Comparison of pancreatic morphology and exocrine functional impairment in patients with chronic pancreatitis

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Abstract
A comparative analysis of pancreatic morphology and exocrine function was performed prospectively in 48 patients. All patients had transabdominal ultrasound, computed tomography, endoscopic retrograde pancreatography, and a secretin-caerulein test. Classification of ultrasound, computed tomography, and pancreatogram findings was based on the Cambridge classification. In 10 patients, no pancreatic duct changes were detected on pancreatography. Equivocal (Cambridge I), mild to moderate (Cambridge II), and considerable ductal changes (Cambridge III) were found in 10, 12, and 16 patients, respectively. Computed tomography and ultrasound changes were found to correlate in 40–50%, 67%, and 94–100% of patients with Cambridge I, II, and III abnormal duct morphology, respectively. In patients with a normal pancreatogram, no patient had a functional impairment. Seventy per cent of the patients with equivocal pancreatic duct changes had dissociated, and 30% global, pancreatic insufficiency, while 50% of those with mild to moderate abnormal duct morphology manifested dissociated, and 50% global, functional impairment. All patients with considerable pancreatic duct changes had global pancreatic insufficiency. The results of this study confirm that normal endoscopic retrograde pancreatographic findings and Cambridge III ductal changes on endoscopic retrograde pancreatography correlate extremely well with normal pancreatic function and advanced functional insufficiency, respectively. As diagnostic tools, ultrasound and computed tomography are as sensitive as pancreatography only in chronic pancreatitis with considerable morphological changes.
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Endoscopic retrograde pancreatography (ERP), ultrasound, and computed tomography are complementary diagnostic means in the evaluation of disease severity in patients with chronic pancreatitis.[1 2] Additional pancreatic function tests are usually necessary, however, to establish the degree of exocrine insufficiency, which is an important prognostic factor.[1 2] As the evaluation of pancreatic function using direct or tubeless tests is a technique with a number of method related

problems, it is necessary to find out if the degree of exocrine pancreatic insufficiency and morphological findings correlate, and if function tests are not required in some groups of patients with chronic pancreatitis. In general, a correlation has been shown between functional impairment and morphological changes in chronic pancreatitis by a number of previous studies most of which, however, did not take the severity grade of the disease into consideration.[3–12] The main purpose of this study was to investigate prospectively the usefulness of the morphological changes in chronic pancreatitis compared with differing degrees of functional impairment measured by the secretin-caerulein test with the aim of identifying a possible correlation.

Patients and methods
A group of patients with suspected or proved chronic pancreatitis but not clinical or biochemical evidence of acute pancreatitis was investigated to clarify recurrent epigastric pain or weight loss, or both. None of the patients had previous history of necrotising pancreatitis. After admission to the department, all patients had transabdominal ultrasound and computed tomography examinations of the pancreas, as well as ERP and secretin-caerulein test. Only patients with a technically successful secretin-caerulein test and pancreatograms with adequate demonstration of the pancreatic duct system were included in the study. The group contained 48 patients (39 males and 9 females) with an average age of 47 (range 23–79) years. The primary grading was based on the morphological changes seen in the pancreatogram. The results of all other imaging techniques and the secretin-caerulein test were compared with the ERP findings.

Transabdominal ultrasound of the pancreas was performed by an experienced examiner using a real time scanner – Picker LSC 7000 or Picker CS 192 (3·5-/5·0-MHz convex transducer) – as the first imaging procedure of the diagnostic investigation. Abdominal computed tomography was done using Siemens Somatom plus and Siemens Somatom HiQ-S with a 5 mm layer thickness. Scans were reviewed by two experienced radiologists who were blinded to the ultrasound findings. A revised Cambridge classification of chronic pancreatitis was used for the grading of ultrasound findings and computed tomography changes (Table 1).[13]

ERP was carried out using an Olympus JF 1T10 oder JF 1T20 fibrescope using the

TABLE I Revised Cambridge classification of chronic pancreatitis[13]

