# Clinical experience of use of $^{13}$C-breath tests in oesophagogastroduodenal diseases: selective questions

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## Abstract

**Introduction:** Motility disorders can be an important factor in the occurrence of symptoms of of dyspepsia that consequently require evaluation of clinical significance of noninvasive diagnostic approaches when observing patients with functional dyspepsia (FD), gastroesophageal reflux disease (GERD), and *Helicobacter pylori*-associated diseases of the stomach and duodenum.

**Aim:** To determine the relationship between various motility disorders and to improve the diagnostics and treatment with the use of $^{13}$C-urea (UBT) and $^{13}$C-octanoic breath tests (OBT).

**Material and methods:** A total of 591 patients, aged 18–83 years, who underwent upper gastrointestinal endoscopy at our department were evaluated. Age, sex, and duration of symptoms of dyspepsia were recorded. UBT and OBT were examined in patients with dyspepsia, GERD, and *H. pylori*-associated diseases.

**Results:** Patients with dyspepsia syndrome had *H. pylori* infection in 70 ±1.3% of cases. The strategy of "test-and-treat" using UBT can be applied in 76.5% of cases of unexplained dyspepsia in the Ukrainian population. In patients with GERD, slowing down of the gastric emptying (GE) prevails (overall 79.7 ±4.4%), which is a reliable predictor of early relapse of GERD symptoms (OR = 4.9, 2.4–7.0). In the case of *H. pylori*-associated diseases, the slowing down of GE according to OBT data is a prognostic sign of the return of the symptoms of dyspepsia after successful eradication of *H. pylori* (OR = 2.1, 1.9–2.3). In *H. pylori*-associated diseases with a slow GE, recurrence of dyspeptic syndrome after *H.pylori*-eradication therapy is observed in 33.1% of cases; the appointment of prokinetics reduces this probability to 9.2% ($p$ = 0.0074).

**Conclusions:** Investigations into the clinical use of new facilities of $^{13}$C-breath tests in gastroenterology are shown. The clinical efficacy of urea and octanoic breath tests in FD, GERD, and *H. pylori*-associated diseases was proven experimentally among patients of the Ukrainian population. New simplified diagnostic and treatment approaches were proposed for certain groups of patients with gastric dyspepsia syndrome, based on the results of the UBT and the OBT.

## Introduction

Gastroenterology is currently developing at a rapid pace and constantly presents new challenges and tasks to practitioners and scientists. The methods of visualisation of internal organs (endoscopy, capsular endoscopy, magnetic resonance and computer tomography, positron emission tomography, ultrasound scanning) have reached their greatest development today. A somewhat more complicated situation has arisen with regard to methods for evaluating the functional state of the organs of the digestive system because their diagnostic accuracy depends on many factors, and in order to increase the accuracy of the investigation it is often necessary to use a significant number of complementary diagnostic techniques. This stretches the diagnostic process over time and increases its cost. Many studies aimed at simplifying diagnostic algorithms for certain groups of gastroenterological patients are ongoing [1, 2]. Non-invasiveness and simplicity of implementation, together with safety, high efficacy, sensitivity, and specificity, have become requirements for diagnostic methods [1, 3]. Some of the most promising methods for the investigation of the gastrointestinal tract, the liver, and

the pancreas are so-called carbon or $^{13}$C-breath tests. The general principle for all breath tests based on the use of the $^{13}$C-isotope is that the patient takes a $^{13}$C-labeled substrate, which ultimately metabolises to $^{13}CO_2$, which can be quantified in the exhaled air [4–6].

Today, one of these breath tests – the $^{13}$C-urea breath test (UBT) – has become generally accepted as the gold standard for the diagnosis of *Helicobacter pylori* (*H. pylori*) infection, due to its almost 100% sensitivity and specificity, and due to its non-invasiveness. It is officially recommended by international consensus (Maastricht V/Florence Consensus, 2016) as the method of choosing to diagnose the presence of *H. pylori* infection and assessing the effectiveness of eradication therapy. In our opinion, this allows us to investigate and introduce new simplified diagnostic and treatment algorithms for certain groups of patients with gastric dyspepsia syndrome, based on the results of UBT, without the use in most cases of endoscopy or investigation of acid-forming function of the stomach. Another test available in Ukraine that can be used to assess the functional state of the oesophagogastroduodenal zone is the $^{13}$C-octanoic breath test (OBT), which allows assessment of the gastric emptying function (because motility disorders can be the main factor in the occurrence of symptoms of dyspepsia) [3, 6, 7–9]. The investigation of $^{13}$C-OBT as a method of objectification of indications for medical correction of motor activity and evaluation of the effectiveness of treatment with prokinetic drugs is highly relevant.

