Gastric emptying in patients with gastroesophageal reflux disease and postprandial distress syndrome – preliminary results

Ocena opróżniania żołądkowego u pacjentów z chorobą refluksu i zespołem dyskomfortu popośniwowego – wstępne wyniki

Background: Gastric motor disturbances are observed in patients with both Gastroesophageal Reflux Disease (GERD) forms - with (ERD) and without (NERD) esophageal inflammatory changes, and in Functional Dyspepsia (FD) patients, particularly in those with Postprandial Distress Syndrome (PDS). Gastric Helicobacter pylori infection is often present in these entities. We tried to evaluate if there is any influence of Hp on gastric emptying (GE) in reflux and dyspeptic patients. Material and methods: 25 GERD patients aged 45.7±13.1 yrs (10 NERD; 5 Hp+ and 5 Hp- and 15 ERD patients with grade A esophagitis according to Los Angeles classification; 5 Hp+ and 10 Hp- and 15 PDS patients (5 Hp+ and 10 Hp-) aged 47.9±14.0 yrs participated in our study. All patients underwent upper gastrointestinal tract endoscopy, Hp status verification, stationary esophageal manometry, 24-hour ambulatory pH-metry and gastric scintigraphy with a liquid test meal. Results: In general, both GERD groups and PDS patients had prolonged GE (T1/2 - NERD-54.9±16.3 [min]; ERD-41.7 ± 14.8 [min] and PDS-54.3±24.8 [min] vs. 35.2 ± 13.9 [min] in control; p<0.05). According to Hp infection, we found in both NERD and PDS groups prolonged GE in Hp+ subjects in comparison to Hp- ones (respectively: T 1/2 - 66.5 ± 21.2 [min] vs. 43.8±11.4 [min] in NERD; p<0.05; 63.5 ± 29.0 [min] vs. 48.0±27.7 [min] in PDS; p<0.05). These differences were less pronounced in ERD subjects: 44.5±17.7 [min] Hp+ vs. 37.4±15.2 [min] in Hp- ERD; p<0.05). Conclusions: Both NERD and PDS patients had more decreased GE halftime compared to those with inflammatory esophageal changes. In particular groups, Hp infection was associated with slower GE rate and elongated T 1/2 in NERD and PDS group but with no effect in ERD patients.
Introduction

Gastroesophageal reflux disease (GERD) and Functional Dyspepsia (FD) are the most common disturbances which affect the upper part of the gastrointestinal tract. About 10% of the adult population experiences daily typical symptoms of gastric regurgitation [20] while even 30% reports clinical features of FD [14]. GERD may be generally defined as the involuntary passage of gastric contents into the esophagus, producing characteristic or sometimes atypical symptoms and possible complications [30]. It is usually divided into two main subclasses, with (GERD – Erosive Reflux Disorder) or without mucosal inflammatory changes (NERD – Non Erosive Reflux Disorder).

FD patients are characterized to complain of epigastric pain or postprandial discomfort centered in the upper abdomen with no evidence of organic disease (Rome II guidelines [25]). The present Rome III criteria also maintain FD as the presence of dyspeptic symptoms mentioned above that are considered to originate from the gastroduodenal region, in the absence of any organic, systemic or metabolic disease that is likely to explain the symptoms. According to Rome III arrangements, two main FD subclasses may be distinguished: Epigastric Pain Syndrome (EPS) and Postprandial Distress Syndrome (PDS) [24].

Etiology of GERD and FD is complex, involving many various factors. The lack of efficient antireflux barrier, with the special role of the phenomenon of transient lower esophageal sphincter relaxations (TLESRs) and diminished esophageal clearance seems to be the most important GERD factors [30]. Abnormal gastroduodenal motor activity, impaired gastric accommodation, visceral hypersensitivity, local inflammatory processes and disturbed brain-gut interactions may play an important role in FD etiology [23].

