INTERLEUKIN-18 AND CAROTID THICKNESS IN HELICOBACTER PYLORI POSITIVE PATIENTS WITH DYSPEPSIA IN SULAIMANI- KURDISTAN

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Abstract

Background: Helicobacter pylori (H. pylori) infection stimulates the production of proinflammatory cytokines associated with the development of atherosclerosis. Levels of circulating interleukin-18 (IL-18) have been positively correlated with carotid intima-media thickness (CIMT) and coronary plaque area and have been identified as important predictors of coronary events and cardiovascular mortality. This study aimed to examine the relationship between serum IL-18, carotid intima thickness and H. pylori-IgG antibody as a sign of H. pylori infection in dyspeptic patients.

Methods: This cross sectional- case control study was conducted in Kurdistan Teaching center for Gastroenterology and Hepatology (KCGH) in Sulaimani city from January 2014 to March 2015. One hundred dyspeptic patients with positive H. pylori infection and 100 apparently healthy asymptomatic volunteers with negative H. pylori tests were enrolled in this study. Sera were tested for H. pylori IgG & IgA antibodies at Sulaimani Central lab., using ELISA tests. Interleukin 18 (IL-18) was measured based on immunoenzymometric assay. All participants
were evaluated for both internal carotid (IC) and common carotid (CC) arteries thickness by using high resolution grey-scale Doppler ultrasonography.

**Results:** A significant difference (P<0.01) was found between patients and controls in the mean serum IL-18. A significant correlation between *H. pylori* IgG level and IL-18 was found (p < 0.01), but not with *H. pylori* IgA level. A significant correlation was found between IL 18 level and ICA, CCA thickness in *H. pylori* positive patients (p < 0.01).

**Conclusion:** *H. pylori* infection was significantly associated with higher serum IL-18. There was significant correlation between IL-18 and Carotid intima-media thickness.

**Keywords:** H. pylori, IL-18, Carotid Thickness, Sulaimani.

**Introduction**

The immunoinflammatory response plays an important role in the development, progression, and complication of atherosclerotic disease (Hansson and Libby, 2006; Herbin et al., 2012). Several studies have demonstrated the association between *H. pylori* infection and coronary heart disease (CHD) (Ayada et al., 2009; Al-Ghamdi et al., 2011), while some studies indicated that there was no correlation between *H. pylori* infection and coronary atherosclerosis (Ozdogru et al., 2007; Szklo et al., 2009).

Interleukin 18, previously known as IFN-γ inducing factor, is a proinflammatory member of IL-1 super family which plays role in the initiation and progression of atherosclerosis (Mallat et al., 2001; Packard and Libby, 2008). Carotid artery intima-media thickness (CIMT) measured by ultrasound are predictive of cardiovascular disease in individuals without clinically evident disease. CIMT is now widely used as an early marker for atherosclerotic disease (Kastelein et al., 2003).

This study aimed to examine the relationship between serum IL-18, carotid intima thickness and *H. pylori*-IgG antibody as a sign of chronic *H. pylori* infection in dyspeptic patients.
Materials and Methods

This cross sectional case control study was conducted in Kurdistan Teaching center for Gastroenterology and Hepatology (KCGH) in Sulaimani city during the period of January 2014 to March 2015. One hundred dyspeptic patients with positive H. pylori infection (IgG) and 100 apparently healthy asymptomatic volunteers with negative H. pylori tests were enrolled in this study. Both groups were comparable in age distribution and gender.

Exclusion Criteria: Pregnant women, smokers, patients previously treated for H. pylori infection and who had received antibiotics; proton pump inhibitors or bismuth compounds in the preceding 4 weeks. This study was approved by the Ethics Committee of Faculty of Medicine, University of Sulaimani and Directory of Health in Sulaimani. Written informed consents were obtained from all the participants.

A special form used to obtained demographic data (name, age, gender, history of dyspepsia, and drug history).

After overnight fasting, 10 ml venous blood aspirated then centrifuged at 5000 r/min for 5 min. Sera were tested for H. pylori IgG & IgA antibodies at Sulaimani Central lab., using ELISA tests (Nova Lisa, NovaTec, Germany), according to the standard operating procedures. That has a sensitivity of 97% and a specificity of 98.8%.

Interleukin 18 (IL-18), using RayBio_ Human IL-18 ELISA Kit (ELH-IL18BPA-001), USA was measured based on immunoenzymometric assay. Subjects were evaluated for both internal carotid (IC) and common carotid (CC) arteries and plaque occurrence by using high resolution grey-scale Doppler ultrasonography (Philips, En visor, Version C.1.3, 2007), In a semi-dark room, the subject lay supine with slightly hyperextended neck and rotated away from the imaging transducer. Both carotid arteries were scanned. CIMT was defined as the distance between the leading edge of the lumen intimal interface and the leading edge of the media adventitia interface of the far wall.

