Studing the Influence of Helicobacter.pylori in Celiac Disease Patients

Farah Hamza Mahdee* Shurooq Rayyis Kadhim* Wassan Abdulkareem Abbas*
Department of Laboratory Sciences, College of Pharmacy, Al-Mustansiriyah University

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Corresponding Author email:
shurooqbiotech@gmail.com
Orcid: https://orcid.org/0000-0002-5697-5670

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Abstract:

Celiac disease an autoimmune disease; it occurs in Europe at 1%, and in the world people (0.3–1.3%). It causes histopathological changes in the mucosa of the intestine (villi atrophy). The findings showed that it occurs due to the reduction of the absorbed nutrients. Helicobacter pylori are colonized in human gastric mucosa, which mainly causes stomach injury. The rate of H. pylori is as high as almost 50%, and it also occurs in childhood. Vitamin/mineral deficiencies, weight loss, and Malabsorption characterize classical celiac disease. The study aimed to detect the effect of H. pylori in celiac patients and determine vitamin B12, D3, and Ferritin in celiac patients infected with H. pylori. The study includes 41 celiac patients with H. pylori and 31 celiac cases without H. pylori of both genders and 52 apparently healthy individuals of comparable age and gender to save as a control group. The vitamin D3, B12, and ferritin levels were measured for each participant. The study found a positive correlation between celiac and H. pylori, with decreased ferritin levels in patients with celiac disease. Also, the patient group showed a significant decrease in Vitamin D3. Also, the B12 level in the patient group decreased. There was no significant gender-related variation between males and females regarding the patient and control groups' Ferritin, vitamin D3, and Vitamin B12 levels. There was no significant age-related variation between individuals under 35 years of age and those over 35 years of age regarding the ferritin and vitamin B12 levels in the patient and control groups. However, vitamin D3 level was lower in patients less than 35 years of age than in cases with more than 35 years of age. Minerals and vitamin deficiencies are observed in untreated CD cases irrespective of age and gender and irrespective of H. pylori. All CD patients had one or more nutritional deficiencies. Serum nutritional parameters like iron, Vitamin B12, and D3 should be included in the clinical workup of CD patients in addition to the serological markers. It was found that H.pylori does affect the levels of ferritin ,vitamin B12 and vitamin D3 in celiac patients .This study confirmed that there is a positive correlation between H. pylori and celiac disease. In addition, H. pylori infection may aggravate some symptoms of CD.

Keywords: Celiac disease, Helicobacter pylori, Vitamin B12, Vitamin D3, Ferritin.

دراسة تأثير البكتيريا البوابية الحلزونية في المرضى المصابين بحساسية الحنطة

فرح حمزة مهدي*,شروق ريس كاظم*,وسن عبد الكريم عباس*
***فرع العلوم المختبرية / كلية الصيدلة / الجامعة المستنصرية**

الخلاصة:

تم تصميم سلسلة جديدة من ٤-امبنوفينيل كينازولينون مرتبطة بشق الالديهايد الاروماتي زتم تصنيع المركب (ZA) عن طريق تفاعل البنزين-١-٤-ديامين مع حمض ٢-١-امينوبنزويك. يعتبر التفاعل بين الالديهايدات الاروماتية و المركب الوسطي (ZA) احد التفاعلات الكيميائية الاكثر شيوعا لتخليق مركب الايمين (قواعد شيف بيس) لانتاج المركبات (ZA1-ZA6). تم استخدام (FTIR, ^{1}H-CNMR, ^{13}C-NMR) لتاكيد الهياكل الكيميائية للمواد المختلفة.التقيم في

المختبر كنشاط مضاد للتكاثر لمستقبلات هرمون الاستروجين الفا باستخدام مقايسة(MTT).كشفت دراسة مكافحة التكاثر عن تاثير يعتمد على الجرعة على الخلايا السرطانية لسرطان الثدي (MCF-7) مع تركيزمثبط بالمقارنة مع الدواء المرجعي تاموكسيفين (IC_{50} من ٤.١٣٣ µg\mL) ، كشفت مقايسة السمية الخلوية أن IC_{50} للمركبات (ZA1، ZA2، ZA3) كان ٠,٠٧٩٦٤ ، ٥٧,٤٣ و٠,٠٠٢٧١٧ µg\mL ، على التوالي في٧٢ ساعة على نفس خط الخلية المذكور اعلاه مما يشير الى تاثير اعلى بكثير لمركب (ZA1) على نوع خط الخلية هذه.

الكلمات المفتاحية: استروجين ريسبتر الفا,MCF-7, كوينازولينون.

