

Impact of Serum Interleukin 6 among Helicobacter Pylori-Positive Adult Patients in Relation to upper gastrointestinal endoscopy findings

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Abstract

Background: Helicobacter pylori (H. pylori) is one of the most common chronic bacterial infections in humans and has a major etiologic role for several gastroduodenal diseases. Interleukin-6 (IL-6) is a multifunctional cytokine and H. Pylori may stimulate its production. **Aim:** to assess the serum level of IL-6 in H. pylori infected patients and to study its relation to gastric endoscopy findings. **Subjects and Patients and Methods:** Eighty-four participants were enrolled; 42 patients with positive H. pylori (patient group "B"), and 42 age and gender-matched subjects with negative H. pylori (control group "A"). Out of 42 patients in the group B, 21 patients were subjected to upper gastrointestinal endoscopy due to persistent gastric upset. Serum concentration of IL-6 was measured in all subjects by ELISA. **Results:** serum IL-6 was significantly higher in patients' group compared to control group (4.3 ± 0.7 vs 1.5 ± 0.3 pg/ml, $p < 0.05$). The prevalence of IL-6 in infected patient with H. Pylori was 92%, with highest levels in those with gastric ulcer. **Conclusion:** H. Pylori infection is associated with high serum level of IL-6 especially in those with gastric ulcer.

Keywords: Helicobacter pylori; interleukin 6

Introduction

Helicobacter pylori (H. pylori) is one of the most common chronic bacterial infections in humans. It occurs throughout the world and has a major etiologic role for several gastroduodenal diseases, including gastric ulcer, duodenal ulcer, gastric mucosa associated lymphoid tissue lymphoma, and gastric carcinoma⁽¹⁾. H. pylori currently infects more than 50% of the

world's populations, and in the last decade, it has been recognized as one of the most common chronic bacterial infections worldwide⁽²⁾. Evidences for effectiveness gained from randomized controlled trials suggested that treating H. pylori is more effective and less expensive than continuous use of proton pump inhibitor therapy⁽³⁾, significantly reduced peptic ulcer diseases and improved dyspeptic symptoms and quality of life^(4,5). H. pylori infection induces an inflamma-

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tory response that is also oxidative, induces chronic active inflammation with a mixture of neutrophils, plasma cells, T-cells and B-cells with production of interleukins (1, 2, 6, 8), tumor necrosis factor (TNF α) and interferon γ (IFN- γ)⁽⁶⁾. Interleukin-6 (IL-6) is a multifunctional cytokine (26 kDa glycoprotein) that is produced by many different types of cells, including monocytes, lymphocytes, fibroblasts, endothelial cells, keratinocytes, mesangial cells, and endometrial cells⁽⁷⁾. The current study was conducted to look up and evaluate the level of serum IL-6 in *H. pylori* infected patients and to assess its relation to gastric endoscopy findings.

Subjects and Methods

This cross-sectional descriptive study was conducted in the outpatient clinic and gastrointestinal endoscopy unit of the Suez Canal University hospitals on 84 patients (group "B"). All individuals were tested for *H. Pylori* fecal antigen and 42/84 patients tested positive *H. pylori* stool antigen (confirmed by rapid urease test). Similar number of age and gender-matched healthy persons with negative *H. pylori* served as control group "A". Out of 42 patients in the group B, 21 patients underwent upper gastrointestinal endoscopy due to persistent gastric upset.

Assessment of serum IL-6

Serum concentration of IL-6 was measured by commercial enzyme-linked immunosorbent assay (ELISA) kit (Abcam IL-6 Human ELISA Kit ab100572). IL-6 Human ELISA kit is an in vitro assay for the quantitative measurement of Human IL-6 in serum, plasma, and cell culture supernatants. This assay employs an antibody specific for Human IL-6 coated on a 96-well plate. Standards and samples were

pipette into the wells and IL-6 present in a sample was bound to the wells by the immobilized antibody. The wells were washed, and biotinylated anti-Human IL-6 antibody was added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin was pipetted to the wells. The wells were again washed, a TMB substrate solution was added to the wells and colour developed in proportion to the amount of IL-6 bound. The stop solution changed the colour from blue to yellow, and the intensity of the colour was measured at 450 nm; the detection limit of the ELISA kit for IL 6 is above 2 pg/ml.

Ethical Considerations

The study was approved by the SCU Ethical Committee, patients had their information sheet exploring the purpose, methods, effects, and possible value and complications of this research. A written informed consent was obtained from all participants. who was assured about the confidentiality of their information.

Results

Eighty-four subjects, 57% were males and were 43% females. The age of our subjects range 19-59 years old with mean age was 37.54 \pm 10.19 years old. 54.76% of *H. Pylori* infected patients were male while 45.23% of them were female. About 61.9% of *H. Pylori* infected patients were living in rural areas and 38.09% of them were living in urban areas as shown in (table 1). The mean serum level of IL-6 were significantly higher in *H. Pylori* infected group (4.3 \pm 0.7) than in healthy control group (1.5 \pm 0.3) ($p < 0.05$), (table 2). The highest level of serum IL-6 in group B was 5.8pg/ml, and the highest level of serum IL-6 in group A was 2pg/ml. the lowest level of serum IL-6 was 3.1pg/ml (in group B) and 1pg/ml

(in group A). The highest of serum interleukin 6 was observed in patients with gastric ulcer (5.8pg/ml) (table 2).

