Chronic Pancreatitis: Diagnosis and Staging

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G. MANES*, S. KAHL, B. GLASBRENNER and P. MALFERTHEINER

Department of Gastroenterology, Hepatology and Infectious Disease Otto-von-Guericke University Magdeburg, Germany
Doctor Gianpiero Manes is the recipient of a grant of the Alexander von Humboldt Foundation in the Department of Gastroenterology of the University of Magdeburg, Director Prof. P. Malfertheiner
*The current address of doctor Manes is: Department of Gastroenterology, Cardarelli Hospital, Via Cardarelli 9, 80131 Napoli, Italy

Abstract

Chronic pancreatitis is a dynamic disease characterized on one side by a progressive destruction of the pancreatic parenchyma and change in the architecture of the gland and on the other by the impairment of its function. Diagnosis of chronic pancreatitis may be a quite easy or a very difficult attempt according to the severity and evolutive stage of disease. In fact, while most patients present with a typical history of alcohol abuse, recurrent abdominal pain and steatorrhea, in the late stage of disease it is not rare to see patients with symptoms and signs which may be not typical for pancreatitis. A large number of morphological and functional methods has been developed to allow an easy and early diagnosis of disease. However, while in the advanced stages of disease, where pancreatic insufficiency, calcifications, or pseudocysts are present, diagnosis is easy and most of the procedures show high sensitivity and specificity, in the early disease the degree of pancreatic dysfunction and structural change are too small to be detected by current methods.
The present article aims to evaluate the different morphological and functional methods with their advantages and shortcomings, as well as to establish their role in the diagnostic assessment of chronic pancreatitis.

Riassunto

PANCREATITE CRONICA: DIAGNOSI ED IMAGING

La pancreatite cronica è una patologia evolutiva caratterizzata da un lato dalla progressiva distruzione del parenchima pancreatico con alterazioni della sua architettura e dall'altro dalla perdita della funzione esocrina ed endocrina della ghiandola. La diagnosi di pancreatite cronica può essere molto semplice o estremamente difficile a seconda dello stadio evolutivo della malattia. Infatti mentre molti pazienti mostrano una tipica storia di alcolismo, di dolore addominale ricorrente e steatorrea, non è raro vedere pazienti con sintomi non tipici di malattia. Un gran numero di metodiche funzionali e di imaging è stato sviluppato ai fini di una diagnosi semplice e precoce di pancreatite cronica. In realtà, mentre negli stadi avanzati di malattia, quando calcificazioni, pseudocisti o steatorrea si sono sviluppate, la diagnosi è semplice e quasi tutte le metodiche mostrano elevati valori di sensibilità e specificità, nelle fasi iniziali di malattia le alterazioni morfologiche e funzionali sono troppo lievi per poter essere riconosciute dalle metodiche attuali.

Introduction

Chronic pancreatitis (CP) is a dynamic, evolutive disease in which a progressive destruction of the pancreatic parenchyma due to inflammation and consequent biosynthesis of large amounts of fibrotic tissue leads to a complete change in the architecture of the gland and impairment of its function. The picture of the patient who after years of alcohol abuse and a history of recurrent abdominal pain develops steatorrhea is typical of the end stage of the disease and does not represent a diagnostic problem at the common morphological and functional procedures. However, most of the patients present in an earlier stage of the disease with symptoms and signs which may be not typical for CP. Furthermore, functional and morphological procedures do not provide unequivocal diagnostic information in the early stage of disease. The exact knowledge of the clinical natural history of disease represents an important tool in order to recognize patients who do not show the typical clinical picture of the disease as well as to identify the diagnostic procedures which may provide information in the different phases of CP.

Clinical course

Abdominal pain, pancreatic insufficiency (exocrine and endocrine), and local complications are the three main clinical manifestations of CP. They may occur together or

Il presente articolo ha lo scopo di analizzare le diverse metodiche funzionali e di imaging oggi disponibili nella diagnosi di pancreatite cronica con i rispettivi vantaggi e svantaggi ed il ruolo di ciascuna di esse nell'iter diagnostico della malattia.

separately in the different phases of CP. According to the classical description of Amman et al. (1) the clinical course of CP shows an early, an intermediate and a final stage. In the early phase, patients suffer from recurrent episodes of abdominal pain with a normal pancreatic function. In this phase morphological tests provide equivocal findings, while the pancreatic function tests are still normal. Pain is in this phase usually recurrent and sometimes related to acute relapse of pancreatitis. Inflammation of the gland and inflammatory neural involvement are likely to play a major role in its pathogenesis (2, 3). The evolution of the disease leads to the progressive alteration of the pancreatic architecture with development of ductal stricture and pseudocysts. Pain tends to occur more frequently and becomes even continuous; it is determined by the development of parenchymal hypertension and/or pseudocysts. Pancreatic function is abnormal at function tests but pancreatic insufficiency and steatorrhea are not yet present. Local complications such as pseudocysts, cholestasis, and segmental portal hypertension usually develop in this phase and may influence the clinical presentation of the disease. In the end stage of the disease, the pancreatic gland is totally fibrotic and calcifications are usually present. Exocrine (steatorrhea) and endocrine (diabetes mellitus) pancreatic insufficiency appear, while pain tends to disappear in the so-called "burning out pancreas". In this phase, diagnosis of CP is easy and the biggest problem is usually to differentiate CP from pancreatic cancer. Some differences in the clinical course can be detected according to the etiology of CP. In alcoholic CP, the onset is typically characterized by an episode of acute pain during the third or fourth decade of life. Pain is the first symptom of disease in 80-90% of individuals with alcoholic CP, and in about 50% of patients the disease begins with an episode of acute pancreatitis. After some years during which pain may occur at intervals of months or years, it tends to become less intense but more frequent or even continuous, or conversely to decrease in intensity and frequency paralleling the fibrotic transformation of the gland (1, 4, 5). In the idiopathic CP, the clinical features of disease depend on the age of patient at the onset of disease (6, 7). In patients with the early-onset form, pain is the first symptom, occurring usually before the age of 35, and pancreatic insufficiency appears 10-20 years later. In the late-onset form, steatorrhea or diabetes mellitus are the first clinical symptoms usually in individuals with a median age of 55 (4, 5).

