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Association of *H. pylori* IgG and CagA-IgG with Some Immunological and Biochemical Parameters in Diabetic Patients

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ABSTRACT

Helicobacter pylori is a gram-negative bacteria that can cause gastric and extra-gastric diseases. The study aimed to find the relationship between infection with *H. pylori* and the progression of diabetes type II (DMII) with other immunological markers. **Method** This study was conducted in Kirkuk City from Nov. 2022 to Apr. 2023 and included 106 individuals, 26 as a control group and 80 patients (34 males and 46 females) suffering from (DMII) with *H. pylori* infection. Five ml of venous blood were taken for HbA1c, fast serum glucose, serum *H. pylori* IgG, *H. pylori* CagA IgG, Interlukin-1 β , and IL-10 tests. **Results** The correlation factor ($p < 0.01$) had shown that there was a weak positive correlation between HbA1c and *H. pylori* IgG titer, as well as a moderate positive correlation between the levels of *H. pylori* CagA IgG and IL-1 β . There was a moderate negative correlation between the levels of HbA1c and IL-10, also between IL-1 β and IL-10 levels. **Conclusion** There was a relationship between the severity of infection with *H. pylori* and high HbA1c levels. In addition, CagA has a significant impact on increasing the severity of inflammation by increasing IL-1 β secretion.



Introduction

About half of the world's population is infected with *Helicobacter pylori* (*H. pylori*), a gram-negative, microaerophilic, spiral-shaped, and flagellated bacteria whose primary reservoir is the human stomach. Geographical location, age, ethnicity, and socioeconomic position all affect the prevalence of infection; in fact, the prevalence is higher in the developing world and in areas with low socioeconomic status [1,2]. Both invasive diagnostics, including endoscopy of the upper gastro-intestinal tract and gastric biopsy, as well as non-invasive testing, like the urea breath, blood, and stool antigen tests, are available in clinical practice to detect this infection [3]. *H. pylori* infection may affect human health in a variety of ways, including gastric and extra-gastric diseases. Examples of gastric disorders include gastritis, peptic ulcers, functional dyspepsia, reflux, and gastric cancer, while extra-gastric complications of *H. pylori* infection include Asthma, dermatological problems (like chronic spontaneous urticaria), Hematologic conditions (like iron deficiency anemia), cardiopulmonary conditions (like coronary artery disease), and neurological conditions (like Alzheimer's, ischemic stroke and Parkinson's), and metabolic conditions (like Diabetes and insulin resistance) [3-5]. As a result of *H. pylori* infection, the stomach and gastrointestinal tract have chronic inflammation and immunological responses, according to the findings of numerous research [6-8]. Tumor necrosis factor-alpha, leptin, and other inflammatory cytokines (interleukin-1 β , IL-6, IL-8, IL-10 and IL-17) and adipokines are consequently participating in this inflammation and immunological responses [6,9,10].

The cytotoxin-associated gene A (Cag-A) is an important component of *H. pylori*'s pathogenicity. It is encoded genes of the type IV secretion system. Additionally, it has the ability to strongly elicit an inflammatory reaction, inflammatory cytokines such interleukin-1, IL-6, and IL-8 and tumor necrosis factor alpha [11]. Globally, diabetes is a serious health issue, chronically high blood glucose levels are the result of the body's cells' inability to effectively utilize insulin or the beta cells' (or cells) inability to make enough of it, Type I diabetes (TDI) and type II diabetes (TDII) are the two common types of diabetes, respectively [12-15]. IL-1 β major product during immune responses [16]. It has strong pyrogenic effects and is necessary for the effective induction of innate immune responses and the development of adaptive immune responses when dealing with acute inflammation [17-19]. However, the discovery that gain-of-function mutations in the inflammasome component generate excessive IL-1 β production that contributes to autoimmune [20], and induces autoinflammatory disorders [16].

