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Pancreatic function assessment

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Abstract. Several non invasive tests are available to assess pancreatic function, but no one is routinely used in clinical practice to diagnose chronic pancreatitis, due to their poor sensitivity in diagnosing mild pancreatic insufficiency. ^{13}C breath tests share the same limits of the other non invasive functional tests, but the mixed triglyceride breath test seems to be useful in finding the correct dosage of enzyme substitutive therapy to prevent malnutrition in patients with known pancreatic insufficiency.

Keywords:
^{13}C breath tests, Chronic pancreatitis, Pancreatic insufficiency, Mixed triglyceride.

Introduction

Pancreatic exocrine function could be impaired in several pancreatic diseases, first of all in chronic pancreatitis but also in cystic fibrosis, pancreatic tumours, acute necrotising pancreatitis, diabetes mellitus or after surgery (partial or total gastrectomy and pancreatoduodenectomy) as well as in extrapancreatic conditions such as celiac disease, Crohn's disease and Zollinger-Ellison syndrome. Tests measuring pancreatic function are usually performed to evaluate pancreatic insufficiency in patients with known pancreatic disease or with other above mentioned conditions and to find the correct dosage of pancreatic enzyme substitution therapy and to assess its efficacy[1]. The use of functional tests to diagnose chronic pancreatitis in case of inconclusive morphological findings is the most challenging use of these tests, but also the most controversial, due to their poor sensitivity in early phases of chronic pancreatitis, in which negative morphological tests are more frequent. The ideal functional test should be non invasive, quantitative, specific for pancreatic maldigestion, able to indicate the need and the appropriate dosage of substitutive enzymes even during therapy, cost-effective and broadly available. Among nowadays available tests, no one has all these features[2].

In this review we will focus on tests that seem to be the most challenging for clinical practice

Direct and indirect tests

Functional tests are divided into direct and indirect tests based on their mechanism. Direct tests determine pancreatic secretory capacity quantifying pancreatic secretion of volume, bicarbonate and/or enzymes after stimulation or measuring pancreatic enzyme levels in blood or stool. Indirect tests measure the effect of pancreatic enzymes on digestion, searching signs of maldigestion[3] Table I. Direct tests, specially secretin-pancreozymin test, are the gold standard for the assessment of exocrine pancreatic function. In fact, the secretin-pancreozymin test and the endoscopy-based pancreatic function test are the only functional tests sensitive enough to be used in the diagnosis of chronic pancreatitis in case of inconclusive or normal morphological test, despite a strong clinical suspicion. In spite of their good sensitivity, these tests are invasive, time-consuming and expensive and they are not useful in monitoring the response to enzyme substitutive therapy, because they do not assess the digestive ability[1]. Furthermore, they are not standardized because of lack in consensus about protocol and a wide variation in results[3] and they are not broadly available; thus, few centres could perform them. Among direct tests, magnetic resonance pancreatography after intravenous secretin infusion (s-MRP) deserves to be mentioned because it is able to provide both morphological and functional information, showing ductal changes and measuring pancreatic secretion volume [1], while the measurement of pancreatic enzymes such as elastase or chymotrypsin in stool has the enormous advantage to be not invasive and relatively cheap compared to

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Table I. Pancreatic function test measurements.

Direct		Indirect (all non invasive)
Invasive	Secretin test Secretin-cholecystokinin test Secretin-caerulein test Secretin-bombesin test Intraductal secretin test 75 Se-methionine test Serum pancreatic polypeptide Lundh test	Pancreolauryl test Bentiromide test Dual-label Schilling test Quantitative faecal fat excretion Faecal fat analysis Serum glucose level Breath tests
Non-invasive	Serum trypsin assay Amino acid consuption test Faecal chymotrypsin Faecal elastase-1 MR after secretin infusion	

Modified from Chowdhury RS, Forsmark CE[3]

tests that required intubation, so their use is particularly intriguing for the physician managing suspected pancreatic insufficiency.

