Abbreviated $^{13}$C-mixed triglyceride breath test for detection of pancreatic exocrine insufficiency performs equally as standard 5-hour test in patients after gastrectomy performed for gastric cancer

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Background. $^{13}$C-mixed triglyceride breath test ($^{13}$C-MTGT) is a non-invasive test for the detection of moderate and severe pancreatic exocrine insufficiency (PEI), but it requires prolonged breath sampling. The aim of this study was to determine the diagnostic power of abbreviated $^{13}$C-MTGT in detecting PEI in patients after subtotal and total gastrectomy performed due to gastric cancer.

Subjects and methods. This cross-sectional observational study included 3 groups of subjects: healthy controls, patients with subtotal and patients with total gastrectomy. Demographic and clinical data of patients were collected. Stool samples to determine faecal elastase (Fe-1) and chymotrypsin were collected and measured by ELISA. All subjects performed 5-hour $^{13}$C-MTGT breath test. The concentration and relative content of $^{13}$C in exhaled air was measured by isotope ratio mass spectrometer (IRMS). PEI was confirmed as values of $^{13}$C-exhalation < 26.8% after 5 hours.

Results. Overall, 65 participants were included into analysis, 22 having PEI (n = 11 after subtotal and n = 11 after total gastrectomy, both performed for gastric cancer). $^{13}$C-MTGT breath test showed difference in percent of exhaled $^{13}$C between PEI and non-PEI patients already after 60 minutes (p = 0.034). Receiver operating characteristic (ROC) curve analysis showed that cut-off value of 13.74% after 150 minutes is showing equivalent diagnostic power to the longer test with sensitivity and specificity both above 90% for the exclusion of PEI in patients after subtotal and/or total gastrectomy.

Conclusions. In this study abbreviated $^{13}$C-MTGT test could be shortened from 5 to 2.5 hours without decrease in its diagnostic accuracy for detection of PEI in patients after subtotal or total gastrectomy performed for gastric cancer. This allows significant time savings in the diagnostics of PEI in this subgroup of patients.

Key words: abbreviated $^{13}$C-mixed triglyceride breath test; pancreatic exocrine insufficiency; gastrectomy; faecal elastase; gastric cancer

Introduction

Pancreatic exocrine insufficiency (PEI) is a malabsorption syndrome caused by deficiency or inactivation of pancreatic enzymes and/or bicarbonate in the gastrointestinal tract. This leads to maldigestion, malabsorption, and malnutrition with consequent higher morbidity, higher long-term mortal-
ity, and reduced quality of life. We distinguish primary PEI, in which the mechanism is tied to the pancreas itself (various diseases of the pancreatic parenchyma or pancreatic duct) and secondary PEI, which is often unrecognized because the mechanisms of PEI are extrapancreatic.

Secondary PEI also includes PEI in patients with altered anatomy due to gastric surgery (subtotal and total gastrectomy). Subtotal and total gastrectomy are common surgical procedures, very often performed in patients with gastric tumours, mostly with resectable adenocarcinoma. Thus, besides chronic pancreatitis, diabetes mellitus (DM), coeliac disease, cystic fibrosis, inflammatory bowel disease and pancreatic cancer, the surgical procedures are the most common causes of PEI. In these diseases, there is a presence of decreased exocrine secretion.

The pathophysiology of PEI post-gastrectomy is attributed to several factors. Firstly, the loss of the gastric reservoir leads to an absence of the initial mechanical digestion of food and faster transit of osmotically active food particles into the small intestine. The less digested food particles are less potent stimulators of cholecystokinin (CCK), resulting in a decrease in endogenous stimulation to release digestive enzymes. Secondly, loss of duodenal transit of food with reconstructive techniques bypassing the duodenum, such as Billroth-II (B2) and Roux-en Y (RY) reconstructions, leads to less CCK being released in response to the detection of chyme in the duodenum and upper jejunum. Thirdly, the release of pancreatic enzymes is not coordinated with the intestinal transit of food and inadequate mixing occurs (post-cibal asynchrony), leading to ineffective digestion. Finally, truncal vagotomy has been shown to reduce secretin-stimulated pancreatic trypsin and lipase secretion by 50-60%. This is attributed to the interruption of the cephalic phase of pancreatic digestion, during which sensory inputs are transmitted to the exocrine pancreas through the vagus nerve.