Imaging in chronic pancreatitis

Imaging procedure play nowadays a leading role in the diagnosis and staging of CP, as well as in the early detection and follow-up of complications of the disease.

From abdominal Ultrasonography and Endoscopic Ultrasound

Ultrasonography (US) is inexpensive, non-invasive and well-tolerated and therefore is usually the first diagnostic procedure in patients with symptoms suggestive of chronic pancreatitis. In addition, it is of particular value for monitoring the course of disease and the development of complications.

The pancreas size, shape and echo-texture, as the main duct morphology and the presence of complications can be identified by US. However, the US findings in CP may be very variable, depending on the cause of CP, as well as on its stage.

The size of the pancreas may be enlarged in the early and moderate stage of disease, especially during an acute relapse. The pancreas size returns to normal or even smaller with the progression of the disease when atrophy develops (8, 9). In most cases the enlargement is focal, usually localized at the head of the gland (10). Alterations of the pancreas size due not a specific sign of CP since they present in only 38-55% of patients (8, 11) and can be found occasionally without disease. The pancreas shape is usually described as altered in advanced stages of CP. However, this finding is not constant and an altered pancreatic shape is described in other pathological conditions such as neoplasms and in anatomic variations (8, 12).

An increased or heterogeneous echogenity with multiple tiny hyperechoic spots is usually considered as a typical finding of CP. According to different authors, only 53-74% of patients with CP have an altered echo-texture (8, 13). On the other hand an increased echogenicity of the gland may be observed in healthy individuals, especially in elderly and in obese (14, 15).

The main pancreatic duct appears at US as an anechoic structure delimited by an echogenic wall. In the early phase of CP an increased echogenicity of the wall due to increased surrounding fibrotic tissue is described as a sign of disease. This sign is far to be specific and sensitive (8, 11). In advanced disease the main duct becomes irregularly dilated, with abnormally visible edges. Hyperechoic areas with US shadowing can be observed within the dilated duct due to the presence of calcifications. These aspect is quite specific for CP (16). The diffuse irregularity of the duct helps in the differential diagnosis with pancreatic cancer in which the upstream dilatation to the stenosis is smoothly regular.

An attempt to improve the diagnostic value of US has been made by introducing the secretin stimulation of the pancreatic gland. The lack of increase in the diameter of the main duct following intravenous bolus injection has

been interpreted as sign of the disease (17, 18). On the other hand, a prolonged dilatation of the pancreatic duct is described in patients with pancreas divisum and abdominal pain, who might benefit from sphincterotomy of the minor papilla.
Detection of local complications of CP is a domain of US. Stenosis of the common bile duct and portal hypertension are easily detected by US. US is the most suitable in the detection of pancreatic pseudocysts as well as their size, localization, and evolution. Pseudocysts appear at US as hypo-anechoic spheric areas within or outside the pancreas. The pattern of the content allows detection of complications: a more echoic zone in the lower part of the cyst, especially if associated with its enlargement and development of abdominal pain, is suggestive of a bleeding. A cyst completely filled with echoic material is probably an infected pseudocyst or an abscess (19).
The differential diagnosis between CP and pancreatic cancer is usually easy by US, due to different US findings. However, cancer may develop on a preexisting CP. In this case, diagnosis becomes more difficult, since the hypoechoic area of the cancer may be not easily recognizable in the heterogeneous echogenicity of the pancreas.
In the diagnosis of CP, US has an accuracy that ranges between 60-80%. Stage of disease and adopted US diagnostic criteria influence the accuracy of the method (11, 13, 20-22). In the early stage of CP a large number of false negative occurs; conversely, false positive may occur if too much confidence is given to single less specific signs. In the follow up of CP and in the detection of complications, US plays surely a more important role and, due to its non-invasiveness, has to be considered the most important diagnostic tool.
Endosonography offers a better imaging of the pancreatic tissue. Hyperechoic parenchymal spot, multialveolar shape, and the thickened duct wall are recognized earlier and allow a diagnosis in the early stages of disease (23, 24). However, the better sensitivity is accompanied by a low specificity due to the fact that the same parenchymal alterations are present also in diabetes, alcoholism and in elderly. Endosonography is also likely to permit a more accurate differential diagnosis with pancreatic cancer, although opinions are still discordant (25).

Computed tomography

The introduction of high resolution CT scans and the new spiral technique provide excellent images of the pancreas parenchyma and ductal system. In particular, CT allows a very reliable evaluation of the parenchyma, similarly to US; the main duct can be also assessed, while the small ducts are usually not detected. Peripancreatic structures such as vessels and fat are also evaluated by CT. The pathological feature of CP by CT are similar to those obtained by US. The considerations reported above for US regarding the shape, size and duct system of the pancreas can therefore be applied to CT. The normal pancreatic duct caliber varies from 2 to 3 mm, in the elderly up to 4 mm. A dilation of the main pancreatic duct is found in up to two thirds of cases of CP (26); while a mild dilation (up to 4 mm) of the main duct is not specific for CP, an irregular duct dilation greater than 4 mm is a pathognomonic CT finding (27). CT is not able to detect ectatic side branches, which are usually better assessed by ERCP.
CT shows a higher sensitivity than US in detecting pancreatic calcifications, even small (27). This finding is highly specific for advanced CP.
Also in the detection of pancreatic pseudocysts CT is very accurate (26, 27). By CT, it is possible to evaluate their size, localization (intra- or extrapancreatic; involvement of adjacent organs), and other characteristics (cystic wall, septa, content); development of cyst complications, such as cyst infection (development of gas within the cyst), rupture, fistulae, and bleeding is assessed with reliability by CT.
Similar to US, CT accuracy in diagnosing CP is highly variable (22, 28-30), depending primarily on the criteria used in the diagnosis and on the stage of the disease. In early stage, the accuracy is about 50% (30); in this stage of disease, recognition of single alterations is non-specific and could lead to false positive diagnosis. In advanced stages of disease, CT becomes accurate in detecting the organ damage and it is valuable to follow the further progresses of CP. Although, some clinicians recommend US because of its lower cost, CT clearly is superior in the broad spectrum of information it provides and in the rarity of technically unsatisfactory examination. CT is helpful in differentiating pancreatic cancer from CP and for detecting the complications of CP. Furthermore, CT appears to be an essential method for planning the strategy of surgical intervention.
The recently introduced magnetic resonance (MR) and MR cholangiopancreatography (MRCP) have been also applied to patients with CP. MRCP can display the main pancreatic duct and its findings agree with those of ERCP in about 80-90% of cases with dilation, narrowing and filling defects (31). However, the exact role of MR and MRCP vis a vis ERCP and CT has not yet been defined and they may probably serve as an alternative form of imaging (32).