Faecal chymotrypsin

Quantification of chymotrypsin activity is performed on a single stool sample; thus, it is simple and easy to use in clinical routine. A faecal chymotrypsin activity less than 3 U g^{-1} of stool is consistent with diagnosis of pancreatic insufficiency. As a diagnostic test for chronic pancreatitis, most studies reported a specificity ranging from 49% to 100% and a sensitivity ranging from 72 to 90%[3]. Chymotrypsin is inactivated during the passage through the intestinal tract in a non-predictable way and is diluted by diarrhoea of any etiology, thus, faecal activity does not directly correspond to pancreatic secretion of the enzyme. Whereas this test shows a sensitivity of 57% in patients with moderate and severe chronic pancreatitis, it is not able to detect any case in mild disease, showing a sensitivity of 0%[4]. Finally, substitutive exogenous enzyme interfere with the determination of chymotrypsin activity, thus the patient should interrupt enzyme therapy at least 48 hours before the test. This feature allows the test to be used in monitoring patient's compliance to enzyme substitution therapy – in this case the faecal chymotrypsin activity should increase[5] – and the need of dose adjustment. Instead, the use of this test in clinical practice to diagnose exocrine pancreatic insufficiency should not be recommended[1].

Faecal elastase

Pancreatic elastase concentration in stools seems the most reliable test in clinical practice among non-invasive tests. A faecal elastase concentration > than 200 mg^{-1} is considered as normal. It is more stable than chymotrypsin in gastrointestinal tract, so its faecal concentration correlates with pancreatic secretion of the enzyme. Furthermore exogenous enzymes do not interact with the human-specific monoclonal antibodies used to quantify elastase, thus the patient should not interrupt the therapy to perform the test. As chymotrypsin, elastase measurement is limited by the dilution effect of diarrhoea[1]. For all these reasons, faecal elastase is considered superior to faecal chymotrypsin[4,6,7]. In spite of these advantages, even faecal elastase is not a decisive test in clinical practice, because it has the same limit as chymotrypsin about sensitivity in mild pancreatic insufficiency. In fact, even if its sensitivity in the severe forms ranges between 73% and 100%, in mild insufficiency several studies have shown a sensitivity ranging from 0 to 47%[8].

Breath tests

After these data, we understand that we do not have a non invasive test that could help physicians in the suspect of chronic pancreatitis in early stage, when morphological findings are inconclusive and pancreatic exocrine insufficiency is mild. In this contest, looking for a better test, several breath tests have been developed, using different ^{13}C-labelled substrates Table II. The rational for the use of breath test is that the ^{13}C-labeled substrate, given orally with the meal, reaches the duodenum where it is hydrolyzed by specific pancreatic enzyme in ^{13}C-labeled metabolites, that are absorbed through the gut and oxidized in $^{13}CO_2$ within the liver. $^{13}CO_2$, absorbed in the blood stream, reaches the lungs and

Table II. ^{13}C-labeled substrates for breath tests assessing pancreatic exocrine function.

Substrate		Enzyme	Dosage	Duration
Carbohydrate starch		Amylase	50g natural starch	5 h
Peptide/protein benzoyltyrosylalanine eggwhite		Peptidase	5 mg per kg /22 g egg white	90 min/ 6 h
Lipids				
	Tripalmitin	Lipase	10 mg/kg	8 h
	Triolein	Lipase	10 mg/kg	9 h
	Hiolein	Lipase	2 mg/kg	10 h
	Trioctanoin	Lipase	7,5 mg/kg	4 h
	Cholesteryl octanoate	Esterase	500 mg	6 h
	Mixed triglycerides	Lipase	250 mg (4 mg/kg)	4-6 h

Modified from Braden[2]

is eliminated with expired air. Thus, the measurement of $^{13}CO_2$ in the expired air, by mass spectrometry or infrared analysis, is an indirect measure of pancreatic digestion[1] Figure 1.

Theorically, all digestive pathways could be used to evaluate pancreatic function. In fact, breath tests measuring carbohydrates, proteins or peptides and lipids digestion exist.

Carbohydrates breath tests

The ^{13}C-labeled starch test studies the amylase activity. The advantage of this test is that naturally ^{13}C-enriched substrate, as maize starch, could be used as substrate. Unfortunately, this test is not sensitive nor specific enough to be used in clinical practice, resulting inferior to faecal elastase test. In fact, pancreatic amylase activity is generally