Introduction

Gluten enteropathy, also called celiac disease, is a genetically based autoimmune of the small intestine. It is connected to intestinal mucosa alterations characterized by villi atrophy. A decrease in the body's capacity to absorb nutrients leads to numerous deficiencies. The protein portion of Gluten, specifically its prolamine gliadin, sets off the immune reaction. Prolamins from rye, barley, and oats are blamed for the abnormal response. 90% of oats are a safe crop for people living with celiac disease. Introducing a gluten-free diet is the treatment of the disease (1).

There are four kinds of CD, typical are included villus atrophy in young children with bloating and diarrhea (2). Atypical villus atrophy in adolescents is also associated with iron deficiency or vitamin B12. It is often accompanied by infertility, chronic inflammation, and osteoporosis. The silent doesn't include clinical signs; however, the villus atrophy is occurring. The latent showed normal mucosa without clinical signs; the celiac disease is likely to develop in the future (3).

Celiac disease of the small intestine is included atrophy of the villi after taking the Gluten (4). The histopathological changes are included diverse degrees of atrophy and enteritis with lymphocytes. The damage degree of the villi will result a wide range of clinical signs (5).

Immune reactions to gliadin fractions trigger an inflammatory response in CD patients. The innate and adaptive immune systems mediate this reaction. G protein-coupled receptor CXCR3 on enterocytes and gliadin peptides interact to cause the release of zonulin, a potent modulator of intestinal barrier function. As a result, the immune system is triggered by the translocation of gliadin peptides into the lamina propria. tTG interacts with gliadin peptides in the lamina propria to deamidate them into immunogenic, negatively charged glutamic acid residues. Gliadin peptides stimulate the humoral immune response after tTG-induced deamidation, producing antibodies against gliadin and tTG, as well as pro-inflammatory cytokines like IFN, IL17, and TNFa (6).

Gluten is a complex mixture of proteins found in wheat, rye, oats, and barley. Gluten has high proline and glutamine rates. By digestive proteases, these proteins are degraded to peptides in the intestine (7).

Chronic inflammation occurs in the intestine leading to villous atrophy. The villi become flattened, and the absorption area is decreased, resulting in malnutrition, mineral, and Vitamin deficiencies, and showing some clinical signs such as bloating, abdominal discomfort, nausea, and disappearing intestine movements. Untreated patients showed chronic non-gastrointestinal clinical signs such as fatigue, infertility, anemia, eczema, osteoporosis, and lymphoma. CD Symptoms occur at any age. Some diseases associated with CD include type I diabetes, Grave's disease, Hashimoto's thyroiditis, Down syndrome, Turner syndrome, and cirrhosis (8). One of the most prevalent infectious human pathogens, *H. pylori*, carries a high risk of morbidity and mortality.*H. pylori* is one of the most significant causes of upper gastrointestinal illnesses, including dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GRD), and gastric mucosa-

associated lymphoid tissue (MALT) lymphoma. It is well known that H. pylori may cause inflammation (9).

Materials and Methods

In this study, 72 samples were collected from patients with celiac disease diagnosed by endoscopic and serologic tests; the samples were divided into two groups based on *H. pylori* presence and a control group. Blood samples were taken for detection of *H.pylori* and assessment of the CD markers (Vitamin D3,B12 and ferritin).The serum was stored at -20°C to analyze vitamin D3, B12, and ferritin levels.

RESULTS

Seventy-two patients (41 with *H. pylori*, 31 without *H. pylori*) fulfilled the clinical and serological criteria for the diagnosis of celiac disease. A statistical comparison using the paired t-test was carried out of the data for all the parameters between subjects that have been marked as true celiac during the study and matched controls for the same.

The analysis of the demographic features doesn't demonstrate marked differences between the experimental and the control group based on gender, as table (1).

Table (1): the age and gender features of the study groups

Demographic feature	Study Group		P value
	Patient	Control	
Men Women	24 (33 %) 48 (67 %)	14 (27 %) 38 (73 %)	0.554
Age (years)	31.1 ± 10.6	30.3 ± 4.16	0.608

The serum level of Ferritin in patients with CD group (13.9 ± 3.4 ng\ml) was lower than that of the control group(24.3 ± 6.7 ng\ml) with significant differences(P<0.01). There was a marked lower Vitamin D3 level in the patient group(19.7 ± 9.3 ng\ml) than that of the control group(32.1 ± 11.3 ng\ml) with significant differences(P<0.01). The vitamin B12 level in the patient group(269.6 ± 29.9 ng\ml) is decreased than that of the control group (373.5 ± 44.1 ng\ml) with significant differences(P<0.01) as shown in Table 2.

