

The effect of Helicobacter pylori eradication on symptoms and gastric emptying in patients with non-ulcer dyspepsia

Helicobacter pylori eradikasyonunun nonülser dispepsili hastalarda semptomlara ve mide boşalım zamanına etkileri

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Background/aims: This study was undertaken to evaluate the effect of eradication therapy on the symptoms of Helicobacter pylori positive non-ulcer dyspepsia patients. **Methods:** Twenty-four patients participated in the study and the symptoms of daytime epigastric pain, night or hunger pain, nausea, vomiting, regurgitation, bloating, belching, early satiety and anorexia were scored at the beginning, the 15th day after starting eradication therapy (amoxicillin 2 gr bid, clarithromycin 2 gr bid and omeprazole 40 mg daily for two weeks) and during the third and sixth months. Gastric emptying of radiolabelled solid meal was determined at baseline and during the third month. **Results:** The Helicobacter pylori eradication rate was 79% and symptom scores significantly decreased during the follow-up period in both of the groups, irrespective of Helicobacter pylori status. The mean symptom scores of the 24 patients at baseline, day 15 and at months three and six were as follows: 1.275, 0.274, 0.496 and 0.238 respectively. Symptom scores for the 19 patients with Helicobacter pylori eradication were 1.084, 0.263, 0.347 and 0.215 respectively while in the five patients in whom Helicobacter pylori eradication therapy failed it was 2.0, 0.314, 1.06 and 0.32 respectively. Of the 16.6% Helicobacter pylori positive non-ulcer dyspepsia patients who had delayed gastric emptying of solids, there was no change after eradication therapy. Nine patients, including all of those in whom eradication therapy failed, required further medication (antacids/prokinetics) for continuing symptoms one month after completion of treatment. **Conclusions:** The results of this study suggest that Helicobacter pylori is a causal factor in symptoms of non-ulcer dyspepsia and that eradication therapy improves symptoms and endoscopic findings but has no effect on gastric emptying.

Key words: Helicobacter pylori eradication, non-ulcer dyspepsia symptoms, gastric motility.

Amaç: Bu çalışmanın amacı Helicobacter pylori (+) non-ülser dispepsili hastalarda semptomlara etkisini araştırmaktır. **Yöntem:** Bu çalışmada 24 (18'i kadın, ortalama yaş: 39.7 yıl) Helicobacter pylori (+) nonülser dispepsili hastaya, gündüz epigastrik ağrı, gece veya açlık ağrısı, bulantı, kusma, regürjitasyon, şişkinlik, geyirme, erken doyma, iştahsızlık semptomları başlangıçta, eradikasyon tedavisi (amoksisilin 2 gr/gün, klaritromisin 1 gr/gün, omeprazol 40 mg/gün 2 hafta) başlanmasından sonra 15. gün, 3. ve 6. aylarda skorlandı. Mide boşalımına başlangıçta, ve 3. ayda radyoaktif işaretli katı yemekle bakıldı. **Bulgular:** Helicobacter pylori eradikasyon oranı %79 idi. 24 hastanın ortalama semptom skorları başlangıçta, 15. gün, 3. ay ve 6. aylarda sırası ile; 1.275, 0.274, 0.496 ve 0.238, Helicobacter pylori eradike edilebilen 19 hastada; 1.084, 0.263, 0.347 ve 0.215, eradikasyonun başarısız olduğu 5 hastada; 2.0, 0.314, 1.06 ve 0.32 idi. Helicobacter pylori (+) nonülser dispepsili hastaların %16.6'sında katılar için gecikmiş mide boşalımı saptandı, eradikasyon tedavisi sonrasında ise değişiklik olmadı. Eradikasyonun başarısız olduğu hastaların hepsi dahil, 9 hasta tedavinin tamamlanmasından 1 ay sonrasında semptomlar nedeni ile ilaç (antiasit/prokinetik) almak zorunda kaldı. **Sonuç:** Bu çalışmanın sonuçları; Helicobacter pylori'nin nonülser dispepside potansiyel bir rol oynadığını, eradikasyonun semptomlar ve endoskopik bulguları düzelttiği fakat mide boşalımını etkilemediğini gösterdi.

