Gastrin, Cholecystokinin (CCK) and H. Pylori in Nonulcer Dyspepsia.


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Abstract:

Introduction: One of the etiological causes of nonulcer dyspepsia (NUD) is H. pylori infection. The role of H. pylori infection in dyspepsia and its accompaniment with hormonal disorders remain controversial. We studied the association between existence of H. pylori and variation of Colecystokinin (CCK) and gastrin in NUD patients.

Methods: One hundred consecutive out patients with NUD that referred to Taleghani Hospital in Tehran from May 2002 to January 2003 were studied. Demographic and clinical examinations were fulfilled and basal serum gastrin and CCK level and IgG anti H. pylori were measured. After through endoscopic evaluation, gastric mucosal biopsies were taken from all patients for investigation of H. pylori (Rapid urease test (R.U.T), direct exam and IgG Anti H. pylori tests) and histological assessment.

Results: 100 NUD patients including 48 (48%) male and 52(52%) female were studied. 11 patients were smoker. Fullness (62%) was the predominant symptoms in them. 59% of patients complained of abdominal pain, 57% of early satiety, 42% of anorexia, 17% of dysphagia, 46% of nausea and 20% of vomiting. 78 (78%) of patients were H. Pylori positive.

In H. pylori positive group, the mean± SD of CCK was 1.06± 0.40 and gastrin was 6.68 ± 7.82. In H. pylori negative group the mean ± SD of CCK was 0.92 ± 0.31 and gastrin 8.20 ± 12.58. There was no significant difference in gastrin and CCK serum level between H. pylori positive and H. pylori negative in nonulcer dyspeptic patients.

Conclusion: According to high frequency of H. pylori in NUD patients, the investigation of patients for the presence of H. pylori in patients is recommended. We didn’t find any relation between H. pylori infection and the serum level of gastrin and CCK in NUD patients.

Keywords: H. pylori, NUD, Gastrin , CCK.
Introduction:

Dyspepsia is persistent or recurrent pain or discomfort centered in the upper abdomen.\(^1\) For dyspepsia to be considered chronic, symptoms should be present for at least 3 months. Of patients with chronic dyspepsia 50% to 70% do not have a significant focal or structural lesion identified at upper endoscopy. These patients are labeled as having functional dyspepsia.\(^1\) The pathogenesis of none ulcer dyspepsia is unclear. Although a possible role for Helicobacter pylori (H. pylori) infection in functional dyspepsia is suggested by several potential pathogenic mechanisms, a clear association among these factors, H. pylori, and functional dyspepsia has not been established.\(^2\) H. pylori infection is closely related to gastrointestinal hormones and involves the formation of gastritis, gastric carcinoma and peptic ulcer.\(^3\) H. pylori infection is usually accompanied by an increased plasma level of gastrin.\(^4\) Gastrin is a basic stimulus to parietal cells in producing gastric acid, and show two ways in acid production: one directly stimulates parietal cell and the other acts on enterochromaffin-like (ECL) cell to release histamine by which stimulates parietal cells. H. pylori infection in patients leading to increased release of gastrin from antral G cells and hypergastrinemia formation is currently an interesting medical problem.\(^3\)

Since the discovery of cholecystokinin (CCK)\(^5\) of its action on the gallbladder and structural characterization\(^6\), similar to the closely-related peptide, gastrin and its acid-releasing activity\(^7\) and structural characterization there have been many studies to attempt to define their roles in both physiological and pathological gastrointestinal processes.\(^8\)-\(^11\) There are different ideas about the relationship between H. pylori infection with the serum level of CCK and gastrin.\(^12\)-\(^14\)

Therefore, we evaluated the relationship between H. pylori infection and gastrin and CCK, which may be important pathophysiologic factors in NUD.

Materials and Methods:

Patients (Study site and selection of participants): 250 consecutive outpatients with dyspepsia who referred to endoscopy clinic of Taleghani Hospital in Tehran, Iran, from May 2002 to January 2003, were underwent upper GI endoscopy. 100 of 250 patients met
the inclusion criteria and signed the informed consent. All patients underwent careful history taking and physical examination. 
Inclusion criteria were 1) Presence of dyspepsia symptoms for ≥3 months according to have two or more symptoms such as early satiety, postprandial fullness, delayed emptying sense, nausea, vomiting and epigastric pain.\(^6\) 2) Absence of clinical, biochemical, or radiological evidence of organic causes and absence of symptoms predominantly suggesting gastroesophageal reflux disease. If the patient had 1) history of existence obvious sign and symptoms of reflux and heartburn, 2) definite disease, 3) using antibiotic during two previous weeks, 4) taking Omeprazol during one previous week excluded from the study.

The aim of study was described for each patient. After completion informed consent, two doctors of research center of gastroenterology to assess symptoms interviewed all participants. The questionnaire consisted of questions that pertained to the sociodemographic profile of each patient (age, sex, smoking behavior, the intake of antibiotics), the dyspepsia symptoms and the past medical history of dyspepsia. Then patients underwent upper GI endoscopy.