		ERP		Ultrasound and computed tomography
Normal		Visualisation of the whole gland without abnormal features		
Equivocal	(Cambridge I)	Fewer than three abnormal branches	one sign only	Main duct enlarged (less than 4 mm) Gland enlarged (up to twice normal) Cavities (less than 10 mm)
Mild Moderate	(Cambridge II)	More than three abnormal branches Abnormal main duct and branches	two or more signs	Irregular ducts Focal reduction in parenchymal echogenicity Echogenic foci in parenchyma Increased or irregular echogenicity of wall of main duct Irregular contour to gland, particularly focal enlargements
Considerable	(Cambridge III)	As above with one or more of: Large cavities (greater than 10 mm) Intraductal calculi Ductal obstruction with stricture Gross irregularity of main pancreatic duct		Large cavities (greater than 10 mm) Calculi Ductal obstruction (greater than 4 mm) Major ductal irregularity Gross enlargements (greater than 4 mm) Contiguous organ invasion

accepted technique. Written informed consent was obtained from each patient. x Rays were taken in the supine position and, if necessary, in the right or left oblique positions. In all patients with pancreas divisum, the pancreatic duct system was visualised through the major and accessory papillae. The pancreatograms were reviewed independently by two gastroenterologists, each of whom had performed at least 1000 ERCPs, and a single radiologist, all three blinded to the ultrasound and computed tomography results. The classification of pancreatogram findings was also based on the revised Cambridge terminology (Table 1).[13] In accordance with morphological changes of the duct system, the severity of chronic pancreatitis was graded into three types such as equivocal (Cambridge I), mild to moderate (Cambridge II), and considerable (Cambridge III) (Table 1).

After an overnight fast, the secretin-caerulein test was performed as the final diagnostic procedure according to current standardisation. A double lumen tube was placed under fluoroscopic guidance with its tip at the ligament of Treitz. A bolus injection of synthetic secretin (1 CU/kg body weight (bw), Sekretolin Diagnosticum, Hoechst AG, Frankfurt, Germany) was given during the first 60 minutes to estimate volume secretion and bicarbonate output. In the period from 60 to 120 minutes, coinfusion of secretin (CU/kg/h bw) and caerulein (25 ng/kg/h bw, Takus, Farmitalia Carlo Erba GmbH, Freiburg, Germany) was applied to measure volume secretion and enzyme outputs. Enzyme activities of amylase and lipase as well as concentrations of bicarbonate were measured using current methods and substrates.[14–16] Normal values for volume secretion (>300 ml/h, range 302–686 ml/h), bicarbonate (>30 mmol/h, range 31–72 mmol/h), and enzyme outputs (amylase: >5000 IU/h, range 5024–11680 IU/h, lipase: >100 000 IU/h, range 100 676–287 542 IU/h) have been previously reported in 40 healthy subjects in our laboratory. Dissociated pancreatic insufficiency was defined as an impairment of function if not more than two parameters were abnormal in the secretin-caerulein test. In the case of three to four abnormal parameters, pancreatic insufficiency was considered to be global.

All results were expressed as means (SEM). Statistical analyses were carried out using the Fisher's exact probability test. Significance was set at the 5% value.

Results

Chronic alcohol abuse was the cause of chronic pancreatitis in 29 (76%) patients, of whom four had a pancreas divisum. No aetiological cause was apparent in the remaining nine (24%) patients. In patients with normal pancreatic duct morphology, six (60%) were known to be chronic alcohol abusers. Among the patients as a whole, the diagnostic investigation was necessary in 30 (63%) patients because of recurrent epigastric pain and weight loss. Twelve (25%) patients suffered only from epigastric pain, and six (12%) only from rapid weight loss. In patients without pancreatic duct changes, the mean body weight was 6·3 (19·9)% higher than normal in accordance with Broca's formula. Among the patients with Cambridge I, II, and III morphology as shown by ERP, the mean body weight was 1·0 (3·7)%, 3·3 (9·4)%, and 4·7 (11·3)% lower than normal, respectively. Diabetes mellitus was found in 30% (n = 3) 42% (n = 5), and 56% (n = 9) of patients with Cambridge I, II, and III morphological changes, respectively. Of the patients with normal pancreatic duct morphology, none was diabetic.

In 10 of 48 patients, ERP showed no pancreatic duct changes. Equivocal (Cambridge I), mild to moderate (Cambridge II), and considerable ductal changes (Cambridge III) were found in 10, 12, and 16 patients, respectively (Table II). Ultrasound and computed tomography showed morphological changes in 38 and 37 cases, respectively. In patients with normal pancreatograms, computed tomography and ultrasound suggested equivocal changes in 40% and 50% of the cases, respec-

TABLE II ERP findings in patients with chronic pancreatitis

Cambridge classification	Morphological changes	(n)
Cambridge I (n = 10)	Fewer than three abnormal branches	10
Cambridge II (n = 12)	More than three abnormal branches	2
	Abnormal main duct and branches	10
Cambridge III (n = 16)	Abnormal main duct and branches	10
	Ductal obstruction with stricture	8
	Intraductal calculi	7
	Gross irregularity of main duct	7
	Large cavities	4