Endoscopic retrograde cholangio-pancreatography (ERCP)

Abnormalities of the main pancreatic duct and its side branches are highly specific features of CP and occur early in the course of disease. In this way, ERCP appears to be the most reliable method in the early diagnosis of CP. As a matter of fact, ERCP is considered the gold standard among the different imaging methods in the diagnosis of CP. The typical ERCP findings in CP have been defined in the Meeting of Cambridge in 1983 (33, 34). Caliber and contour of the main pancreatic duct and side branches,

number and length of side branches, parenchymal opacification, presence of cavities, and the bile duct system in the region of the head of the pancreas should be analyzed. Focal or diffuse irregular dilatation of the main duct and its branches is a specific feature of CP. If alterations are limited to the side branches they indicate mild CP. In case of abnormal main pancreatic duct, CP is moderate. Severe CP is characterized by an abnormal main duct with at least one of the following findings: cavity, obstruction, filling defects, severe dilation or irregularity.

ERP has a higher accuracy than US and CT in the diagnosis of CP (35), with a sensitivity and specificity that are about 80 and 90% respectively (20, 30, 36-40). The benefits of ERCP also include the possibility of discovering additional finding in the stomach, duodenum and papilla, the simultaneous evaluation of the bile duct, and the extension of diagnosis by biopsy, collection of pancreatic juice for cytology and detection of biochemical markers. Manometry and pancreatoscopy are other highly specialized investigations performed by using the ERCP access. To limit the use of ERCP is the fact that it is more difficult to perform and more invasive; furthermore, in the early stages of CP, ERCP has a limited sensitivity, and its overall accuracy is reduced in individuals with pancreatic cancer and in elderly (27, 41). In spite of the fact that the ductal patterns of CP and pancreatic cancer are quite different at ERCP (Tab. I), problems sometimes arise in differentiating ductular changes determined by CP from those of pancreatic cancer (42); on one side a chronically destructed duct system may mask a supervening malignant lesion; on the other hand, chronic inflammatory changes particularly in focal pancreatitis are able to mimic the ductal patterns usually displayed by carcinoma (43).

In conclusion ERCP is the most accurate imaging method in the diagnosis of CP. Furthermore, it provides a number of information on the pancreatic duct system and bile duct that may help in understanding symptoms and planning endoscopic or surgical treatment. Limitations of ERCP regard the early stage of CP and the differential diagnosis with cancer. In this case, ERCP findings may be interpreted by means of US, CT and function tests.

Sensitivity and specificity values of different imaging procedures in the diagnosis of chronic pancreatitis are reported in Table II.

Functional diagnosis of CP

In the pre-US and -CT era, diagnosis of CP was based primarily on the recognition of a reduced pancreatic function, usually by invasive tests such as secretin-cerulein test (SC test). The introduction of new imaging methods has relegated the functional tests to a secondary role and even the introduction of newer, non-invasive tests did not promote the use of functional testing in the clinical

Tab. I – DUCTAL PATTERN IN CHRONIC PANCREATITIS AND PANCREATIC CANCER AT ERCP

Aspect of pancreatic duct	*Chronic pancreatitis*	*Pancreatic cancer*
Obstruction contour	Smooth, hemispheric	Irregular, tapered, blunt, pointed, or serrated
Stricture		
Number	Multiple	Singular
Contour	Smooth transition of caliber, flat rod- or spindle-like	Abrupt change of caliber, irregular, eccentric, or serrated
Length	Short (< 5mm)	Usually > 10 mm
Pancreatic duct		
Upstream	Tortuosity, irregular dilation	Regular dilation
Downstrean	Tortuosity, irregular, “chain of lakes”	Normal aspect
Side branches		
At level of stricture	Ectatic, irregular	Lost or destructed
Downstream	Ectatic, irregular	Normal aspect
Upstream	Ectatic, irregular	Regular dilation
Calcifications	Frequent	Rare
Extravasation pattern	Regular contour, cystic	Irregular cavity, Diffuse extravasation
Common bile duct		
Stenosis	Medium to high grade	Mostly high grade
Contour	Smooth, tube-like, symmetric	Irregular, asymmetric
Length	Mostly > 1mm	Mostly short

Tab. II – ACCURACY OF IMAGING PROCEDURES IN THE DIAGNOSIS OF CHRONIC PANCREATITIS

	Sensitivity (%)	*Specificity (%)*
Ultrasonography	48-90	75-90
Computed tomography	56-95	85-90
Endoscopic retrograde pancreatography	68-100	89-100
Endosonography	85%	85-100%
*Magnetic resonance		
*MR cholangiopancreatography		

*Not yet sufficienthy defined

diagnostic routine. Testing of pancreatic function remains controversial; these tests are widely used in Europe, while in USA the use are quite limited. Two problems are inherent in each of the tests: First, in minimal disease the degree of pancreatic dysfunction is too small to be detected by current tests, with the exception of the SC-test; secondy, pancreatic tumors, which cause obstruction of the pancreatic duct system also determine pancreatic dysfunction. However, it seems clear that imaging procedures combined with function tests provide the best diagnosis and the most accurate means of staging CP. Functional evaluation in CP may be assessed by performing intubation tests with stimulation of the pancreas, by oral tests, by measuring serum and fecal pancreatic enzyme, as well as by evaluating the endocrine function of the gland.

