decarboxylase
T1 DM---------------------------------Type I diabetes mellitus
T2 DM---------------------------------Type 2 diabetes mellitus
MODY ------------------------------maturity onset diabetes of the young
HLA ----------------------------------human leucocyte antigen
GK ------------------------------------glucokinase
WP ----------------------------------western pacific
SEA-----------------------------------Southeast Asian
lDDNI2---------------------------------Insulin locus
ICA----------------------------------islet cell antibody
GABA-------------------------------glutamic acid to amino butyric acid
IAA----------------------------------insulin autoantibodies
FPG-------------------------------Fasting Plasma Glucose
OGTT--------------------------------oral glucose tolerance test
DKA---------------------------------diabetic Ketoacidosis
HHS---------------------------------Non ketotic hyperosmolar coma
Po---------------------------------per oral
CSII------------------continuous subcutaneous insulin infusion
MDD--------------------------------multiple day injection
Abstract

This study included 50 diabetic pediatric patients (age ranged from 4 to 16 years) complained of gastrointestinal symptoms, who presented to the endocrinology unit at Cairo University Specialized Pediatric Hospital with gastrointestinal complaints and had been tested for the presence of H. pylori infection by the C 13 urea breath test. Only Twelve positive cases approved for undergoing endoscopy for confirming H. pylori infection by biopsy specimens obtained by upper gastrointestinal endoscopy and for assessment of gastritis. The overall incidences of H.pylori infection in all children (cases and controls) we have studied were 55 %. In our study no statistically significant difference was found regarding H .pylori positivity between diabetic cases and controls, as 60% of cases were positive compared to 45% of controls.

Key words: H.pylori , gastrointestinal symptoms, urea breath test, endoscopy
Introduction

Helicobacter Pylori is a worldwide bacterium that infects human gastric mucosa, generally persists for life in the infected tissue unless adequately treated (Yakoob et al., 2008). Fifty percent of the world’s population carry Helicobacter pylori in their stomach with the incidence up to 80% in developing countries (Adrienne et al., 2007).

The prevalence of H. Pylori varies greatly among countries and among population groups within the same country (Feldman, 2001). Its prevalence is extremely high among Egyptian schoolchildren and is one of the main causes of growth failure in Egyptian children (Abu zekry et al., 2000, Mohammad et al., 2005).

With regard to malignant diseases, H. pylori has been recognized as a class 1 human carcinogen as identified by the international Agency for Research on Cancer (Xiao-Qin et al., 2011), this actually due to extensive epidemiological data, showing an association between H. pylori seropositivity and increased gastric cancer risk. However, it seems plausible that H. pylori colonization might also promote tumor formation in extra gastric target organs such as the colorectal mucosa, pancreas, and liver through stimulation of circulating growth factors or other local, more site-specific mechanisms (Suerbaum and Michetti, 2002).
On the other hand, H. Pylori is considered the most important risk factor for non-cardia gastric mucosa-associated lymphoid tissue (MALT) lymphomas (Moss, 2007).

Type 1 diabetes is an autoimmune disease in which destruction of pancreatic islet beta cells leads to insulin deficiency (Fourlanos et al., 2004).

In children with type 1 diabetes, gastrointestinal symptoms are frequently observed although their prevalence and impact on glycemic control are poorly defined (Quan et al., 2008), Delayed gastric emptying and antral dysmotility is recognized as a major cause of H.pylori colonization in diabetes mellitus (Quid, 1998).

Alteration of glucose metabolism in diabetes has been suggested as promoting H.pylori colonization (Dore et al., 2000).

Several studies have investigated the prevalence of H.pylori in diabetic patients and a possible role of the infection in their metabolic control with discordant results (Ojetti et al., 2001), some studies did not exhibit a higher prevalence of H.pylori in diabetics patients and did not support any correlation between metabolic control and infection (Peach et al, 2011), while others have demonstrated a higher seroprevalence of the infection in diabetic patients and significantly worsens metabolic control in children and adolescents with type 1 diabetes mellitus (Toporowska, 2007).
Aim of Work

Our Aim in this study to:

1-Evaluate the period prevalence rate of H.pylori in type 1 diabetes patients with gastrointestinal trouble at the diabetic endocrine metabolic pediatrics unit (DEMPU).