Anahtar kelimeler: Helicobacter pylori eradikasyonu, nonülser dispepsi semptomları, gastrik motilite

INTRODUCTION

Dyspepsia occurs in 25-30 % of the general population and in 50% of these people, no peptic ulcer, eosophagitis, cancer or other organic disease is found and they are therefore diagnosed as non-

ulcer dyspepsia (NUD). Helicobacter pylori (H. pylori) is the most common gastrointestinal bacterial disease in the world. It has been shown that infection is associated with chronic active gastri-

tis, duodenal ulcer, gastric ulcer, gastric carcinoma and low grade MALT-B cell lymphoma etiopathogenesis (1,2). Many studies have been undertaken to evaluate the potential etiological relationship between NUD and H. pylori and the following questions in particular are being investigated:

1. What is the prevalence of H. pylori in cases with dyspeptic complaints, compared with the general population?
2. Is there a relationship between specific subgroups of NUD and H. pylori?
3. How does eradication of H. pylori infection in the patient with NUD affect symptoms and gastric physiology?

In this study, the effect of eradication therapy on symptoms and gastric emptying was evaluated in H. pylori positive NUD patients. In particular, the following questions were considered:

- a. is there any etiological relationship between H. pylori and NUD?
- b. is H. pylori eradication necessary in such patients?

MATERIALS AND METHODS

The study included 24 patients attending Ankara University Gastroenterology Department diagnosed as H. pylori positive NUD between June 1997 and January 1999. Patient evaluation included detailed history taking, physical examination, upper gastrointestinal endoscopy and abdominal ultrasonography. Hematologic and chemical analyses were also performed. A diagnosis of NUD was made according to the following criteria:

1. A history of specific dyspeptic symptoms, or upper abdominal pain or discomfort either continuously or episodically for at least three months.
2. Exclusion of esophageal, gastric or duodenal ulcer on endoscopic examination
3. Normal ultrasonography.
4. Exclusion of organic, systemic, metabolic or psychiatric disease
5. Exclusion of a history of peptic ulcer, chronic nonsteroidal antiinflammatory drug usage and abdominal surgery, except appendectomy.
6. Exclusion of gastroesophageal reflux disease or irritable bowel disease.

None of the patients were drug users and none had received previous eradication therapy. In the three days prior to commencement of the study, none of them took any medicine. Amoxicillin 1 g bid, clarithromycin 500 mg bid and omeprazole 20 mg bid was prescribed to all patients for two weeks. Symptoms were evaluated prior to the study and on the 15 th day, third month and sixth month. This consisted of a questionnaire about the presence, duration and severity of five dyspeptic symptoms: daytime epigastric pain, night-time or hunger type epigastric pain, nausea and vomiting, regurgitation and upper abdominal discomfort (early satiety, bloating, belching, anorexia).

These symptoms were scored as 0=absent, 1=one or two times per week but not interfering with daily activity or feeling well with medicine, 2=several times per week, interfering with daily activity.

The NUD patients were divided into subgroups as follows:

1. Dysmotility like dyspepsia (DLD): Epigastric pain, discomfort and two or more of the following symptoms; nausea and/or vomiting, early satiety and/or anorexia, postprandial fullness, belching
2. Reflux like dyspepsia (RLD): Pyrosis and/or acid regurgitation with epigastric pain or discomfort.
3. Ulcer like dyspepsia (ULD): Hunger and/or night-time localised epigastric pain, periodic pain and improvement of pain with food or antacids consumption.

Endoscopy with a GIF-K 20 gastroscope was performed initially and three months after the treatment period, during which antral biopsies were taken for histological and microbiological examination (Gram stain, culture and rapid urease test).

