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STUDY OF HELICOBACTER PYLORI INFECTION AND CORONARY HEART DISEASE ASSOCIATION IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS

Thesis

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By

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بسم الله الرحمن الرحيم

(سنريهم آياتنا في الآفاق وفي أنفسهم حتى يتبين لهم
أنه الحق، أولم يكف بربك أنه
على كل شيء شهيد)

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INTRODUCTION

It is now broadly accepted that infection with Helicobacter pylori is one of the most common chronic infections worldwide. Helicobacter pylori causes gastritis and has been actiologically linked to peptic ulcer, gastric carcinoma, and primary gastric B-cell lymphoma [1,2].

Recent published studies discuss some of the extragastric association of infection caused by Helicobacter pylori including coronary heart disease [3].

The results of many workers proved this association and many explanations were suggested including the presence of a low grade chronic inflammatory response [4,5], hyperhomocysteinaemia [6], and the development of coronary atheroma [7]. On the other hand the results of other workers lead to the suggestion that this accociation is likely to be spurious and can be explained by age and social class association[8,9].

Diabetes mellitus may be associated with increased incidence of Helicobacter pylori colonization caused by reduced gastric motility [10], or due to chemical changes in the gastric mucosa caused by alterations in glucose metabolism [11].

It is clear from the previous studies that the evidence for the association between the H. pylori infection and the coronary heart disease is conflicting.

Hence it is of importance to assess the association between the Helicobacter pylori infection and the coronary heart disease in the diabetic and non diabetic patients and aiming also at evaluation of the indirect added risk factor for the coronary heart disease caused by the increased incidence of Helicobacter pylori infection in the diabetic patients.

REVIEW OF LITERATURE

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HISTORICAL REVIEW

Although the association between Helicobacter pylori and ulcers was discovered by Warren in 1979 and the organism was cultured in 1983, the historical origin of its discovery is rooted in the latter half of the nineteenth century [12]. In 1875 one of the first gastric bacteriologists was Bottcher who demonstrated bacterial colonies in the ulcer floor and its mucosal margins [13]. In 1881 Klebs reported a bacillus like organism evident both free in the lumen of gastric glands and between the cells of the glands and tunica propria [14].

In 1889, Jaworski, was the first to describe in details spiral organisms in the sediment of washings obtained from humans, which he named vibrio rugula[15].

In 1893, Bizzero noted the presence of spirochaetes organisms in the gastric glands and both in the cytoplasm and vacuoles of parietal cells in the specimens of gastric mucosa of six dogs [16]. In 1896, Salmon reported a paper entitled spirochaetes in the gastric mucosa of dogs, cats and rats [17].

Muhlen and independently Luger and Neuberger, had all reported these organisms to be evident in the stomach contents of patients with ulcerating carcinomas of the stomach and the rarity of these organisms in the gastric mucosa and gastric juice of healthy individuals [18].

In 1921 Edkins studied the spirochaetes organisms in different parts of the stomach and named spirochaete regaudi [19].

In 1925, Hoffman investigated whether the causative agent of ulcer disease was a member of bacillus family and named his organism bacillus Hoffmani[20]. In 1984, Steer identified bacteria in close contact with the epithelium and suggested that white cells migrated in response to these bacteria, he also attempted to isolate and culture the organism but failed [21].

In 1985 Steer reported an apparent association between "active gastritis" and a gram negative bacterium with simultaneous occurrence of bacteria in the stomach and peptic ulceration [22].

In 1984 Marshal et al, introduced S-shaped campylobacter- like organism [23], and in the same year he isolated and cultured H. pylori utilizing the knowledge that these bacteria resemble the species of compylobacters rather than spirochaetes[24]. In 1984, Jones and et al isolated H.pylori from gastric mucosa and confirmed the relationship between H.pylori and ulcers [25]. In the same year Pearson et al reported that H.pylori can be cultured under microaerophilic conditions [26]. By light microscopy study of these spiral bacteria and by guanine plus cytosine contents of their DNA, these microaerophilic organisms resembled compylobacters, and so were named compylobacter pyloridis [27], which latter changed to compylobacter pylori (C.pylori) [28,29].