## Aim

The aim of this scientific research: to improve the diagnosis and treatment of patients with functional dyspepsia, gastroesophageal reflux disease, and *H. pylori*-associated diseases of the stomach and duodenum by exploring new aspects of the use of UBT and OBT.

## Material and methods

The tasks of the study were formulated in accordance with the aim of the research, for which 591 patients were examined in general.

For justification the choice of age and gender groups, 7664 patients' histories of the disease were analysed previously; patients had upper endoscopy performed (Olympus, EVIS-160). An analysis of the examined patients by age, sex, and duration of symptoms of dyspepsia was conducted (Table I).

The statistical analysis showed that upper gastrointestinal endoscopy has clinical expediency for patients with dyspepsia syndrome over 39 years of age, male sex (OR = 1.7), age over 51, and female sex (OR = 1.4). Thus, the strategy of "test-and-treat" [10, 11] using $^{13}$C-UBT can be used for patients of the corresponding sex under the specified age.

A total of 312 patients (156 men, 156 women) were examined for the decision of the task of evaluating the clinical effectiveness of the new diagnostic and treatment algorithm for managing patients with gastric dyspepsia syndrome, based on data from the UBT as a method to detect *H. pylori* infection. They were divided into three groups according to the therapeutic tactics that they had applied. First group (110 patients) – *H. pylori*-positive patients who were treated by eradication of *H. pylori* according to the schemes: proton pump inhibitor (PPI) in standard dose two times a day + clarithromycin 500 mg two times a day + amoxicillin 1 g two times a day (or ornidazole 500 mg two times a day). Second group (110 patients) – *H. pylori*-positive patients who were treated by PPI monotherapy. Third group (92 patients) – *H. pylori*-negative patients who

**Table I.** Gender, age, and anamnestic analysis of cases requiring upper endoscopy

| Disease | Number of patients | Percentage from the total number of disease histories | Age (95% CI) [years] | Sex | | Duration of symptoms [months] (95% CI) |
|---|---|---|---|---|---|---|
| | | | | Male | Female | |
| Gastric cancer | 99 | 1.3 | 44–83 (45–80) | 69 | 20 | 1–14 (3–7) |
| Barrett's oesophagus | 114 | 1.4 | 18–70 (43–65) | 67 | 15 | 30–144 (60–120) |
| Hernia of the oesophagus aperture | 315 | 4.1 | 32–72 (46–64) | 203 | 112 | 12–144 (12–132) |
| Gastric atrophy | 858 | 11.2 | 27–79 (48–71) | 532 | 326 | 60–360 (120–240) |
| Cancer of the oesophagus | 11 | 0.2 | 59–74 (59–74) | 9 | 2 | 1–3 (1–3) |
| Oesophageal varices | 47 | 0.6 | 40–64 (45–64) | 32 | 15 | Not defined |
| Gastric polyps | 91 | 1.3 | 39–70 (47–70) | 47 | 44 | Not defined |

*CI – confidence interval, OR – odds ratio.*

were treated by PPI monotherapy. PPIs (omeprazole, rabeprazole, esomeprazole, pantoprazole) were used in recommended doses [12]. UBT was performed according to the standard method [6, 13, 14].

To determine the nature of violations of the motility and empty functions of the stomach in patients with functional dyspepsia, gastroesophageal reflux disease (GERD) and *H. pylori*-associated diseases using $^{13}$C- OBT, as well as objectification by means of OBT indications to the appointment of prokinetics and the selection of their dose and assessment of the quality of differential correction options of motility dysfunction in diseases of the oesophagogastroduodenal zone, 279 people were examined. The disease spectrum included functional dyspepsia (FD) – 54 patients, GERD – 84 persons, *H. pylori*-associated diseases (chronic gastritis, type B (60 men, 44 women), peptic ulcer of the duodenum (23 men, 14 women)).