Additionally, persistent IL-1 β in the presence of chronic inflammation may favor tumor induction as well as later tumor propagation through a variety of mechanisms [17,18]. IL-10 is a pleiotropic cytokine known for its potent and immunosuppressive effects and anti-inflammatory [21]. T helper2 cells were initially the original biological source, but it was soon discovered that additional CD4 and CD8 T cells can also produce this cytokine, IL-10 is secreted by the lymphoid and myeloid lineages in response to various stimuli. In addition to CD4 and CD8 T cells and B cells, this also comprises macrophages, monocytes, Dendritic cells (DCs), neutrophils, mast cells, eosinophils, and natural killer cells [22]. Therefore, This study aimed to evaluate some immunological markers such as IL-1 β and IL-10 in order to find a correlation between *H. pylori* infection and its virulence factor (cagA) and the progression of type II diabetes mellitus.

Materials Methods

Study design

This study was conducted in Kirkuk City from November 2022 to April 2023 and included a total of 106 participants, divided into two groups: 80 participants as a patient group (34 males and 46 females) suffered from type II diabetes mellitus more than five years ago with a positive *H. pylori* stool antigen test, whose ages ranged from 37 to 78 years, and 26 healthy persons (13 males and 13 females) as a control group, with a mean age of 45.26, attended the Azadi Teaching Hospital and the Kirkuk General Hospital in Kirkuk City. The questionnaire was filled out, and information was voluntarily obtained from all 106 participants during the drawing of the blood sample. The age, sex, and BMI (weight/ height²).

Exclusion criteria

Patients with type 1 diabetes (history of the disease), Antibiotic treatment for *H. pylori*, and patients who already had *H. pylori* infection and were receiving treatment for it before being selected as participants were included in the exclusion criteria by asking them during the questionnaire.

Sampling

Two types of samples were taken from both groups:

1. Stool sample for quick detection of *H. pylori* antigen in stool.

2. Five ml of venous blood samples were taken and divided into two parts:

A) 2 mL were placed in EDTA (ethylene diamine tetra acidic acid) tubes in order to perform the HbA1c.

B) 3 ml of blood were placed in plain tubes and spun at 3000 rpm for 10 minutes to separate the serum samples using a centrifuge. The serum sample was split into two portions; one portion was used to measure fast serum glucose (FSG), (The participant result for HbA1c greater than 6.5% and 126 mg/dL for FSG was considered a diabetic patient). while the other portion was placed in Eppendorf tubes and kept at -20 C for *H. pylori* IgG, *H. pylori* CagA IgG, Interlukin-1 β , and Interleukin-10 analysis (Table 1).

Detection of *H. pylori* antigens

Immunochromatographic method is an in vitro qualitative for quick detection of *H. pylori* antigen in stool sample, It takes approximately 10 minutes to visualize the test results on a cassette. It was used in accordance with the manufacturer's instructions (Neo nostics cassette, China). The test began with a sample that was immediately added to a sample diluent buffer bottle and then applied to a sample well. The results were then interpreted based on the formation of two colored bands in the test and control zones for positive samples and just one colored band in the control region for negative samples. This was carried out for both the patients and the control group.

Estimation immunological parametres

The concentration of human serum parameters (*H. pylori* IgG, CagA IgG, IL-1 β and IL-10) were quantitatively measured by using a sandwich ELISA technique, carried out according to the manufacturer company instructions (Sunlong Kits, China).

Statistical analysis:

Using IBM version 26 statistical analysis program SPSS, one way ANOVA was used to measure the mean and standard deviation (Mean $\pm$ SD) between groups, P value < 0.01 is highly statistically significant. Correlation was done by using Pearson's bivariate test, IBM version 26. Pearson's r varies between +1 and -1, where +1 is a perfect positive correlation, and -1 is a perfect negative correlation. 0 means there is no linear correlation at all [40].

r : 0.7 < |r| < 1 : strong correlation

0.4 < |r| < 0.7 : moderate correlation

0.2 < |r| < 0.4 : weak correlation

0.0 < |r| < 0.2 : very weak correlation

|r|=0.0: no correlation

Results:

The results revealed that FSG mg/dL was significantly higher in type II diabetic patients with a positive *H. pylori* stool antigen test (patients group) (255.1 $\pm$ 18.8) than in healthy control (97.69 $\pm$ 8.23). In addition, there was a highly significant increase in the level of HbA1c% (9.045 $\pm$ 1.874) in patients compared to control (5.396 $\pm$ 0.605).