Direct function tests

Direct tests, based on duodenal intubation and analysis of duodenal aspirate following hormonal stimulation of the pancreas, still remain, after many years from their introduction, the most reliable tests for pancreatic function. Furthermore, they represent without a doubt, the best means of defining the diagnosis and stage of CP, being superior to current imaging methods, which show an insufficient sensitivity in mild disease (44-48). Maximal, or near maximal stimulation of the pancreas is usually achieved by the combined iv infusion of secretin with cholecystokinin (CCK) or cerulein (SC test). Amylase, lipase, trypsin, chymotrypsin and bicarbonate are determined in the sampling fractions of duodenal aspirate. In early stages of CP, only one or two parameters are reduced, usually lipase (44) or, according to other authors, amylase (45) or bicarbonate (48). In advanced stages, all these parameters are decreased. SC test has a high accuracy in the diagnosis and staging of CP with values of sensitivity and specificity higher than 90% (44-48). However, the test is invasive, time consuming, and expensive, and is performed only in specialized centers. Its use is, as a consequence, very limited and restricted to special cases in which the current imaging and functional procedures are not conclusive. The Lundh test has been developed with the aim of overcoming these disadvantages. The hormonal stimulation of the pancreas has been substituted by the administration of a test meal, and only the mean tryptic activity but not the overall output of trypsin is determined in the duodenal aspirate (47, 49, 50). However, the test is not substantially easier than the SC test and its accuracy appears to be lower, especially in the mild CP (47, 50).

Indirect function tests

Exocrine pancreatic function can be indirectly assessed measuring the concentration of pancreatic enzymes in serum or feces, or evaluating their effect on a test meal, by determining the concentration in urine, serum or breath of the products of their enzymatic activity.

Serum and fecal pancreatic enzymes

In CP, serum concentration of different pancreatic enzymes may be increased, normal or decreased (51-53). Increased concentrations are present in 22-39% of patients with CP, decreased in 20-32% and normal in 49-71% (54). A decreased serum concentration is very specific for pancreatic insufficiency, but not enough sensitive (51, 53-55). A decreased P-amylase/lipase ratio has been described in one study to be very specific for CP and to have a high accuracy in differentiating mild/moderate from severe forms of CP (54), but no further confirmation from other studies has been added.

Measurement of chymotrypsin activity in feces is a simple, cheap and non invasive method to assess the exocrine pancreatic function. The diagnostic accuracy of this test is however low; false normal values occur in mild CP and when oral pancreatic enzymes are ingested. False positive results appear in diarrhea, protein-losing enteropathy and in diseases where the pancreas is only insufficiently stimulated (cachexy, resection of the stomach, anorexia nervosa, obstructive jaundice) (56). This fact limits the use of this test that can be performed to differentiate pancreatic from intestinal steatorrhea.

In the last years a new ELISA method has been developed to measure concentration of human specific pancreatic elastase in feces. Pancreatic elastase is highly stable along the intestinal tract and its concentration in feces is not influenced by pancreatic enzyme supplementation. Its specificity in the diagnosis of CP is significantly higher than that of fecal chymotrypsin, ranging from 80 to 90%, and it makes this test of special value in the assessment of exocrine pancreatic function in patients with other GI disease or under oral enzyme substitution. However, the detection of mild forms of CP remains a problem (57,58) and the diagnostic accuracy of the test in a prospective clinical population of patients with abdominal pain is limited (59). It is an error to suppose that fecal elastase enables us to diagnose CP by a simple stool test.

Oral function tests

These tests are based on the oral administration of a substrate, and on the determination in serum or urine of the concentration of the products that are liberated from this substrate by specific pancreatic enzymes and absorbed from the gut. The NBT-PABA (nitro blue tertrazolium-*para*-aminobenzoic acid) test is based on the urinary recovery of PABA after the oral administration of a complex NTB-PABA. PABA is liberated by pancreatic chymotrypsin, and then after being adsorbed in the intestinal lumen and conjugated in the liver, is excreted in the urine. In the pancreolauryl test (PLT) the substrate is represented by fluorescein esterified with two molecules of lauric acid. This complex is hydrolyzed by a specific pancreatic cholesterol-esterase and the fluorescein, liberated into the intestinal lumen, is absorbed by the intestinal mucosa and then excreted *via* the kidneys. These tests are cheap, easy to perform, with a high reliability in recognizing severe exocrine pancreatic insufficiency. However, they have a low sensitivity in mild/moderate CP and a relatively high number of false positive in the GI diseases that can influence the gastrointestinal transit, and the intestinal absorption (60-64). To overcome the limitations related to urine sampling, new methods to measure serum concentration of PABA and fluorescein have been introduced (63, 64). Furthermore, the duration of the serum pancreolauryl test has been shortened, and its sensitivity in detecting mild/moderate forms of CP improved by means of intravenous administration of metoclopramide and secretin to stimulate gastric emptying and pancreatic secretion respectively (65, 66). Our procedure in performing the serum PLT is reported in Table III. In our series, this test shows overall sensitivity and specificity near to 90% in the diagnosis of CP in different stages. However, false positive results are frequently obtained in postgastrectomy patients, in patients with extensive intestinal inflammatory disease or in general in all patients with gastrointestinal and hepatobiliary diseases that interfere with the gastrointestinal transit and the intestinal absorbitive capacity (65-67).