As a test breakfast for OBT, a sandwich with butter was used, to which was added 100 mg of $^{13}$C-octanoic acid. The collection of alveolar air was carried out in plastic bags. The first 2 h of investigation an air was being collected every 15 min, next 2 h – every 30 min. Air analysis in the performance of UBT and OBT was carried out on an Iris infrared analyser (Wagner-Analysen-Technik, Germany). As a result of the analysis, the curve of concentration of $^{13}CO_2$ was constructed and the half-life for gastric emptying of solid food was calculated. Assessment of the severity of symptoms of dyspepsia was performed by questioning the patients using a 10-point scale. The general severity of discomfort consisted of the sum of scores obtained for each symptom.

### Statistical analysis

The data are presented in the form of average and relative values, medians, and interquartile confidence intervals (CI). The reliability of the data difference in repeated measurements was evaluated using the Wilcoxon method. The reliability of the data difference when comparing different groups was estimated using the Mann-Whitney method. The difference was considered probable at $p < 0.05$. The data was processed using Statistica 7.0 software.

## Results and discussion

The percentage infected by *H. pylori* among patients with dyspepsia syndrome was 70 ±1.3%. For men, this indicator was 76.3 ±1.4% and for women – 64.2 ±1.4%. Moreover, the difference in the incidence rate of *H. pylori* among men and women was statistically significant ($p = 0.0233$). Perhaps a higher number of infected men combined with a higher incidence of bad habits and a less healthy diet leads to a higher frequency of complications in the future.

In group 1, the frequency and severity of all symptoms after 7 days ($p < 0.001$) decreased, and after one month this effect was maintained for both men and women. In the group of men the effectiveness of eradication therapy was 90.8 ±2.6% (108 men), and in the group of women – 87.1 ±1.4% (88 women). In the group in which the eradication therapy was successful, complete regression of symptoms 1 month after the end of treatment was noted by 92 men (85.1 ±3.4%). Among women, this indicator was 49 (55.7 ±5.3%) ($p < 0.05$).

In group 2, the frequency and severity of all symptoms after 1 month ($p < 0.001$) decreased, and after 2 months there were no observed significant differences, compared with the rates before treatment, among women. Among men, the frequency and severity of heartburn decreased ($p < 0.001$). Significant differences of the frequency and severity of other symptoms were also not observed among men.

In group 3 after one month, there were no fixed significant changes of frequency of symptoms, such as the feeling of postprandial overflow and bloating, and even a tendency to increase the intensity of postprandial discomfort was observed. The frequency of abdominal pain decreased, but no significant changes in its severity occurred. In group 3, after 2 months, no significant differences in symptoms were observed in women compared to those before treatment. Among men, the frequency and severity of heartburn decreased ($p < 0.001$). Significant differences in other symptoms were not observed in the group of men also. Consequently, the strategy of appointing of empirical antisecretory treatment was not effective – 1 month after its completion, most patients had a relapse of clinical symptoms of varying intensity.

Thus, the data obtained by us indicate that in 76.8 ±0.5% of cases of unexplained dyspepsia the use of upper endoscopy is not appropriate. Among these patients, the UBT was sufficient to determine further therapeutic tactics that could effectively cure 87% of men and 55% of women. Thus, in this percentage of individuals, further therapeutic tactics will depend on the *H. pylori* status to a greater extent than other factors. Among the latter, considerable attention must be paid to the violation of the motility-evacuation function of the stomach.

According to the data obtained earlier, the sensitivity of OBT = 93.6 + 4.3%, specificity = 92.5 + 3.5%, reproducibility = 88.6 ±2.1%, positive predictive value (PPV) = 89.9%, and negative (NPV) = 94.8%, meaning that the test is a reliable method for determining the rate of gastric emptying.

