

**Role of cytokines in pathogenesis of *H. pylori* induced gastric mucosal inflammation.**

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**ABSTRACT**

*Helicobacter pylori* gastritis is characterized by colonize the stomach and induce strong, specific local and systemic humoral and cell-mediated immunity. The aim of this study was to evaluate the level of several cytokines and their role in the pathogenesis of *H. pylori* gastritis and whether *H. pylori* stimulate the release of these cytokines. The levels of TH1 (IFN- $\gamma$  and TNF- $\alpha$ ) and TH2 (IL-4, IL-6 and IL-10) cytokines, as well as, inflammatory cytokines (IL-1 $\alpha$  and IL-8) were determined. Most of the investigated cytokines (IL-1 $\alpha$ , IL-6, IL-8, IL-10, IFN- $\gamma$ , TNF- $\alpha$  and GM-CSF) showed a significantly increased level in the sera of *H. pylori* gastric patients as compared to subjects (control) with no infection which showed normal serum interleukin levels. While IL-10 showed significant decrease when compared to subjects. These results conclude the pro-inflammatory cytokines have a central role in the pathogenesis of *H. pylori*-induced mucosal inflammation.

**INTRODUCTION**

Gastritis is an inflammation of the stomach lining. Many factors can cause gastritis. Most often the cause is infection with the same bacteria which called *Helicobacter pylori* (*H. pylori*) that also causes stomach ulcers. An autoimmune disorder, a backup of bile into the stomach, or long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen can also cause gastritis (1,2).

In recent years, *Helicobacter pylori* has been identified by researchers as the

cause of the majority of gastrointestinal ulcers. *H. pylori* is a bacterium that lives in the stomach and duodenum. Gastric juice is composed of digestive enzymes and concentrated hydrochloric acid, which can readily digest food or kill microorganisms. Low levels of stomach acid increase the chance an organism's survival. It used to be thought that the stomach contained no bacteria and was actually sterile (3).

The stomach is protected from its own gastric juice by a thick layer of mucus that covers the stomach lining. *H. pylori* takes advantage of this protection by living in the mucus lining (2, 3). Once *H. pylori* is safe in

the mucus, it is able to fight the stomach acid that does reach it with an enzyme it possesses called urease. Urease converts urea, of which there is an abundant supply in the stomach (from saliva and gastric juices), into bicarbonate and ammonia, which are strong bases. This creates a cloud of acid-neutralizing chemicals around the *H. pylori*, protecting it from the acid in the stomach. The breath test method of diagnosis relies on this reaction being present (4). Contributing to the protection of *H. pylori* is the fact that the body's natural defenses cannot reach the bacterium in the mucus lining of the stomach. The immune system will respond to an *H. pylori* infection by sending white cells, killer T cells, and other infection fighting agents. However, these potential *H. pylori* eradicators cannot reach the infection, because they cannot easily get through the stomach lining. They do not, however, go away - the immune response just grows and grows. White cells die and spill their destructive compounds (superoxide radicals) on stomach lining cells. Extra nutrients are sent to reinforce the white cells, and the *H. pylori* can feed on this (2, 5). *Helicobacter pylori* is estimated to infect over one-half of the world's population (4,6). The factors that determine the outcome of an *H. pylori* infection are still relatively unknown (7). There are indications that *H. pylori* strains differ in their ability to induce cytokine production; e.g., an important feature of the bacteria for the clinical outcome of the infection seems to be the presence of the cytotoxin-associated gene A (*cagA*) and the *cagA*-associated *ice* gene, which are associated with ulcer disease (5, 8). Chemokines which specialize in mobilizing leukocytes to areas of immune challenge (9, 10, 11). In spite of its relatively low toxic activity, *H. pylori* LPS has been shown to activate inflammatory cells to produce different

cytokines and chemokines, such as TNF- $\alpha$ , IL-8, IL-1, and monocyte chemoattractant protein-1 (12, 13, 14, 15). The aim of this study was to evaluate the level of several cytokines and their role in the pathogenesis of *H. pylori* gastritis, whether *H. pylori* stimulate release.