Table (2): The level of Ferritin, vitamin D3, and B12 in the study groups

Group	N	Ferritin (ng\ml)	vitamin D3 (ng\ml)	vitamin B12 (ng\ml)
Patient group	72	13.9 ± 3.4*	19.7 ± 9.3**	269.6 ± 29.9***
Control group	52	24.3 ± 6.7	32.1 ± 11.3	373.5 ± 44.1

***< 0.001, ** < 0.01, * < 0.05

There was no significant gender-related variation between males and females regarding the serum concentration of Ferritin, vitamin D3 and B12 in the patient and control groups, as shown in Table 3

Table (3): The effect of gender on the Ferritin, vitamin D3 and B12 levels in the study group

Parameter	Group	Mean ± SD		P value
		Male	Female	
Serum level of ferritin (ng/ml)	Patient group	14.5 ± 2.8	13.6 ± 3.6	0.288
	Control group	25.2 ± 7	24 ± 6.6	0.601
Serum level of Vitamin D_3 (ng/ml)	Patient group	19.3 ± 8.7	19.9 ± 9.7	0.789
	Control group	27.7 ± 7.7	33.6 ± 10.3	0.093
Serum level of Vitamin B_{12} (ng/ml)	Patient group	277.1 ± 29.1	265.9 ± 30	0.136
	Control group	381.1 ± 47.7	370.6 ± 43.1	0.445

There was no significant age-related variation between individuals under 35 years of age and those over 35 years of age regarding the level of ferritin and vitamin B12 in the patient and control groups, as shown in Table 4. However, the vitamin D3 was lower in cases less than 35 years(13.6 ±5.5 ng/ml)than in cases more than 35 years (29.3 ± 5.1 ng/ml)with significant differences(P<0.01) , as shown in Table 4.

Table (4): The influence of age on Ferritin, vitamin D3 and B12 levels in the study group

Parameter	Group	Mean ± SD		P
		< 35 years	> 35 years	
ferritin (ng/ml)	Patient	13.8 ± 3.1	14.1 ± 3.8	0.731
	Control	23.3 ± 6.7	30 ± 1.6	0.089
Vitamin D_3 (ng/ml)	Patient	13.6 ± 5.5*	29.3 ± 5.1	**0.000**
	Control	32.9 ± 10.5	27 ± 2.1	0.123
Vitamin B_{12} (ng/ml)	Patient	274.7 ± 29.2	261.6 ± 30	0.169
	Control	369.6 ± 47	394.5 ± 5.3	0.145

For estimating the effects of *H. pylori* and CD on the used parameters, the patients were subdivided into those with *H. pylori* and those without *H. pylori*, as shown in Table 5.

Table (5): Effect of *H-pylori* on study parameters in the study groups

	Serum level of ferritin (ng/ml)	Serum level of Vitamin D_3 (ng/ml)	Serum level of Vitamin B_{12} (ng/ml)
Patient with H-pylori	11.38 ± 1.16 *	17.58 ± 7.9 *	253.14 ± 26.7 *
Patient without H-pylori	17.2 ± 2.12	22.66 ± 10.4	291.4 ± 17.5
P value	0.000	0.021	0.000

* statistical analysis using Student's t-test, P < 0.001 (significant).

Table (5) depicted a significant decrease in the Ferritin, vitamin D3, and B12 levels in celiac disease patients infected with H. pylori than in the patients without H. pylori.

Discussion:

Gluten-sensitive enteropathy is currently the preferred term because the gastrointestinal system bears the brunt of celiac disease's main symptoms due to the damaging effects of ingested gliadin. The majority of these patients experience impaired nutrient absorption. Water-soluble vitamin deficiencies, like those of the B vitamins, would be anticipated given that CD patients most frequently experience damage to the proximal small bowel, where these vitamins are absorbed (10).

The current study found a positive correlation between *H. pylori* and celiac disease; however, the difference was not statistically significant (11). Another study found that the rate of *H. pylori* was 63% of patients with CD and 44% with non-celiac peptic ulcers. Compared to first-degree relatives, controls, and duodenal biopsy samples from adult CD patients, *H. pylori* were extremely prevalent (12). Many systemic and cohort studies provide a strong association, but the case-control reports provide the majority of data about the relationship between *H. pylori* and CD. Another study confirmed the results of some earlier studies showing a mildly negative relationship between H. pylori and CD (13).

In this work, the gender and age were of comparable range according to the inclusion criteria. Accordingly, demographic features don't show marked differences between the patients and control groups based on gender and age. The female patients have more frequent gastrointestinal clinical signs than the male patients. The gastrointestinal clinical signs include heartburn, dyspepsia, vomiting, nausea and constipation, which

are related to the female. The classical clinical signs of CD in females differ from the silent of CD men, as well as a higher rate of anemia and dyspepsia in CD females (14).

