



# Pathological and Clinical Correlation between Celiac Disease and *Helicobacter Pylori* Infection; a Review of Controversial Reports

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## ABSTRACT

There are overwhelming reports and descriptions about celiac associated disorders. Although there is a clear genetic association between celiac disease (CD) and some gastrointestinal disorders, there are controversial reports claiming an association between CD and *Helicobacter pylori* (*H. pylori*) infection. Different studies indicated the possible association between lymphocytic gastritis and both CD and *H. pylori* infection, although this evidence is not consistently accepted. Also it was shown that an increase in intraepithelial lymphocytes count is associated with both *H. pylori* infection and celiac disease. Therefore the following questions may raise: how far is this infection actually related to CD?, which are the underlying patho-mechanisms for these associations? what are the clinical implications? what is the management? and what would be the role of gluten free diet in treating these conditions? PubMed (PubMed Central), Ovid, ISI of web knowledge, and Google scholar were searched for full text articles published between 1985 and 2015. The associated keywords were used, and papers described particularly the impact of pathological and clinical correlation between CD and *H. pylori* infection were identified. In this review we tried to answer the above questions and discussed some of the recent developments in the pathological and clinical aspects of CD and *H. pylori* infection.

## KEYWORDS

Celiac disease, *Helicobacter pylori*, Pathological feature

Please cite this paper as:

Rostami-Nejad M, Ehsani-Ardakani MJ, Assadzadeh H, Shahbazkhani B, Ierardi E, Losurdo G, Zojaji H, Mohammad Alizadeh AH, Naderi N, Sadeghi M, Zali MR. Pathological and Clinical Correlation between Celiac Disease and *Helicobacter Pylori* Infection; a Review of Controversial Reports. *Middle East J Dig Dis* 2016;8:85-92. DOI: 10.15171/mejdd.2016.12

## INTRODUCTION

Celiac disease (CD) is a T-cell-mediated disorder, which is induced by gluten ingestion in genetically predisposed individuals.<sup>1</sup> Different studies showed that the prevalence of CD is approximately 1% in many populations worldwide.<sup>2</sup> New diagnostic tools increased the consciousness and improved the diagnosis of the disease, thus causing an apparent real increase in the incidence of CD.

CD is diagnosed by abnormal histology of duodenal biopsy specimens as well as with diagnostic tools, including serologic tests for antibodies against tissue transglutaminase (anti-tTG Ab) and deamidated gliadin peptide (DGP).<sup>3</sup> In suspicious cases for example in first degree relatives of patients with CD and in patients with autoimmune disorders, evaluation of HLA-DQ2 and HLA-DQ8 haplotypes are useful

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 Received: 18 Sep. 2015  
 Accepted: 12 Mar. 2016

tools.<sup>4</sup> According to recent guidelines by Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), clinical symptoms of CD and other gluten related disorders can be relieved by adherence to a gluten-free diet and a diagnosis can be made without biopsy taking in certain circumstances, especially in those cases with an increase value of anti-tTG antibodies (IgA) more than 10 time than upper limit.<sup>5</sup>

*Helicobacter pylori* (*H. pylori*), the causative agent in more than 90% of patients with gastroduodenal disorder, is responsible for many disorders ranging from asymptomatic histological chronic gastritis to some histologically important disorders such as peptic ulcer, upper gastrointestinal bleeding, primary gastric mucosa-associated lymphoid tissue (MALT) lymphoma, chronic gastritis with atrophy, intestinal metaplasia, and adenocarcinoma.<sup>6-9</sup> To date there is no known pathogenic mechanism to explain these diverse abnormalities.

Although native immune inflammatory response is identified in both *H. pylori* infection and CD, systemic humoral immune reaction is also involved.<sup>10</sup> Increased numbers of intestinal intraepithelial lymphocytes (IELs) and subsequently villous atrophy, are not specific histological findings in *H. pylori* infection or CD. They may be found in a large number of other disorders, such as *Giardia* infection, IgA deficiency, and Crohn's disease.<sup>11,12</sup> Patients with increased IELs without serology confirmation do not have CD, but those with positive serological tests and suggestive symptoms are considered as potential cases of CD.<sup>13,14</sup>

Various studies reported a high prevalence of *H. pylori* infection in patients with CD and vice versa.<sup>15-18</sup> But others have failed to find any correlation to support this statement.<sup>19-25</sup> Some studies reported that a clinical presentation like atrophic gastritis is common in patients with CD<sup>26</sup>, but others have found poor evidence to support this presentation.<sup>19</sup>