## MATERIALS AND METHODS

### **Subjects**

Fifty patients with *H.pylori* gastritis (age range: 25 – 50 years) were investigated. The patients were referred to the hospital. The diagnosis was made by the consultant medical staff, which was based on a history inspection, clinical examination and other laboratory tests. A control sample of 25 healthy samples free of diseases included in the study.

### **Collection of Blood Samples**

From each subject, 5ml of blood were obtained by venepuncture, using a 10 ml disposable syringe. The blood sample was dispensed in a plain tube, and left for 15 minutes at 4°C to clot. Then, it was centrifuged at 3000 rpm for 10 minutes to collect serum. The serum was divided into aliquots (0.5 ml) and stored in the freezer (-20°C) until use.

### **Laboratory Methods**

#### **Biological Materials and Kits**

ELISA kits for quantitative determination of IL-1 $\alpha$ , IL-8 and GM-CSF in serum (Immunotech Company, France). ELISA kits for quantitative determination of IL-4, IL-6, IL-10, TNF- $\alpha$  and IFN- $\gamma$  in serum (Mabtech Company, Sweden) were used.

### **Serum Level of Cytokines**

Serum levels of eight cytokines (IL-1 $\alpha$ , IL-4, IL-6, IL-8, IL-10, TNF- $\alpha$ , IFN- $\gamma$  and GM-CSF) were quantitatively determined in patients and control subjects by means of

indirect sandwich ELISA test using ready kits manufactured by the French company Immunotech (IL-1 $\alpha$ , IL-8 and GM-CSF) and Swedish company Mabtech (IL-4, IL-6, IL-10, TNF- $\alpha$ , IFN- $\gamma$  and TNF- $\alpha$ ).

Serum Level of IL-1 $\alpha$ , IL-8 and GM-CSF:

- Assay Procedure

Before carrying out the assay procedure of a cytokine (IL-1 $\alpha$ , IL-8 or GM-CSF) determination, the kit was left at room temperature (18-25°C) for 30 minutes to equilibrate, as suggested by the manufacturer. Then, the assay was carried out following the instructions in the kit's leaflet, which are summarized in the following steps: Serial concentrations (0, 15.6, 62.5, 250 and 1000 pg/ml for IL-1 $\alpha$ , 0, 31.2, 125, 500 and 2000 pg/ml for IL-8 and 0, 7.8, 31.3, 125 and 500 for GM-CSF) of the standard were made using the diluent. An aliquot (50  $\mu$ l) of the standard or sample was added to the well, and the plate was incubated for two hours at room temperature with shaking. The well was washed with three cycles of washing using the washing solution, with the aid of a micortiter plate washer. An aliquot (50  $\mu$ l) of biotinylated antibody was added to the well and the plate was incubated for 30 minutes at room temperature. The washing step was repeated (step iii). An aliquot (100  $\mu$ l) of streptavidin-HRP conjugate was added to the well and the plate was incubated for 30 minutes at room temperature. The washing step was repeated (step iii). An aliquot (100  $\mu$ l) of substrate was added to the well and the plate was incubated for 20 minutes at room temperature with shaking. An aliquot (50  $\mu$ l) of stop solution was added to the well and the absorbance was read at a wave length of 405 (IL-1 $\alpha$ ) or 450 nm (IL-8 and GM-CSF) using ELISA reader.

- Calculations: The sample results were calculated by interpolation from a standard curve that was performed in the same assay as that for the sample, using a curve fit equation.

Serum Level of IL-4, IL-6, IL-10, TNF- $\alpha$  and IFN- $\gamma$  :

- Assay Procedure

Before carrying out the assay procedure of a cytokine (IL-4, IL-6, IL-10, TNF- $\alpha$  or IFN- $\gamma$ ) determination, the kit was left at room temperature (18-25°C) for 30 minutes to equilibrate, as suggested by the manufacturer. After that, the assay was carried out following the instructions in the kit's leaflet, which are summarized in the following steps: The wells of a high binding ELISA plate were coated with anti-cytokine monoclonal antibody (anti-IL-4, -IL-6, -IL-10, -TNF- $\alpha$  or -IFN- $\gamma$  antibody) that was diluted with PBS to a concentration of 2 pg/ml. For each well, 100  $\mu$ l of antibody was added and the plate was incubated overnight at 4-8°C. The day after, each well was washed gently with 200  $\mu$ l of PBS. The well was blocked by adding 200  $\mu$ l of PBS-Tween solution containing 0.1% bovine serum albumin (incubation buffer). The plate was incubated at room temperature for an hour. Each well was washed five times with PBS containing 0.05% Tween. The recombinant human cytokine standard was diluted with incubation buffer to prepare five concentrations, which were 1, 10, 100, 1000 and 10000 pg/ml. Then, 100  $\mu$ l of serum samples or diluted human cytokine standards were added to each well and incubated at room temperature for two hours. The washing step was repeated. To each well, 100  $\mu$ l of biotinylated

