

• *H pylori* •

Effects of *Helicobacter pylori* infection on gastric emptying rate in patients with non-ulcer dyspepsia

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Abstract

AIM: The pathogenesis of delayed gastric emptying in patients with non-ulcer dyspepsia (NUD) remains unclear. We aimed to examine whether gastric emptying rate in NUD patients was associated with *Helicobacter pylori* (*H pylori*) infection and whether it was affected by eradication of the infection.

METHODS: Gastric emptying rate of a mixed solid-liquid meal was assessed by the paracetamol absorption method in NUD patients and asymptomatic controls ($n=17$). *H pylori* status was assessed by serology and biopsy urease test. *H pylori*-positive NUD patients ($n=23$) received 10-day triple eradication therapy. *H pylori* status was re-assessed by biopsy urease test four weeks later, and if eradication was confirmed, gastric emptying rate was re-evaluated.

RESULTS: Thirty-three NUD patients and 17 controls were evaluated. NUD patients had significantly delayed gastric emptying compared with controls. The mean maximum plasma paracetamol concentration divided by body mass (C_{max}/BM) was 0.173 and 0.224 mg/L·kg respectively ($P=0.02$), the mean area under plasma paracetamol concentration-time curve divided by body mass (AUC/BM) was 18.42 and 24.39 mg·min/L·kg respectively ($P=0.01$). Gastric emptying rate did not differ significantly between *H pylori*-positive and *H pylori*-negative NUD patients. The mean C_{max}/BM was 0.172 and 0.177 mg/L·kg respectively ($P=0.58$), the mean AUC/BM was 18.43 and 18.38 mg·min/L·kg respectively ($P=0.91$). Among 14 NUD patients who were initially *H pylori*-positive, confirmed eradication of the infection did not significantly alter gastric emptying rate. The mean C_{max}/BM was 0.171 and 0.160 mg/L·kg before and after *Hp* eradication, respectively ($P=0.64$), the mean AUC/BM was 17.41 and 18.02 mg·min/L·kg before and after eradication, respectively ($P=0.93$).

CONCLUSION: Although gastric emptying is delayed in NUD

patients compared with controls, gastric emptying rate is not associated with *H pylori* status nor it is affected by eradication of the infection.

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INTRODUCTION

Dyspepsia is defined as pain or discomfort centered in the upper abdomen, according to the Rome II criteria^[1]. Discomfort refers to a subjective, unpleasant feeling that the patient does not interpret as pain and which can include any of the following: upper abdominal fullness, early satiety, bloating, or nausea. Functional or non-ulcer dyspepsia (NUD) is defined as persistent or recurrent dyspepsia for at least 12 wk, which need not to be consecutive, within the preceding 12 mo of persistent or recurrent dyspepsia, with no evidence of organic disease that is likely to explain the symptoms, and no evidence that symptoms are exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (*i.e.*, not irritable bowel syndrome)^[1].

NUD is a common healthcare problem: The estimated annual prevalence in Western countries is 15%^[2]. Despite a great deal of scientific attention, little is known about the pathogenesis of NUD. *Helicobacter pylori* (*H pylori*) infection and delayed gastric emptying have both been documented to have higher prevalence in patients with NUD compared with asymptomatic controls^[3, 4]. However, it is unknown if *H pylori* infection and/or delayed gastric emptying are involved in the pathogenesis of NUD. Furthermore, it is still unclear whether there is a causal association between these two factors in patients with NUD.

Therefore, we designed this study to investigate whether gastric emptying rate in patients with NUD was associated with the presence of *H pylori* infection, and whether the eradication of the infection affected the gastric emptying rate in these patients. We also sought to confirm in our population the well-known finding of delayed gastric emptying in patients with NUD compared with asymptomatic controls.

