# Cytokine Profile in Patients with Concurrent *Schistosoma mansoni* Infection with *Helicobacter pylori* Associated Chronic Gastritis

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**Abstract:** The response of the host to parasitic infections represents a complex interaction between non specific inflammatory mechanisms and specific immunologically adaptive events. The type of effector mechanisms involved depends on the type of organism. *Schistosoma mansoni* infection is characterized by a strong T-helper type 2 (Th2) cell-associated immune response. However, bacterial infection is associated with induction of Th1 immune response. Few data are available about the immune response of cases infected with combined *Helicobacter pylori* (*H. pylori*) and schistosomiasis. Thus, the investigation of the cytokine pattern in patients coinfected with both *H. pylori* and schistosomiasis was our rationale. This study included four patient groups: Group I included 24 patients infected with chronic schistosomiasis alone, Group II included 24patients infected with *H. pylori* alone, Group III included 24 healthy control individuals with matched age and sex and Group IV patients with chronic *H. pylori* and schistosomiasis. Serum levels of IFN-gamma, interleukin (IL)-4were measured in all groups by enzyme-linked immunosorbent assay. The results showed that the patients infected with *H. pylori* had significantly higher serum levels of IFN-gamma compared with the controls and the patients with schistosomiasis and coinfection ($P < 0.001$). On the other hand, serum levels of IL-4 were significantly higher in patients with schistosomiasis and coinfection compared with the control group and with the *H. pylori* patients. Schistosomiasis appeared to induce a Th2 cytokine profile, with increase in serum levels of IL-4, even in the presence of *H. pylori* coinfection. In conclusion, schistosomiasis may down regulate the stimulatory effect of *H. pylori* on Th1 cytokines.

[Gouda M. A.; Nassef N.; Sharaf S. A.; Saad A.E.; Sahar S. and Zaghla H.E. **Cytokine profile in patients with concurrent *Schistosoma mansoni* infection with *Helicobacter pylori* associated chronic gastritis**. *J Am Sci* 2014; 10(8):163-168]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 22

**Key words:** cytokines, Schistosomiasis and *H. pylori*.

## 1. Introduction

Most Helminthic infections are chronic, where the worms are long living and may survive within their host for many years. To survive such extended periods of time, these organisms have developed sophisticated survival substances that induce anti-inflammatory and/or regulatory immune responses **(Maizels *et al*., 2004).** This ability of helminthic parasites to modulate immune response and immune responsiveness has generated a great deal of interest **(Helmby, 2009),** The beneficial effects of helminthic infections and /or products have been demonstrated using experimental models in conditions such as inflammatory bowel disease, diabetes and allergy (**Zaccone *et al*., 2006).**

Schistosomiasis is a helminthic infection caused by the blood fluke of the genus *Schistosoma*. Despite intensive control efforts, disease caused by these worms remains a major public health concern in Egypt and so many other developing countries **(ElSaied *et al*., 2009).** Although, schistosomiasis is endemic in Egypt where *Helicobacter pylori* (*H. pylori*) is a widespread problem and coinfections are frequent, limited data exists on the effect of schistosomiasis on the severity of *H. pylori* infection **(Elshal *et al*., 2004).**

*H. pylori* causes gastritis, peptic ulceration and is an important risk factor for gastric adenocarcinoma (the second highest cause of cancer deaths worldwide). The disease process is thought to have a multifactorial etiology **(Hussein, 2010).** The presence of *H. pylori* invariably induces gastric inflammation with the release of chemokines and cytokines, which in turn recruit and activate lymphocytes. It has been reported that *H. pylori* causes a predominant Th1 type response which enables it to eliminate the organism and might even benefit the bacteria by providing nutrients and growth factors. A prolonged Th1 response damages the mucosa and may lead to gastroduodenal disease (**Torres *et al*., 2003).**

An imbalance between Th1/Th2 immune response caused by helminth infection has been found to play a role in immune activation and /or dysregulation of the host immune response to concurrent bacterial infection**.** The increased pathology observed with concurrent *S. mansoni* and *H. pylori* infection demonstrates that the severity of *H. pylori* infection is exacerbated by the concurrent infection with *S. mansoni* and that schistosomiasis may be a risk factor for aggravated *H. pylori* pathogencity **(Brady *et al*, 1999: Mansfield *et al*.,**

**2003).** This work was done to clarify changes in immune response in patients with combined *S. mansoni* and *H. pylori* infections.