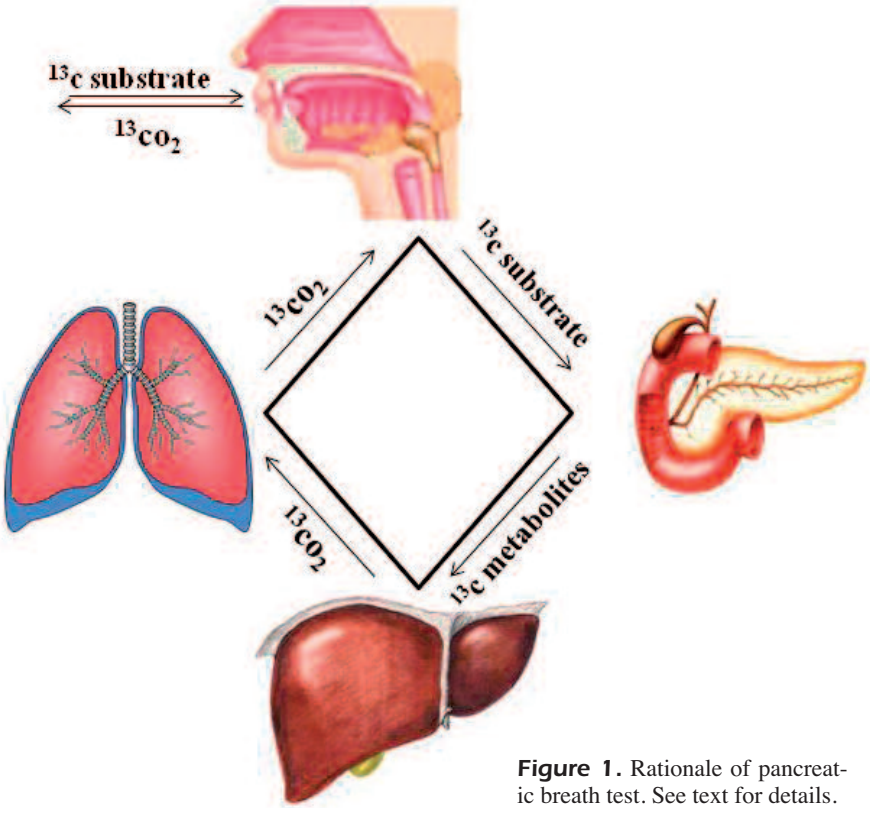

Figure 1. Rationale of pancreatic breath test. See text for details.

normal in early stage of pancreatic insufficiency and malabsorbed ^{13}C-starch could be metabolized by colonic flora, thus these features reduced sensitivity of the test. Furthermore, starch digestion involves also salivary amylase, thus this test is not specific for pancreatic enzymes[2].

Protein and peptides breath tests

The ^{13}C-labeled protein test studies the trypsin activity, using chicken egg white enriched with ^{13}C. The six hour cumulative $^{13}CO_2$ excretion significantly correlates with trypsin activity after maximal pancreatic stimulation[9]. Nevertheless, protein digestion depends not only on pancreatic enzymes, but also on enzymes from stomach and intestinal brush border and on gut microbiota metabolism[2]. A new ^{13}C-dipeptide (N-benzoyl-L-tyrosyl-1-(13)C-L-alanine) test studying the pancreatic carboxypeptidase has been developed[10-12]. This test is promising mainly because of its short duration (90 minutes compared to 4-6 hours of other breath tests), but data showing its capacity to detect mild pancreatic insufficiency are still lacking.

Lipid breath tests

Lipid breath tests generally investigate the function of lipase. Since pancreatic lipase is the first enzyme impaired in pancreatic insufficiency,[2] breath tests evaluating lipid maldigestion are the most sensitive for the assessment of pancreatic function. Furthermore, gastric lipase participates only to 15% of lipid digestion in duodenum[2], and even if preduodenal lipases compensate for pancreatic lipase deficiency[13], they could compensate only partially pancreatic lipase insufficiency[2]. For these reasons, several ^{13}C-lipids substrates have been developed, ^{13}C labelled at the carboxy group of the fatty acids.

Tripalmitin and triolein

Tripalmitin and triolein are triglycerides containing long chain fatty acids, whose digestion requires lipase activity and bile salt solubilisation. Triolein breath test requires 9 hours of sampling, while tripalmitin requires 8. The triolein breath test is a reproducible method to quantify fat absorption, thus it could be used to monitor the compliance and the efficacy of the substitutive enzyme therapy, finding the lowest effective dose of enzymes[2].

