The relationship between *Helicobacter pylori* infection and development of Rheumatoid Arthritis

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Abstract

Background: *Helicobacter pylori* is a spiro-helical, gram-negative & microaerophilic bacteria that particularly lives in the stomach. It has helix form is thought to have developed to puncture the mucoid lining of the stomach and transmit infection. Almost around world about half of population infected with these bacteria, which is broadly dispersed. The interplay of genetic predisposition and environmental exposures results in autoimmune disorders. Infectious triggers have been linked and thoroughly explored among environmental exposures. **Objective:** To identify the frequency of peoples infected with *Helicobacter pylori* and autoimmune disorders like rheumatoid arthritis and to determine how this bacterial infection may affect the immune system and contribute to autoimmune disease. **Materials and Methods:** 100 Stool samples were collected from patients (50) & control group (50) having mild to severe abdominal symptoms also they have pain in joints and bones in order to detect *H. pylori* infection by stool antigen (Ag) test also urea breath test done to confirm the diagnosis, the patients also diagnosed for rheumatoid arthritis (RA) via anti -CCP test by blood samples collection. **Results:** A total of 50 patients were infected by *H.pylori*, Females have higher rate of infection with 60% and males 40%. (40-49) years old age patients have higher rate of infection. (30%) of patients with positive *H. pylori* and chronic gastritis suffered from Pain in bones and joints and diagnosed with RA , while only 6% of controls without *H. pylori* infection diagnosed with RA and showed less gastrointestinal symptoms and no joints inflammation. **Conclusions:** In our study we can conclude that there is a strong association between gastritis in patients caused by *helicobacter pylori* and development of autoimmune diseases represented by rheumatoid arthritis.

Keywords: Rheumatoid arthritis (RA), *Helicobacter pylori (H.pylori),* Anti-Cyclic Citrullinated Peptide Antibody Test (ACCP).