**2. Subjects and methods**

The present study included 96 individuals of different age groups ranging from 18-65 years old. They were selected from those attending National Liver Institute Hospital, and Shebin El-Kom Educational Hospital (Hepatology Department). They divided into four groups; Group I included 24 patients infected with chronic schistosomiasis *mansoni* alone, Group II included 24patients infected with *H. pylori* alone, Group III included 24 healthy control individuals with matched age and sex and Group IV patients with concurrent chronic *H. pylori* and *S. mansoni*. Patients and controls were subjected to:

**Full clinical examination**

History and clinical data with special attention to gastrointestinal complaints as well as abdominal examination and assessment of the severity of the liver disease and its complications such as cirrhosis were performed. History of parasitic infection within the previous three months was excluded.

**Diagnosis of Schistosomiasis:**

Diagnosis of *S. mansoni* infection was carried out through detection of *S. mansoni* ova in stool by using Both Formol ether concentration technique (FEC) (**Garcia, and Bruckner, 1998**) and examination of three smears of Kato Katz slides **(Katz *et al*., 1970).** In addition of performing rectal snip and *Schistosoma* antibodies using indirect haemagglutination assay (Femouz Laboratories, Asniéres, France).

**Diagnosis of *H. pylori* in serum**: *H. pylori* infected patients were screened for the presence of anti- *H. pylori* antibodies. enzyme-linked immunosorbent assay (ELISA) classic IgG kit was used (ELISA; Sorin Biomedica, Sallugia, Italy).).

**Assessment of cytokine profile.**

A blood sample was taken from each patient and control. Sera were separated and cryopreserved at 70 $^{o}$C till tested by ELISA Kits (**Pomi *et al*., 1997).**

**Quantitative determination of serum IFNγ and serum IL-4**

The levels of IL-4 and IFN-γ were measured by use of a capture ELISA (ELISA; R&D Systems, Minneapolis, Minn.). Samples and standards were incubated in microtitre wells coated with a mouse mAb against human IFN-γ. or IL4. Samples and standards of known IFN-γ and IL-4 concentration were pipetted into the wells, and incubated. After washing, a biotinylated mAb specific for IFN-γ and IL-4 was added and incubated. Then, the enzyme streptavidin peroxidase was added. After incubation and washing to remove all unbound enzyme, a substrate solution was added to induce a colored reaction product.

Optical densities of duplicate wells, measured at 450 nm, were converted to picograms of IL-4 or IFN-γ per milliliter, using standard curves constructed with the recombinant human cytokines as recommended by the manufacturer.

**Histopathology for gastric mucosa:**

Biopsy specimens were done through upper gastroinestinal endoscopy, frozen in Tissue Tek OCT compound (Miles, Inc., Elkhart, IN) and then stored at −80°C. Then, 5-μm sections were cut on a 2800 Frigocut cryostat (Reichert-Jung, Germany) and were stained with hematoxylin and eosin. Pathology was scored by using a modified histology scoring system (**Loher *et al*., 2003**).

**Statistical analysis**

Data were coded and analyzed using the SPSS computer program. Quantitative data were presented as mean ±SD for patients and control. Qualitative data were compared using frequency and percentage. Student *t* test for comparison of means and Pearson correlation test for comparing the serum levels of both cytokines in the patient group were used.

**3. Results**

The study included analysis of 96 Egyptian patients. Table (1) summarizes the demographic and clinical findings of all patients. The study population included 65 (76.7%) men and 31 (32.3%) women. The male: female ratio was 2.1: 1. The age of the patients enrolled ranged from 18-65 years, mean age 41.31 ±11.06 years.

Some patients enrolled in the study had different degrees of liver cirrhosis (as diagnosed by their clinical, laboratory, and radiological findings).

Schistosomiasis was assessed in all groups using FEC, Kato thick smear, rectal snip and IHAT. Results revealed that all group I and IV were positive by IHA test, followed by rectal snip (17 cases), then Kato thick smear (11 cases) and lastly FEC (8 cases) and other groups were negative as shown in table (2).

The patient groups II and IV only attend to endoscopy unit were examined for histopathology. The prevalence of gut mucosal damage caused by *H. pylori* alone was significantly higher than that with concurrent *S. mansoni* infection. 58.3% of cases in group II had grade 2 pathological features with neutrophils in the lamina propria (LP) and glandular epithelial lining, while 20.8% of cases in group IV had neutrophils and glandular epithelial lining in LP (Table 3).

The mean value of IL-4 was 70.87±30.83 in group I, 15.5±8.37in group II, 10.71±9.16 in group

III and 58.29±13.33 in group IV. A significant increase in serum level of IL-4 was found in studied schistosomiasis cases compared to controls and *H. pylori* infected patients ($p$ <0.001). The co-infected patients have the highest levels of IL-4 than *H. pylori* infected patients and control group (Table 4).

In the current study serum level of INF γ in patients with schistosomiasis and *H. pylori* infection and its role in disease progression was assessed. The mean value of INF- γ was 1.54±1.54 in group I, 13.77±11.82 in group II, 2.15±1.85 in group III and 3.28±1.66 in group IV. INF- γ was significantly higher in group II in comparison with other studied groups (Table 5).