^{13}C-Hiolein

^{13}C-Hiolein is a mixture of triglycerides composed by different long-chain fatty acids, such as oleic acid (that is present in the major percentage), palmitic acid, linolic acid, linoleic acid, stearic acid and palmitoleic acid. It is extracted from algae growing under a $^{13}CO_2$ atmosphere, an expensive techniques that provides that all carbon atoms are uniformly labelled, while the other triglyceride substrates have the ^{13}C label only at the carboxy group of 1 fatty acid. This test depends on pancreatic lipase activity and is able to identify patients with steatorrhea. It could be used to monitor the efficacy of substitutive enzyme therapy[2]. A similar test described by Nakamura et al[14] has been shown to be superior to faecal elastase in patients who underwent pancreatic surgery.

Trioctanoin

^{13}C-labeled trioctanoin breath test has been used in patients before and after pancreatoduodenectomy and in these patients it was as sensitive as secretin test[15].

Cholesteryl Octanoate

This breath test evaluates the activity of cholesterol esterase. It could be impaired also in patients without pancreatic disease because the hydrolysis of the substrate requires bile acids, thus all conditions that alter duodenal bile salt concentration, such as celiac disease (in which there is an impaired cholecystokinin release) or liver disease, could be associated to false positive results.

Mixed triglyceride (1,3-distearyl [^{13}C octanoyl] glycerol)

The mixed triglyceride is the most investigated pancreatic breath test. This triglyceride is called "mixed" because it is composed by a ^{13}C-labeled medium-chain fatty acid (octanoic acid) at position 2 of the glycerol and by two long-chain fatty acids (stearine) at position 1 and 3

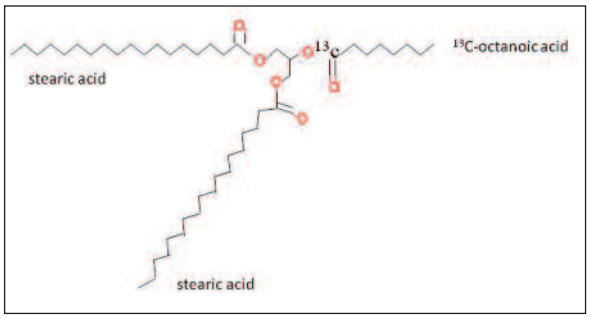

Figure 2. Molecular structure of mixed triglycerides.

(Figure 2). Lipase has to separe the two stearyl groups from the glycerol (this hydrolysis is the rate limiting step), to release ^{13}C-octanoyl monoglyceride, that is rapidly absorbed and finally metabolized in $^{13}CO_2$ [2]. The mixed triglyceride is not contained in our common diet, and octanoic acid is only little represented in normal diet, thus the labelled tracer is not therefore diluted by unlabelled substrate. Octanoic acid, as a medium chain fatty acid, is rapidly and completely absorbed by the intestine and small bowel disease did not affect its mucosal uptake, so intestinal absorption is not a major limiting step in this process[16].

Compared to breath tests using labelled long-chain fatty acids, such as triolein, tripalmitin and hiolein, the sampling period of the mixed triglyceride breath test could be shorter, because the oxidation of the shorter octanoic acids is faster, thus the peak excretion is observed on average after 3.5 hours[2].

This test was originally described by Ghoos et al[19] in 1981 using a ^{14}C-labeled substrate and lasting 10 hours. The mean $^{14}CO_2$ excretion in breath, expressed as the cumulative percentage of the administered dose, was only 32.9% in patients with pancreatic disease, while it was 68.3% in healthy subjects. The results of the test were impaired also in severe malabsorption due to gluten enteropathy, a condition characterized by functional pancreatic insufficiency due to reduced pancreatic stimulation. In 1989, Vantrappen et al[20] described a test with a non radioactive ^{13}C-labeled substrate. In the diagnosis of advanced chronic pancreatitis, this study reported a sensitivity of 89% and a specificity of 81% for diagnosis of pancreatic steatorrhea. Furthermore, there was an excellent correlation between lipase output in the duodenum and the 6-h cumulative $^{13}CO_2$ excretion in breath.

Some factors such as baseline $^{13}CO_2$ enrichment, gastric emptying rate, CO_2 production rate, physical exercise and meal consumption during the test could affect test results. About the possible effect of gastric emptying on test results, Keller et al[17] performed a ^{13}C-octanoic acid breath test to asses gastric emptying 3-14 days before a mixed triglyceride breath test and found that time until maximal ^{13}C excretion (T max), maximal ^{13}C excretion rates or cumulative ^{13}C excretion exhalation rates over 1 to 4 hours after ingestion of both breath test meals were not correlated. Furthermore, correction for gastric emptying parameters did not improve sensitivity or specificity of the mixed triglyceride breath test.