1. Introduction

The stomach is frequently home to the *Helicobacter pylori* bacteria, which is gram-negative, microaerophilic, and spiral (helical). Its helical form is thought to have developed to puncture the mucoid layer of the stomach and transmit infection. *H. pylori* has been linked to cancer of the mucosa-associated lymphoid tissue in the stomach, esophagus, colon, rectum, or tissues around the eye. *H. pylori* disease normally has no symptoms, although it can potentially lead to gastritis (1). In 2015, it was estimated that more than 50% of people worldwide have *H. pylori* colonized or infected in their upper gastrointestinal tracts, in higher rates in non-developed countries. However, gastrointestinal tract *H. pylori* colonization has become less common recently in many countries (2). The helix-shaped Gram-negative bacterium *Helicobacter pylori* can be seen in tissue using the Gram stain, Giemsa stain, and phase-contrast microscopy. *H. pylori* possesses 4-6 flagella in same directions, making it has biofilms creating features and changing from spiral to other coccoid form. As a result, all Helicobacter species involving gastro-enterohepatic mainly are motile. Fla-A and Fla-B, two copolymerized flagellins, make up the Helicobacter's distinctive sheathed flagellar filaments (3). *Helicobacter pylori* requires oxygen due to its microaerophilic nature, but with low level than atmospheric O_2. It has a hydrogenase that converts the H2 produced by intestinal bacteria into energy. Urease, catalase, and oxidase are produced. (4). *Helicobacter pylori* utilizes own flagellum to breach the mucus layer of the stomach to gain access to less acidic epithelial cells beneath. The production of copious urease amounts to make NH_3 is a main role of *H. pylori's* adaptive techniques for fending off stomach acidity. Additionally, it has the capacity to detect the pH acidity range of mucus layer (5). The linings of the duodenum and stomach are damaged by *Helicobacter pylori* in a number of different ways. The colonization of the stomach by *H. pylori* can result in chronic gastritis, an inflammation of the stomach lining, at the site of infection, in addition to the biochemicals produced by the organism, such as proteases, which are toxic to epithelial cells. Additionally, researchers are examining two interrelated mechanisms by which *H. pylori* may promote cancer. One pathway involves a rise in the formation of free radicals and the rate of host cell mutations around *H. pylori* (6). The bacteria is the one of most distributed infection in the world, affecting about half of the population. Actual infection rates vary by country; in the impoverished world, they are substantially higher than in the developed world, where they are thought to be around 25%. Infections are typically contracted in infancy in all of these countries (7). When the immune system responds in an inappropriate way to a healthy physiological part, an autoimmune disorder results. There are at least 80 different types of autoimmune illnesses, and they can present with a variety of mild to severe symptoms, such as exhaustion and low-grade fever (8). Joints and cartilages can be synthesized by special cells in the body that invade other areas of the body and cause local inflammation in rheumatoid arthritis. Further malignant transformation of other cells is further encouraged by the milieu created by persistent inflammation and overactive immune system. This explains the links to skin and lung cancer. Additionally, there is a higher risk of developing other hematologic cancers, none of which are specifically impacted by joint inflammation (9).Antigenic resemblance between certain disease-causing bacteria and particular, previously healthy bodily tissues or cells. One hypothesis for autoimmune disorders is molecular mimicry. When the body is infected with a bacterium that has antigens on its surface that are similar to those on its own, the immune system may react improperly by trying to harm cells that have these antigens on their surface in joints, blood vessels, or other organs that are otherwise healthy (10) . The interplay of genetic predisposition and environmental exposures results in autoimmune disorders. Infectious triggers have been linked and thoroughly explored among environmental exposures. Bacteria, viruses, and parasites are examples of infectious agents. They can also include other species found in the natural flora. There have been several hypothesized methods by which viral pathogens may trigger autoimmune disease, one of these is molecular mimicry (11).Cross-reactive T lymphocytes in autoimmune gastritis were activated by molecular mimicry of *H. pylori* antigens. It has been demonstrated that *H. pylori* components, particularly urease, stimulate B cells and cause them to create IgM rheumatoid factor, anti-ds-DNA, and anti-phospholipid choline antibodies. The earlier findings are among the few, in comparison to the vast majority of other studies, that partially explain how the pathogen might cause immunological tolerance loss, which is a crucial precursor to antigen-driven autoimmunity (12). Non-steroidal anti-inflammatory drug use and an elevation in IgM rheumatoid factor in B cells persistently activated with *H. pylori*

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urease are most likely linked to an increased prevalence of peptic ulcer disease in autoimmune disease patients. Considered to be one of the infectious diseases connected to rheumatoid arthritis is *Helicobacter pylori* (13).

2. Patients and methods

2.1. Samples collection

Case-control study of 100 stool samples collected from 50 patients & 50 as control having mild to severe abdominal symptoms diagnosed for *H. pylori* by rapid Ag test from stool samples and urea breath test as conforming test, then all study groups tested for autoimmune disease (Rheumatoid arthritis) by anti-CCP antibodies detected by blood samples collection.

Inclusion criteria: Any patients suffering from chronic gastritis that diagnosed with *H. Pylori* bacteria and autoimmune diseases, adult patients and controlled middle age years old, all patients & controlled prevented from taking treatment.

Exclusion criteria : Children, patients taking any medications for last three months, patients with chronic diseases like diabetes and other autoimmune disorders, those subjected with gastrointestinal disorder or inflammatory bowel diseases, all should be excluded .

2.2. Bacterial Infections diagnosis

2.2.1. Antigen test for *H. pylori*

A small sample of the patient's stool was combined with a specific buffer and added to a quick cassette. According to immune-chromatograph lateral flow, if the targeted bacteria present in the sample that are regarded antigens will bind to specific antibodies in the cassette, positive results two lines appear control and test, while negative results one line only show as control as in figure (1) .