Assessment of gastric emptying of solids and liquids was made at the Nuclear Medicine Center on two different days with a 24 hour interval. Solid emptying time was calculated by taking static images in the anterior and posterior position for two hours at 10 minute intervals after giving a standard test meal mixed with 500 microcuri (8.15MBq) of sulphur colloid. The next day, 500 microcuri Tc-99m of sulphur colloid was given in 200 ml liquid and gastric emptying time was calculated. The normal T1/2 for laboratory was 45-90

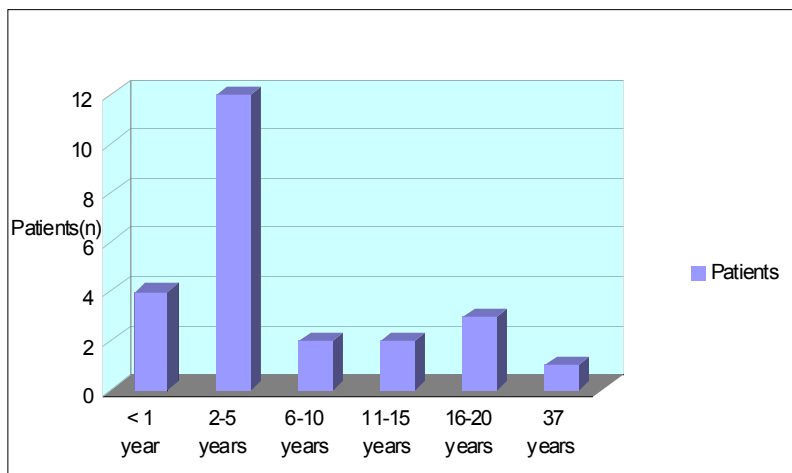


Figure 1. Distrubition of patients according to symptom duration

minutes for solids, and five-30 minutes for liquids. Higher values were evaluated as delayed emptying time.

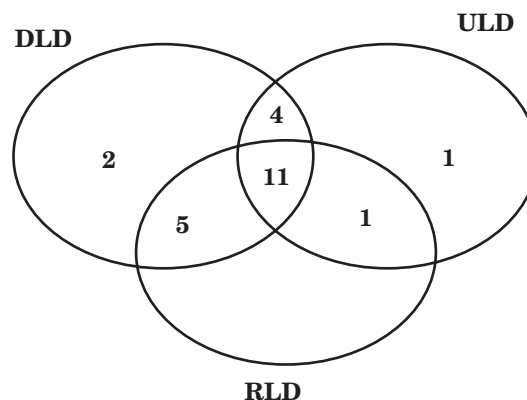
Statistical Analysis was made by using SPSS for Windows Mean age, symptom duration, symptom score (at the beginning, 15th day, third month, sixth month) and emptying time for solids and liquids was quoted as mean±SE. Mann Whitney-U test was used to compare the duration of symptoms in the H. pylori eradication and non-eradication groups. Friedman test was used to evaluate the difference in symptom scores at four different times in all of the groups and in the H. pylori group, eradication was successful. The effect of Helicobacter pylori infection eradication on the mean symptom score initially and during the observation period was analysed with Student’s t test. In the group with delayed gastric motility, initially and at the sixth month, the difference in mean gastric emptying time was analysed initially and at the sixth month with Wilcoxon-Rank-Sum. Student’s t test was used to investigate any difference between the two groups (H. pylori eradication or non-eradication) at the beginning of the study and p<0.05 was accepted to be significant in all analyses.

RESULTS

Six (25%) of the patients were men and 18 (75%) were women with a mean age of 39.7 years (range 18-65). Patients’ symptom durations are shown in Figure 1.

The H. pylori eradication rate was 79%. In the five patients in whom eradication therapy failed, the mean age was 48.5±5.35 years and mean symptom duration was 100.8±9.0 months (=8.4 years), while in those where eradication therapy was successful, the mean age was 38.05±12.32 and mean symptom duration was 68.4±108.4 months. The difference between the groups was not significant (p>0.05).

Patient distribution according to subgroups of dyspepsia are shown in Figure 2.



DLD: Dysmotility like dyspepsia
 ULD: Ulcer like dyspepsia
 RLD: Reflux like dyspepsia

Figure 2. Distribution of patients according to subgroups of dyspepsia

Table 1. Evaluation of mean symptom scores in follow-up period

Patients (n)	At start	15 th day	3 rd month	6 th month
Helicobacter pylori eradication achieved (n=19)	1.084±0.307	0.263±0.313	0.347±0.431	0.215±0.291
Helicobacter pylori eradication failed (n=5)	2.0±1.456	0.314±0.271	1.06±0.343	0.320±0.363
Total (n=24)	1.275±0.76	0.274±0.3	0.496±0.5	0.238±0.301

One of the patients in whom H. pylori eradication therapy failed was in the ULD group while the other four were DLD+ULD+RLD. Four of the patients were smokers and eradication therapy was successful in all of them.