Tab. III – PROCEDURE FOR THE MODIFIED SERUM PLT (64, 65)

- After an overnight fasting, basal blood collection;
- assumption of a standard test meal: 40g of white bread spread with 20 g of butter and 200 ml of tea without sugar. The content of two capsules of fluorescein dilarate is mixed with the butter;
- intravenous administration of secretin (1U/kg body weight) and metoclopramide (10 mg) in
- bolus;
- serum collection at 30, 60, 90, 120, 150, 180, 180, and 240 min for fluorescein measurement;

A fluorescein peak of 4.5µg/ml is considered as cutoff between normal (>) and abnormal (<)

Other indirect pancreatic function tests

A recently introduced indirect pancreatic function test is based on the measurement of plasma amino acids consumption following pancreas stimulation. In fact, under stimulation with secretin and/or cerulein, the pancreas assumes large amount of plasma amino acids to produce and secrete proteins, i.e. pancreatic enzymes. In patients with severe pancreas insufficiency, a significantly lower decrease in amino acids plasma concentration than in controls is detectable (68, 69) and it has been suggested that concentration of some amino acids (serine, isoleucine and histidine) is mainly related to the degree of pancreatic insufficiency. The accuracy of this test in detecting pancreatic insufficiency varies according to different authors (68-70), and the good results found in the first studies (68, 69) were not confirmed by other groups (70). This test is usually not performed in the clinical routine. Quantitative fecal fat analysis after appropriate fat rich diet is a low sensitive test, usually able to recognize only an end-stage pancreatic insufficiency, when the exocrine pancreatic capacity is reduced by more than 85% from normal. In clinical practice its use is seldom relevant in the diagnosis of the disease, but in patient's management quantification of fecal losses is relevant for therapeutic purpose and for monitoring the efficacy of an oral enzymatic substitution treatment. The daily fat excretion is adopted as index of malabsorption, though measurement of fecal fat does not differentiate between pancreatic and non-pancreatic dysfunction. The 72-hour stool collection is the gold standard. However, for an accurate fat balance, complete fecal collection, weighting, homogenization, and then fat assay are steps needed under a five-day standard diet with a defined fat content (71). This is actually not easy, it is time consuming, the assay is uncomfortable, and it explains why fecal fat balance is seldom carried in the clinical routine.

To overcome these problems, new non-invasive tests have been proposed based on the administration of a ^{14}C or of a non-radioactive ^{13}C labeled substrate. It is administrated orally, digested by pancreatic enzymes, absorbed, metabolized, and then labeled CO_2 excreted with breath within some hours. The CO_2 recovery in the expired air, is assumed as index of pancreatic function. Different breath tests with different substrates have been developed with the aim of obtaining a simple test, easy to perform, rapid, and specific for the pancreatic function.

Mixed triglyceride (72, 73), triolein (74, 75) and hiolein (76) breath test are based on the administration of lipids similar to the triglycerides found in the normal diet. The cholesteryl octanoate breath test utilizes a substrate which is metabolized by a pancreatic cholesterol esterase activity. In spite of the different substrates, all these tests share some characteristics: In patients with normal fat excretion or with mild steatorrhea, the pattern of expired $^{13}CO_2$ is normal, while in those with moderate or severe steatorrhea $^{13}CO_2$ excretion is reduced and the recovery curve may be even flat. These tests have a relatively high sensitivity

and specificity in recognizing a deficit of the lipolytic activity when compared with fecal fat measurement; but their sensitivity is very low in the diagnosis of mild and moderate CP. In the management of CP, breath tests have been used in the early phases of the diagnostic work-up of patients with chronic diarrhea to rule out the presence of fat malabsorption, as well as in monitoring the efficiency of therapy with pancreatic enzymes in advanced CP. A two-stage breath test, based on the comparison of the results before and after the administration of pancreatic enzymes, has been advocated to differentiate pancreatic insufficiency from non-pancreatic causes of steatorrhea (77). A ^{13}C-starch breath test has been also developed to evaluate the pancrease amylase activity (78). This test is interesting because ^{13}C-labeled starch is readily and cheaply available as naturally ^{13}C-enriched starch. However, since amylase is redundantly produced by the gland, a reduced activity during CP is not so easily observed as that of pancreatic lipase, results of this breath test have been disappointing in the diagnosis of CP. A not negligible limitation for all these tests is the cost, even not considering the cost of the assay equipment (that is covered by other more frequently used breath tests, i.e. ^{13}C urea breath test); moreover, these pancreatic function tests are not listed in Italy among the diagnostic tests charged on the National Health Service.

Endocrine function tests

In advanced stages of CP, impairment of the endocrine pancreatic secretion frequently develops. Determination of glucose blood levels, C peptide blood levels and glucose tolerance test has no value in the diagnosis and staging of CP. Assessment of plasma glucagone levels after arginine infusion seems to be useful in differentiating primary diabetes from diabetes secondary to CP, since the glucagone response to arginine is impaired only in CP (79). The integrated plasma pancreatic polypeptide (PP) response to a test meal, secretin or cerulein infusion, may be valuable in the diagnosis and staging of CP (80, 81), but the sensitivity of the test in the early stages of disease is too low (82). Endocrine function tests are usually not performed in the clinical routine.
In Table IV are reported the values of sensitivity and specificity of the different tests in the diagnosis of CP. There is a high variability among different studies, mainly due to the different stages of CP in the considered groups, as well as to the different diagnostic criteria applied to define CP.

Tab. IV – SENSITIVITY AND SPECIFICITY OF THE DIFFERENT FUNCTIONAL TESTS IN THE DIAGNOSIS OF CHRONIC PANCREATITIS

	Sensitivity (%)	*Specificity (%)*
Direct function tests		
Secretin/cerulein test	80-97	90-98
Lundh test	70-90	80-90
Indirect function tests		
Serum enzymes	20-83	92-100
Fecal chymotrypsin	50-100	73-89
Fecal elastase	80-93	83-94
NBT-PABA test	85-94	82-100
Pancreolauryl test	55-100	39-100
Amino acid consumption test		69-96
54-100		
Breath tests	?	?
Endocrine function		
Pancreatic polypeptide	70-80	80-93
Arginine test	70-80	–

Conclusion

Diagnosis of CP may be a quite easy or a very difficult attempt according to the severity of disease. In the advanced stages of disease, where pancreatic insufficiency, calcifications, or pseudocysts are already present, a plain abdominal roentragenogram, an abdominal ultrasound and (not necessarily) an indirect pancreatic function test are sufficient to set the diagnosis. A CT and/or an ERCP should be performed if the diagnosis is still not clear, or in cases, such as the suspicion of a cancer, a ductal stenosis, or a bile duct involvement, as well as for planning an endoscopic or surgical treatment. Conversely, the diagnosis of CP may require expensive and invasive imaging and functional tests, even direct function tests, if the disease is in an early stage. In all these cases, it is advisable that an expert pancreatic radiologist and pancreatologist in a tertiary center interpret the different radiograms and findings, and plan the different therapeutic options.