In both GERD and FD cases, pathological changes of gastric motor function are observed, resulting in delay of gastric emptying (GE). Delayed GE and antral meal retention is responsible for an increase in intragastric pressure, which overcomes Lower Esophageal Sphincter (LES) pressure and leads to stress reflux. It may also contribute to the augmented gastric afferent signals and to dyspeptic symptoms development in FD.

Furthermore, still unclear role in GERD and FD plays Helicobacter pylori (Hp) infection. This bacteria colonises gastric mucosa and seems to contribute to many pathophysiological consequences involving gastric dysmotility and secretion due to hypergastrinemia [1]. However, it appeared that this infection leads to more profound changes including modification of afferent neural signals and specific hormone release [26]. In infected patients, low ghrelin plasma level together with parasympathetic dysfunction were observed, which may affect esophageal and gastric motor activity [10]. Thus, a link between Hp infection and gastric secretary and motor functioning undoubtedly exists.

There is a question if disorganized gastric motility is more stressed in GERD or FD patients infected with Hp. The aim of our study was to find an answer to the issue stated above. We aimed to determine gastric emptying rate in patients with both GERD forms and FD with and without Helicobacter pylori infection.

Material and methods

Subjects: Forty patients with upper gastrointestinal tract symptoms participated in our study. There were 25 GERD patients (45.7±13.1 yrs) and 15 PDS patients aged 47.3±14.0 yrs. According to upper endoscopy results, performed before, 10 GERD patients had no esophageal inflammatory changes (NERD group), 15 GERD patients had grade I esophagitis, according to Los Angeles classification (EDR group). The brief characteristic of studied patients is given in the table I.

GERD patients had typical acid reflux symptoms including heartburn, pyrosis, acid regurgitation together with postprandial epigastric dyscomfort. The predominant symptoms in FD patients concerned mostly early postprandial fullness and early satiety at least 12 weeks with onset at least 6 months previously, according to Rome III criteria. All participants answered a detailed, structured questionnaire administered for general patients’ complaints characteristic. 73% of all GERD patients (65% NERD and 80% EDR) complained of pyrosis, 67% - of acid belching (70% NERD, 64% EDR) and 41% - of acid re-gurgitation (48% NERD and 34% EDR) as predominant symptoms. Moreover, 46% of them (42% NERD and 50% EDR) reported early postprandial fullness and 64% (68% NERD and 60% EDR) - epigastric postprandial pain or distress. On the other hand, 72 % of FD patients reported early postprandial fullness and 76% - epigastric postprandial distress as predominant complaints. Thus, we were able to recognise Postprandial Distress Syndrome (PDS) in studied dyspeptics. None of the patients had other gastroesophageal diseases or had previous abdominal operations. They were untreated patients or patients with interruption in drug administration (proton pump inhibitors, H2 antagonists) lasting 14 or more days. They had no co-existing chronic disorders and were in general good condition.

Study protocol: All participants underwent general medical examination with the gastrointestinal complaints questionnaire fulfillment, upper gastrointestinal tract endoscopy, esophageal stationary manometry, 24-hour ambulatory esophageal pH monitoring and gastric scintigraphy.

In the first step, esophageal manometry was performed to localise LES before pH-monitoring study. Additionally, LES basal pressure (LESp) and its lenght were estimated. It was performed using Synectics Medical software and equipment, water-perfused, 4-channel catheters and step-up method, described elsewhere [12]. In the next stage, potential reflux was verified using 24-hour esophageal pH monitoring in ambulatory circumstances. The pH probe (Synectics Medical Multi-Use pH Catheter) was inserted in locally anaesthetized patient through the nasal cavity and pharynx to distal esophagus and located 5cm above the upper LES margin, previously determined in manometry. The probe was connected to

Figure 1

<table>
<thead>
<tr>
<th>GERD Emptying Half-time (T1 [min])</th>
<th>Compliance With Helicobacter pylori Status</th>
</tr>
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<tbody>
<tr>
<td>HP +</td>
<td>48</td>
</tr>
<tr>
<td>HP -</td>
<td>66.5</td>
</tr>
<tr>
<td>HC +</td>
<td>44.5</td>
</tr>
<tr>
<td>HC -</td>
<td>37.4</td>
</tr>
</tbody>
</table>

p<0.05

Gastric emptying half-time (T1 [min]) complying with Helicobacter pylori status.