monoclonal antibody was added, and the plate was incubated for a further hour at room temperature. Streptavidin alkaline phosphatase was diluted (1:1000) with incubation buffer, and 100  $\mu$ l of the diluted enzyme was added to each well. The plate was incubated for an hour at room temperature. The washing step was repeated. To each well, 100  $\mu$ l of the substrate p-nitrophenyl-phosphate was added. After 1.5 hour, the absorbance was read at a wave length of 405 nm using ELISA reader.

- Calculations: The sample results were calculated by interpolation from a standard curve that was performed in the same assay as that for the sample, using a curve fit equation.

#### Differences between Means

The data of other parameters were tabulated in a data sheet, and the data were analyzed using the computer programme SPSS (Statistical Package for Social Sciences) version 11.5. The investigated

parameters were presented in terms of means  $\pm$  standard errors (S.E.), and differences between means of patients and controls were assessed by ANOVA test and the Least Significant Difference (LSD). The difference was considered significant when the probability (P) value was  $\leq 0.001$ . Other data was analyzed using Chi-square test.

## RESULTS

### Serum Cytokine Levels

The serum levels of interleukin-1 $\alpha$  (IL-1 $\alpha$ ), IL-4, IL-6, IL-8, IL-10, interferon- $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and granulocyte-monocytes colony stimulating factor (GM-CSF) were assessed in gastric patients and controls.

### Interlukin-1 $\alpha$ (IL-1 $\alpha$ )

A highly significant ( $P \leq 0.001$ ) increased mean serum level of IL-1 $\alpha$  was observed in the patients as compared to control subjects (85.61 vs. 15.20 pg/ml), (Table 1).

Table 1: Serum level (mean  $\pm$  S.E.) of IL-1 $\alpha$  in gastric patients and controls.

GROUPS	NUMBER	SERUM LEVEL OF IL-1A (PG/ML)			PROBABILITY $\leq$
		Mean $\pm$ S.E.	Minimum	Maximum	
Controls	25	15.20 $\pm$ 0.04	12.50	18.50	
patients	50	85.61 $\pm$ 1.10	39.40	160.80	0.001

### Interlukin-4 (IL-4)

A not significant increased mean serum level of IL-4 was observed in the patients

(12.17 pg/ml) as compared to the controls (11.34 pg/ml). (Table 2).

Table 2: Serum level (mean  $\pm$  S.E.) of IL-4 in gastric patients and controls.

GROUPS	NUMBER	SERUM LEVEL OF IL-4 (PG/ML)			PROBABILITY $\leq$
		Mean $\pm$ S.E.	Minimum	Maximum	
Controls	25	11.34 $\pm$ 0.18	8.10	12.50	
patients	50	12.17 $\pm$ 1.18	8.90	15.70	N.S.

N.S.: Not significant.

### Interlukin-6 (IL-6)

A highly significant ( $P \leq 0.001$ ) increased mean serum level of IL-6 was observed in the patients as compared to

control subjects (85.17 vs. 21.90 pg/ml), (Table 3).

Table 3: Serum level (mean  $\pm$  S.E.) of IL-6 in gastric patients and controls.

GROUPS	NUMBER	SERUM LEVEL OF IL-6 (PG/ML)			PROBABILITY $\leq$
		Mean $\pm$ S.E.	Minimum	Maximum	
Controls	25	21.90 $\pm$ 0.08	15.20	33.60	
patients	50	85.17 $\pm$ 2.18	20.60	108.80	0.001

### Interlukin-8 (IL-8)

A highly significant ( $P \leq 0.001$ ) increased mean serum level of IL-8 was observed in the total patients as compared to

control subjects (124.68 vs. 19.30 pg/ml), (Table 4).