Overall, the prevalence of IL-6 in infected patient with H. Pylori was 92% (table 3).

Table 1: The relation between H. Pylori infection and gender

Group	Gender		Total
	Male No. (%)	Female No. (%)	
Study (B)	23 (54.76%)	19 (45.23%)	42 (100%)

Discussion

Regarding the gender, Current data showed that H. Pylori Positivity had predominance in males (54.76%) compared to females (45.23%); the results which in agreement with other previous records. Woodward *et al*, Kaore *et al.*, valliani *et al.*, reported that higher prevalence of H. pylori in male gender⁽⁸⁻¹⁰⁾. In addition, more comprehensive meta-analysis of large population-based studies concluded a male predominance of H. Pylori related diseases. In contrast, Zhu *et al*, reported that female had a higher H.

Pylori infection rate than male⁽¹¹⁾. The explanation for this difference can only speculative at this moment, being most probably related to the hormonal differences between the two genders, as recent studies identified an important role of oxytocin in the gastric evacuation rate⁽¹²⁾. The present study showed that H. pylori infected patients had a higher concentration of serum IL-6. Other study reported the same result; Hiroko *et al* reported that higher H. pylori IgG levels were significantly associated with higher serum IL-6 levels among H. pylori-infected individuals⁽⁷⁾.

Table 2: Serum IL-6 (pg/ml) level in study populations

IL-6 (pg/ml)	Group	Highest Level	Lowest level	Mean	SD	P value (T-test)
		Control (Group A)	2	1	1.595	0.3561
	Patients (Group B)	5.8	3.1	4.329	0.7286	

Similarly, Siregar *et al*, reported that Serum IL-6 level was significantly higher in H. Pylori positive group compared to H. pylori negative group in a study which had done at 80 patients admitted to endoscopy units at Adam Malik General Hospital and Permata Bunda Hospital, Medan, Indonesia from May-October 2014⁽¹³⁾. In addition, Yamaoka *et al*, showed that mucosal IL-6 levels were higher in early gastric cancer with active H. pylori

infection than without H. pylori infection⁽¹⁴⁾. Moreover, Azadegan Dehkordi *et al*, reported that the mucosal IL-6 mRNA level increased in patients with H. pylori infection compared with uninfected patients and correlated positively with the grade of chronic gastritis in patients with H. pylori infection⁽¹⁵⁾. However, Bayraktaroglu *et al* could not detect statistically significant differences in the serum levels of IL-6, IL-8 and TNF- α

with respect to the presence or absence of H. pylori determined by Giemsa staining of gastric tissues⁽¹⁶⁾. Also, Akgun *et al.*, reported that serum levels of IL-8 did not differ between H. Pylori infected and uninfected persons, this finding may indicate that this infection remains local without inducing systemic inflammation⁽¹⁷⁾. Regarding another associated multifunctional cytokine (IL-8), Fan *et al.*, found that IL-8 concentrations in gastric juice and biopsy homogenate supernatant fluid were increased in

patients with H. Pylori infection compared with the patients without infection, but this difference was not observed for plasma IL-8 concentration⁽¹⁸⁾. As well, Audibert *et al.*⁽¹⁹⁾ and Crabtree *et al.*⁽²⁰⁾, acknowledged that there is an increased mucosal production of IL-8 that may be an important mediator of the inflammatory response. They also confirmed the finding that CagA positive H. Pylori strains induce significantly higher levels of IL-6 and IL-8 on Hep-2 cell cultures than CagA negative strains.

Table 3: Serum level of IL-6 and result of gastric Endoscopy

Endoscopy Findings (n=21)	Normal No (%)	Erosive gastritis No (%)	Atrophic gastritis No (%)	Gastric ulcer No (%)	p*
	8 (38.1%)	4 (19.1%)	4 (19.1%)	5 (23.7%)	0.000
IL 6 (pg/ml) (highest level)	3.1	4.4	3.5	5.8	

*T-test

As a final point, up to date studies have shown that H. pylori activates signal transducer and activator of transcription 3 (STAT3) that plays an imperative role in gastric carcinogenesis. Yet, the molecular mechanism underlying H. pylori-mediated STAT3 activation is still not fully unstated. Riao *et al.*, recognized that, H. pylori-induced STAT3 activation is mediated, at least in part, through reactive oxygen species-induced up regulation of IL-6 expression⁽²¹⁾. These results provide a novel molecular mechanism accountable for H. pylori-induced gastritis and gastric carcinogenesis. The main limitation of the study was the sample size. A wider study is required with reassessment of IL-6 levels after eradication of H. pylori and to evaluate its prognostic values.

Conclusion

Serum IL-6 is significantly higher in H. Pylori infected patients and the highest levels were observed in patients

with gastric ulcer than in those with erosive or atrophic gastritis.

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