The concentrations of *H. pylori* IgG and CagA IgG pg/ml were significantly higher in the patient group (93.16 $\pm$ 9.62 and 333.7 $\pm$ 24.0) than in the control group (55.09 $\pm$ 8.54 and 224.4 $\pm$ 27.7), respectively. Furthermore, the results of serum interleukin-1 β and IL-10 pg/ml show a highly significant increase in the patient group (88.81 $\pm$ 14.61 and 67.57 $\pm$ 9.79) in comparison to the control (47.87 $\pm$ 15.90 and 46.99 $\pm$ 9.37), respectively. see table 1.

Table 1. Results of DMII with positive *H. pylori* stool antigen test (patients group).

Parameters	Patients M $\pm$ SD	Control M $\pm$ SD	P- value 0.01**
FSG mg/dL	255.1 $\pm$ 18.8	97.69 $\pm$ 8.23	
HbA1c %	9.045 $\pm$ 1.874	5.396 $\pm$ 0.605	
<i>H. pylori</i> IgG Pg/ ml	93.16 $\pm$ 9.62	55.09 $\pm$ 8.54	
<i>H. pylori</i> CagA IgG Pg/ ml	333.7 $\pm$ 24.0	224.4 $\pm$ 27.7	
Interleukin-1 β Pg/ml	88.81 $\pm$ 14.61	47.87 $\pm$ 15.90	
Interleukin-10 Pg/ml	67.57 $\pm$ 9.79	46.99 $\pm$ 9.37	

P- value = 0.01** highly significant different. DMII: type II diabetes mellitus, FSG: fast serum glucose.

There was a strong positive correlation between blood sugar concentration and HbA1c; P< 0.01 (r = 0.737). In addition, there was a weak positive correlation between HbA1c and the *H. pylori* IgG titer, meaning

that if IgG levels increase, so will HbA1c levels ($r = 0.321$) $p < 0.01$. Figure figure (1) shows that the correlation is significant at 0.01 ($r = 0.0321$, $P = 0.004$).

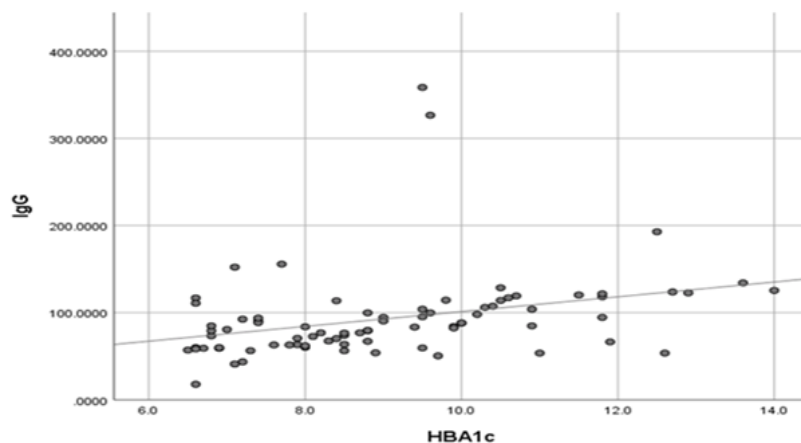


Figure 1. Positive correlation between HbA1c and *H. pylori* IgG antibody concentration. $r = 0.321$, $P = 0.004$

There was a moderate positive correlation between the *H. pylori* CagA IgG virulence factor and the concentration of interleukin-1 β ($r = 0.579$) $P < 0.01$. as obvious in figure (2).