**Table (1): demographic and clinical data of all patients**

| Variables | NO % |
|---|---|
| Demography | |
| Age (years) [mean± SD (range)] | 41.31 ±11.06 (18-65) |
| Males | 65 (76.7%) |
| Females | 31 (32.3%) |
| Cirrhosis | 8 (8.3%) |
| No Cirrhosis | 88 (91.7%) |
| Viral hepatitis | 39 (40.6%) |
| Schistosomiasis | 48 (50%) |

**Table 2: Comparison between the studied groups as regards stool analysis by FEC, rectal snip, Kato thick smear and IHA results for diagnosis of schistosomiasis**

| | Stool examination(FEC) | | Rectal snip | | Kato thick smear | | IHA | |
|---|---|---|---|---|---|---|---|---|
| | Positive NO % | Negative NO % | Positive NO % | Negative NO % | Positive NO % | Negative NO % | Positive NO % | Negative NO % |
| **Group I** | 5 (20.8) | 19 (79.2) | 9 (37.5) | 15 (62.5) | 7 (29.2) | 17 (70.8) | 24 (100) | 0 (0.0) |
| **Group II** | 0 (0.0) | 24 (100) | 0 (0.0) | 24 (100) | 0 (0.0) | 24 (100) | 0 (0.0) | 24 (100) |
| **Group III** | 0 (0.0) | 24 (100) | 0 (0.0) | 24 (100) | 0 (0.0) | 24 (100) | 0 (0.0) | 24 (100) |
| **Group IV** | 3 (12.5) | 21 (87.5) | 8 (33.3) | 16 (66.7) | 4 (16.7) | 20 (83.3) | 24 (100) | 0 (0.0) |

**Table 3: Comparison between the studied groups as regards activity of gastritis diagnosed by histopathology.**

| Activity of gastritis | The studied groups | | | | $X^2$ | P value |
|---|---|---|---|---|---|---|
| | Group II N = 24 | | Group IV N = 24 | | | |
| | No | % | No | % | | |
| **Histopathology of gastric mucosa** | | | | | | |
| 0 | 5 | 20.8 | 5 | 20.8 | | |
| 1 | 3 | 12.5 | 14 | 58.3 | 13.38 | 0.004 |
| 2 | 14 | 58.3 | 5 | 20.8 | | |
| 3 | 2 | 8.3 | 0 | 0.0 | | |

**$X^2$ = Chi square test** Activity refers to presence of neutrophils in the lamina propria (LP). The activity was graded on a scale of 0-3 (modified from **Bayerdorffer *et al.*1992** ).

0: Chronic inflammatory cells with no neutrophilic infiltration (chronic gastritis only).

1: Neutrophils in LP only. 2: Neutrophils in LP and glandular epithelial lining only (cyrptitis).

3: Neutrophils in LP, glandular epithelial lining and lumina (cryptitis and crypt abscesses).

**Table 4: Serum levels (pg/ml) of IL-4 in Schistosomiasis, *H.pylori* infected patients and control**

| | The studied groups | | | | Test of significance | P value |
|---|---|---|---|---|---|---|
| | Group I N = 24 | Group II N = 24 | Group III N = 24 | Group IV N = 24 | | |
| IL4 | | | | | 5.94 | <0.001[1] |
| (Pg/ml) | 70.87±30.83 | 15.5±8.37 | 10.71±9.16 | 58.29±13.33 | 5.94 | <0.001[2] |
| X ± SD | 39 – 160 | 2 – 36 | 1 – 38 | 39 – 87 | 1.17 | 0.24[3] |
| Range | | | | | 2.18 | 0.03[4] |
| | | | | | 5.94 | <0.001[5] |
| | | | | | 5.94 | <0.001[6] |

1 = Comparison between group I and group II. 2 = Comparison between group I and group III

3 = Comparison between group I and group IV. 4 = Comparison between group II and group III

5 = Comparison between group II and group IV. 6 = Comparison between group III and group IV

**Table 5: Serum levels (pg/ml) of INF- γ in Schistosomiasis, *H.pylori* infected patients and control.**

| | The studied groups | | | | Mann Whitney U test | P value |
|---|---|---|---|---|---|---|
| | Group I N = 24 | Group II N = 24 | Group III N = 24 | Group IV N = 24 | | |
| INF γ (Pg/ml) X ± SD Range | 1.54±1.54 0.1 – 5 | 13.77±11.82 5.9 – 63 | 2.15±1.85 0.2 – 5.2 | 3.28±1.66 0.3 – 5.6 | 5.94<br>1.31<br>3.48<br>5.94<br>5.94<br>2.20 | <0.001[1]<br>0.19[2]<br>0.001[3]<br><0.001[4]<br><0.001[5]<br>0.03[6] |