MATERIALS AND METHODS

Subjects

Consecutive patients with dyspeptic symptoms who attended the self-referred out-patient clinic of the 2nd Department of Internal Medicine, General Regional Hospital of Alexandroupolis were candidates for inclusion in the study. Inclusion criteria were: (1) age between 18 and 65 years; (2) presence of dyspeptic symptoms, defined as upper abdominal pain, upper abdominal discomfort, upper abdominal fullness, early satiety, or nausea/vomiting, continuously or intermittently for at least three mo; (3) no relevant findings revealed by physical examination other

than epigastric tenderness; (4) normal gastroscopy except mild erythema of gastric or duodenal mucosa; (5) normal abdominal ultrasound scan; (6) normal full blood count, liver function tests, fasting glucose, urea, creatinine, electrolytes, amylase and thyroid function tests. Exclusion criteria were: (1) presence of any organic or psychiatric disease that could affect the evaluation, treatment or compliance of the patient; (2) heartburn as the predominant symptom; (3) predominant symptoms being compatible with the diagnosis of irritable bowel syndrome or functional constipation as defined by Rome I criteria^[5]; (4) pregnancy or breast feeding; (5) chronic alcoholism or drug abuse; (6) past medical history of peptic ulcer disease, oesophagitis, pancreatitis, abdominal trauma, or abdominal surgery other than uncomplicated appendectomy; (7) intake of antibiotics 4 wk prior to inclusion; (8) regular intake of non steroidal anti-inflammatory drugs, including aspirin, or other medications that could cause dyspepsia during the 3 mo prior to inclusion.

The asymptomatic controls were recruited from the employees of General Regional Hospital of Alexandroupolis. Eligibility criteria were: (1) age between 18 and 65 years; (2) absence of dyspeptic symptoms; (3) absence of any organic or psychiatric disease that could affect the evaluation, treatment or compliance of the participant; (4) intake of antibiotics 4 wk prior to inclusion.

Proton pump inhibitors and H₂-receptor antagonists were withheld from all participants for 7 d before gastroscopy or gastric emptying testing. Paracetamol and all medications with any known potential effect on gastrointestinal motility were withheld for, respectively, two and three days before gastric emptying testing.

Study protocol

Study procedures were timed as follows: NUD patients underwent gastroscopy and two biopsy specimens were collected, one from the antrum and one from the corpus, for urease testing for *H. pylori* (CLOtest®, Delta West Ltd, Australia). The presence of *H. pylori* IgG antibodies in serum was assessed by ELISA (*H. pylori* GVE 573II IgG, PLK, Italy). On the following day, gastric emptying rate was assessed by the paracetamol absorption method as described below. *H. pylori*-positive NUD patients received 10 d of *H. pylori* eradication therapy consisting of omeprazole 20 mg twice daily, amoxicillin 1 000 mg twice daily and clarithromycin 500 mg twice daily. Four weeks later, *H. pylori* status was re-assessed by biopsy urease test. If eradication of *H. pylori* infection was confirmed, gastric emptying rate was re-evaluated. Asymptomatic controls were tested for *H. pylori* infection by serology (*H. pylori* IgG ELISA) and had gastric emptying rate assessed by the paracetamol absorption method.

The study protocol conformed to the World Medical Association Helsinki Declaration in 1964 as amended in 1996 and was approved by the regional Ethics Committee. Informed consent was obtained from all study subjects. This work was not financially supported by any outside agency or pharmaceutical company.

Assessment of gastric emptying rate

Gastric emptying rate was assessed by the paracetamol absorption method, which was conceived by Heading *et al.*^[6,7] and recently re-evaluated^[8,9]. The test meal was administered following overnight fasting and consisted of: (1) three cream crackers (total mass is 35 g); (2) a 200-mL carton of Fortimel® (Nutricia Clinical, Holland; liquid nutritional supplement; 410 mOsm/L; 4.184×10³ kJ/L; containing 19.4 g of protein, 4.2 g of fat and 20.8 g of carbohydrates per carton); (3) 1 g of paracetamol as two tablets 500 mg Depon®, Bristol-Myers Squibb; (4) 100 mL of tap water. Peripheral venous blood samples were obtained *via* a heparinised cannula immediately after the

ingestion of paracetamol (time 0) and at 30 min intervals over a 3-h period (7 samples in total). During the 3-h test period, the subjects were free to sit, stand or walk; they were not allowed to eat, drink or smoke.