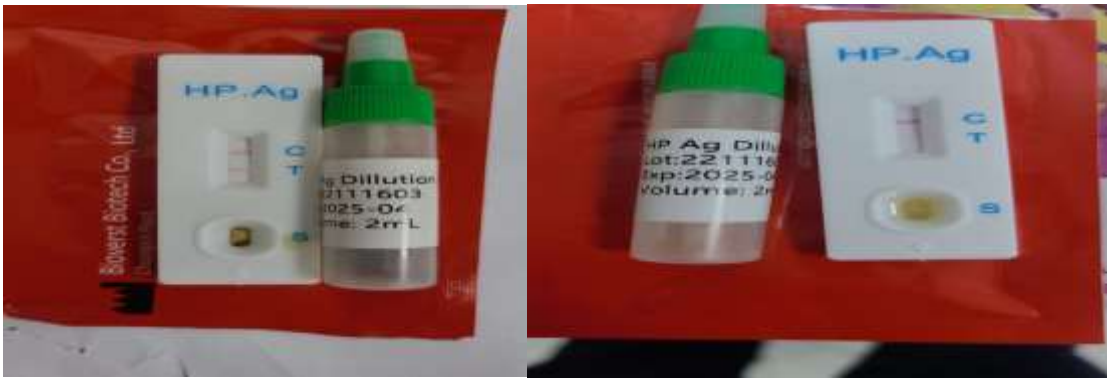

Figure (1): *H. pylori* stool Ag test negative and positive results

2.2.2 Urea breathing test

The urea breath test can be used to quickly, confirmatory identify *Helicobacter pylori* infections connected to gastritis, stomach and peptic ulcers. Depending on the *H. pylori* role in returning urea to CO2 & ammonia (NH_3). As the principal non-breaching approach for detecting *H. pylori* with or without therapy , leading society guidelines endorse urea breath testing as in figure (2) (14) .

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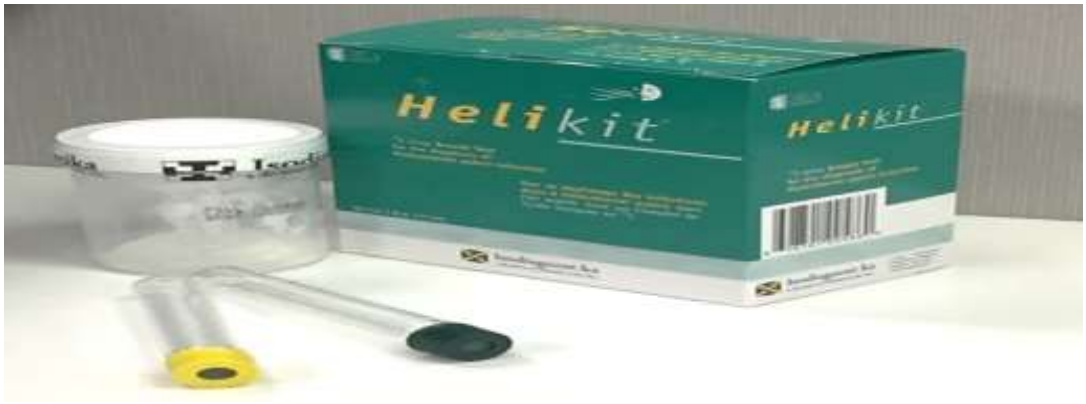

Figure (2): Heli-kit, a 13C breath test is used in detecting *H. pylori* bacterium.

2.3. Patients diagnosis with rheumatoid arthritis (RA)

All study participants underwent a RA test; of the first group of patients, 50% had *H. pylori* infection, whereas the second group, 50%, had no such infection. In order to diagnose RA, a particular test called the Anti-Cyclic Citrullinated Peptide Antibody Test (ACCP) is performed. Readings demonstrated that 30% of patients with chronic gastritis caused by *H. pylori* had positive ACCP readings, compared to 6% in the control group of research participants who were not infected with *H. pylori*. ACCP test are measured by Ichroma II kit & instrument as in figure (3).

