Leading article

A perspective on the use of tubeless pancreatic function tests in diagnosis

For many years, gastroenterologists have searched for the holy grail of pancreatic function tests—the tubeless test. The quest is to find an accurate, simple, easy, sensitive, and specific non-invasive test that can detect mild to moderate decreased exocrine function in patients without signs of pancreatic disease on imaging tests. Such a test would increase the possibility of diagnosing early chronic pancreatitis and perhaps pancreatic cancer as pancreatic function may decrease in pancreatic diseases before imaging tests become abnormal. However, tests based on decreased exocrine function can never be one hundred per cent sensitive for the diagnosis of chronic pancreatitis; even some patients with pancreatic calcification, a recognised hallmark of advanced chronic pancreatitis, have normal exocrine function.¹

Generally, modern tubeless tests satisfactorily distinguish pancreatic from non-pancreatic malabsorption as they are sensitive indicators of pancreatic disease when pancreatic function is severely decreased. However, for pancreatic insufficiency to be severe enough to produce malabsorption, secretion of pancreatic enzymes must be 5–10% or less than normal.^{2,3} In this case, pancreatic disease is advanced and the diagnosis often is obvious by other means. Therefore, tubeless tests are highly sensitive only when malabsorption is present and generally are not a useful clinical test with which to make the diagnosis of chronic pancreatitis.

The foundation of non-invasive tubeless tests rests on decreased pancreatic function increasing the amounts of unabsorbed food (fat, protein, carbohydrate) in stool or decreasing the amount of enzymes (for example, chymotrypsin, elastase, amylase, lipase) in the blood or faeces. Compounds also have been designed and synthesised that are hydrolysed within the gut lumen by pancreatic enzymes. Use of these compounds as pancreatic function tests is based upon measuring decreased amounts or concentrations of the products of the synthetic compounds (for example, *N*-benzoyl-L-tryptophyl-*p*-amino benzoic acid (NBT-PABA), fluorescein dilaurate (pancreolauryl)) that appear in the stool, urine or blood after intraluminal hydrolysis and gut absorption.^{4–6} Breath tests have also been developed that measure ¹³CO₂ or ¹⁴CO₂ in breath after ingestion of a labelled substrate (triolein, cholesteryl octanoate, mixed triglyceride (distearyl, octanoyl glycerol) or starch).^{7–15}

None of these tests is used routinely in clinical practice because they are usually complex requiring a number of samples of blood, urine or stool and because they generally lack sensitivity and specificity. Several more recent examples of non-invasive, tubeless tests of exocrine pancreatic function including the amino acid consumption test (AACT),^{16–22} the faecal pancreatic elastase 1^{23–29} and the fluorescein dilaurate (pancreolauryl) tests epitomise how these tests are at first promoted as accurately assessing pancreatic function because they are initially tested in patients with malabsorption due to exocrine insufficiency. Later, they are found to be insensitive for

mild to moderate insufficiency and non-specific when they are tested in patients with mild to moderate exocrine insufficiency and in appropriate control groups who have malabsorption not due to exocrine pancreatic insufficiency.

The AACT is based on the premise that stimulating the pancreas with exogenous hormones increases uptake of amino acids from the circulation and that a healthy pancreas depletes plasma amino acids more than an impaired gland. Several investigators reported that intravenous infusion of secretin and cholecystokinin (CCK),^{16,17} secretin and cerulein¹⁸ or cerulein alone¹⁸ decreased amino acids in normal subjects but not in patients with chronic pancreatitis, and that this was an accurate measure of exocrine pancreatic function and discriminated among patients with varying degrees of pancreatic insufficiency. However, we²⁰ and others¹⁹ found that the AACT in response to CCK-OP²⁰ or cerulein and secretin¹⁹ did not reliably predict pancreatic function or discriminate between normal subjects and patients with chronic pancreatitis. Furthermore, Kemmer *et al* found that AACT did not discriminate between subjects with normal and abnormal pancreatic function classified by the pancreolauryl test.¹⁹ At present, most pancreatologists, including one of the former proponents of this test, have concluded "...the sensitivity of the AACT is relatively high, but...the specificity is low, making the test unsuitable for clinical use...".²²