Paracetamol plasma concentration was determined with the TDxFLx® System (Abbott, IL, USA) by using fluorescence polarization immunoassay technology. The following parameters were calculated: time to detect paracetamol in plasma (lag phase), maximum plasma paracetamol concentration divided by body mass (C_{max}/BM); time to reach maximum plasma paracetamol concentration (T_{max}), area under the plasma paracetamol concentration – time curve divided by body weight (AUC/BM).

Primary outcomes were the absolute difference in gastric emptying rate as assessed by C_{max}/BW and AUC/BW in *H. pylori*-positive and *H. pylori*-negative NUD patients, and in *H. pylori*-positive NUD patients before and after eradication.

Secondary outcomes were the absolute difference in gastric emptying rate as assessed by C_{max}/BM and AUC/BM in NUD patients compared to asymptomatic controls. We also assessed gastric emptying lag phase and T_{max} in all study groups.

Sample size calculation

Sample size was calculated *a priori* with the Altman nomogram^[10]. A pilot study of five *H. pylori*-positive NUD patients provided an estimate of mean C_{max}/BM (19.0 mg·min/L·kg) and standard deviation (5.0 mg·min/L·kg). We calculated that at least 10 subjects were required in each study group (*H. pylori*-negative NUD patients, *H. pylori*-positive NUD patients, post-eradication NUD patients, asymptomatic controls) in order to detect a clinically important relative difference (*a priori* set as $\geq 25\%$) between two study groups or within person comparison before and after *H. pylori* eradication ($1-\beta=0.8$, $\alpha=0.05$, two tailed significance).

Statistical analysis

Statistical analysis was carried out according to a pre-established analysis plan. Proportions were compared by χ^2 test with Fisher's exact test when appropriate. Regarding continuous outcomes, study groups were compared by the Mann-Whitney *U* test, while differences before and after *H. pylori* eradication were assessed by Wilcoxon matched pairs signed rank test. Two sided significance tests were used throughout. The software used was Statistical Package for the Social Sciences 10.0.1 for Windows (release 1999, SPSS Inc., Chicago, IL). Confidence intervals were calculated with Confidence Interval Analysis software 2.0.0 (release 2000, T. Bryant, Univ. of Southampton).

RESULTS

Thirty-three patients with NUD and 17 asymptomatic volunteers were included in the study during two recruitment periods (January to March 1997 and March to April 1998). All participants were Caucasian. Twenty-three of the NUD patients (70%) had both a positive serum anti-*H. pylori* IgG and biopsy urease test and were considered *H. pylori*-positive. The remaining 10 NUD patients had both tests negative and were considered *H. pylori*-negative. The baseline characteristics of the study groups are displayed in Table 1. The only significant difference found was a difference in age between control group and NUD group ($P=0.02$). Nevertheless multiple regression (ANOVA) revealed that age had no effect on any of the study outcomes. There was, therefore, no need for adjustment for age.

All study subjects underwent evaluation of gastric emptying. There was no significant difference in gastric emptying rate between *H. pylori*-positive and *H. pylori*-negative NUD patients as assessed by the primary study parameters C_{max}/BM and

AUC/BM (Table 2). NUD patients had significantly delayed gastric emptying compared with asymptomatic controls as assessed by C_{\max} /BM and AUC/BM (Table 3). Gastric emptying lag phase and T_{\max} did not differ significantly in any comparison (data not shown).