However, in our centre, to increase standardization of the test, we do not allow our patients to smoke and to eat foods naturally enriched of ^{13}C, such as pineapple, mais or brown sugar the day before the test. After 8 hours fasting, they blow into 2 vacutainers (basal samples) and then they assumed 250 mg of ^{13}C-labeled substrate with a gluten-free cracker spread with a cream containing chocolate and nuts (30 g). After that, the patients blow in a vacutainer every 30 minutes until the 240th minute. During the test, the patient should be at rest and he/she cannot eat, smoke or sleep and can drink only still water, because physical exercise demonstrated to influence the $^{13}CO_2$ response. Data demonstrating the influence of an additional meal during the test are not so strong, in fact, Kalivianakis et al[18] showed that 9th hour ^{13}C expiration rates and cumulative ^{13}C expiration were similar after 9 hours fasting and when an additional meal 3 hours after the start of the test was consumed (43.4% ± 7.2% vs 38.3 ± 5.3%, respectively). All these factors could make the intraindividual repeatability of the test low.

When evaluating a new test, the first problem to resolve is the definition of normal values in the general population. Jonderko et al[21] performed the ^{13}C-mixed triglyceride breath test in two age groups each composed by 12 healthy subjects to find normal values of $^{13}CO_2$ excretion. A maximum momentary $^{13}CO_2$ breath excretion of 9.6 ± 0.5% dose/h at 295 ±19 min in the young subjects and of 9.4 ± 0.4%dose/h at 270 ± 15 min in the middle-aged volunteers was observed. At the 6th hours, the cumulative ^{13}C recovery was 32.01 ± 1.78% dose and 31.84 ± 1.73% dose in the young and middle-aged groups, while at the 9th hour it was 47.59 ± 2.26% dose and 48.28 ± 2.36% dose, respectively. In another study including healthy adults, the cumulative ^{13}C excretion over 9 hours was 42.2 ± 8.4% (when substrate used was cream) and 47.7 ± 6.3% (when substrate used was bread and butter)[18]. Dominguez Munoz et al[22] used a cut off value of 58% of $^{13}CO_2$ recovered at the 6th hour to indicate the presence of fat maldigestion, with a sensitivity and specificity higher than 90%. Weaver et al[16] stated that in normal subjects the percentage dose recovered over 5 or 6 hours is between 20 an 40%, while the remaining 60-80% is deposited within the body in adipose tissue and other carbon pools or is not absorbed (Figure 3).

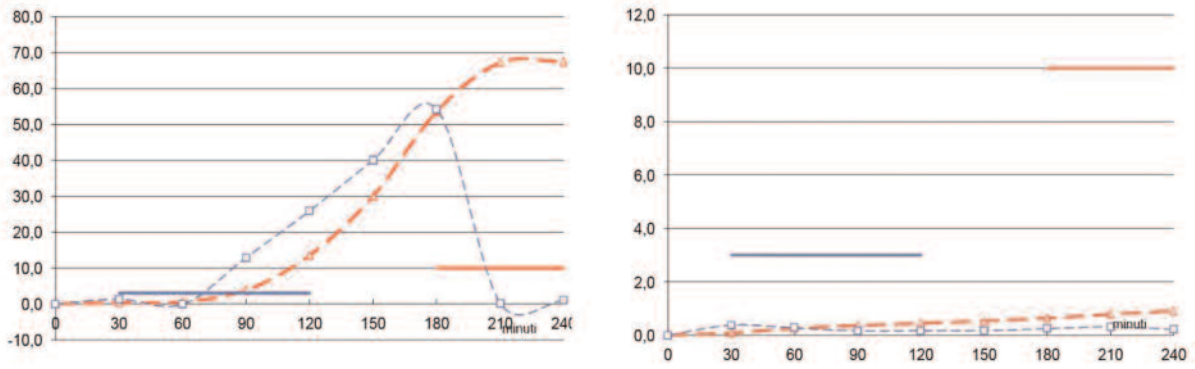

Figure 3. Examples of mixed triglycerides breath test results. X-axis shows time in minutes. Y-axis shows percentage of dose recovered. Short-dash line corresponds to Percent Dose Recovery (PDR), that is the percentage of the total dose of 13C recovered in each breath sample. Long-dash line corresponds to cumulative Percent Dose Recovery (cPDR), that is the percentage of the total dose of 13C recovered in breath in a determined time interval (240 minutes). A. Normal result. B. Result in one patient with severe pancreatic insufficiency.