Currently, there is controversy regarding whether the measurement of faecal pancreatic elastase 1 with an enzyme linked immunosorbent assay is an accurate measure of exocrine pancreatic function. Loser *et al* cite excellent sensitivity to detect mild to moderate exocrine insufficiency, confirmed by an invasive pancreatic function test,²⁹ but Lankisch *et al* find very low sensitivity in patients with mild to moderate exocrine insufficiency.²⁸ Similarly, some investigators found relatively high sensitivity,^{24,25} whereas others found low sensitivity (0 to <50%)^{23,26} in subjects with the diagnosis of mild to moderate chronic pancreatitis made on the basis of imaging studies such as computed tomography, endoscopic retrograde pancreatography or roentgenograms of the pancreatic area. As with most non-invasive pancreatic function tests, the faecal elastase test has been found to be non-specific; the majority of patients with non-pancreatic malabsorption have false positive test results.²⁷

Among the tubeless exocrine pancreatic function tests, the pancreolauryl test (PLT) is perhaps the best, distinguishing among all degrees of exocrine function and detecting patients with moderate insufficiency. The basis of this test is that fluorescein dilaurate, after ingestion with a standard breakfast, is hydrolysed by pancreatic cholesterol esterase, releasing fluorescein, which is readily absorbed by the gut, conjugated by the liver, released into the circulation, and excreted into the urine. Most commonly,

serum concentrations are measured, which can be done within several hours thereby avoiding prolonged collection of urine and has the same sensitivity and specificity as the urine collection.⁴

However, there is general agreement that the sensitivity of PLT for detecting patients with mild degrees of exocrine pancreatic function or mild to moderate chronic pancreatitis is about 50%⁴⁻⁵; in severe insufficiency or advanced, severe chronic pancreatitis sensitivity exceeds 85%.⁴⁻⁶ In the study comparing PLT with exocrine pancreatic function,⁴ function was measured by the combining the results of a quantitative faecal fat collection and the secretin-CCK test. Degrees of exocrine function were classed as mild (reduced output of at least one enzyme and normal fat excretion), moderate (low enzyme output and bicarbonate concentration with a normal fat excretion) and severe (low enzyme output, bicarbonate concentration and steatorrhoea). In the studies to test the sensitivity and specificity of PLT compared with severity of chronic pancreatitis,^{5,6} severity of chronic pancreatitis was assessed by the ductal changes observed with endoscopic retrograde cholangiopancreatography.

In addition, PLT, in common with most tubeless tests, is non-specific because of the indirect nature of the test. Before the indicator is measured in either blood or urine, the original substance generally must undergo mixing with pancreatic secretions, digestion, micellar solubilisation, absorption by the gut, and conjugation by the liver. Hence, with PLT and many other tubeless tests false positive results occur in patients who have a gastrectomy, hepatobiliary disease or a mucosal small bowel disease such as coeliac disease and inflammatory bowel disease. With breath tests, false positive test results also occur in patients who have a respiratory or a metabolic disease (diabetes mellitus, thyroid disease) with reduced pulmonary function or altered production of CO₂.

This discussion highlights the general dilemma with non-invasive pancreatic function tests. Usually non-invasive pancreatic function tests are sensitive for the detection of severe exocrine insufficiency or chronic pancreatitis. However, no non-invasive pancreatic function test, including faecal elastase 1, has been found to be consistently sensitive by a number of investigators in mild to moderate exocrine or mild to moderate chronic pancreatitis. Therefore, non-invasive tests are not useful in this latter group of patients who are most difficult to diagnose.

Thus, at present the only uses for non-invasive tests are to use them in a general medical or surgical practice to screen for pancreatic insufficiency (because of their high positive predictive value in some studies) or to assess the efficacy of pancreatic enzyme replacement in patients with known severe exocrine insufficiency who are being treated with exogenous enzymes.⁷⁻¹⁵ However, in the former case even if a test is abnormal, the high false positive rate in non-pancreatic malabsorption reduces the usefulness and an invasive pancreatic function test may be needed if a non-pancreatic explanation for malabsorption is not found or if the non-invasive test is normal and there is a persistent suspicion of pancreatic disease. In our gastroenterology practice where detection of definite pancreatic disease in patients who are suspected, but not proved to

have pancreatic disease is paramount, we only use a highly sensitive and specific invasive pancreatic function test.^{2-20,30}

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