References

1) Amman R., Akovbiatz A., Largiadier F., Schüler G.: *Course and outcome of chronic pancreatitis.* Gastroenterology, 1984, 86:820-828.

2) Bockmann D.E., Büchler M., Malfertheiner P., Beger H.G: *Analzsis of nerves in chronic pancreatitis.* Gastroenterology, 1988, 94:1459-1469.

3) Manes G., Büchler M., Pieramico O., Di Sebastiano P., Malfertheiner P.: *Is increased pancreatic pressure related to pain in chronic pancreatitis?.* Int J Pancreatol, 1994, 15:113-117.

4) Amman R.W., Bühler H., Münch R., Freiburghaus A.W., *Siegenthaler W. Differences in the natural history of idiopathic (nonalcoholic)and alcoholic pancreatitis.* Pancreas, 1987, 2:368-377.

5) The Copenhagen Pancreatic Study Group.: *An interim report from a prospective epidemiological multicenter study.* Scand J Gastroenterol, 1981, 16:305-312.

6) Layer P., Kalthoff L., Clain J.E., Di Magno E.P.: *Nonalcoholic chronic pancreatitis-two diseases?* Dig Dis Sci, 1985, 30:980-985.

7) Layer P., Yamamoto H., Kalthoff L., Clain J.E., Bakken L.J., Di Magno E.P.: *The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis.* Gastroenterology, 1994, 107:1481-1487.

8) Otte M.: *Ultrasound in chronic pancreatitis.* In: Malfertheiner P., Ditschunheit H., eds. *Diagnostic procedures in pancreatic disease.* Springer Verlag: Berlin-Heidelberg, 1986, 143-148.

9) Swobodnik W., Mezer W., Brecht-Kraus D. et al.: *Ultrasound, computed tomography and endoscopic retrograde cholangiopancreatography in the morphologic diagnosis of pancreatic disease.* Klin Wochenschr, 1983, 61:291-296.

10) McCain A.H., Berkman W.A., Bernardino M.E.. *Pancreatic sonography: Past and present.* JCU, 1984, 12:325-332.

11) Bolondi L., Priori P., Gullo L. et al.: *Relationship between morphological changes detected by ultrasonography and pancreatic exocrine function in chronic pancreatitis.* Pancreas, 1987, 2:222-229.

12) Bolondi L.: *The pancreas.* In: Bolondi L., Gandolfi L., Labo G., eds. *Diagnostic ultrasound in gastroenterology: Instrumentat5ions, clinical problems and atlas.* Butterworths: Padove, 1984:261.

13) Alpern M.B., Sandler M.A., Heiman G.M. et al.: *Chronic pancreatitis: Ultrasonic features.* Radiology 1985, 155:215-219.

14) Worthen N.J., Beaben O.: *Normal pancreatic echogenicity: relation to age and body fat.* AJR, 1982, 139:1095-1098.

15) Marks W.M., Filly R.A., Callen P.W.: *Ultrasonic evaluation of normal pancreatic echogenicity and its relation to fat deposition.* Radiology, 1980, 137:475-479.

16) Bolondi L., Bassi S., Gaiani S., Barbara L.: *Sonography of chronic pancreatitis.* Radiol Clin North Am, 1989, 27:815-833.

17) Glaser J., Hogemann B., Krummenerl T. et al.: *Sonographic imaging of the pancreatic duct. New diagnostic possibilities using secretin stimulation.* Dig Dis Sci, 1987, 32:1075-1081.

18) Bolondi L., Bassi S., Gaiani S., Santi V., Gullo L., Barbara L.: *Impaired response of main pancreatic duct to secretin stimulation in early chronic pancreatitis.* Dig Dis Sci, 1989, 34:834-840.

19) Segal I., Epstein B., Lawson H.H., Solomon A., Patel V., Oettle G.J.: *The syndromes of pancreatic pseudocysts and fluid collections.* Gastrointest Radiol, 1984, 9:115-122.

20) Gowland M., Kalantzis N., Warwick F., Braganza J.: *Relative efficiency and predictive value of ultrasonography and endoscopic retrograde pancreatography in diagnosis of pancreatic disease.* Lancet, 1981, 2:190-193.

21) Foster P.N., Mitchell C.J., Robertson D.R.C. et al.: *Prospective comparison of three non-invasive tests for pancreatic disease.* Br Med J, 1984, 289:13-16.

22) Hessel S.J., Siegelman S.S., McNeil B.J. et al.: *A prospective evaluation of computed tomography and ultrasound of the pancreas.* Radiology, 1982, 143:129-133.

23) Lee W.R.: *Endoscopic ultrasonography of chronic pancreatitis and pancreatic pseudocysts.* Scand J Gastroenterol, 1986, 21 (suppl. 123):123-129.

24) Kaufman A.R., Sivack M.V.: *Endoscopic ultrasonography in the differential diagnosis of pancreatic disease.* Gastrointest Endosc, 1989, 35:214-219.

25) Laugier R.: *Role of ultrasonography in the diagnosis, staging and detection of complications of chronic pancreatitis.* In: Malfertheiner P., Dominguez-Munoz J.E., Schulz H.U., Lippert H., eds. *Diagnostic procedures in pancreatic disease.* Springer Verlag: Berlin-Heidelberg, 1997, 183-188.

26) Luetmer P.H., Stephens D.H., Ward E.M.: *Chronic pancreatitis: reassessment with current CT.* Radiology, 1989, 171:353-357.

27) Malfertheiner P., Buechler M.: *Correlation of imaging and function in chronic pancreatitis.* Radiol Clin North Am, 1989, 27:51-64.