In spite of the relative low cost, the non-invasiveness and the good acceptance by the patients, the mixed triglyceride breath test shares the same limitations of the other non invasive functional tests. In fact, although this test showed a good sensitivity in the advanced pancreatic insufficiency, it had poor sensitivity in mild pancreatic disease. Löser et al[23] compared the mixed triglyceride breath test with the secretin-caerulein test as the gold standard of pancreatic function testing and with faecal elastase and chymotripsin in 13 patients with mild and 13 with severe pancreatic insufficiency. The specificity of the mixed triglyceride breath test (69% in mild and 85% in severe chronic pancreatitis) was equal to faecal chymotrypsin (82%), but lower than faecal elastase (90%), while the sensitivity for total (total, 69-81%) and separately for mild (46%) and severe (100%) exocrine pancreatic insufficiency was higher than that of faecal chymotrypsin (total, 56%), but lower than faecal elastase (total, 92%).

Under the circumstances, the mixed triglyceride breath test could not to be helpful to the physician to diagnose mild chronic pancreatitis, but it seems promising in other situations such as the management of enzyme replacement therapy. Modification of the enzyme therapy to normalize fat absorption as assessed by breath test in 20 patients affected by chronic pancreatitis with malnutrition despite an adequate clinical response to the enzyme therapy was associated with a significant increase of body weight and a major serum concentration of retinol binding protein and prealbumin[22].

A new modified mixed triglyceride breath test has been proposed to improve sensitivity and to detect also moderate pancreatic insufficiency. This test used a higher lipid dose compared to that used by Loser et al, consisting in 100 g of white bread, 20 g of butter, 30 g of chocolate and nutcream and 250 mg of ^{13}C-mixed triglycerides and breath samples were collected for 8 hours while subjects remained seated. With all these devices, sensitivity was 100% and specificity 92%, compared to secretin test. These promising results, derived from a study including 10 healthy volunteers and 9 patients with heterogeneous pancreatic disease (3 with longstanding chronic pancreatitis, 3 with first diagnosis of chronic pancreatitis, 1 with recurrent acute pancreatitis) of unknown etiology and 1 complaining abdominal pain with hyperlipasemia and a previous acute pancreatitis, so they need to be confirmed in a larger and more homogenous group of patients[17].

Conclusions

None of the non-invasive pancreatic function tests is sensitive enough to diagnose a mild to moderate exocrine pancreatic insufficiency[24]. The ^{13}C-mixed triglyceride breath test, the most studied among pancreatic breath tests, could only diagnose pancreatic insufficiency with maldigestion, that typically occurs in advanced stages of pancreatic disease. Breath tests could not be used in clinical practice to early diagnosis of chronic pancreatitis, but they could have a role in the individually modulated enzyme replacement therapy in patients with known pancreatic insufficiency.

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Conflict of interest

The Authors disclose that they have no conflict of interests.