PEI has great impact on the quality of life, morbidity and mortality of these patients also in patients after gastrectomy, especially if the condition remains unrecognized. Diagnostic tests for the direct pancreatic function are gold standard as they are most sensitive for the detection of PEI but are invasive. The alternative are non-invasive tests such as faecal elastase-I (Fe-I), however with low sensitivity and specificity falls in diagnosing mild to moderate PEI. The specificity of this test seems to be even reduced after total and subtotal gastrectomy.

Therefore, diagnostics of PEI patients after gastrectomy may be difficult, as faecal elastase (Fe-I), the standard of PEI detection, may be of normal range values. The sensitivity of these tests is low due to its extrapancreatic mechanism of PEI in these patients. On the other hand, the $^{13}$C mixed triglyceride breath test ($^{13}$C-MTGT) is a non-invasive assay that indirectly evaluates pancreatic lipase activity and pancreatic exocrine function. The disadvantage of this breath test is the long time required for the test (5-6 hours). This is time consuming for patients and for medical staff, so there is a great need for a test that will be of shorter duration and therefore more patient-friendly. Limited number of studies have tested patients with suspected PEI who underwent a long 6-hour or modified, shortened $^{13}$C-MTGT breath test and showed some good results for shortening the test from 6 to 4 hours. As mentioned, the long time period of breath sampling and immobilization is a drawback and the period less than 6 hours led to decreased sensitivity of $^{13}$C-MTGT. Even though with shorter times (1-5 hours), sensitivity and specificity ranged from 73% to 85% and 83% to 100%, respectively. However, none of these studies were performed in a subgroup of patients after subtotal and total gastrectomy with test whether even shorter duration of test can be performed. We hypothesised that in this specific subgroup of post-gastrectomy patients the $^{13}$C-MTGT breath test could be significantly shortened due to the changed anatomy after resection of the stomach. Since this has not been explored before we performed this prospective observational study that specifically focused on patients with resectable gastric cancer.

Therefore, the purpose of our study is to determine the diagnostic value of abbreviated $^{13}$C mixed triglyceride respiratory test ($^{13}$C-MTGT) for the evaluation of PEI in patients after subtotal and total gastrectomy performed for gastric cancer. The goal was to determine and confirm the equivalence of the sensitivity of the shortened and standard $^{13}$C-MTGT breath test in detecting PEI, while determining the optimal required cut-off time of the abbreviated $^{13}$C-MTGT breath test with preserved sensitivity and specificity of PEI determination.

**Subjects and methods**

**Participants**

The study was designed as a cross-sectional, observational study from a single centre, University Medical Centre of Ljubljana. The subjects were
divided into three groups: healthy controls, subjects with subtotal gastrectomy and subjects with total gastrectomy. The group of healthy controls served as a base population for better estimation of diagnostic accuracy for abbreviated $13C$-MTGT breath test. All subjects were adults, 18 years of age or older. Before voluntary participation all participants needed to give the written informed consent. The study design and execution were approved by National Ethics Committee of Republic of Slovenia for Medical Ethics (registration number 140/02/10).

Exclusion criteria for patients in both gastrectomy groups, as well as in the group of healthy individuals, were conditions often associated with PEI (type 1 and 2 diabetes, celiac disease, acute pancreatitis, chronic pancreatitis, surgical conditions such as pancreatectomy, pancreatic head tumours, etc.). Since we studied the impact of changed anatomy after gastric surgery on the performance of $13C$-MTGT breath test we excluded patients with primary metastatic gastric cancer. The other exclusion criteria were other metastatic diseases, liver disease in which bile secretion is impaired, inability to participate in research due to psychiatric illness, pregnancy, lactation and allergy to butter or chocolate (these patients are unable to performed the test). Healthy controls were without any clinical signs and symptoms of gastric diseases, normal pancreatic elastase and without concomitant diseases.