Statistical Analysis
All data were analyzed using Excel and SPSS (Version 20 software) computer program. To assess the correlation between different variables, bivariate correlation coefficient analysis was performed. In this analysis, the statistical significant association was determined. All p values were based on 2-sided tests and p < 0.05 was considered statistically significant.
Results

Both groups of *H. pylori* seropositive and seronegative groups were comparable in mean age and gender (p>0.05).

The mean serum Interleukin 18 among patients and controls were (19.7 ± 8.9) and (8.9 ± 1.96) pg/ml respectively, with highly significant difference (P< 0.01), Table 1.

Table 1. Interleukin 18 in study population.

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Patients</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 18 (pg/ml)</td>
<td>19.7±8.9</td>
<td>8.9±1.96</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

A moderate correlation between *H. pylori* IgG level and Interleukin 18 was found (r = 0.341), which is statistically significant (p < 0.01), Figure 1

![Figure 1. Relationship between *H. pylori* IgG level and Interleukin 18 in patients](image)
A negative correlation between *H. pylori* IgA level and Interleukin 18 was found (r = -0.084), (p >0.05), Table 2.

### Table 2. Relationship between *H. pylori* IgA level and IL-18 in patients.

<table>
<thead>
<tr>
<th><em>H. pylori</em> IgA (Ndx)</th>
<th>Correlation coefficient (r)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 18 (pg/ml)</td>
<td>-0.084</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Correlation between serum interleukin 18 level and ICA, CCA thickness was found (r = 0.545), (r = 0.502) respectively, which is statistically significant (p < 0.01), Figure 2 & 3.

![Figure 2](image.png)

**Figure 2.** Relationship between interleukin 18 level and ICA thickness in patients.
Figure 3. Relationship between interleukin 18 level and CCA thickness in patients.

**Discussions:**

In the present study the mean serum Interleukin 18 concentration was higher in *H. pylori*-infected patients than in control group, this observations is consistent with findings of other studies (Jafarzadeh and Sajjadi, 2006; Sakai et al., 2008; Chen et al., 2013; Rezaeifar et al., 2013). A significant correlation between Interleukin 18 and *H. pylori* IgG level was found, but not with *H. pylori* IgA level. Those may be explained by *H. pylori* infection induces IL-18 in the gastric mucosa (Sakai et al., 2008). IL-18 may play an important role in the inflammatory response and promote the chronic and persistent inflammatory changes in the stomach. This may ultimately influence the outcome of *H. pylori*-associated diseases that arise within the context of gastritis (Bagheri et al., 2013).

Also *H. pylori* have been shown to induce a strong cytokine response in both human gastric epithelial cells and gastric epithelial cell lines. Chronic infection with *H. pylori* is associated with gastric IFN-γ producing T cells and increased mucosal IL-12, indicating a predominant Th1
response. IL-12 mRNA levels are increased in infection with cag-positive H. pylori. This results in up-regulation of the expression of IL-18 receptors in both Th1 (T-helper 1) and NK cells. It seems that in chronic H. pylori infection, mucosal production of IL-18, together with IL-12, would be important in promoting Th1 responses and IFN-γ secretion. Moreover, it has been demonstrated that Th cells respond to H. pylori antigen by secreting high levels of IFN-γ. (Smythies et al., 2000; Jafarzadeh and Sajjadi, 2006).

A statistically significant correlation between interleukin 18 and ICA, CCA thickness was found. Yamagami et al., 2005 found that elevated serum IL-18 levels are associated with increased carotid IMT (Intima media thickness) as evaluated by B-mode ultrasound, suggesting their link with carotid atherosclerosis. However IL-18 is highly expressed in human carotid atherosclerotic plaques predominantly colocalized with macrophages. Thus, increased IL-18 production from severe atherosclerotic lesions could contribute to the higher IL-18 (Mallat et al., 2001). Also, experimental studies have shown that IL-18 enhances atherosclerosis through release of interferon-γ (Whitman et al., 2002) and induces expression of IL-6 in vascular endothelial and smooth muscle cells (Gerdes et al., 2002). Inversely, IL-18 deficiency reduces the extent of atherosclerosis in apolipoprotein E-knockout mice. These findings are in accordance with the studies that IL-18 plays a key role in atherogenesis, supporting the link between IL-18 and carotid atherosclerosis (Elhage et al., 2003).

**Conclusion:** H. pylori infection was significantly associated with higher serum IL-18. There was significant correlation between IL-18 and Carotid intima-media thickness.

The author disclose that, they have no conflict of interest.
References