On initial endoscopic examination, 17 (70.83%) patients had gastritis and/or duodenitis, but at three month follow-up, only three (12.5%) had gastritis and/or duodenitis. All patients in whom H. pylori was successfully eradicated and three patients in whom it was not had normal endoscopy findings at three month follow-up, with only one patient with unsuccessful H. pylori eradication showing no improvement in endoscopy findings. Table 1 and Figure 3 show mean symptom scores during the follow-up period.

Mean symptom scores of the 24 patients were statistically different at the four different times ($\chi^2=54.576$, $p=0.000$) and in the 19 patients with H. pylori eradication, this difference was significant ($\chi^2=42.487$, $p=0.000$). When patient symptom scores for two different times were compared, although the 15th day and sixth month differences between the H. pylori eradicated and non-eradicated group were insignificant, they were significantly different for other times. When the symptom scores of patients with successful H.

pylori eradication therapy were compared for different times, all of them were significant (Table 2).

When the symptom scores of patients with successful and failed H. pylori eradication were compared, the initial and 3rd month mean symptom score was significantly lower in the successful than the failed eradication group ($p=0.0015$ vs $p=0.008$), but the 15th day and 6th month score differences were insignificant ($p=0.739$ vs $p=0.572$).

Mean gastric emptying time of solid meal for all patients was 70.4±23.9 minutes (45-135 minutes) and for liquids 12.04±5.3 minutes (5-30 minutes). In four of the patients, solid gastric emptying times were longer, with a mean value of 110.2±18.9 minute. At three month follow-up, the mean emptying times for solids and liquids were 110.0±11.5 and 12.0±3.5 minutes respectively. There was no significant difference between the baseline and three month follow up period ($p=0.713$ for solids, $p=0.317$ for liquids).

Three of the patients with motility disorder were in DLD+RLD+ULD group and one in the RLD+ULD subgroup of NUD: H. pylori was not eradicated in only one of the patients with motility disorder. When the mean gastric emptying

Table 2. Comparison of symptom scores at different times

Symptom scores that are compared	Symptom score in all patients (n=24)	Symptom score H. pylori eradicated (n=19)
Start and 15 th Day	1.275 ve 0.274 $p=0.000$	1.084 ve 0.263 $p=0.000$
Start and 3 rd Month	1.275 ve 0.496 $p=0.000$	1.084 ve 0.347 $p=0.000$
Start and 6 th Month	1.275 ve 0.238 $p=0.000$	1.084 ve 0.215 $p=0.000$
15 th Day and 3 rd Month	0.274 ve 0.496 $p=0.008$	0.263 ve 0.347 $p=0.176$
15 th Day and 6 th Month	0.274 ve 0.238 $p=0.600$	0.263 ve 0.215 $p=0.509$
3 rd Month and 6 th Month	0.496 ve 0.238 $p=0.03$	0.347 ve 0.215 $p=0.039$

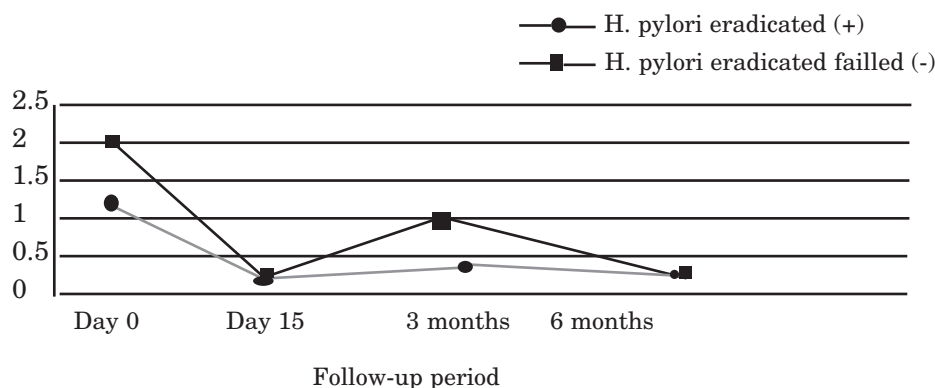


Figure 3. Evaluation of mean symptom scores of *H. pylori* eradicated or not in follow-up period

times for solids and liquids were compared in groups with and without successful eradication therapy, no significant difference was found ($p > 0.05$, $p > 0.05$).