Upon inclusion, demographic and clinical data on patients (gender, age, associated diseases, regular therapy, eating habits, smoking, coffee drinking, physical activity, weight, height, calculated body mass index (BMI)) were collected. Gastrointestinal symptoms and the degree of expression (diarrhoea, steatorrhoea, abdominal pain, weight loss, flatulence, anorexia, increased appetite) were also recorded.

Blood analyses

Moreover, peripheral blood for haemogram, amylase, lipase, CRP, hepatogram (AST, ALT, total and direct bilirubin, AF and GGT, prothrombin time, INR), electrolytes, urea, creatinine, calcium, lipidogram was drawn from all subjects in the morning after a 12-hour fast. Subjects submitted the first morning urine for amylase, lipase, glucose and stool to determine faecal elastase and faecal chymotrypsin. Analysing pancreatic faecal elastase (FE-1) and chymotrypsin levels subjects needed to pass the stool samples. The concentrations were measured by Enzyme-Linked ImmunoSorbent Assay method (ELISA) and detected photometrically.

Performance of $13C$-mixed triglyceride breath test ($13C$-MTGT)

All subjects underwent our standardized $13C$-MTGT breath test that took in total 5 hours (= 300 min). This is in line to already published procedure and is standard of care in our institution.12 The first exhalation is done as a baseline, before eating test meal and then at 30-minute intervals. After the first exhalation the subject ate a test meal consisting of two slices of white bread, each weighing 100 g, with one piece of bread accompanied by a piece of butter weighing 20 g. With another piece of bread, subjects consumed 30 g of chocolate spread (Nutella, Ferrero Rocher, Germany). The chocolate cream was mixed with 250 mg of a substrate of mixed triglycerides (1,3-distearin-2-octanoyl glycerol) labelled with the isotope $13C$ (Euriso-top, Saarbrücken, Germany). After eating the bread, the subjects drank 200 mL of water. They were requested to sit throughout the whole examination. The subjects blew exhaled air into test tubes at intervals of 30 minutes. Based on the difference in concentration between $13C$ and $12C$, the relative isotope ratio (IRMS) mass spectrometer was used to determine the relative $13C$ content of exhaled CO$_2$. The concentration of $13C$ in exhaled air and measurement of the ratio of $13C$ to $12C$ in exhaled CO$_2$ were analysed. The measured isotope ratio in the samples were expressed as the relative difference (δ per mL in %) and subtracted from the baseline. The values of $13C$ exhalation were compared with the standard parameter of $13C$ of healthy volunteers. PEI was confirmed according to Keller et al. if patients had a ratio of $13C$ below 26.8%.17

Statistical analysis

Statistical analyses were performed using the software package SPSS 21.0 (IBM Inc., Chicago, USA). Normally distributed variables were expressed as arithmetic mean and standard deviation, and One-Way ANOVA test was used for comparisons between variables. In case of abnormally distributed variables the differences between continuous variables were analysed by the nonparametric Mann-Whitney test. Differences between categorical variables and calculation of the positive/negative predictive values (PPV, NPV) were performed by using the Pearson’s chi-square test. The optimal time of the $13C$ MTGT breath test was tested with a receiver operating characteristic (ROC) analysis with area under curve (AUC), sensitivity and specificity. Respective cut-off values were performed for each
Overall, 65 participants were included into analysis and were then divided into 3 groups: (i) healthy controls (n = 20), (ii) group of patients with subtotal resection (n = 23) and (iii) group of patients with total gastrectomy (n = 22). Baseline characteristics

### Results

Overall, 65 participants were included into analysis and were then divided into 3 groups: (i) healthy controls (n = 20), (ii) group of patients with subtotal resection (n = 23) and (iii) group of patients with total gastrectomy (n = 22). Baseline characteristics
According to the baseline the groups of patients with gastrectomy differed in age and in gender ratio when compared to the healthy controls. Moreover, PEI were identified in patients after subtotal and total gastrectomy with $^{13}$C-MTGT breath test, FE-1, and faecal chymotrypsin, but not with 100% coverage. $^{13}$C-MTGT breath test after 300 minutes with a score < 26.8% was taken as a reference to determine PEI17,18, and at the end determined 22/45 (48.9%) patients with PEI. Approximately half of the patients in group of patients after subtotal and total gastrectomy had PEI confirmed. Meanwhile, no significant differences in patients’ characteristics or habits were determined between patients with PEI and patients without PEI (Table 2).