Females are more likely than males to have celiac disease, with a ratio of about 2-2.5:1. (15). Inconsistent findings were found that attempted to determine the gender differences at the CD detection in the children and adults. According to some authors, male patients present with "atypical" CD presentations more frequently (16). There have also been conflicting findings regarding the delay in CD detection. Males tend to reach CD at a younger age than females do (17), while other studies find no discernible gender differences (16).

The present study showed that the serum level of Ferritin in cases with CD was decreased than that of the control group (13.9 ± 3.4 ng\ml, P<0.01) (24.3 ± 6.7 ng\ml), respectively.

Insufficient iron intake causes anemia. A gluten-free diet improves nutrient absorption, but it is poor in iron consumption in boys (18). The pseudo cereals Teff supplements the amino acids Fe, Ca, Mg, and fiber (19).

There was a marked decrease of the vitamin D3 level in the patient group to that of the control group (19.7 ± 9.3 ng\ml, P<0.01) (32.1 ± 11.3 ng\ml) respectively; these results were in disagreement with another study that showed the levels of Vitamin D3 low in CD patients, the difference from the control group was not so statistically significant (p < 0.042479). This can be explained by a high prevalence of Vitamin D3 deficiency in our normal population (20). But this result was in agreement with another study that found. Many reports found that vitamin D levels are decreased in patients with CD compared with the control group (p=0.001) (21).

The low vitamin D intake and hypocalcemia will increase bone resorption. The density of the mineral improves in the bones after using the without-gluten diet (22).

In the current study, it was shown that the vitamin B12 level in the patient group decreased than that of the control group (269.6 ± 29.9 ng\ml) (373.5 ± 44.1 ng\ml) respectively; these results were in agreement with another study that showed vitamin B12 deficiency was observed in CD patients group (86%), in accordance with previous studies. Vitamin B12 is predominantly absorbed in the terminal ileum. Contrary to popular belief, the finding of low serum vitamin B12 indicates that the distal small intestine is functionally more affected. This is true based on histopathological examination of distal small intestinal biopsies in previous studies (10).

There was no significant gender-related variation between males and females regarding the serum concentration of Ferritin, vitamin D3, and vitamin B12 in both patient and control groups; this result was in agreement with another study that showed no marked difference in the Vitamin and mineral level between males and females, although Vitamin used before the diagnosis in the females and males (30% vs. 13%) (23).

In the current study, there was no significant age-related variation between individuals under 35 years of age and those over 35 years regarding the serum concentration of ferritin and vitamin B12 in both the patient and control groups.

The vitamin D3 level was lower in patients less than 35 years than in patients more than 35 years (13.6 ±5.5 ng/ml, P < 0.001) (29.3 ± 5.1 ng/ml); vitamin D deficiency has an important role in childhood less than fifteen years in the celiac disease. It causes an irregular immune response with increased intestinal barrier damage due to the impaired immune response that causes increased gastrointestinal infection (24).

Children with CD and children without CD (aged 3 to 12) have the same levels of vitamin D (25). Children did not exhibit

any vitamin D deficiency, but adults did. Children who have CD consume a lot of vitamin D (26).

H. pylori is a significant problem for public health because it can lead to a number of diseases. All groups, including the control group, were predicted to have widespread H. pylori infections based on the data collected. Given that H. pylori is the most common chronic infection in humans, this finding has been supported by a number of publications (27).

The relationship between CD and *H. pylori* is not clear. *H. pylori* influence of gluten-related pathological changes in the small intestine (28). Some reports showed no relationship between these two diseases (29). Lebwohl et al. found that CD development was decreased with *H. pylori*; wherever *H. pylori* were 4.4% in CD cases and 8.8% in cases without CD(30). *H. pylori* rate of 26.4% in CD cases but 20% in the control g group; the *H. pylori* rate increased in CD cases (31). The patients with CD were subdivided into those with *H. pylori* and those without *H. pylori*.

The current study showed a significant decrease in the serum level of Ferritin, vitamin D3, and vitamin B12 in celiac disease patients that were also infected with *H-pylori* compared to patients without *H-pylori*. In previous studies, *H. pylori* have related to anemia and gastritis in CD cases (32). *H. pylori* causes iron deficiency anemia by bleeding and decreased iron absorption (33). The relationship between CD and *H. pylori* has not been demonstrated. *H. pylori* rates in CD cases are higher than those without CD cases (34).

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