**Upper GI Endoscopy:** All of the patients underwent the upper GI endoscopy by gastroenterologist or fellowship of gastroenterology. Endoscopy was performed by standard procedures after an overnight fast, using Olympus and Pentax Video endoscopes, which were sterilized with glutaral disinfectant 2% solution for 20-30 minutes. If there was not any ulcer or esophagitis in endoscopy, three mucosal biopsies were taken from the antrum, body and angularis. The biopsy forceps were sterilized in glutaral disinfectant between patients. These biopsy samples were investigated for the presence of the H. Pylori according to the rapid urease test (RUT), direct observation. The specimens for histological assessment was placed in 10% formalin and sent for standard histopathologic examination by a single pathologist.

**Helicobacter pylori infection:** R.U.T, Anti-H. pylori immunoglobulin (IgG) and direct exam tests were used for detection of the H. pylori\(^{15}\). One positive result in each test was considered as H. Pylori positive and negative results in all tests were considered as H. pylori negative.

**Laboratory exams:** Whole blood was obtained from all participants for checking of gastrin, CCK and anti H. pylori immunoglobulin (IgG). All
fasting blood was taken before the endoscopy. All of blood samples were centrifuged and serum of them was frizzed in –70 C. Anti-H. pylori immunoglobulin (IgG) was determined by EIA, Genesis kit, UK. (X1: 6.2, SD: 0.4895, CV: 7.9%, X2: 29.8, SD:1.9837, CV: 6.7%) Basal serum Cholecystokin in was determined by RIA, Euro Diagnostica kit, Sweden. (X1: 3.4, SD: 0.3356, CV: 9.9%, X2: 22.3, SD: 2.3761, CV: 10.7%) Basal serum Gastrin was determined by ELIZA, BIOHIT kit, Finland. (X1: 10.3, SD: 0.9633, CV: 9.4 %, X2: 31.6 , SD:3.0567, CV: 9.7%)

**Statistical Analysis:** All above-mentioned data will be filled in data sheet with SPSS for Windows Version 11 software. Student t Test was used for data analysis.

**Ethical consideration:** The protocol was approved by the RCGLD (Research center of Gastroenterology department) ethics committee at Shaheed Beheshti University, and a written informed consent was obtained from each patient at the time of enrollment. All of these examinations and evaluations were free and the results of tests where given back to the patients.

**Results:**

A total of 100 Non ulcer dyspeptic patients referred to the Taleghani’s Hospital clinic of endoscopy, the Shaheed Beheshti University of Tehran, Iran which they had the inclusion criteria, enrolled in the study. Of the enrolled patients, 48 (48) patients were male and 52 (52) of them were female. 11 patients (11%) was smoker and 5 patients (5%) had the history of taking alcohol. 7% of them was drug abuser. The frequency of different age groups in dyspeptic patients was shown in table 1.

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>valid percent</th>
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<tbody>
<tr>
<td>&gt;25</td>
<td>24 (24)</td>
<td>24</td>
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<tr>
<td>26-45</td>
<td>43 (43)</td>
<td>43</td>
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<tr>
<td>46-65</td>
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<td>&gt;65</td>
<td>7 (7)</td>
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<tr>
<td>Total</td>
<td>100 (100)</td>
<td>100</td>
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</table>

Figures in parentheses are percentages.

Among the patients with nonulcer dyspepsia, fullness (62%) was the predominant symptoms. 59 patients (59%) complained of abdominal pain, 57 patients (57%) of early satiety, 46 patients (46%) of nausea, 42 patients (42%) of anorexia, 20 patient (20%) of vomiting and 17 patients (17%) of dysphagia.

78 patients (78%) were H. pylori positive according to Rapid urease test (R.U.T), Anti-H. pylori
immunoglobulin (IgG) and direct exam tests that 40 patients were male and 38 patients were female. Abdominal pain in 9% of patients was before food and in 31% of patients was immediately after food. 49% of patients had previous history of dyspepsia in their past medical history that 48% of them tried for treatment. 37 patients (37%) had at least one dyspeptic patient in their relatives that 11 cases (11%) had seen in father, 15 cases (15%) in mother, 1 case (1%) in brother, 5 cases (5%) in sister, 1 case (1%) in child.

H. pylori infection: 78 patients (78%) were H. pylori positive. 40 patients were male and 38 patients were women. The frequency of H. pylori infection in different age groups is shown in table 2. No significant difference in H. pylori positive and negative was found between men and female.

Serum Gastrin and CCK level: In H. pylori positive group, the mean ± SD of CCK was 1.1±0.40 and gastrin was 6.7 ± 8.2. In H. pylori negative group the mean ± SD of CCK was 0.9 ± 0.3 and gastrin 8.2 ± 12.6. No significant statistical differences between H. pylori negative and positive group in serum gastrin and CCK level was found. (Table 2)

<table>
<thead>
<tr>
<th>Table 2: The frequency of Helicobacter pylori infection in different age groups, sex, hormonal changes in nonulcer dyspepsia.</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
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<td>Female</td>
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<td><strong>Age</strong></td>
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<td>&gt;66</td>
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<tr>
<td><strong>Hormones</strong></td>
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<tr>
<td>Gastrin (pg/ml)</td>
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<tr>
<td>Cholecystokinin (pmol/L)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentage or standard deviation.