In 1989 the Royal Perth Hospital team produced evidence to justify the creation of the new genus and they renamed the organism Helicobacter pylori (H.pylori) [29,30]. It was found that the organism produces urease [31]. Luck and Seth [32], in1924, and an extensive review by Kornberg and Davies [33] in1955 concluded that gastric urease was located mainly in the corpus of the stomach and was of bacterial origin. Human studies confirmed that there was an association between the presence of the enzyme and ulcer disease [34].

More than 15 years after the start of the modern Helicobacter era, many of the important issues remain unresolved.

General cellular morphology :

H.pylori is a motile, gram-negative organism that can be cultured in microaerophilic (low o_2) conditions, although it adapts to high o_2 at higher culture densities [30,35]. As such it has an outer membrane, the outer leaflet of which is lipopolysaccharides, a cell wall and periplasmic space, an inner membrane, and cytoplasm. The organism possesses 6-8 flagellae at one end.

Flagellar function depends on the activity of a flagellar motor, also driven by the proton motive force generated across the cytoplasmic membrane of the organism [23,25].

H. pylori are non-sporulating in vitro, S shaped, curved rod or helical in shape (0.5-0.9 um wide by 2-4um long) and it transformed to coccoid form under unfavourable circumstances like increased oxygen tension, alkaline pH, increased temperature , extended incubation or treatment with omeprazol or antibiotics [30]. The coccoid form is non culturable but alive and metabolically active as it synthesizes DNA. Both spiral and coccoid forms can be found in the human stomach and duodenum but coccoid H.pylori is found attached to severely damaged gastric epithelial cells and around margins of gastric tumours .The coccoid form is non motile, however it has flagellae raising the possibility that it could be motile under some circumstances .So the role of coccoid form in pathogenesis remains unclear [36,37].

Membrane potential:

Fluorescent dyes have been used to measure transmembrane potential, which staining the organism with a lipophilic fluorescent cation, this dye is taken up and its fluorescence quenched as a function of internal negative potential [38,39]. When membrane potential was measured as a function of medium PH , was found to extend between PH 4.0 and PH 8.0 ,exactly the PH range over which the organism survives[40,41].

Urease is essential for H.pylori:

The elimination of urease activity by either growth selection for urease negative mutants or intentional removal of one of the urease enzyme genes results in strains that are unable to infect animal models. It is possible to obtain some infections with these urease negative mutants if acid is severely inhibited by proton pump inhibitors , but the infection does not persist after removal of the drugs. So all current data suggest that H. pylori is an acid tolerant neutralophile rather than being a facultative acidophil[42].

EPIDEMIOLOGY OF HELICOBACTER PYLORI

H. pylori infection occurs throughout the world and it appears that all populations are affected to a greater or lesser extent. Although detection methods have differed between populations casting doubt on the validity of some epidemiological findings, a number of important patterns have emerged. However it must be borne in mind that strain differences may occur between or within individual populations, and serology has often been used in studies based upon antigens of strains taken from completely different countries [43,44].

Host and habitate:

Humans are the only host for H. pylori where it is found beneath the mucous layer of the gastric epithelium in the stomach, it is firmly attached to some cells on the tissue surface through the formation of predestals mediated by specific adhesion [45,46]. The bacterium is also found on areas of metaplastic gastric epithelium which may be present in the duodenal bulb, adhering to columnar – lined epithelium in the oesophagus, meckel's diverticulum and rectum,the duodenal bulb location being by far the most important clinically, in contrast, the organisms do not ovely absorpative-type duodenal epithelial cells, even when these are metaplastic in the stomach [47]. In the human stomach, the organism rests in and beneath the surface mucus layer of where it is protected from gastric acid, to which it is sensitive, because gastric mucus is relatively impermeable to acid and has a strong buffering capacity [48,49]. H. pylori also produce protease that modifies the gastric mucus and further reduce the ability of acid to diffuse through the mucus [50]. H. pylori have been isolated occasionally in different animal species, including the rhesus monkey, pig, baboon and domestic. cat. However there is no evidence that individuals with domestic cats or those in contact with other animals are more likely to be colonized by H. pylori, Thus a zoonotic reservoir for H. pylori seems unlikely [51]. Other Helicobacter species have been cultured successfully from animals.