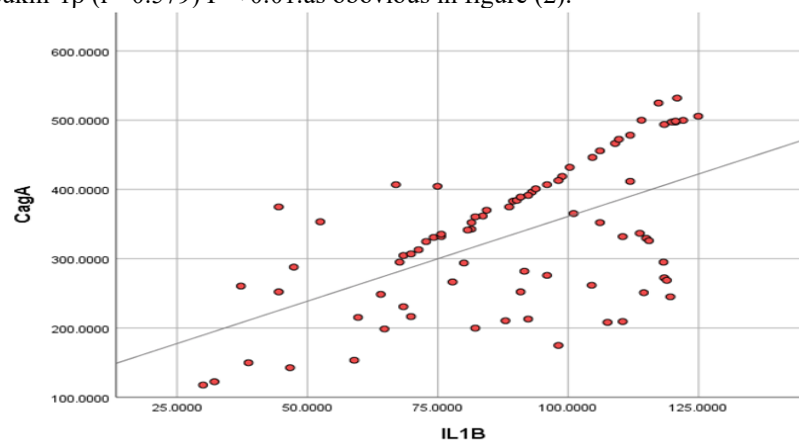


Figure 2. Positive correlation between IL-1 β concentration and *H. pylori* CagA IgG antibody concentration. $r = 0.579$, $P = 0.000$.

Although, A moderate negative correlation was found between glycated hemoglobin and concentration of interleukin-10, meaning when the level of glycated hemoglobin increases the concentration of IL-10 decreases ($r = -0.500$), as is clear from Figure (3).

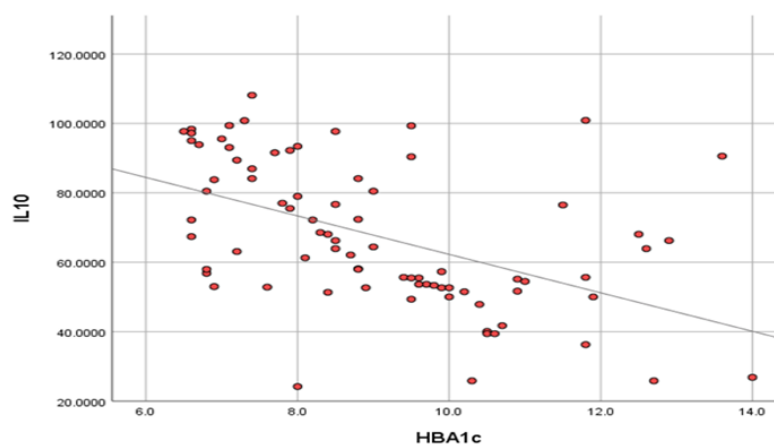


Figure 3. Negative correlation between level of HbA1c and IL-10 concentration. $r = -0.500$, $P = 0.000$

Additionally, as shown in Figure (4), Negative moderate correlation between IL-1 β and IL-10 concentrations, ($r = -0.485$) $P < 0.01$, Indicated that when the level of anti-inflammatory cytokine decreased, there was an increase in the concentration of pro-inflammatory cytokine.

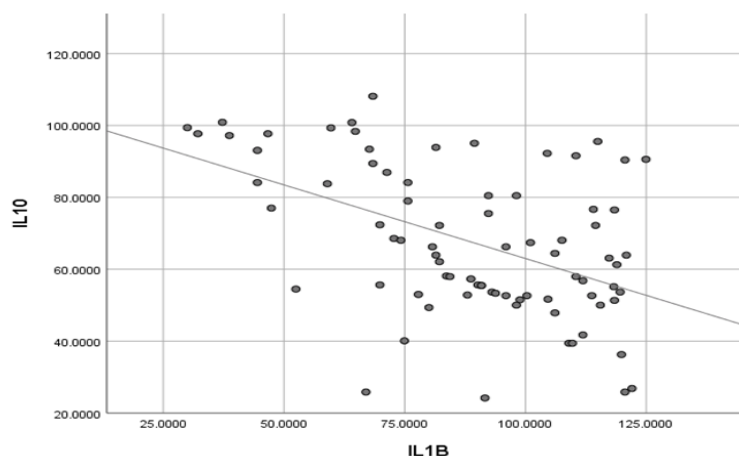


Figure 4. Negative correlation between IL-1 β and IL-10 concentrations. $r = -0.485$, $P = 0.000$