2-Study the correlation of H.pylori with the age, duration of diabetes, clinical, laboratory and histopathological findings.
**Helicobacter Pylori**

### I. Historical background:

In 1875, German scientists found spiral bacteria in the lining of the human stomach; the bacteria could not be grown in culture and the results were eventually forgotten (*Blaser, 2005*).

Spiral organisms had been found at first incidentally in the stomachs of the dogs in 1893 (*Bizzozero, 1893*).

Nearly one decade ago, the pathogenesis of peptic ulcer disease as gastritis, gastric ulcer, duodenitis and duodenal ulcer was attributed to an imbalance between acid secretion and mucosal defense mechanism till Professor Walery Jaworski of the Jagiellonian University in Krakow investigated sediments of gastric washings obtained from humans. In 1899 he also found bacteria with a characteristic spiral shape, which he called *Vibrio rugula*. He was the first to suggest a possible role of this organism in the pathogenesis of gastric diseases. Jaworski was not able to culture the organism (*Konturek, 2003*).

The bacterium was rediscovered in 1983 by two Australian scientists Robin Warren and Barry Marshall; (*Marshall and Warren, 1983*). They isolated the organisms from mucosal specimens from human stomachs and were the first to successfully culture them. Warren and Marshall assumed that most stomach ulcers and gastritis—were caused by colonization with this bacterium, not by stress or spicy food as had been
assumed before. In 2005, Warren and Marshall were awarded the Nobel Prize in medicine for their work on H. pylori.

In the next three years the organisms had been isolated from patients with gastritis and peptic ulcer in England (Jones et al., 1994), Holland (Langenberg et al., 1994), USA, Canada, Japan and Peru (Pearson et al., 1995).

The bacterium was initially classified as a Campylobacter but was placed in a new genus Helicobacter, on the basis of its ultrastructure and morphology, fatty acid composition, growth characteristics, regulatory quinines and enzymatic properties as well as the 16 subunit ribosomal RNA (16s RNA) sequences of these organisms (Marshall and Warren, 1983).

The new name reflects the helical appearance of this organism in vivo but often rod like in vitro as well as its most common isolation place, the pylorus (Heatley and Wyatt, 1995).

Milosavljevic (2001) found at least 24 species formally named Helicobacter have been identified and an additional 35 or more novel Helicobacter await formal naming. H pylori is the best known and the most important in terms of global impact on human disease. However, two other gastric Helicobacter; heilmannii and H. felis are associated with gastric disease in humans. Nineteen named species colonize the lower intestinal tract of animals, many of which also colonize humans, such as H. cinaedi, H. cams, H. pullorum, H. fennelliae, H. canadensis and H. rappini.
II Morphology:

Helicobacter pylori is a spiral-shaped, Gram-negative rod and catalase-positive organism, 0.5-0.9 mm wide by about 3 mm long (O’Rourke et al, 2004).

It has smooth surface, and one to six unipolar sheathed flagella emerge from one of its rounded ends. The sheath is continuous with the outer membrane of the cell wall. Some flagella have a terminal bulb (Figure 1) (Kusters et al., 1997).

![Figure 1: H.pylori with its flagella by electron microscope.](image)

Structurally, the flagella of H. pylori (30-35 nm in diameter) consists of a central filament 15 nm wide and up to 3 nm long (Kusters et al., 1997), which is composed of flagellin (a protein monomer of mol. wt 51,000Dalton), a hook, and cell anchored basal plate and a sheath. The majority of flagellated bacteria are unsheathed, the bacterium drills into the mucus layer of the stomach, and then can either be found suspended in the gastric mucosa or attached to epithelial cells (O’Toole et al., 2000).

The bacterium can appear as a rod, while coccoid shapes appear after prolonged vitro culture, a long inoculation period or milk samples, or antibiotic treatment (Kusters et al., 2006).
It excretes the enzyme urease, which converts urea into ammonia and bicarbonate. The release of ammonia is beneficial to the bacterium since it partially neutralizes the very acidic environment of the stomach whose very purpose is to kill bacteria. Ammonia is, however, toxic to the epithelial cells, and other products of H. pylori, including protease, catalase, and phospholipase, cause damage to those cells. A recent finding is that some strains of the bacteria have a particular mechanism for injecting the inflammatory agent peptidoglycan from their own cell wall into epithelial stomach cells. It remains unknown how this mechanism is advantageous to the bacterium (Viala et al, 2004).