28) Ferrucci J.T., Wittemberg J., Black E.B., Kirkpatrick R.H., Hall D.A.: *Computed body tomography in chronic pancreatitis.* Radiology, 1979, 130:175-182.

29) Freeny P.C., Marks W.M.: *Compured tomography of chronic pancreatitis.* In: Sarles H., Singer M., Gyr K., eds. *Pancreatitis - Concepts and classification.* Elsevier: Amsterdam, 1984, 219-223.

30) Malfertheiner P., Buechler M., Stanescu A., Ditschunheit H.: *Exocrine pancreatic function in correlation with ductal and parenchymal morphology in chronic pancreatitis.* Hepatogastroenterol, 1986, 33:110-114.

31) Takehara Y., Ichijo K., Tooyoama N. et al.: *Breath-hld MR cholangiopancreatography with a long echo-train fast spin-echo sequence and a surface coil in chronic pancreatitis.* Radiology, 1994, 192:19-21.

32) Soto J., Barish M., Yucel E. et al.: *Pancreatic duct: MR cholangiopancreatography with a three-dimensional fast spin-echo technique.* Radiolog, 1995, 196:459-464.

33) Axon A.T.R., Classen M., Cotton P.B., Cremer M., Freeny P.C., Less W.R.: *Pancreatography in chronic pancreatitis: internationals definitions.* Gut, 1984, 25:1107-1112.

34) Axon A.T.R.: *Endoscopic retrograde cholangiopancreatography in chronic pancreatitis. Cambridge classification.* Radiol Clin North Am, 1989, 27:39-50.

35) Malfertheiner P., Buechler M., Beger H.G., Ditschunheit H.: *Exocrine pancreatic function in correlation to morphological findings (assessed by different imaging procedures) in chronic pancreatitis.* In: Sarles H., Singer M., Gyr K., eds. *Pancreatitis - Concepts and classification.* Elsevier: Amsterdam, 1984, 291-299.

36) Cotton P.B., Less W.R., Vallon A.G., Cottone M., Croker J.R., Chapman M.: *Gray-scale ultrasonography and endoscopic pancreatography in pancreatic diagnosis.* Radiology, 1980, 143:453-459.

37) Valentini M., Cavallini G., Vantini I. et al.: *A comparative evaluation of endoscopic retrograde cholangiopancreatography and the secretin-cholecystokinion test in the diagnosis of chronic pancreatitis: a multicentre study in 124 patients.* Endoscopy, 1981, 13:64-67.

38) Braganza J.M., Hunt L.P., Warwick R.: *Relationship between pancreatic exocrine function and ductal morphology in chronic pancreatitis.* Gastroenterology, 1982, 82:1341-1347.

39) Girwood A.H., Hatfield A.R.W., Bornman P.C. et al.: *Structure and function in noncalcific pancreatitis.* Dig Dis Sci, 1984, 29:721-726.

40) Heij H.A., Obertop H., Van Blankenstein M., Nix G.A.J.J., Westbroek D.L.: *Comparison of endoscopic retrograde pancreatography with functional and histologic changes in chronic pancreatitis.* Acyta Radiol, 1987, 28:289-293.

41) Schmitz-Moormann P., Malchow H., Himmelmann G.W. et al.:

Pancreatitis-like changes in ERCP and their morphological patterns: The validity of ERCP. Digestion, 1983, 28:60-64.

42) Neff C.C., Simeone J.F., Wittemberg J. et al.: *Inflammatory pancreatic masses.* Radiology, 1984, 150:35-38.

43) Jowell P.S.: *Assessment of pancreatic duct strictures.* Gastrointest Endosc Clin Am, 1995, 5:125-143.

44) Gullo L.: *Value and clinical role of intubation tests in chronic pancreatitis.* In: Beger H.G., Büchler M., Ditschuneit H., Malfertheiner P. (Eds.), *Chronic pancreatitis.* Springer-Verlag, Berlin-Heidelberg, 1990, pp. 287-290.

45) Nagata A., Homma T., Oguchi H. et al.: *Study of chronic alcoholic pancreatitis by means of serial pancreozyminsecretin tests.* Digestion, 1986, 33:135-145.

46) Lankisch P.G.: *Exocrine pancreatic function tests.* Gut, 1982, 23:777-798.

47) Gyr H., Agrawal N.M., Felsenfeld O. et al.: *Comparative study of secretin and Lundh tests.* Am J Dig Dis, 1975, 20:506-512.

48) Wormsley K.G.: *Test of pancreatic secretion.* Clin Gastroenterol, 1978, 7:529-544.

49) Ashton M.G., Axon A.T.R., Lintott D.J.: *Lundh test and ERCP in pancreatic disease.* Gut, 1978, 19:910-915.

50) Arvanitakis C., Cooke A.R.: *Diagnostic tests of exocrine pancreatic function and disease.* Gastroenterology, 1978, 74:932-948.

51) Johnson S.G., Levitt M.D.: *Relation between serum pancreatic isoamylase concentration and pancreatic exocrine function.* Dig Dis Sci, 1978, 23:914-918.

52) Ventrucci M., Pezzilli R., Gullo L. et al.: *Role of serum pancreatic enzyme assays in diagnosis of pancreatic disease.* Dig Dis Sci, 1989, 34:39-45.

53) Fahrenkrug J., Margid E.: *Concentration of immunoreactive trypsin and activity of pancreatic isoamylase in serum compared in pancreatic diseases.* Clin Chem, 1980, 26:1573-1576.

54) Dominguez-Munoz J.E., Pieramico O., Büchler M., Malfertheiner P.: *Ratios of different serum pancreatic enzymes in the diagnosis and staging of chronic pancreatitis.* Digestion, 1993, 54:231-236.

55) Lankisch P.G., Koop H., Otto J.: *Estimation of serum pancreatic isoamylase: its role in the diagnosis of exocrine pancreatic insufficiency.* Am J Gastroenterol, 1986, 81:365-368.

56) Dürr H.K., Otte M., Forell M.M., Bode J.C.: *Fecal chymotrypsin: a study on its diagnostic value by comparison with the secretin-cholecystokinin test.* Digestion, 1978, 17:404-409.