Discussion

Many studies have demonstrated that *Helicobacter pylori* infection results in immunological responses in addition to chronic inflammation of digestive system [23]. Compared to healthy individuals, those who had *H. pylori* infections had higher levels of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8 and tumor necrosis factor-alpha) and lower levels of leptin [24]. Previous research has demonstrated that an elevation in the level of pro-inflammatory cytokines and increased leptin may develop insulin resistance (IR) and initiate the metabolic syndrome [25]. A natural *H. pylori* infection can last a lifetime, although an immune response is elicited. As a result, *H. pylori*-induced activation of inflammatory signaling in immunological and epithelial cells can lead to an accumulation of cytokines and chemokines during the chronic inflammatory phase [26, 27]. Among the cytokines that were reportedly raised were IL-1, IL-4, IL-6, IL-10, IL-11, IL-12, and TNF-alpha. many of which act as trophic agents for epithelial cells and could stimulate the proliferation of gastric epithelial cells [28].

In diabetic individuals, chronically high levels of glucose above normal can lead to low-grade systemic inflammation (notably increased blood concentrations of cytokines, acute phase proteins, and mediators with endothelial activation capabilities) that affects other body organs [29,30]. For instance, IL-1 β levels may rise in the majority of diabetics who have high levels of glycated hemoglobin[31]. Since this interleukin impacts the gastric cells and decreases the secretion of stomach acid, it creates the perfect conditions for *Helicobacter pylori* development and colonization[32]. Additionally, the majority of diabetic patients have low levels of interleukin-10, a sign of an imbalance between pro- and anti-inflammatory cytokines due to pro-inflammatory cytokines like IL-6, IL-1, CRP, and TNF-alpha rising when interleukin-10 levels drop[33]. And this explains what we have found regarding the association between high IL-1 β , HbA1c and low IL-10 levels. The study done by Tong H. et al. confirmed our findings regarding the association between the high level of IL-1 β and the low level of IL-10. He found that there was a correlation IL-1 β and IL-10 cytokines, where serum IL-1 β in type 2 diabetes increased while serum IL-10 decreased[34]. IL-1 β performs a variety of essential roles in the control of inflammatory processes and metabolism. It can also control insulin secretion and trigger beta-cell apoptosis, which can result in type 2 diabetes mellitus [34].

As previously discussed, the consequences of increased pro-inflammatory cytokines and how they relate to *Helicobacter pylori* infection. a study has hypothesized that the release of a number of inflammatory cytokines may rise in response to infection with *H. pylori* have a virulence factor CagA [35]. So, this supports our results, which explain the high level of IL-1 β that accompanies the high level of *H. pylori* cagA IgG virulence factor. Furthermore, the result for the correlation between *H. pylori* IgG and the level of HbA1c was in agreement with the result of research performed by J. Chen et al. A meta-analysis found a correlation between glycated hemoglobin A levels in diabetes and *Helicobacter pylori* infection[36]. Increased inflammation brought on by an *H. pylori* pathogen may lead to IR and diabetes because of the hypothalamus' sex-dimorphic insulin action. A study (using a rat model) has shown that inflammation may affect the hypothalamus's reduced ability to produce insulin [37]. The systemic inflammation caused on by *H. pylori* infection may specifically elevate the expression of pro-inflammatory cytokines (such as IL-6, IL-1, and tumor necrosis factor-alpha). These cytokines' effects on the hypothalamus caused hypothalamic inflammation [38,39]. Inflammation in the

hypothalamus, which may reduce insulin signaling, was a major contributor to the disruption of the neuroendocrine control of metabolism that resulted in systemic IR [39].

Conclusions

The patients suffering from diabetes mellitus type II and whose stool antigen test for *H. pylori* was positive had higher levels of serum *H. pylori* IgG and CagA IgG, in addition to higher levels of interleukin-1 β and IL-10 concentrations compared to the control group. Furthermore, there was a positive correlation between the level of HbA1c and *H. pylori* IgG and a positive correlation between *H. pylori* CagA IgG and IL-1 β . In contrast, there was a negative correlation between concentration of HbA1c and IL-10 and a negative correlation between level of IL-1 β and IL-10. Through the correlation between the titer of *H. pylori* IgG and the elevation of HbA1c levels, in addition to the high levels of inflammatory mediator IL-1 β that are associated with an increase in the level of *H. pylori* Cag A virulence factor, we conclude that there is a relationship between *H. pylori* infection and the development of DMII.

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