There is increasing evidence that distinct variants of H. pylori exist and that these may be associated with the pathogenicity of the bacterium (Gatti et al, 2006).

There are 2 phenotypically distinct H.pylori groups; type 1 bacteria, which express the cytotoxin associated gene antigen (cagA) and the vacuolating cytotoxin associated gene antigen (vacA), type 2 bacteria, where cagA is absent and vacuolating cytotoxin activity is not manifested although vacA gene is present. The type I bacteria are more strongly pathogenic than the type II and induce a more intense inflammatory response (Xiang et al, 1995).

Virtually, the presence of vacA gene has been reported in all H. Pylori strains; various strains show marked differences in production of vacuolating cytotoxins (Mahboob et al, 2005).
III Epidemiology of Infection

A-Prevalence of infection:

H. pylori is considered as the commonest chronic bacterial infection in man, one half of the world’s population has helicobacter pylori infection (Adrienne et al, 2007).

Prevalence estimates vary greatly, depending on the location of the study group and the characteristics of the population studied, in general prevalence correlates positively with a low socioeconomic status during childhood (Feldman et al, 2001).

Across populations of children, H. pylori prevalence ranges from 20% to 80%. Regarding the worldwide distribution of H. pylori, the overall prevalence of H. pylori is about 70-90% in North Africa, 80% in South Africa, 70-80% in Asian countries, 30-70% in European countries, 20% in Australia, 30-70% in north American countries and 80-90% in South America (Torres et al, 2000).

In Egypt (Mohammed et al, 2006) studied the prevalence of H. pylori among 286 schoolchildren, the overall prevalence was 72.38% attending school in an overcrowding was the major risk factor for infection.
1-Prevalence of H. pylori according to sex:

Several large epidemiological studies indicate a 5-20% higher prevalence of infection in males than in females, there is no apparent biologic reason why males would have greater exposure or greater susceptibility to infection, perhaps one reason is that in certain populations H. pylori infection may be eliminated inadvertently because of more frequent antimicrobial treatment of women for urogenital infections (James, 2000).

However, other studies show non-significant differences in the prevalence of H. pylori between males and females (Yasuhiro et al., 2001).

2-Prevalence in relation to age

Prevalence of H. pylori is variable there are two patterns of H. pylori prevalence with respect to age depending on the geographical region studied. The first is widespread infection early in childhood with elevated prevalence rate close to 80% throughout adulthood, and the second is increasing prevalence with age. The variability in pattern suggests a difference in infectivity or transmissibility of H. pylori. Potential determinants of these differences include environmental, bacterial, and host factors. The most important determinant is likely socioeconomic class which affects living conditions and sanitation, thus altering exposure to bacterium (Abbolito et al 1999, Fallone 1999), stated that the prevalence of H. pylori was increasing with age with an overall prevalence of 78.6%.
3-Prevalence in relation to Racial and Ethnic differences:

The prevalence of Pylori varies between races and ethnic group, but it is not known if this difference is a result of different exposures e.g. cultural background, social and environmental factor or genetic predisposition (Rothenbacher et al., 1998).

4-Prevalence in relation to socioeconomic status:

The prevalence of H. pylori is inversely related to socio economic status, the major variable being the status during childhood and the period of Highest risk (Malaty, 2007).

It is note worth that the effect of both parental origin and socioeconomic status on a child’s probability of being seropositive is considerably stronger when the mother’s status was considered than when the father is taken into consideration. This observation is consistent with a predominant mother-child transmission pattern (Tindberg, et al., 2001).

Goodman et al, (2002) found that children born within 4 years of an older sibling were 4 times more likely to be infected with H. pylori. The fact of having H. pylori infection seems to increase almost steadily with the total number of 2-9 year-old siblings in the home.

In support of the horizontal transmission of H. pylori among siblings, a study from Northern Ireland (Farrel et al., 2005) showed that sharing a bed or bedroom with an infected parent or siblings significantly increases the risk for H. pylori infection.