57) Dominguez-Munoz J.E., Hieronymus C., Sauerbruch T., Malfertheiner P.: *Fecal elastase test: Evaluation of a new noninvasive pancreatic function test.* Am J Gastroenterol, 1995, 90:1834-1837.

58) Stein J., Jung M., Sziegoleit A., Zeuzem S., Caspary W.F., Lembcke B.: *Immunoreactive elastase I: clinical evaluation of a new noninvasive test of pancreatic function.* Clin Chem, 1996, 42:222-226.

59) Amman S.T., Bishop M., Curington C., Toskes P.: *Fecal pancreatic elastase 1 is inaccurate in the diagnosis of chronic pancreatitis.* Pancreas, 1996, 13:226-230.

60) Toskes P.P.: *Bentiromide as a test of exocrine pancreatic function in adult patients with pancreatic exocrine insufficiency. Determination of appropriate dose and urinary collection interval.* Gastroenterology, 1983, 85:565-569.

61) Malfertheiner P., Peter M., Junge U., Ditschuneit H.: *Indirect Pancreatic function test: pancreolauryl - its value in diagnosis of chronic pancreatitis.* Klin Wschr, 1983, 61:193-198.

62) Lankisch P.G., Schreiber A., Otto J.: *Pancreolauryl test. Evaluation of atubeless pancreatic function test in comparison with other indirect and direct tests for exocrine pancreatic function.* Dig Dis Sci, 1983, 28:490-493.

63) Lang C., Gyr K., Tonko I. et al.: *The value of serum PABA as a pancreatic function test.* Gut, 1984, 25:508-512.

64) Lagger A., Bastian L., Prager J. et al.: *Pankreas-Funktionsdiagnostik. Vereinfachtes Screening mit Fluorescein-Dilaurat durch Serumkonzentrationsbestimmungen.* Fortschr Med, 1981, 99:589-591.

65) Malfertheiner P., Büchler M., Müller A., Ditschuneit H.: *Fluorescein dilaurate serum test: a rapid tubeless pancreatic function test.* Pancreas, 1987, 2:53-60.

66) Dominguez-Munoz J.E., Pieramico O., Büchler M., Malfertheiner P.: *Clinical utility of the serum pancreolauryl test in diagnosis and staging of chronic pancreatitis.* Am J Gastroenterol, 1993, 88:1237-1241.

67) Malfertheiner P., Büchler M., Müller A., Ditschuneit H.: *Influence of extrapancreatic digestive disorders on the indirect pancreatic function test with fluorescein dilaurate.* Clin Physiol Biochem, 1985, 3:166-173.

68) Domschke S., Heptner G., Kolb S. et al.: *Decrease in plasma amino acids level after secretin and pancreozymin as an indicator of exocrine pancreatic function.* Gastroenterology, 1986, 90:1031-1038.

69) Gullo L., Pezzilli R., Ventrucci M., Barbara L.: *Cerulein induced plasma amino acids decrease: a simple, sensitive, and specific test of pancreatic function.* Gut, 1990, 31:926-929.

70) Kemmer T.P., Malfertheiner P., Haberle H. et al.: *The diagnostic value of the amino acid absorption test in detection of a disorder of exocrine pancreatic function.* Z Gastroenterol, 1992, 30:391-396.

71) Benini L., Caliari S., Bonfante F. et al.: *Fecal fat concentration in the screening of steatorrhoea.* Digestion, 1992, 53:94-100.

72) Ghoos Y.F., Vantrappen G.R., Rutgeerts P.J., Schurmans P.C.: *A mixed triglyceride breath test for intraluminal fat digestive capacity.* Digestion, 1981, 22:239-247.

73) Vantrappen G.R., Rutgeerts P.J., Ghoos Y.F., Hiele M.I.: *Mixed triglyceride breath test: a noninvasive test of pancreatic lipase activity in the duodenum.* Gastroenterology, 1989, 96:1126-1134.

74) Newcomer A.D., Hofmann A.F., DiMagno E.P., Thomas P.J., Carlson G.L.: *Triolein breath test: a sensitive and specific test for fat malabsorption.* Gastroenterology, 1979, 76:6-13.

75) Mylvaganam K., Hudson P.R., Ross A., Williams C.P.: *14C triolein breath test: A routine test in the gastroenterology clinic?* Gut, 1986, 27:1347-1349.

76) Lemcke B., Braden B., Caspary W.F.: *Exocrine pancreatic*

insufficiency: accuracy and clinical value of the uniformly labeled ^{13}C-Hiolein breath test. Gut, 1996, 39:668-674.

77) Fleming S.C., Kapembwa M.S., Griffin G.E.: *Combined single day 14C-triolein breath test and PABA test in the diagnosis of malabsorption.* Ann Clin Biochem, 1990, 27:50-55.

78) Patel V.P., Jain N.K., Agarwal N., Gee Varghese P.J., Pitchumoni C.S.: *Comparison of bentiromide test and rice flour breath hydrogen test in the detection of exocrine pancreatic insufficiency.* Pancreas, 1986, 1:172-175.

79) Keller U., Szollosy E., Verga L., Gyr K.: *Pancreatic glucagon, secretin and exocrine function (BT-PABA test) in chronic pancreatitis.* Dig Dis Sci, 1984, 29:853-857.

80) Campbell D., Slaff J., McGuigan J. et al.: *Integrated pancreatic polypeptide response in pancreatic diseases.* Gastroenterology, 1985, 88:1341A.

81) Adrian T.E., Besterman H.S., Mallinson C.M. et al.: *Impaired pancreatic polypeptide release in chronic pancreatitis with steatorrhea.* Gut, 1979, 20:98-101.

82) Imrie C.W., Devine B., McKenzie J.: *The assessment of chronic pancreatitis.* Int J Pancreatol, 1989, 5:11-15.

Address for correspondence:

Prof. P. MALFERTHEINER
Department of Gastroenterologie
Otto-von-Guericke-University
Leipziger Str. 44
D-39120 MAGDEBURG, GERMANY