A total of nine (37.5%) patients, including the five (100%) with unsuccessful *H. pylori* eradication therapy and four (21.05%) where *H. pylori* eradication was achieved, required further medication (antacid or H_2 receptor blocker) during the follow up period due to continuing symptoms.

DISCUSSION

Non-ulcer dyspepsia has a prevalence of 7-41% (3) in the population. *Helicobacter pylori* is two three times more common in NUD cases than in normal individuals (2). Symptoms of NUD may be severe whatever the endoscopic findings and can continue despite treatment with antisecretory agents (4). The pathophysiology of the disease is thought to include motility disorder, psychologic factors and gastroduodenal mucosal inflammation gastrointestinal hypersensitivity. Unless these etiologic factors are addressed, treatment is unlikely to be successful. The reported prevalence of *Helicobacter pylori* in NUD ranges from 34% to 87% in clinical studies (5,6). Since the aim of this investigation was to evaluate the effect of triple eradication therapy and as there is a high prevalence of *Helicobacter pylori* in Turkey, only *H. pylori* positive patients with NUD were included in the study.

In many studies, *H. pylori* seroprevalence has been found to be similar in ULD, RLD and DLD subgroups. There is no symptom profile specific to NUD (2,7). In our study most of the cases (83.3%)

were in more than one subgroup. Talley et al (8) investigated subgroups of dyspepsia in a 30-64 years old population and found that 66 % had combined symptoms while with 43% being in more than one subgroup and 23% being defined as non-specific dyspepsia. However, *H. Pylori* status was not determined in this study. Perri et al (5) also suggested that classification criterias have little value in practice and that NUD can not be divided into simple and specific subgroups. There is a wide range of symptoms in NUD and according to many studies, there appears to be no specific symptom of bacterial infection. In Dağlı et al's study, *H. pylori* positive patients were reported to have significant chronic dyspepsia, epigastric pain and burning while *H. pylori* negative patients had more significant postprandial and night abdominal discomfort symptoms (9). Tucci et al. found epigastric pain and burning to be more common in *H. Pylori* positive patients and postprandial fullness more common in *H. pylori* negative cases (10). In another study from Belgium (5), *H. pylori* positive NUD patients' predominant symptom was epigastric pain and these cases had normal gastric emptying time. Patients with the predominant symptom of abdominal discomfort however, had delayed gastric emptying time. All of our cases were *H. pylori* positive and there was no predominant symptom.

In the literature there are several studies evaluating the effects of *H. pylori* suppression and eradication on symptoms. Although most of them reported an improvement in symptoms following eradication therapy, the nature of decreasing symptoms is unclear and results are conflicting due to different follow up periods (in particular,

short follow-up periods) failure of bacteria eradication, diagnostic criteria for NUD and inadequate study protocols. In this study a six month follow up period was considered appropriate to properly evaluate treatment given the chronic nature of NUD and H. pylori infection.

In Talley's study, 16 investigations were evaluated, and he reported that eight of them found eradication treatment to be successful while the other eight did not (11). In some studies, treatment with colloidal bismuth subcitrate has been reported to result in a decrease in symptom score and histological recovery in short periods (such as one month) (4,12). Marshal et al (13) reported a 65% suppression in symptoms rate with colloid bismuth subcitrate in their placebo controlled study; after one month the symptom score was lower in the suppressed group than the others. Trespi et al (14) reported that H. pylori colonisation was more intensive in ULD and RLD subgroups than a DLD group and found more significant symptom improvement at three and six month follow-up in the ULD group. Thus they suggested that H. pylori has an effect on symptoms in ULD and RLD groups but that in DLD, there are different mechanisms. There is no Turkish study to date about the long term effect of H.pylori eradication on symptoms in NUD. Studies with short follow-up periods (one-two months) have mostly found symptomatic improvement after eradication therapy (15-17). Also, most of them report that symptomatic improvement was also seen in groups where H. pylori was not eradicated.