Czas połowicznego opróżniania żołądka (T1 [min]) u pacjentów (Hp+) i bez infekcji Helicobacter pylori (Hp-).
a pH meter (Digitrapper Mk III, Synectics Medical). During the study, patients kept their normal daily activity and diet. Standard reflux parameters were calculated (Polygram for Windows, Synectics Medical) [8,21]. According to reported clinical symptoms and results of both endoscopy and pHmetry, patients were classified to an appropriate group (NERD, ERD or PDS). In the last step, gastric emptying was assessed in each patient in Nuclear Medicine Department of the 5th Military Hospital in Cracow. Gastric emptying was estimated with dynamic abdominal external scintigraphy started immediately after the meal ingestion. Images of the radioactivity in the anterior abdomen were collected from subject laying under collimator with the wide-spectrum gamma camera. Images corresponding to the anterior projection of stomach were identified, the total stomach was outlined from all acquisitions. Scintigraphy was performed at the rate of 5-minute intervals for the first 45 minutes and, thereafter, at every 10 minutes for 1.5 hours. From obtained data "activity versus time" curve was derived and major gastric emptying parameters – gastric emptying half-time (T 1/2); the time [min] needed for the initial activity in the total stomach to fall by 50% was calculated. The same study protocol was assessed in healthy subjects. Results obtained in the control group were comprising in the range 15-45 minutes with the average GE half time (T 1) carrying out 35.2 [min] ± 13.9 [min].

Helicobacter pylori infection: In 32 studied patients, Helicobacter pylori infection was detected using CLO-test and the biopsy specimen obtained during endoscopy. 8 patients had previously done specific anti Hp Ig level estimation. According to these findings, we were able to subdivide the entire study group into subpopulation of patients with Helicobacter pylori (Hp+) and without Hp (Hp-) confirmed infection. Finally, we obtained 15 Hp+ patients (5 NERD, 5 ERD and 5 PDS) and 25 Hp- patients there were 12 persons after effective eradication of patients Hp- (5 NERD, 10 ERD and 10 PDS). Among Hp- patients there were 12 persons after effective eradication of Hp and the Hp+ patients in particular subgroups using Student’s t-test. They were considered to be statistically significant at p<0.05.

Results
Esophageal manometry: PDS patients and NERD ones had slightly different value of basal lower esophageal sphericity pressure (LESP) – 22.3 ± 12.6 [mmHg] and 25.3 ± 11.6 [mmHg]. The lowest LESP value was observed in ERD patients (19.1 ± 8.6 [mmHg]). All results were still located in normal range, when compared to literature published data related to manometry findings in healthy volunteers [12]. The total LES length was the largest in NERD patients (2.7 ± 0.6 [cm]) and similar in remaining groups (2.2 ± 0.4 [cm] in ERD and 2.5 ± 1.3 [cm] in PDS). The both subdiaphragmatic and thoracic LES region was the longest in NERD patients (1.5 ± 0.3 and 1.2 ± 0.3 [mmHg], respectively); whereas the subdiaphragmatic part was briefest in ERD ones (0.9 ± 0.3 [mmHg]). The manometric findings are given in the table II.