After performing $^{13}$C-MTGT breath test there has been an observation of difference in percent of exhaled $^{13}$C between the patients without PEI and patients with PEI soon after 2 measurements at 60 minutes (Table 3). In later timepoints, after 3<sup>rd</sup> measurement at 90 minutes the differences were increasing (p < 0.001) confirming that the abbreviated $^{13}$C-MTGT breath test to exclude PEI can be reliably used in patients after gastrectomy.

The required test time was not shorter in patients with total gastrectomy than in those after subtotal gastrectomy (Table 4) as no differences were observed in any of the timepoints.

The optimal duration of the abbreviated $^{13}$C-MTGT breath test was determined by cut-off values and ROC analysis showing that shortening the test to 150 minutes with the cut-off value of 13.74% is showing high sensitivity and specificity, both above 90% and high PPV and NPV for the exclusion of PEI in patients after subtotal and/or total gastrectomy. The reliability of the abbreviated $^{13}$C-MTGT breath test showed an equivalence of sensitivity in comparison to the standard, 5-hour $^{13}$C-MTGT breath test (Table 5, Figure 1) in this subgroup of patients.

### Discussion

PEI in patients after subtotal and total gastrectomy should be detected as early as possible and with a highly sensitive test as early treatment of PEI improves outcome for these patients. Diagnostic of measuring fecal elastase in stool is most commonly performed, but it is important to supplement or even substitute it with more sensitive tests such as the $^{13}$C-MTGT breath test as it is crucial to treat PEI.
early in these patients. However, the execution of this test takes significant time, generally 5–6 hours. The test is feasible as soon as patients are able to eat, and all of our patients have passed the test within 6 months of gastrectomy.

All patients underwent a C13 breath test less than 6 months after gastrectomy. Previously it has been shown that the time required for a breath test in patients with fast food passage in the upper gastrointestinal tract may be shorter\(^1\)\(^6\),\(^1\)\(^7\), so it is still necessary to determine the most optimal time required for breath test in patients with gastrectomy where changed anatomy impacts test meal transition time even more. The aim of the current study was to find the optimal duration and cut-off value for the 13C-MTGT breath test in secondary PEI at respective timepoints in two groups of patients, namely with subtotal and with total gastrectomy performed for gastric cancer. Because the time after gastrectomy in which patients underwent 13C-MTGT breath test after gastrectomy was too short, laboratory-detectable malnutrition had not yet occurred. If the 13C-MTGT breath test would be performed after a longer period of time, we would expect reduced laboratory nutritional markers at the same time as the pathological 13C-MTGT breath test, which in principle would not affect the 13C-MTGT breath test itself.

Other conditions that could simultaneously lead to PEI and consequently a change in the 13C-MTGT breath test could be ruled out by additional investigations (DM, etc).

Our analysis showed that the diagnostic sensitivity and specificity of the abbreviated 13C-MTGT breath test for detection of PEI was equivalent to the sensitivity of the longer 5-hour 13C-MTGT breath test.