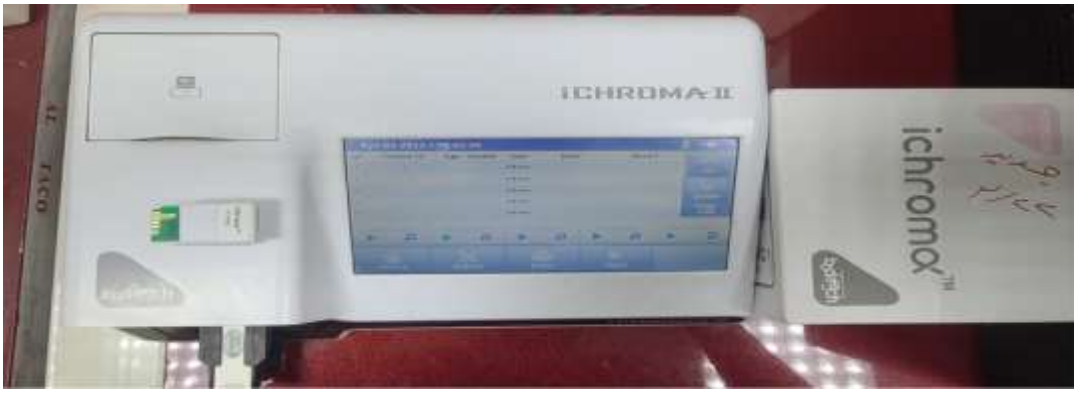

Figure (3): I chroma II using for diagnosis rheumatoid arthritis by ACCP kit test.

2.4. Statistical analysis

The statistical data analysis approaches were used to analyze and assess the results of the study under the application of (SPSS) ver. (26.0), to analyze the association between the frequency of *Helicobacter pylori* gastritis and development of rheumatoid arthritis in all studied patients. *P* values ≤0.05 were regarded as statistically significant (S), *P* values >0.05 were non-significant (NS) and *P* values ≤0.01 considered statistically highly significant (HS).

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3. Results

Table (1): Samples collected depending on gender

Age	H.pylori patients	Control group	Total	*p.value*
Male	20(40%)	30(60%)	50	0.4*NS
Female	30(60%)	20(40%)	50	
Total	50(100%)	50(100%)	100	

*p-value > 0.05 considered statistically non-significant (NS)

Fifty *H. pylori* detected patients including 40% males and 60% females having severe abdominal symptoms diagnosed as gastritis by H. pylori infection. 50 patients appeared to have *H. pylori* infections with chronic gastritis, females showed higher rate of infection about 60% at non-significant (p=0.4) distribution.

Table (2): Patients samples distributed depending on age

Age / years	*H. pylori* infection
< 20	5(10%)
20-29	6(12%)
30-39	8(16%)
40-49	14(28%)
50-59	10(20%)
> 60	7(14%)
Total	50(100%)

Fifty gastritis patients they conformed to have infection with *H. pylori* they grouped according to age into six groups, higher infection rate was 28% at (40-49) years old patients group.

Table (3): Diagnosis of bacterial samples in all study groups

Isolates	Antigen test	Urea breath test
H. pylori patients	50	50
Control group	50	50
Total	100	100

The diagnosis of *H. pylori* bacteria confirmed by several techniques. Basically antigen test was done by using stool samples were 50% of patients having *H. pylori* with severe infection with positive Urea breath test and 50% controls were negative results of both stool antigen test & urea breath test . Urea breath test were done as conforming test for *H. pylori* gastritis.

Table (4): Diagnosis of rheumatoid arthritis distributed in all study groups

Study group	Positive ACCP test	Negative ACCP test	Total	p-value
H. pylori patients	15(30%)	35(70%)	50	0.00005
Control group	3(6%)	47(94%)	50	X^2= 19.5
Total	18 (18%)	82(82%)	100	

*p-value ≤ 0.01 considered statistically highly-significant (HS)

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The anti CCP test done for specific diagnosis of patients with rheumatoid arthritis (RA). Study samples divided in to two groups, the first group were patients infected with *H. pylori* and they have chronic gastritis, ACCP test showed 30% of this group with positive anti CCP results five times more than the control group accompanied with only 6% positive anti CCP results at statistically highly significant differences in distribution of *H .pylori* along with rheumatoid arthritis development in all study groups (p. 0.00005).