24-hour ambulatory esophageal pH-monitoring results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NERD</th>
<th>ERD</th>
<th>PDS</th>
<th>ALL GROUPS (Bartlet’s test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total reflux episodes amount</td>
<td>181.2 ± 54.3</td>
<td>175.6 ± 81.9</td>
<td>56.9 ± 33.8</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Upright reflux episodes amount</td>
<td>144.3 ± 47.7</td>
<td>142.8 ± 77.0</td>
<td>47.1 ± 32.3</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Supine reflux episodes amount</td>
<td>36.8 ± 25.8</td>
<td>33.3 ± 17.1</td>
<td>9.9 ± 6.4</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Number of episodes &gt; 5 minutes</td>
<td>2.9 ± 1.9</td>
<td>10.4 ± 6.1</td>
<td>2.2 ± 1.5</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Time of longest acid reflux episode</td>
<td>8.8 ± 4.4</td>
<td>46.5 ± 30.1</td>
<td>1.5 ± 0.9</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Fraction of time with pH &lt; 4 [%]</td>
<td>11.0 ± 3.5</td>
<td>12.9 ± 9.4</td>
<td>1.9 ± 1.2</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NERD</th>
<th>ERD</th>
<th>PDS</th>
<th>ALL GROUPS (Bartlet’s test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>47.0 ± 14.7</td>
<td>44.4 ± 11.4</td>
<td>47.9 ± 14.0</td>
<td></td>
</tr>
<tr>
<td>Height [cm]</td>
<td>167.4 ± 4.9</td>
<td>170.7 ± 8.2</td>
<td>166.1 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>72.1 ± 14.7</td>
<td>75.7 ± 11.8</td>
<td>65.8 ± 12.6</td>
<td></td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>25.6 ± 5.0</td>
<td>26.8 ± 4.0</td>
<td>23.8 ± 4.0</td>
<td></td>
</tr>
</tbody>
</table>

Table I

Characteristic of studied populations.
**Discussion**

**Esophageal manometry and pH-metry**: NERD and PDS patients had similar resting LESP values, whereas ERD patients were characterized by lower LES pressure. However, LESP were in each of the studied group from normal range. The published data describes normal LES to have a pressure of about 20 mmHg, ranging between 15 and 40 mmHg [30,12]. It was also consistent with our pH-metry findings, which revealed that all GERD patients were upright refluxers – acid regurgitation was mostly observed during the day period and in standing position (79 % in NERD, 81 % in ERD and 83 % in PDS of all noted reflux episodes occurred in these circumstances). Thus, the resting LESP was high enough to prevent from night reflux in GERD patients in supine position. Reflux episodes appeared most likely in TLESRs (Transient Lower Esophageal Sphincter Relaxations) mechanism in GERD patients (dyspeptic group had normal results of pH-metry, excluding pathologic acid reflux pressure). This manometric and pH-metric results suggest that gastric emptying disturbances may play an important role by triggering excessive TLESRs episodes in GERD patients.

**Gastric emptying**: The literature data related to the GE in GERD is partly consistent with the delayed gastric emptying findings in most patients. In children with GERD, Cucchiaro et al. [5] revealed prolonged GE, estimated in ultrasonography, together with abnormal postprandial gastric myoelectrical activity. Soykan et al. [19] also found the disturbances of GE in about 40% of the studied adult GERD patients. Additionally, some studies have been done demonstrating intragastric food distribution. Herculanu et al. [8] and van der Schaar et al. [29] in their research works discovered abnormally decreased retention of gastric contents in the proximal stomach. Thus, theory of delayed GE, which is also treated as one of the pathophysiological factors leading to GERD development (probably by triggering TLESRs) seems to be true. Our results also support common belief of decreased postprandial gastric motor function. Analysing our GERD patients as a homogeneous population we noticed that GE in this group was smaller of about 60% in comparison to control. Moreover, analysis NERD and ERD patients seperately showed that prolonged GE time was more attenuated in NERD group (delayed GE of even 83%) than in ERD ones (of about 39%).