All 23 *H. pylori*-positive NUD patients received eradication therapy. Of those, 18 completed the 10-d course and 4 wk later underwent repeat gastroscopy and biopsy urease test, eradication was confirmed in 14 patients (per protocol eradication rate 77.8%). Of the remaining five patients who received eradication therapy, 4 did not consent to repeat gastroscopy and 1 discontinued the course on the third day due to severe diarrhea (*C. difficile* toxin negative). No other side effects of the eradication regimen were reported on direct questioning.

All 14 NUD patients with confirmed *H. pylori* eradication underwent repeat assessment of gastric emptying. No significant difference was found in the gastric emptying parameters C_{\max} /BM and AUC/BM compared with the values prior to eradication (intra-individual comparisons) as shown in Table 4. Neither gastric emptying lag phase nor T_{\max} differed significantly compared with the values prior to eradication (data not shown).

DISCUSSION

This study confirmed that gastric emptying is significantly delayed in patients with NUD compared to asymptomatic controls (Table 3). This has been well established for years^[3, 11].

In fact, our results showed that the 95% confidence interval (CI) for the absolute difference between the medians of gastric emptying parameters, C_{\max} /BW and AUC/BW, was compatible with a relative difference encompassing the predefined limit of clinical importance (*i.e.* 25%). Consequently, our results need to be interpreted as evidence of a statistically significant difference in gastric emptying rate between patients with NUD and asymptomatic controls, which however is unclear if it is clinically relevant. The above comparison was not the primary outcome of our; Nonetheless the fact that these results are in agreement with the current medical literature corroborates the methodological validity of our study and the credibility of the main outcomes.

The pathophysiology of delayed gastric emptying in patients with NUD, as well as its clinical implications, remains unknown. *H. pylori* gastritis - which was also more prevalent in patients with NUD^[3] - has been suggested as a causal factor for the gastric motility disorders found in these patients. There is no solid evidence supporting this hypothesis although there is some biological plausibility since a mucosal inflammatory reaction could affect the function of enteric nerves and smooth muscle^[12].

In our attempt to investigate the potential role of *H. pylori* in the above mentioned motility disorders, we found that the gastric emptying rate in patients with NUD did not differ significantly between *H. pylori*-positive and *H. pylori*-negative patients (Table 2). Furthermore, eradication of *H. pylori* infection in patients with NUD did not induce any significant modification

Table 1 Baseline characteristics of patients with non-ulcer dyspepsia (NUD)

Characteristics	Controls (n=17)	All NUD pts (n=33)	Hp positive NUD pts (n=23)	Hp negative NUD pts (n=10)
Sex (Male:Female)	9:8	20:13	13:10	7:3
Age (yr) (mean±SD)	27.7±6.7	37.3±14.5	39.3±14.2	35.2±18.4
Body mass (kg) (mean±SD)	66.6±13.8	74.3±10.0	75.6±9.8	71.2±10.1
Hp(+) (%)	9 (52.9)	23 (69.7)	23 (100)	0 (0)
Smokers (%)	8 (47.1)	10 (30.3)	7 (30.4)	3 (30)

Table 2 Gastric emptying: *H. pylori*-positive NUD patients vs *H. pylori*-negative NUD patients

parameters (mean±SD, M)	Hp positive NUD pts (n=23)	Hp negative NUD pts (n=10)	Mann-Whitney U test	95% CI for difference between medians (Hp pos. -Hp neg.)
C_{\max} /BM(mg/L·kg)	0.172±0.070 (0.153)	0.177±0.050 (0.176)	P=0.58	-0.050 to 0.037
AUC/BM(mg·min/L·kg)	18.43±6.93 (18.53)	18.38±5.94 (19.42)	P=0.91	-5.36 to 4.62

C_{\max} /BM: maximum plasma paracetamol concentration divided by body mass; AUC/BW: area under the plasma paracetamol concentration-time curve divided by body mass. M: median.