Discussion:

In some studies, the role of Helicobacter pylori infection in nonulcer dyspepsia was described but the role of H. pylori infection in dyspepsia and its accompaniment with serological findings remain controversial. In one study, it is suggested that delayed gastric emptying is partly associated with H. pylori infection and that the infection may contribute to the development of non-ulcerative dyspepsia. In our study, fullness was the the
most frequent symptom in nonulcer dyspeptic patient that was seen in one half of patients. The most frequent symptom in nonulcer dyspeptic patients in another study was fullness, early satiety, bloating and nausea.\(^{(17-18)}\) In one study said that the H. pylori infection and increasing of basal serum level of gastrin, accompanied with gastrointestinal symptoms.\(^{(3)}\)

In our study one fifth of patients had mucosal erythema in endoscopy that about 75 percent of them were H. pylori positive. Endoscopic features associated with H. pylori were a vascular pattern, edema, rugal hypertrophy, nodularity, rugal atrophy, erythema with reddish streaks excluded, flat erosions, and exudate.\(^{(19)}\)

In one study, it was seen that the frequency of gastritis after H. pylori infection in nonulcer dyspepsia was about one half of cases.\(^{(2)}\) Serology and histological assessment for H. pylori infection assessment was used in this study. Some different methods of detection of H. pylori consist of culture of H. pylori, PCR, rapid urease test, and urea breath test.\(^{(21)}\) Use of more than one test increases the specificity of detection of H. pylori.\(^{(22)}\) Usage of more tests may increase our test accuracy. In one study invasive tests (culture, histological assessment and rapid urease test) with non-invasive test (serology and urea breath test) was used for H. pylori infection detection.\(^{(23)}\)

In our study 78 percent of nonulcer dyspeptic patients was H. pylori positive. H. pylori infection was a frequent chronic bacterial infection in human that was seen in any age.\(^{(24-25)}\) There was many studies about the presence of the relation between dyspepsia symptoms and H. pylori infection.\(^{(20, 26-29)}\) The reduction of dyspepsia symptoms after H. pylori eradication is the most reason for the presence of this relationship.\(^{(29)}\) H. pylori had exact relation with GI hormones, gastritis, gastric cancer and gastric ulcer.\(^{(3)}\)

CCK is known to effect gastric secretary and motor functions.\(^{(30)}\) CCK has been implicated in the feedback control of gastric acid secretion\(^{(31)}\) gastrin and somatostatin release\(^{(30)}\) in healthy subjects. The interaction between gastrin and H. pylori was shown to be specific, essential and dependent on defined gastrin sequence.\(^{(33)}\)

Competition for the gastrin effect by pentagastrin and cholecystokinin (CCK-8) resulted in inhibition of bacterial growth. This effect was mediated by the four C-terminal amino acids that are shared by gastrin, CCK-8 and pentagastrin. The interaction between gastrin and H. pylori was shown to be specific, essential, and dependent on a
defined gastrin sequence.\textsuperscript{(34)} In the patients whose infection was eradicated, serum gastrin decreased significantly, but the CCK level did not change significantly, although there was a non–significant trend for CCK to increase.\textsuperscript{(16)}

The gastric meal and CCK enhance the release of leptin in H. pylori positive patients and this leptin is capable of inhibiting basal and meal-stimulated gastric H+ secretion, while raising plasma gastrin and reducing the plasma CCK levels. The eradication of H. pylori reduces the postprandial gastric H+ and plasma gastrin responses as well as the release of leptin in response to CCK and meal.\textsuperscript{(35)} H. pylori infection seemed not to cause alternations in gastric emptying, but rather alternations in gastrin levels. In contrast, the altered levels of CCK account for its involvement in the pathophysiology of H pylori negative dyspepsia.\textsuperscript{(13)}

In our study the mean basal serum levels of gastrin and CCK were higher than normal but there was not any significant statistical difference between H. pylori positive and negative groups. The role of H. pylori infection in dyspepsia and its accompaniment with serological findings remain controversial. According to some study, H. Pylori infection induces increased release of gastrin\textsuperscript{(12,13)} and CCK and causes somatostatin deficiency in patients with nonulcer dyspepsia and the level of gastrin was higher in H. pylori positive than H. pylori negative subjects.\textsuperscript{(12)} But in another study there was no significant difference in the serum gastrin level between H. pylori positive patients and H. pylori negative patients. They reported that the inhibitory effects of cholecystokinin on gastrin release were induced by H. pylori infection.\textsuperscript{(14)}

In conclusion, H. pylori infection is a frequent infection in nonulcer dyspeptic patients. Although the mean basal serum level of gastrin and CCK in nonulcer dyspepsia is higher than normal, but there are not significant difference in H. pylori positive and negative patient in nonulcer dyspepsia.

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**References:**


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