### TABLE 4. Percent of exhaled 13C according to diagnosis of in respective timepoint of C13 measurement

| Healthy controls (n = 20) | Subtotal resection (n = 23) | Total resection (n = 22) | p-value* | p-value** |
|--------------------------|-----------------------------|--------------------------|----------|----------|
| 30 min 0.54 ± 0.74       | 0.32 ± 0.71                 | 0.38 ± 0.51              | 0.700    | 0.936    |
| 60 min 2.28 ± 2.32       | 1.27 ± 1.88                 | 1.92 ± 1.86              | 0.193    | 0.534    |
| 90 min 5.12 ± 3.76       | 3.15 ± 3.12                 | 4.32 ± 3.45              | 0.202    | 0.495    |
| 120 min 8.63 ± 4.76      | 5.66 ± 4.54                 | 7.04 ± 4.63              | 0.162    | 0.593    |
| 150 min 20.60 ± 7.09     | 13.96 ± 9.00                | 15.87 ± 8.11             | 0.056    | 0.714    |
| 180 min 24.91 ± 7.86     | 16.94 ± 10.74               | 18.77 ± 9.00             | 0.031    | 0.790    |
| 210 min 29.31 ± 8.61     | 20.45 ± 12.33               | 21.51 ± 9.55             | 0.023    | 0.937    |
| 240 min 33.67 ± 9.26     | 24.18 ± 13.81               | 24.14 ± 10.11            | 0.014    | 1.000    |
| 270 min 37.71 ± 9.82     | 28.04 ± 15.26               | 26.47 ± 10.63            | 0.010    | 1.000    |
| 300 min 41.14 ± 10.40    | 32.01 ± 17.21               | 28.51 ± 11.00            | 0.008    | 0.658    |

* Mann-Whitney test; ** Tukey Post-hoc analysis between subtotal and total resection groups

### TABLE 5. Cut-off values for prediction of non-pancreatic exocrine insufficiency (non-PEI) within respective timepoints in all subjects

| cut-off | AUC   | 95% Cl | p-value | Sensitivity | Specificity | PPV   | NPV   |
|---------|-------|--------|---------|------------|-------------|-------|-------|
| 30 min  | 0.25  | 0.591  | 0.444–0.737 | 0.233 | 53.5% | 68.2% | 42.9% | 76.7% |
| 60 min  | 1.16  | 0.662  | 0.522–0.801 | 0.034 | 67.4% | 54.5% | 46.2% | 74.4% |
| 90 min  | 3.79  | 0.776  | 0.654–0.898 | < 0.001 | 67.4% | 81.8% | 56.3% | 87.9% |
| 120 min | 4.71  | 0.845  | 0.738–0.952 | < 0.001 | 88.4% | 72.7% | 74.2% | 86.4% |
| 150 min | 13.74 | 0.929  | 0.853–1.000 | < 0.001 | 93.0% | 90.9% | 87.0% | 95.2% |
| 180 min | 16.19 | 0.938  | 0.869–1.000 | < 0.001 | 93.0% | 90.9% | 87.0% | 95.2% |
| 210 min | 18.64 | 0.948  | 0.888–1.000 | < 0.001 | 95.3% | 90.9% | 90.9% | 95.3% |
| 240 min | 20.85 | 0.962  | 0.902–1.000 | < 0.001 | 97.7% | 90.9% | 95.2% | 95.5% |
| 270 min | 25.71 | 0.962  | 0.891–1.000 | < 0.001 | 97.7% | 95.5% | 95.5% | 97.7% |
| 300 min | 26.95 | 0.962  | 0.889–1.000 | < 0.001 | 100%  | 95.5% | 100%  | 97.7% |