In Sheu et al's study (18) with triple therapy, a 75% *Helicobacter pylori* eradication rate was obtained and at two, six and 12 month follow up, symptomatic and histologic improvements were significant in the H. pylori group with H. pylori eradication. Another study reported that with triple therapy, eight week follow-up results were similar in two groups (eradication and non-eradication) (19).

It may be concluded that if H. pylori eradication therapy is unsuccessful, symptomatic improvement lasts for a short period, whereas successful eradication therapy results in a long period of symptomatic improvement. Thus, long follow-up period results are more important. In this study with two weeks triple therapy the eradication rate was 79.1%. In two different studies (20,21) with a one year follow up period of H. pylori positive NUD patients the eradication rate with triple

therapy (omeprazole+two antibiotics) was reported as 79%. After a year, all patients were evaluated for bacteria eradication, improvement of dyspeptic complaints and quality of life. Blum et al (20) reported that improvement of dyspepsia in the omeprazole and omeprazole+antibiotics group were 21% and 27% respectively and that the difference found to be insignificant. Recovery of gastritis was 75% in the triple therapy group, but only 3% in the omeprazole only group and it was suggested that H. pylori does not have a major role in NUD. Mc Coll et al. reported that symptomatic improvement in an omeprazole+antibiotics group was 21%, but only 7% in an omeprazole group and this difference was found to be significant (21). Also the rate was 12% in patients with symptom duration over five years but 27% with a duration period below five years. In our cases, the mean symptom duration was longer, in the H. pylori eradication group it was 5.7 years and in the other group it was 8.4 years. Patients with successful eradication therapy were younger than those where it failed (mean age: 38 vs 48.5 years respectively). Given that H. pylori infection usually occurs in early childhood in Turkey, the finding of failure of eradication therapy in the group with longer symptom duration and older patients is to be expected.

In 70.83% of our cases, endoscopy revealed gastritis and/or duodenitis, while at three month follow-up it was only 16.6%. Symptom scores at the 15th day, third and sixth months were significantly different from the beginning. We suggest that even in patients where eradication therapy failed, proton pump inhibitors other antacids or H₂ receptor blockers prescribed for symptoms later, might be responsible for symptomatic and endoscopic improvement. These drugs might have had a placebo affect or decreased bacteria colonisation might have helped to decrease the symptoms. Although all (100%) of the patients in whom H. pylori eradication failed were prescribed medication after, it was required in only 21% of the other group Gastric emptying time was found to be delayed in four (16.6%) of our patients and after bacterial eradication, the emptying time did not differ. We therefore believe that H. pylori does not affect motility disorders.

For a long time gastrointestinal motility was thought to be responsible for symptoms in some patients with dyspepsia, but no study has proved any clear relationship between H. pylori and

motor abnormality. There are some reports of normal gastric emptying time in *H. pylori* infection (22,23). Wegener et al (24) and Pieromica et al (25) reported postprandial hypomotility in NUD patients, independent of *H. pylori* status and other investigators have reported similar results. Tucci et al (10) reported a delayed gastric emptying rate of 40% in NUD compared with healthy controls. In *H. pylori* negative cases, gastric emptying time for solids was delayed by 70%, whereas it was 20% in *H. pylori* positive cases. Soslow et al (26) reported that *H. pylori* decreased gastric accommodation but did not change gastric motor and sensory functions. In Turkey, Sarıçam et al (27) reported that *H. pylori* did not affect gastric emptying time, while in another study with 73%

Helicobacter pylori prevalence in NUD, they found a higher symptom score and longer gastric emptying time in the *H. pylori* infected group. This is in contrast to our findings that after eradication therapy there was a shortening of gastric emptying time (15).

In conclusion, the present authors believe that *H. pylori* plays a potential role in the symptoms of NUD. Although eradication of *Helicobacter pylori* improves symptoms of dyspepsia and endoscopic findings, it does not affect gastric motility. Symptomatic improvement in patient's with treatment failure may have been due to a decrease in bacteria colonisation and/or acid suppressant therapy.

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