Table (5): Age groups distribution in patients with H .pylori & RA

age / years	*H.pylori* infection	RA patients Positive ACCP	p-value
< 20	5(10%)	0(0%)	0.01 HS
20-29	6(12%)	1(6.7%)	
30-39	8(16%)	2(13.3%)	
40-49	14(28%)	5(33.3%)	
50-59	10(20%)	4(26.7%)	
> 60	7(14%)	3(20%)	
total	50(100%)	15(100%)	

*p-value ≤ 0.01 considered statistically highly-significant (HS)

This table shows the association between age ranges of patients having *H. pylori* infection and frequency of rheumatoid arthritis, the most important age groups were 40-49 years old patients having high rate (28%) of gastritis represented by *H .pylori* along with (33.3%) high ACCP positive results of arthritis at highly significant p.0.01.

4. Discussion

Chronic autoimmune disease (CAD) is typically specified by a lack of immunological tolerance to auto-antigens. It has been found that many bacteria play a role in autoimmunity. Infectious pathogens can cause autoimmunity in two different ways: by mobilizing endogenous antigens or by sending a specific-antigen homologous signal via genetic modeling. Additionally, it leads to inflammation, which generates specific-antigen homologous signal in order to strengthen the response of immunity. *H. pylori* infection considered a key role factors that set off number of autoimmune disorders (15). According to (2018) study by *Wolfgang Fischbach* and *Peter Malfertheiner*, only 10.9% of Germans had *H. pylori* infection, which is disagreed with the results of our study. Of the 100 patients who had abdominal pain, 50% had *H. pylori* tests that were positive. (16). Gender distribution in our study results is in agreement with study by *Pshtewan D. et al*. conducted in Arbil (2019), who found that 64% of patients with positive *H. pylori* infection were females and 36% were males . In our study, females (60%) had a higher rate of infection with *H. pylori* than males (40%) from 50 patients confirmed to have infection (17). The same study by *Pshtewan D.* revealed that *H. pylori* infection was spread among age groups, but that the group of patients aged 41 to 49 years old had the highest rate of *H. pylori* infection, with 24% of them showing positive results that in agreement with patients in our study who were age group 40 to 49 years old were thought to have a greater rate 28% of infections with *H. pylori* (17) . All studies focus on distribution of *H. pylori* infection among rheumatoid arthritis (RA) patients. But in our study trying in diagnosis the patients having chronic *H. pylori* infection and how this can induce autoimmune diseases like rheumatoid arthritis (RA) , our study results revealed about 6% of control group non *H. pylori* infected but have mild symptoms of pain in bone, pain and swelling of cartilage also they have simple abdominal symptoms with positive anti CCP results for (RA) and 30% of patients group having *H. pylori* with chronic gastritis and they have severe symptoms like bone pain, painful swelling cartilage & fever with severe abdominal symptoms as well as positive anti CCP results for rheumatoid arthritis in all patients , these study results agreed with study of *Hongyn wen. et al* , published in (2012) , Tokyo , Japan , who reported that Rheumatic illness patients were substantially more likely (88%) than the general apparently healthy population (42%) to have *H. pylori* infection , your study revealed that 88% of RA patients suffer from *H. pylori* infection (18) , finally these our study results agreed with study of Li Wang , *et al* .. (2022), who decided with his colleagues that gastric infection with *H. pylori* considered the predominant causes for development of many autoimmune diseases like inflammatory bowel disease,

autoimmune thyroiditis, type 1 diabetes, primary biliary cirrhosis, autoimmune hepatitis, rheumatoid arthritis, Systemic lupus erythematosus, Sjogren's syndrome (19).

5. Conclusions

In our study results we can conclude that *H. pylori* infection in patients above 40 years old suffered from moderate to severe pain and swelling in bone and joints can induce triggering of autoimmunity represented by multiple mechanisms like molecular mimicry and other microbial mechanisms that enhance auto reactive T & B cells participating in autoimmune diseases development.

6. Future prospective

Other modern research about the relationship between patients suffering from chronic gastritis and induction of autoimmunity, also other types of autoimmune diseases should be screened in patients infected with *Helicobacter pylori* by phenotypic, antigenic and molecular targeting such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), sjogrens syndrome (SS). Finally in our study we can recommends modern and advanced techniques for isolation and detection of *H . pylori* auto-antigen in rheumatoid patients at DNA & PCR molecular level .