According to the questionnaire, the severity of the postprandial fullness in patients with FD was 7 points

(95% CI: 7–8 points). All patients with FD were prescribed itopride at a dose of 150 mg per day (50 mg three times a day) for 14 days. After the treatment, the severity of the postprandial fullness in patients was re-evaluated and the OBT was performed. The results showed the following: the severity of postprandial fullness was 1 point (95% CI: 0–2 point, $p < 0.0001$ compared with the result before treatment); the half-life for gastric emptying of solid food was 75 min (95% CI: 70–89 min). In this case, in 11 (40.7%) patients, this symptom disappeared, in 11 (40.7%) it decreased by 50% or more, and in 5 (18.5%) patients it decreased by less than 50%. Thus, in 22 (81.5%) patients we evaluated the treatment as effective, and in 5 (18.5%) patients – as ineffective. Thus, 18.5% of patients with FD needed additional therapeutic interventions, so at the next stage of the study, these patients were prescribed itopride at a dose 300 mg/day (100 mg three times daily) for 14 days. At the end of the indicated treatment period the severity of the postprandial fullness in the indicated five patients was re-evaluated and the OBT was performed. The results showed the following: before the treatment with itopride at a dose 300 mg/day, the severity of the postprandial fullness was 7 points (95% CI: 7–7), and after treatment it was 0 points (95% CI: 0–1 point, $p = 0.04$); the half-life for gastric emptying of solid food before the second stage of treatment was 200 min (95% CI: 180–208 min), and after treatment it was 76 min (95% CI: 67–86 min, $p = 0.04$). We also found that in patients whose appointment of an itopride at a dose of 150 mg per day was effective, and in patients whose appointment of an itopride at a dose of 300 mg per day was effective, there were significant differences in the mean half-life for gastric emptying of solid food (125 min, 95% CI**:** 120–124 min vs. 210 min, 95% CI: 186–210 min, $p = 0.0006$). Therefore, we decided to investigate the threshold value (distribution point) of the half-life for gastric emptying of solid food according to OBT data, with which it would be possible to determine the optimal dosage regimen. As a result of the analysis it was found that the highest diagnostic properties had a value of 172 min (diagnostic efficiency 88.6%).

In patients with GERD using OBT, it was found that a reduction in the rate of gastric emptying was detected in 44 patients (55.0 ±4.1%). After the main four-week course of treatment, these patients were divided into two groups, group 1 received itopride at a dose corresponding to the degree of slowdown of the gastric emptying (GE). Group 2 comprised informed, untreated controls. The frequency of heartburn was evaluated in the groups as soon as the treatment was completed and after 4 weeks. One month after the end of the treatment period in the first group, the heartburn recurred in 4 patients (18.1 ±4.2%), whereas in the second group – in 16 patients (72.7 ±7.5%), $p < 0.01$. Thus, the differentiated appointment of itopride on the basis of OBT data can reliably prevent early relapse of GERD.

In patients with *H. pylori*-associated diseases, data was received indicating that, in general, 55 people (39.0 ±4.1%) had reduced rate of GE of varying degrees. Twenty-four persons (17.0 ±3.2%) had accelerated GE, and 62 persons (44.0 ±4.1%) had normal GE. There were no significant differences in the frequency of normal, accelerated, and slow gastric emptying between gender groups. Subsequent observations have shown that the slowing of GE is a prognostic sign of the return of clinical symptoms of dyspepsia, even after successful eradication of *H. pylori*. Concerning the practical significance of this observation, it can be said that the clinical application of OBT in the case of *H. pylori*-associated diseases is required in the presence of symptoms of dysmotility dyspepsia – the feeling of postprandial fullness has the greatest prognostic significance, and the odds ratio is OR = 2.1 (1.9–2.3). The purposes of using OBT before treatment are to determine the indications and to adequately select the dose of a drug with prokinetic action to prevent the return of symptoms.