AUC = area under curve; NPV = negative predictive values; PPV = positive predictive values
test in patients after subtotal and total gastrectomy. Two and half hours have been determined as optimal to detect patients with PEI with the cut-off value of exhaled $^{13}$C at 13.74% after 2.5 hours (Table 5). Taking all that, there was also no difference in the required duration of the $^{13}$C-MTGT breath test when comparing patients after total gastrectomy and the duration of the test in patients after subtotal gastrectomy, even though the transit time in the upper gastrointestinal tract depends on the type of gastrectomy and affects the time required for a breath test. Since the number of patients was small, no significant differences occurred, but with a larger number, we would expect a shorter duration time of the $^{13}$C-MTGT breath test required when used in patients after total gastrectomy compared to subtotal gastrectomy patients. Our study was the first in this regard to perform the sub-analysis of patients with subtotal and total gastrectomy, and at the same time confirming shortening of the test. Keller et al. in 2011 indicated that shortening the test to less than 6 hours, decreases the sensitivity, however, even with considerable shorter sampling, the sensitivity and specificity ranged from 73% to 85% and 83% to 100%, respectively, and reached even higher sensitivity and specificity rates in mild to moderate PEI (100% and 92%, respectively). They also showed that abbreviated version of the test was promising. Abbreviated test as such makes the examination more acceptable and comfortable in time, both for patients and medical staff. Our study contributes to the innovation in the diagnostics and treatment of patients with PEI after gastrectomy and improves their quality of life, as well as facilitates the diagnostic process of these patients. This is important as in patients after gastrectomy, fecal elastase in the faeces may be preserved and the sensitivity of this test is expected to be low because the mechanism of PEI is extrapancreatic. Therefore, there is a presence of the risk that patients may be deprived of appropriate treatment with pancreatic enzyme replacement therapy (PERT). Because PEI has a strong impact on quality of life, additional tests such as $^{13}$C-MTGT breath test in addition to Fe-1 or $^{13}$C-MTGT breath test on its own detects more patients. Meanwhile the $^{13}$C-MTGT breath test is a non-invasive test that indirectly assesses pancreatic lipase activity and pancreatic exocrine, detects levels of undigested or digested products following gastric resection, so it is appropriate for patients after gastrectomy. Other trials have also tested patients with suspected PEI who underwent a modified shortened $^{13}$C-MTGT breath test, but some did not include patients after gastrectomy. On the other hand, they demonstrated high sensitivity for severe PEI ranging 90% to 100% and specificity ranging 80% to 90%. Keller et al. performed their study in 181 patients and revealed that cumulative $^{13}$C-exhalation with $^{13}$C-MTGT breath test over 4 hours had 88% sensitivity and 94% specificity for detection of PEI when compared to the standard 6-hour test. This reliability has been previously confirmed. Thus, the evaluation of pancreatic exocrine function using abbreviated test was in concordance with several studies showing that the abbreviated test might be of diagnostic value and used in clinical practice. However, due to different optimal timepoint more studies need to be evaluated confirming the exact time point for determine PEI as previous studies showed only minor abbreviation when compared to our data showing the abbreviation of more than 3 hours. Nevertheless, our findings are significant for bringing innovation into clinical practice and the study design encompassed two groups of patients.
that might develop PEI, our analysis had limitations. The sample size that was used is relatively small. Out of 65 subjects, only 22 had PEI. Secondly, the patients were not split by the surgical procedure. They had undergone the Roux-en-Y method or the Billroth I (BI) and the types might be associated with differences in fat digestive and absorptive function as BI reconstruction was proven to be superior to that after Roux-en-Y reconstruction.13 Furthermore, the basic characteristics of healthy controls did not match in age with patients’ group. Here it must be highlighted that the controls were used only as a baseline group stimulating statistical power of PPV and NPV in subjects. The testing time was not compared to other treatment modalities and possible diet was not evaluated to impact the testing results. Finally, in our study gastric emptying was not performed so its influence on the duration of the test or on the rates of abbreviated 13C-exhalation was not covered, despite that gastric emptying parameter was proven similar in patients and controls, and correction for these did not improve accuracy of 13C-MTGT.13 One of the limitations was also not regarding the possible concomitant adjuvant/neoadjuvant chemotherapy.

The importance of our study is that it demonstrated the possibility of shortening the 13C-MTGT breath test for patients after total and subtotal gastrectomy, which may make the test less time consuming and therefore more patient-friendly and medical stuff-friendly and suitable for wider clinical use in these two groups of patients for the assessment of PEI.

Conclusions

The negative side of the breath test for detection of PEI is the long 5-hour procedure, which is burdensome for patients and medical personnel. Because of this there is a great clinical need for the test to be shortened. In the study we confirmed that this can be performed in a subgroup of patients with resected stomach due to gastric cancer. The abbreviated 13C-MTGT breath test to 2.5 hours performed equally as the standard 5-hour test in this subgroup of patients. The results of study support the use of abbreviated test in patients after gastrectomy.

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