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Conflict of Interests

The authors affirm that the publication of this paper is not impacted by any conflicts of interest.

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العلاقة بين عدوى البكتريا البابية الملتوية وتطور مرض التهاب المفاصل الرثواني

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الخلاصة:

الخلفية : البكتريا البابية الملتوية هي بكتريا تأخذ شكل حلزوني- لولبي وذات صبغة سالبة الكرام وتحتاج كمية قليلة من الأوكسجين كطبيعة عيشها داخل معدة الأنسان . بواسطة شكلها الحلزوني او اللولبي في بعض الحالات تستطيع ان تثقب الغشاء المخاطي للمعدة مما تؤدي الى حدوث عدوى وانتقالها الى مكان اخر . على الأقل حوالي نصف سكان العالم يعانون من الإصابة المزمنة بهذا النوع من البكتيريا حيث تعتبر من اكثر الأنواع انتشارا . من الواضح لهذه العدوى هنالك دور كبير لمناعة جسم الأنسان والجينات الموروثة في مختلف الظروف البيئية والتي تؤدي الى ربط التعرض للقرحة المزمنة نتيجة هذه البكتريا مع تحفيز وتطور الكثير من امراض المناعة الذاتية كالتهاب المفاصل الرثواني مثلا . **الهدف من البحث:** للتعرف على هوية ومدى انتشار هذه البكتريا البابية الملتوية بين الناس الذين يعانون من الاصابة المزمنة بأمراض المناعة الذاتية كالتهاب المفاصل الرثواني وغيرها ، ومعرفة مدى تأثير هذه العدوى المزمنة على الجهاز المناعي وحثه لكي يفعل المناعة الذاتية المتمثلة بأمراض المناعة الذاتية المختلفة .**المواد وطريقة العمل:** تم جمع عينات الخروج من 100 شخص نصفهم يعانون من مرض القرحة المزمنة بفعل اصابتهم بهذه البكتريا ونصفهم من الواضح مسيطر عليهم لم يصابوا بهذه البكتريا حيث ان جميع العينات التي شملت بهذه الدراسة كانوا يعانون من الام في المفاصل والعظام تتراوح من سطحية الى شديدة الخطورة وقد تم فحص العينات جميعها مختبريا بفحص المستضد المناعي في الخروج لهذه البكتريا وتم تأكيدها بفحص تنفس اليوريا الاكثر تخصصا في التشخيص وقد تم التحري عن الأجسام المضادة المقاومة للببتيد السيترولييني (anti-CCP) بسحب عينات دم للجميع للتأكد من وجود مرض التهاب المفاصل الرثواني . **النتائج:** نتائج هذه الدراسة اظهرت 50 مريضا يعانون من الاصابة بهذه البكتريا مع وجود قرحة مزمنة حيث كان النساء اكثر بنسبة 60% من الرجال وان اكثر معدل للأعمار الذين شهدوا اكثر اصابات يتراوح بين 40-49 ، ومن بين هؤلاء المرضى المصابين بهذه القرحة المزمنة نتيجة هذا النوع من البكتريا حوالي 30% من بينهم يعانون من الام المفاصل والعظام الشديدة وقد ثبت تشخيصهم بمرض التهاب المفاصل المزمن الرثواني بينما كانوا فقط 6% من المتبرعين الاصحاء المسيطر عليهم فقط هذه النسبة من مجموع جميع العينات شهدوا الاصابة بمرض التهاب المفاصل مع الام سطحية غير خطرة مع عدم تشخيص عدوى البكتريا البابية الملتوية. **الاستنتاجات:** تشير نسبة عالية من الاستنتاجات الى وجود علاقة وثيقة بين القرحة المزمنة في مجموعة المرضى المصابين بهذه البكتريا وعلاقتها المناعية بتحفيز وتطور مرض التهاب المفاصل الرثواني المزمن.

الكلمات المفتاحية: التهاب المفاصل الرثواني (rheumatoid arthritis) ، البكتريا البابية الملتوية (*Helicobacter pylori*) ، الأجسام المضادة المقاومة للببتيد السيترولييني (anti-CCP) .