Different studies reported that number of intraepithelial lymphocytes in the duodenal mucosa are more likely to be increased in patients with *H. pylori* gastritis, and this can be controlled by the eradication of *H. pylori*, although epidemiologi-

cal investigations have failed to show the association between gastritis and CD.<sup>20,21,24,27</sup> Other reports have focused on *H. pylori*-related lymphocytic gastritis and anemia in patients with CD.<sup>18</sup>

The following keywords were selected and searched alone or in combination in PubMed (PMC central), Medline, and Google scholar for articles published in English, from January 1985 to October 2015: "celiac disease", "pathogenesis", "*Helicobacter pylori*", "lymphocytic gastritis", "lymphocytic duodenitis", "intraepithelial lymphocytes", "clinical presentation", and "epidemiology." Using the mentioned keywords, only those articles, which reported controversial issues on pathological and clinical aspects of CD and *H. pylori* infection were assessed.

Based on the above-reported controversial point of views, in this article we describe an updated review about pathological and clinical correlation between CD and *H. pylori* infection.

### **Lymphocytic gastritis**

Lymphocytic gastritis (LG) is defined by the presence of 25-30 IELs per 100 epithelial cells, without accounting the mononuclear inflammatory cell infiltration of the lamina propria. Studies showed that LG may be associated with both CD and *H. pylori* infection even if this evidence is not unanimously recognized.<sup>10</sup> LG was reported in 36-45% of children with CD, but *H. pylori* infection was reported only in 13% of patients.<sup>28-30</sup> About 38% and 13% of LG cases were associated with CD and *H. pylori* gastritis respectively. A diagnosis of LG should stimulate the exploration for these two disorders.

Previous studies confirmed that LG was more common in *H. pylori* positive children than in *H. pylori* negative ones, both without CD.<sup>31</sup> They reported that duodenal intraepithelial lymphocytosis persisted but LG counts decreased after treatment of *H. pylori* infection. In a study by Broide and colleagues on 40 patients who were candidate for endoscopy, only IELs positive for peculiar CD3 and CD8<sup>+</sup> intraepithelial T-lymphocyte population increased significantly in CD patients with or with-

out *H. pylori* infection.<sup>10</sup> Drut and co-workers concluded that LG was associated with CD in children with IELs positive for CD8, but was not associated with substantial damage to the epithelial cells.<sup>32</sup> Nenna and others suggested that exposure to gluten for long time was a possible trigger of LG.<sup>33</sup> They evaluated gastric and duodenal mucosa of 226 patients with CD and 154 controls. LG was reported in 7% of the patients with CD and no control subjects, while *H. pylori* infection was found in 6 (2.7%) children with CD (16.7% had LG). In other two studies on children and adults, the prevalence of LG was reported 42% and 84%, respectively.<sup>34,35</sup> Similar to Nenna and colleagues, Prasad and co-workers reported that the prevalence of *H. pylori* in patients with CD and LG was 6%.<sup>34</sup> In contrast to previous studies, in 1999 Wu and colleagues showed that out of 103 patients with LG, 33% had concomitant CD compared with only 4.1% with *H. pylori* and therefore declined any association.<sup>36</sup>

Nielsen and co-workers recently supported these data and demonstrated that lymphocytic gastritis was not associated with active *H. pylori* infection.<sup>37</sup> These inconsistent outcomes could also be attributable to different variability of *H. pylori* virulence genes. So, as demonstrated by Genta and colleagues, a particular attention must be paid to other causes of gastric inflammation, and CD must be taken into account when *H. pylori*-negative gastritis is confirmed.<sup>38-40</sup>

### Lymphocytic duodenitis

In the duodenum, the increased number of IELs, lymphocytic duodenitis, can be a primary presentation of CD as well as the epiphenomenon of *H. pylori* infection itself.<sup>41,42</sup> In accordance with the interpretations of Goldstein<sup>43</sup>, Memeo and colleagues, determined that the patterns of distribution of duodenal IELs in patients with *H. pylori* gastritis overlap to a significant range with the patterns described for CD.<sup>21</sup> Remarkably Goldstein reported the non-gluten-sensitive groups with increased IELs, included patients with *H. pylori* gastritis.