Table 4: Serum level (mean  $\pm$  S.E.) of IL-8 in gastric patients and controls.

GROUPS	NUMBER	SERUM LEVEL OF IL-8 (PG/ML)			PROBABILITY $\leq$
		Mean $\pm$ S.E.	Minimum	Maximum	
Controls	25	19.30 $\pm$ 0.84	8.90	23.50	
patients	50	124.68 $\pm$ 1.14	70.60	134.84	0.001

**Interlukin-10 (IL-10)**

The total patients showed a highly significant ( $P \leq 0.001$ ) decreased mean level

of IL-10 (15.40 pg/ml) as compared to control subjects (24.44 pg/ml). (Table 5).

Table 5: Serum level (mean  $\pm$  S.E.) of IL-10 in gastric patients and controls.

GROUPS	NUMBER	SERUM LEVEL OF IL-10 (PG/ML)			PROBABILITY $\leq$
		Mean $\pm$ S.E.	Minimum	Maximum	
Controls	25	24.44 $\pm$ 0.22	17.25	39.80	
patients	50	15.40 $\pm$ 1.08	10.63	21.76	0.001

**Interferon- $\gamma$  (IFN- $\gamma$ )**

The total patients showed a highly significant ( $P \leq 0.001$ ) increased mean level

of IFN- $\gamma$  (54.81 pg/ml) as compared to control subjects (24.30 pg/ml) (Table 6).

Table 6: Serum level (mean  $\pm$  S.E.) of IFN- $\gamma$  in gastric patients and controls.

GROUPS	NUMBER	SERUM LEVEL OF IFN- $\gamma$ (PG/ML)			PROBABILITY $\leq$
		Mean $\pm$ S.E.	Minimum	Maximum	
Controls	25	24.30 $\pm$ 1.08	12.20	51.56	
patients	50	54.81 $\pm$ 2.18	35.60	90.80	0.001

**Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ )**

A highly significant ( $P \leq 0.001$ ) increased mean serum level of TNF- $\alpha$  was observed in the total patients as compared to

control subjects (145.1 vs. 34.45 pg/ml), (Table 7).

Table 7: Serum level (mean  $\pm$  S.E.) of TNF- $\alpha$  in gastric patients and controls.

GROUPS	NUMBER	SERUM LEVEL OF TNF- $\alpha$ (PG/ML)			PROBABILITY $\leq$
		Mean $\pm$ S.E.	Minimum	Maximum	
Controls	25	34.45 $\pm$ 0.10	30.20	38.50	
patients	50	145.1 $\pm$ 2.18	67.40	204.50	0.001

### Granulocyte-Monocyte Colony Stimulating Factor (GM-CSF)

The total patients showed a highly significant ( $P \leq 0.001$ ) increased mean level

of GM-CSF (120.1pg/ml) as compared to control subjects (34.78 pg/ml) (Table 8).

Table 8: Serum level (mean  $\pm$  S.E.) of GM-CSF in gastric patients and controls.

GROUPS	NUMBER	SERUM LEVEL OF GM-CSF (PG/ML)			PROBABILITY $\leq$
		Mean $\pm$ S.E.	Minimum	Maximum	
Controls	25	34.78 $\pm$ 0.10	24.20	44.50	
patients	50	120.1 $\pm$ 0.18	77.13	210.21	0.001

## DISCUSSION

*H. pylori*-derived factors stimulate chemokine and cytokin release from immune cells in human (1). The effects of bacteria on lymphocytes can be better understood in terms of interleukins, especially those of T-helper lymphocytes, the latter cells can be subdivided into T helper 1 (TH1), T helper 2 (TH2), and T helper 3 (TH3) depending on their interleukins profile. The differentiation, function and polarization of these cells are subjected to the effects of virulence factor derived from *H.pylori* ; therefore, the level of produced interleukins is consequently affected. In the present study, most of the investigated interleukins (IL-1 $\alpha$ , IL-6, IL-8, IFN- $\gamma$ , TNF- $\alpha$  and GM-CSF) were significantly increased in the sera of gastritis patients as compared to control subjects, therefore the gasteritis status had activating effects on cells that produced these cytokines, and the effect was dependent on the period of infection .in contrast the IL-10 level showed a significant decrease as compared to control subjects. However, the mechanism of action may have not been

well defined, and it is subjected to speculations.