Delayed GE, impaired gastric accommodation and hypersensitivity to gastric distention are regarded to be important pathophysiologic factors in dyspepsia, as it was mentioned in the introduction. The proofs which confirm disturbed GE in dyspeptic patients were delivered among others by Chaudhuri et al. [28]. In our study also corroborated these findings, showing that even up to 50% of FD patients had impaired GE [15]. Jones et al. in their research work found that GE in FD was diminished in 21% of studied patients’ population (although differences in T 1/2 between FD and control were only of about 10%) and according to them, FD symptoms are rather associated with psychologic distress than with gastric motor dysfunction [11]. Bromer et al. [2] showed in their study delayed GE in FD group both after solid and liquid meal. T 1/2 in FD was decreased of about 26% in comparison to control. Slowing GE of about 1.5 times also observed Quartero et al. [16] in dyspeptic group. Similar conclusions obtained Herculano et al. [8] who found that GE in FD patients decreased of 30% (although they used ultrasonographic GE estimation). Our results also support the idea of delayed GE in FD - our studied dyspeptic patients had prolonged GE of about 19 [min] when compared to control.

**Helicobacter pylori and gastric emptying**: The influence of Helicobacter pylori on gastric motor function in GERD and FD has not still been clearly explained. Some researches claim that Hp does not affect GE. Saslow et al. [18] studied GE of solids in asymptomatic volunteers finding no change in overall motor function of the stomach. Soykan et al. [19] did not demonstrate any relationship between Hp infection and GE rate in GERD patients, although these patients treated as homogeneous group had disturbed GE. Similarly, Chiloiro et al. [4] showed no evidence of Hp impact on GE rate in dyspeptic patients as well as in control (although Hp increased plasma gastrin level in these patients).

On the other hand, Samelli et al. [17] revealed accelerated GE in Hp positive (Hp+) patients with dyspepsia, in comparison to those ones without Hp infection, although these differences were not statistically significant. Koskenpato et al. [13] found in scintigraphic study that dyspeptic Hp (+) patients had only slightly prolonged GE when compared to Hp (-) ones.

There are also other studies demonstrating link between gastric emptying delaying and Hp infection, such as Tucci et al. [28]. They found that fundic atrophic gastritis observed in profound Hp infection is characterized by progressive deterioration of gastric motor functions. These results confirmed Tosetti et al. [27] who noticed that GE seemed to be less in Hp positive GERD patients also when the analysis was adjusted for Helicobacter pylori status. Summarizing, the effect of Hp on gastric motility and visceral sensation is still unclear and the literature reports are often contradictory. However, our results suggest potential relationship between GE rate and Hp presence in NERD, PDS and FD patients (exactly in PDS subpopulation). In NERD and PDS groups, Hp+ patients had diminished gastric emptying rate, resulting in increased T 1/2 (mostly marked in NERD group). In ERD patients differences between Hp+ and Hp- were not statistically significant, although distinct tendency was also seen. Thus, the key finding of our study is that gastric emptying may be attenuated in Hp+ NERD and PDS patients. It may be also associated with our previous studies concerning the autonomic nervous system disturbances in GERD patients [7]. We revealed low vagal activity in these patients, observed already in the NERD group. The parasymphathetic withdrawal seems to be one of the important GERD pathophysiological factors. Moreover, decreased ghrelin level in Hp+ GERD patients, described in literature as mentioned above, may also reflect diminished cholinergic control of stomach motor function [26, 22].

It must be underlined that the hypothesis of lower gastric emptying rate in Hp positive, non-erosive reflux and dyspeptic patients, requires further investigations. Finally, to ascertain the statement given above, GE studies in Hp positive NERD and PDS participants would have to be repeated after effective Hp eradication which should reveal GE rate improvement, compared to the results obtained before Hp treatment.

It is generally believed, that GE decrease is a unique feature of GERD. Moreover, decreased ghrelin level in Hp+ GERD patients, described in literature as mentioned above, may also reflect diminished cholinergic control of stomach motor function [26, 22].

**References**

11. Jones M.P., Magnenti K.: Symptoms, gastric func-