Guz-Mark et al. proposed that in children with negative CD, lymphocytic duodenitis is common

and is not expressively affected by *H. pylori* infection.<sup>44</sup> However, this explanation is somehow doubtful as they have evaluated the children with functional recurrent abdominal pain as normal control group. Recent study by Simondi and others, showed that *H. pylori* infection is associated with an increase in IELs count in both patients with CD and in subjects with duodenal intraepithelial lymphocytosis.<sup>23</sup> Losurdo and colleagues demonstrated that, during a 2-year follow-up of 81 patients affected by non-specific duodenal lymphocytosis, 5 (6.1%) were exclusively related to *H. pylori* infection.<sup>45</sup> In contrast Ilus and co-workers reported that co-morbidities such as *H. pylori* gastritis did not contribute to the persistent intraepithelial lymphocytosis among patients with normal villous structure who adhere to a long-term strict gluten-free diet.<sup>46</sup>

### Clinical presentation

Several reports have rejected any correlation between severe abnormal histology and severe clinical and typical presentation like diarrhea, abdominal pain, and malabsorption in patients with CD.<sup>23</sup>

In the study by Nielsen and colleagues, the most common presenting symptoms were GERD/reflux (35%), followed by abdominal pain (31%), and anemia (22%).<sup>37</sup> Spee and co-workers undertook a meta-analysis of 38 studies to examine the relationship between *H. pylori*, functional recurrent abdominal pain, and other gastrointestinal symptoms in children.<sup>47</sup> They concluded that *H. pylori* was not associated with functional recurrent abdominal pain.

In our previous study, out of 450 dyspeptic patients, 91.3% had histology-based evidence of *H. pylori* infection, and the most prevalent symptoms were abdominal discomfort (78%), bloating (71.1%), and heartburn (58%).<sup>18</sup> Our recent study also confirmed the previous one and showed that among the 250 studied patients, 232 (93%) were *H. pylori* positive and high prevalent symptoms including abdominal discomfort (80%), and bloating (73%) were reported in the infected patients.<sup>25</sup> In other study, on 226 children with CD, Nenna and

colleagues, demonstrated that the most frequent symptoms were abdominal pain, diarrhea, abdominal distension, and poor weight gain.<sup>33</sup>

Aydogdu and colleagues, showed that bloating was more common at the time of admission of patients with CD and *H. pylori* gastritis and a gluten-free diet recovers the symptoms in all patients regardless of the presence of *H. pylori* infection.<sup>17</sup> On the other hand, it has been shown that an increased number of IELs can be associated with a variety of other gastrointestinal disorders such as syphilis, hypertrophic gastropathy, Ménétrier's disease, and Crohn's disease.<sup>48-50</sup>

### Epidemiology

Evidence suggests a controversial relationship between *H. pylori* infection and CD (Table 1). Few studies support their association and most of them decline any correlation. Lebowhl and colleagues, have recently proposed the hypothesis of decreased risk of CD in patients with *H. pylori* infection.<sup>22</sup> In their cross-sectional study, gastric and duodenal biopsy samples were collected from 136,179 patients who underwent endoscopy. The authors found contrariwise association and showed that *H. pylori* was significantly prevalent in controls compared with patients with CD (8.8% vs 4.4% respectively,  $p < 0.0001$ ). Other recent study by Simondi et al.,<sup>23</sup> did not show a significant difference in *H. pylori* infection between patients with CD (36%) and controls (41%).

Eighty-one children with CD and 81 matched children without CD were studied by Luzzza and co-workers.<sup>51</sup> The result of this study indicated that 18.5% of patients with CD and 17.3% of controls had *H. pylori* infection and therefore the prevalence and clinical presentation of *H. pylori* infection is not increased in children with CD. Similar prevalence have been reported by Diamanti et al. (89% vs. 97%) and Rostami-Nejad et al. (82% vs. 86%). Despite a high prevalence of *H. pylori* infection found in these two studies, the researchers did not find any relationship between *H. pylori* infection and CD in their study population.<sup>18,19</sup> Crabtree and