## Conclusions

The strategy of "test-and-treat" using UBT as the main method in the Ukrainian population can be applied in 76.5% of cases of unexplained dyspepsia and is effective among men because it gives a steady clinical effect in 87.6 ±5.5% of cases. This strategy is clinically insufficiently effective among women, in whom a steady clinical effect is observed in 53.6 ±7.4% of cases. With functional dyspepsia, 96% of patients have impaired GEs of varying degrees, with a slowing of GE in 81.5% of cases of FD, regardless of its variant. Acceleration of GE was detected in 11.1% of patients. In GERD, slowing down of the GE prevails (overall 79.7 ±4.4%), which is a reliable predictor of early relapse of GERD symptoms (OR = 4.9, 2.4–7.0). In the case of *H. pylori*-associated diseases, the slowing of GE according to OBT data is a prognostic sign of the return of the symptoms of dyspepsia after successful eradication of *H. pylori* (OR = 2.1, 1.9–2.3). In *H. pylori*-associated diseases with a slow GE recurrence of dyspeptic syndrome after *H. pylori*-eradication therapy is observed in 33.1% of cases, and the appointment of prokinetics reduces this probability to 9.2% ($p = 0.0074$). Diagnostic efficiency of the half-life for gastric emptying of solid food (T1/2 index) according to OBT results (85--172 min in case of prescribing of standard dose of prokinetics and more than 172 min in case of double dose) is 88.64%.

Objectivised therapeutic correction of the slow GE in cases of FD allows effective clinical remission in 85.5% of patients; in cases of GERD the number of early relapses decreases from 27.8 ±5.1% to 9.1 ±4.2% ($p$ = 0.0114).

## Conflict of interest

The authors declare no conflict of interest.

### References


1. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection – the Maastricht V/Florence Consensus Report. Gut 2017; 66: 6-30.
2. Harvey R, Lane JA, Nair P, et al. Clinical trial: prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia consultations – the Bristol Helicobacter Project. Aliment Pharmacol Ther 2010; 32: 394-400.
3. Talley NJ, Verlinden M, Jones M. Can symptoms discriminate among those with delayed or normal gastric emptying in dysmotility-like dyspepsia? Am J Gastroenterol 2001; 96: 1422-8.
4. Ohara S, Kato M, Asaka M, Toyota T. Studies of 13C-urea breath test for diagnosis of Helicobacter pylori infection in Japan. J Gastroenterol 1998; 33: 6-13.
5. Schadewaldt PB, Schommartz B, Wienrich G, et al. Application of isotope-selective nondispersive infrared spectrometry (IRIS) for evaluation of 13C-octanoic acid gastric-emptying breath tests: comparison with isotope ratio-mass spectrometry (IRMS). Clin Chem 1997; 43: 518-22.
6. Siddiqui I, Ahmed S, Abid S. Update on diagnostic value of breath test in gastrointestinal and liver diseases. World J Gastrointest Pathophysiol 2016; 7: 256-65.
7. Quartero AO, de Wit NJ, Lodder AC, et al. Disturbed solid-phase gastric emptying in functional dyspepsia: a meta-analysis. Dig Dis Sci 1998; 43: 2028-33.
8. Bonfrate L, Grattagliano I, Palasciano G, Portincasa P. Dynamic carbon 13 breath tests for the study of liver function and gastric emptying. Gastroenterol Rep 2015; 3: 12-21.
9. Roda A, Mirasoli M, Guardigli M, et al. Non-invasive panel tests for gastrointestinal motility monitoring within the MARS-500 Project. World J Gastroenterol 2013; 19: 2208-16.
10. Gisbert JP, Pajares JM. Helicobacter pylori 'test-and-treat' strategy for dyspeptic patients. Scand J Gastroenterol 1999; 34: 644-52.
11. Gisbert JP, Calvet X. Helicobacter pylori "test-and-treat" strategy for management of dyspepsia: a comprehensive review. Clin Transl Gastroenterol 2013; 4: e32.
12. Nagaraja V, Eslick GD. Evidence-based assessment of proton-pump inhibitors in Helicobacter pylori eradication: a systematic review. World J Gastroenterol 2014; 20: 14527-36.
13. Wang YK, Kuo FC, Liu CJ, et al. Diagnosis of Helicobacter pylori infection: current options and developments. World J Gastroenterol 2015; 21: 11221-35.
14. Gisbert JP, Pajares JM. 13C-urea breath test in the diagnosis of Helicobacter pylori infection – a critical review. Aliment Pharmacol Ther 2004; 20: 1001-17.


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