Table 3 Gastric emptying: NUD patients vs asymptomatic controls

Parameters (mean±SD, M)	NUD pts (n=33)	Controls (n=17)	Mann-Whitney U test	95% CI for difference between medians (NUD pts-Controls)
C_{\max} /BM (mg/L·kg)	0.173±0.064 (0.163)	0.224±0.076 (0.221)	P=0.02	-0.012 to -0.095
AUC/BM (mg·min/L·kg)	18.42±6.56 (18.53)	24.34±8.06 (25.53)	P=0.01	-2.11 to -10.93

C_{\max} /BM: maximum plasma paracetamol concentration divided by body mass; AUC/BM: area under the plasma paracetamol concentration-time curve divided by body mass. M: median.

Table 4 Gastric emptying: *H. pylori*-positive NUD patients before and after eradication (intra-individual comparisons)

Parameters (mean±SD, M)	Initially Hp positive NUD pts (n=14)		Wilcoxon matched pairs test	95%CI for the median difference (after - before)
	Before eradication	After eradication		
C_{\max} /BM (mg/L·kg)	0.171±0.074 (0.167)	0.160±0.064 (0.146)	P=0.64	-0.047 to 0.278
AUC/BM (mg·min/L·kg)	17.41±5.25 (18.95)	18.02±7.25 (16.88)	P=0.93	-3.04 to 4.38

C_{\max} /BM: maximum plasma paracetamol concentration divided by body mass. AUC/BM: area under the plasma paracetamol concentration-time curve divided by body mass. M: median.

of the gastric emptying rate (Table 4). However, for both comparisons, the 95% CI for the absolute difference between the medians of gastric emptying parameters was marginally compatible with the pre-defined level of a clinically important relative difference of 25%. This should be interpreted, therefore, as insufficient evidence to confirm or exclude a clinically important difference in gastric emptying rate between *H. pylori*-positive and *H. pylori*-negative patients with NUD. The same conclusion applies to the changes of gastric emptying rate following eradication of *H. pylori* infection in patients with NUD.

Our results are in agreement with most previous publications, which did not detect any influence of *H. pylori* status on gastric emptying rate in patients with NUD^[13-23]. However, it is possible that some of these studies were not adequately powered to detect the targeted difference. Some investigators were able to demonstrate significant differences, but their conclusions differed. For example, Fock *et al.*^[24] found that gastric emptying was slower in *H. pylori*-positive NUD patients compared to *H. pylori*-negative NUD patients, while Tucci *et al.*^[25] found the opposite. No meta-analysis has yet addressed this issue.

Regarding the effect of the eradication of *H. pylori* infection on gastric emptying rate in NUD patients, our results are in line with three other trials, which were unable to detect any changes in gastric emptying rate after a follow up period of one^[26], six^[27] and 12 mo^[28]. Nonetheless, other investigators found that eradication of the infection significantly increased gastric emptying rate after a follow-up of 1 mo^[29] or "normalised" previously abnormal (*i.e.* rapid or delayed) gastric emptying after a 2-mo follow up^[30]. There was considerable methodological heterogeneity among these trials, which complicates any attempts to draw a conclusive answer.

Further larger trials would be helpful. These would be facilitated by using safe and non-invasive methods of gastric emptying assessment, such as the paracetamol absorption method, ultrasonography^[31], or ¹³C octanoic acid breath test. Utilization of urea breath testing for confirmation of *H. pylori* eradication^[32], which was not available to us at the time of the research, might improve the compliance of participants and could allow investigators to lengthen the post-eradication follow-up time without a significant dropout rate. Future studies should also explore whether specific *H. pylori* characteristics, such as CagA phenotype^[19], or differences in host response are implicated in the pathogenesis of gastric emptying disorders in patients with NUD.

In conclusion, gastric emptying is delayed in patients with NUD but is unrelated to *H. pylori* status. Eradication of *H. pylori* infection in *H. pylori*-positive patients with NUD does not significantly alter the gastric emptying rate. Although our results are not definitive, they will contribute to a better understanding of the pathogenesis of NUD - especially when quantitatively synthesised with analogous data in future meta-analyses.

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