**Table 1: Prevalence of celiac disease and *H. pylori* in different parts the world**

Country	<i>H.pylori</i> (%)	Celiac disease
Argentina	36-40	1:67-1:681
Australia	32	1:82-1:125
Brazil	63-66.5	1.66:1000
Bulgaria	52.6	2.65% (in IDDM patients)
Canada	23.1	0.9%
Colombia	60.1	1:67-1:681
Croatia	60.4-68	1:519
Czech Republic	33-48	1:218
Chile	43-92	1:67-1:681
Denmark	25.6	6.9:100000
Estonia	73.87	0.34%
France	16.7	1:940
Germany	9-75	0.3%
Hungary	59	1:166
India	12.76.2	0.3-1.04%
Iran	83-97	1:100
Ireland	43	1:300
Italy	13-67.9	1:106
Japan	29	1:20.000
Kazakhstan	79	NA
Korea	75	NA
Latvia	19	0.35-0.49%
Malaysia	26-55	NA
Mexico	41-90	1:67-1:681
Netherlands	16	1:198
Poland	34.5-78.5	1:404 (in children)
Portugal	52.5-80	1:134
Republic of Belarus	10-76	NA
Romania	69	3.9% (IDDM)
Russia	25-92	NA
Saudi Arabia	51	12:100
Singapore	27.9-48.1	NA
Spain	52-69	1:118
Tunisia	80-85	1:18-1:335
Turkey	42-100	1:87
UK	26-27.6	1:100
Ukraine	43	NA
USA	9-32	1:100-1:200
Yemen	82.2	1:18 (chronic diarrhea)
Zambia	61	1:18-1:335

NA: not available; IDDM: insulin-dependent diabetes mellitus

other specified that although *H. pylori* positivity in patients with CD increased with age, the percentage of *H. pylori* seropositivity was not different from similarly blood donors of the same geographic area.<sup>52</sup> Also Nenna, Jozefczuk and their colleagues, recently confirmed that *H. pylori* infection was more prevalent in controls than in pediatric patients with CD.<sup>33,53</sup> Lasa and co-workers, showed that out of 312 patients who underwent endoscopy, 12.5% of patients with CD compared with 30% of patients without CD were infected with *H. pylori* infection. They established that *H. pylori* infection was less frequent in patients with CD.<sup>54</sup>

On the other hand Konturek and colleagues reported a higher frequency of *H. pylori* in patients with CD than in controls (26% vs. 20%)<sup>16</sup>, while Ciacci and co-workers found that 21% of patients with CD and normal diet, 32% with gluten-free diet, and 55% of controls were infected by *H. pylori*.<sup>20</sup> Similar findings were reported by Aydogdu and colleagues.<sup>17</sup> Data of 96 children with CD and 235 control children who underwent endoscopy showed that 21.8% of patients with CD and 23.8% of controls were infected by *H. pylori* infection. They concluded that CD might be associated with *H. pylori* gastritis, and it affected only bloating as associated presentation.

## CONCLUSION

*H. pylori* is a frequent etiological agent of upper gastrointestinal disorders such as gastritis and peptic ulcer.<sup>55</sup> Even CD is a possible cause of gastric inflammatory conditions.<sup>38</sup> Examinations of the correlation between *H. pylori* infection and CD have yielded discordant outcomes, undoubtedly because of the diverse frequency of *H. pylori* prevalence in different studies.<sup>15-20</sup>

Intraepithelial lymphocytosis may remain unchanged for a long time despite a strict gluten-free diet and normalization of the small intestinal villous structure.<sup>56</sup> For this reason, a careful clinical and laboratory examination of cases of intraepithelial lymphocytosis must be performed to distinguish between gluten-related disorders (CD, gluten sensitivity or seronegative CD) and non-gluten-related conditions.<sup>57,58</sup> Indeed, *H. pylori* gastritis, drugs

such as non-steroidal anti-inflammatory drugs, olmesartan, proton pump inhibitors, and viral gastroenteritis are often associated with increasing intraepithelial lymphocytosis.<sup>59-61</sup> It was illustrated that *H. pylori* infection may be the cause of pathogenesis of LG in patients with CD, and its treatment may reduce the number of IELs, and inflammation of the intestine, thus leading to an improvement of dyspeptic symptoms.<sup>31-36</sup>

In conclusion, different studies demonstrate the prevalence of *H. pylori* infection in CD population is similar to control subjects. Various investigations suggested that histological abnormalities including villous atrophy and endoscopic markers are similar in patients with and without *H. pylori* infection. Although some evidence show a potential preventive role of *H. pylori* in the pathogenesis of CD, further studies are needed to clarify some controversial points about this topic.

## CONFLICT OF INTEREST:

The authors declare no conflict of interest related to this work.

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