Our studies demonstrate that *H. pylori* stimulates the release of neutrophil-activating, IL-8 from human. This chemokine is potent leukocyte chemoattractants and may play an important role in regulating inflammatory cell infiltration of *H. pylori*-infected gastric mucosa (9, 17).

A number of studies report that gastric mucosal levels of IL-8 are increased in patients with *H. pylori* gastritis (18, 19). IL-8 and ENA-78 are produced by gastrointestinal epithelial cells, as well as by monocytes and macrophages (20, 21, 22). Activation of epithelial cell IL-8 production seems to require contact between live *H. pylori* and the gastric epithelial cell (20, 21). Chemokines provide a chemoattractant signal to direct neutrophil migration toward an inflammatory focus. However, endothelial cell activation is required also for neutrophils to adhere to the vascular endothelium, migrate between endothelial cell tight junctions, and infiltrate tissues (22, 23, 24). *H. pylori* LPS is a monocyte chemoattractant and mitogen; it activates monocytes to release reactive oxygen

intermediate superoxide anion and upregulates monocyte production of IL-1, TNF, and IL-6 (25, 26, 27). Inflammation by *H. pylori* infection is strongly induced by a cascade of tumor necrosis factor (TNF-), associated with interleukin-1 and other inflammatory cytokines (28): previously reported that a tumor necrosis factor (TNF-) inducing protein (Tip) secreted from *H. pylori* acts as a tumor promoter in stomach cancer development, and thus started to investigate whether Tip is involved in induction of chemokine genes (29). These studies support our results.

Interleukin-10 is an important regulatory cytokine produced by Th2 cells, B cells, macrophages, thymocytes, and keratinocytes(30). It is also a potent inhibitor of macrophage activation in vitro as it impairs the production of inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$  by macrophages stimulated with LPS and IFN- $\gamma$  (31). Accordingly, mice become more sensitive to LPS-induced shock by treatment with anti-IL-10 Abs while lethal endotoxemia and elevated serum TNF- $\alpha$  levels are suppressed upon the administration of IL-10 (31, 32, 33). All these previous studies give us the best explanation to our data which showed high decrease in Interleukin-10 in contrast to the high increase in other inflammatory and pro-inflammatory interleukins. Also enable to understand the role of interleukins in pathogenesis of *H. pylori*-induced mucosal inflammation.

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## دور الحركيات الخلوية في التهاب بطانة المعدة الناجم من بكتريا *Helicobacter pylori*

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### الخلاصة

التهاب المعدة المزمن أو التهاب أغشيتها المخاطية المتسبب من بكتريا *Helicobacter pylori* يتميز باستعمارها من قبل هذه البكتريا والتي تؤدي إلى تحفيز كبير للمناعة الخلوية والأخيطية في كل أنحاء الجسم وتتركز في موقع الألتهاب. هدفت هذه الدراسة على قياس مستويات الحركيات الخلوية (السايتوكينات) ودورها في الأمراض و هل أن هذه البكتريا تؤدي إلى تحفيز إنتاج هذه الحركيات الخلوية:

(IL-1 $\alpha$ , IL-4, IL-6, IL-8, IL-10, TNF- $\alpha$ , IFN- $\gamma$  and GM-CSF).

وقد وجد أن معظم الحركيات الخلوية المدروسة: (IL-1 $\alpha$ , IL-6, IL-8, TNF- $\alpha$ , IFN- $\gamma$  and GM-CSF) أظهرت زيادة معنوية واضحة في مصل المرضى بالتهاب الأمعاء مقارنة بالسيطرة وهذا دليل على حالة الألتهاب في المعدة في الأشخاص المصابين. بينما IL-10 أظهر انخفاض معنوي واضح في مصل المرضى بالتهاب الأمعاء مقارنة بالسيطرة. أستنتج من هذه الدراسة أن الحركيات الخلوية وخاصة الألتهابية تلعب دور رئيسي في أمراضية وزيادة ألتهابه *Helicobacter pylori*.