References

1) Dominguez Munoz JE. Diagnosis of chronic pancreatitis: Functional testing. Best Pract Res Clin Gastroenterol 2010; 24: 233-241.
2) Braden B. (13)C breath tests for the assessment of exocrine pancreatic function. Pancreas 2010; 39: 955-959.
3) Chowdhury RS, Forsmark CE. Review article: Pancreatic function testing. Aliment Pharmacol Ther 2003; 17: 733-750.
4) Dominguez-Munoz JE, Hieronymus C, Sauerbruch T, Malfertheiner P. Fecal elastase test: evaluation of a new noninvasive pancreatic function test. Am J Gastroenterol 1995; 90: 1834-1837.
5) Keller J, Layer P. Pancreatic enzyme supplementation therapy. Curr Treat Options Gastroenterol 2003; 6: 369-374.
6) Glasbrenner B, Schon A, Klatt S, Beckh K, Adler G. Clinical evaluation of the faecal elastase test in the diagnosis and staging of chronic pancreatitis. Eur J Gastroenterol Hepatol 1996; 8: 1117-1120.
7) Loser C, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut 1996; 39: 580-586.
8) Lankisch PG, Schmidt I. Fecal elastase 1 is not the indirect pancreatic function test we have been waiting for. Dig Dis Sci 2000; 45: 166-167.
9) Evenepoel P, Hiele M, Geypens B, Geboes KP, Rutgeerts P, Ghoos Y. ^{13}C-egg white breath test: a non-invasive test of pancreatic trypsin activity in the small intestine. Gut 2000; 46: 52-57.
10) Ishii Y, Kohno T, Ito A, Suzuki S, Kohno T, Takayama T, Asai S. Measurement of extra-pancreatic secretory function by ^{13}C-dipeptide breath test. Transl Res 2007; 149: 298-303.
11) Kohno T, Ito A, Hosoi I, Hirayama J, Shibata K. Synthetic ^{13}C-dipeptide breath test for the rapid assessment of pancreatic exocrine insufficiency in rats. Scand J Gastroenterol 2007; 42: 992-999.
12) Ishii Y, Kohno T, Ito A, Suzuki S, Kohno T, Takayama T, Asai S. Evaluation of pancreatic exocrine secretion using ^{13}C-dipeptide (benzoyl-L-tyrosyl-[1-(13)C]alanine) breath test: focusing on pancreatoduodenectomy cases. Pancreas 2007; 35: 313-319.
13) van Dijk-van Aalst K, Van Den Driessche M, van Der Schoor S, Schiffelers S, van't Westeinde T, Ghoos Y, Veereman-Wauters G. ^{13}C mixed triglyceride breath test: a noninvasive method to assess lipase activity in children. J Pediatr Gastroenterol Nutr 2001; 32: 579-585.
14) Nakamura H, Morifuji M, Murakami Y, Uemura K, Ohge H, Hayashidani Y, Sudo T, Sueda T. Usefulness of a ^{13}C-labeled mixed triglyceride breath test for assessing pancreatic exocrine function after pancreatic surgery. Surgery 2009; 145: 168-175.
15) Kato H, Nakao A, Kishimoto W, Nonami T, Harada A, Hayakawa T, Takagi H. ^{13}C-labeled trioctanoin breath test for exocrine pancreatic function test in patients after pancreatoduodenectomy. Am J Gastroenterol 1993; 88: 64-69.
16) Weaver LT, Amarri S, Swart GR. ^{13}C mixed triglyceride breath test. Gut 1998; 43(Suppl 3): S13-19.
17) Keller J, Bruckel S, Jahr C, Layer P. A modified (1)(3)C-mixed triglyceride breath test detects moderate pancreatic exocrine insufficiency. Pancreas 2011; 40: 1201-1205.
18) Kalivianakis M, Verkade HJ, Stellaard F, van der Were M, Elzinga H, Vonk RJ. The ^{13}C-mixed triglyceride breath test in healthy adults: determinants of the ^{13}CO2 response. Eur J Clin Invest 1997; 27: 434-442.
19) Ghoos YF, Vantrappen GR, Rutgeerts PJ, Schurmans PC. A mixed-triglyceride breath test for intraluminal fat digestive activity. Digestion 1981; 22: 239-247.
20) Vantrappen GR, Rutgeerts PJ, Ghoos YF, Hiele MI. Mixed triglyceride breath test: a noninvasive test of pancreatic lipase activity in the duodenum. Gastroenterology 1989; 96: 1126-1134.
21) Jonderko K, Dus Z, Szymszal M, Kasicka-Jonderko A, Blonska-Fajfrowska B. Normative values for the ^{13}C-mixed triglyceride breath test in two age groups. Med Sci Monit 2009; 15: CR255-259.
22) Dominguez-Munoz JE, Iglesias-Garcia J, Vilarino-Insua M, Iglesias-Rey M. ^{13}C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2007; 5: 484-488.
23) Loser C, Brauer C, Aygen S, Hennemann O, Folsch UR. Comparative clinical evaluation of the ^{13}C-mixed triglyceride breath test as an indirect pancreatic function test. Scand J Gastroenterol 1998; 33: 327-334.
24) Siegmund E, Lohr JM, Schuff-Werner P. [The diagnostic validity of non-invasive pancreatic function tests—a meta-analysis]. Z Gastroenterol 2004; 42: 1117-1128.