1 = Comparison between group I and group II. 2 = Comparison between group I and group III
3 = Comparison between group I and group IV. 4 = Comparison between group II and group III
5 = Comparison between group II and group IV. 6 = Comparison between group III and group IV

**4. Discussion**

Approximately 50% of humanity is infected with *H. pylori*. *H. pylori* gastritis may progress to atrophic gastritis and lead to the development of metaplasia, dysplasia and eventually gastric cancer. Fortunately, only a small percentage of the population developed serious disease due to *H. pylori* infection (**Lee *et al*., 2013).**

Host and environmental factors as well as the virulence properties of particular strains of *H. pylori* probably influence disease outcome in infected individuals. Individuals living in countries with low socioeconomic conditions suffer from high prevalence rates of *H. pylori* acquired at an early age (**Salih, 2009).** Some of these countries have high rates of gastric cancer, whereas some African countries with equally high prevalence rates of *H. pylori* have much lower gastric cancer (**Ghoshal *et al*., 2010)**, this paradox needs further studies.

Diagnosis of schistosomiasis by IHA test was higher than other tests used in diagnosis. This finding is coincident with study of **Coulibaly *et al*., (2013),** who found that the prevalence of anti *S. mansoni* antibodies was more three times than the prevalence of infection estimated by stool examination and finding of **El Ridi (2013),** who reported that immunodiagnostic test led to the diagnosis of the earliest cases of human schistosomiasis**. Carneiro *et al*., (2013)** also found 80 cases to be seroreactive while eggs were identified in only 19 of the samples by parasitological examination. This may be also attributed to closed infection in most chronic schistosomaiasis cases where the eggs are trapped inside the colonic mucosa.

Evidences are conflicting on the effect of concurrent helminthes infection on the immunopathogenesis and outcome of *H. pylori* infection. Some studies were in agreement with our study and have shown that helminthes infection may play protective role against *H. pylori* infection and that infected patients may have a less severe form of the disease as our study **(Fox *et al*., 2000; Elshal *et al*., 2004).**

The impact of concomitant *S. mansoni* infection on *H. pylori* induced gastritis was studied in twenty patients infected exclusively with *H. pylori*. The patients were compared with twenty patients coinfected with the bacteria and *S. mansoni* and twelve patients with schistosomiasis alone. The results revealed that severe gastritis was significantly more common in the patients infected exclusively with *H. pylori* **(Abou Holw *et al*., 2008).**

In contrast, **Chen *et al.* (2005)** reported that coinfected helminthes infection significantly enhances the pathology of colonic bacterial infection.

The current study focused on determining pattern of serum IL-4 in patients with schistosomiasis and its role in disease progression. The results of this work was consistent with those of other studies which reported high level of IL-4 in patients infected with schistosomiasis as IL-4 has a fundamental role in pathogenesis of schistosomiasis (**El-Kady *et al*., 2005)**. There was significant increase in IL-4 levels in studied schistosomal cases compared to controls and this in agreement with previous studies (**Kamal *et al*., 2001 and Emam *et al*., 2006).** Schistosomiasis appears to induce a Th2 cytokine profile, with increase in serum levels of IL-4 even in the presence of HCV co-infection (**El-Kady *et al*., 2005).**

Significant increase in serum level of INF γ was found in cases infected with *H. pylori* alone in comparison with controls, schistosomiasis alone and coinfected individuals ($p$ <0.001).These data were consistent with results of **Eltayeb *et al*., (2013)** which was conducted on population suffering from schistosomiasis, and there was very significant difference between IFN-γ levels between patients and control group.

**Abdollahi *et al.* (2011)** found that the mean of TNF-α and IFN-γ levels in the infected group with *H. pylori* were significantly higher than that of uninfected patients. Increased serum level of IFN-γ indicates the activation of circulating-T cells against

infection. Therefore, they concluded that, *H. pylori* by inducing certain inflammatory cytokines may contribute the process of disease development.

Many studies reported that both IL4 and IFN- γ appeared to have mutually antagonistic effects which were consistent with the present study. Furthermore, IL4 also inhibited the effect of IFN- γ on immunoglobulin production by B cells and vice versa (**Yazdanbakhsh *et al*., 2001)**.

These findings were in contrast to **Epplein *et al*. (2013),** who reported that both IFN- γ and IL4 were increased in *H. pylori* infected patients. However, no significant correlation was detected between serum levels of both cytokines.

It is therefore concluded that concurrent *S. mansoni* infection may modify the inflammatory response to gastric *H. pylori* infection. However, further explanation and clarification of the immune response to co-infection between parasites and bacteria and their beneficial effects to the host should be taken into considerations.

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6/12/2014