TABLE III   *Ultrasound and computed tomography findings (n) in patients with normal pancreatic duct morphology and chronic pancreatitis shown by ERP*

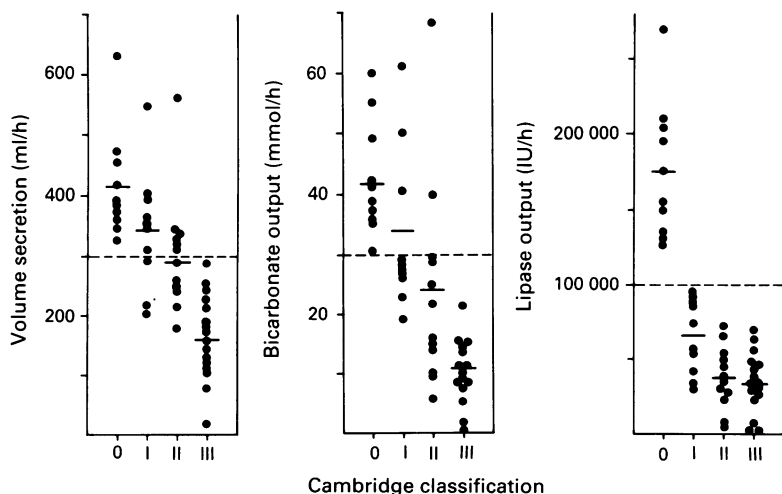| Cambridge classification	Morphological changes	Ultrasound	Computed tomography
Normal (n = 10)	Normal	5	6
	Focal reduction in parenchymal echogenicity	3	2
	Irregular contour to gland	2	2
Cambridge I (n = 10)	Normal	5	5
	Focal reduction in parenchymal echogenicity	3	3
	Irregular contour to gland	2	2
Cambridge II (n = 12)	Focal reduction in parenchymal echogenicity	12	12
	Irregular contour to gland	4	6
	Echogenic foci in parenchyma	4	2
	Gland enlarged	2	2
Cambridge III (n = 16)	Focal reduction in parechymal echogenicity	16	16
	Irregular contour to gland	12	11
	Echogenic foci in parenchyma	7	6
	Gland enlarged	11	12
	Calculi	5	4
	Ductal obstruction (greater than 4 mm)	7	4
	Large cavities (greater than 10 mm)	6	4
	Major duct irregularity	4	2

TABLE IV   *Distribution of abnormal parameters (n) measured by secretin-caerulein test*

Cambridge classification			Volume	HCO$_3$	Amylase	Lipase
Normal		(n = 10)	0	0	0	0
Cambridge I	D	(n = 7)	0	4	3	7
	G	(n = 3)	3	3	3	3
Cambridge II	D	(n = 6)	0	4	2	6
	G	(n = 6)	6	4	6	6
Cambridge III	G	(n = 16)	16	16	13	16

D=Dissociated insufficiency; G=global insufficincy.

the secretin-caerulein test. In 13 patients a dissociated functional impairment was found, while 25 patients were shown to have global insufficiency. Among patients with normal ERP, none had pancreatic functional impairment (Table IV, Figure). Patients with equivocal pancreatic duct changes had dissociated and global pancreatic insufficiency in 70% and 30% of the cases, respectively. In patients with mild to moderate abnormal duct morphology 50% had dissociated, and 50% global functional impairment. Considerable pancreatic duct findings were always accompanied by global pancreatic insufficiency (Table IV, Figure). Among patients with pancreas divisum, ERP showed no further duct changes in one, who also had normal pancreatic function. Three patients with pancreas divisum had equivocal abnormal findings on ERP, accompanied by dissociated impairment of the pancreatic function.

In patients with dissociated pancreatic insufficiency, lipase, bicarbonate, amylase outputs, and volume secretion were abnormal in 100%, 62%, 38%, and 0% of the cases, respectively (Table IV). In comparison with normal pancreatic function, the mean volume secretion, bicarbonate, and amylase outputs in Cambridge I type pancreatitis were reduced by 17%, 19%, and 27%, respectively, while lipase output was impaired by 64% (Table V). In Cambridge II patients, a reduction in mean volume secretion of 30% was found. Bicarbonate, amylase, and lipase outputs were reduced by 43%, 55%, and 78%, respectively (Table V). In the case of considerable chronic pancreatitis, there was a decrease in mean volume secretion, amylase, and bicarbonate outputs of 62%, 72%, and 74%, respectively, while lipase output was reduced by 81% (Table V).

Among the four parameters examined, lipase output was found to be abnormal in all patients with dissociated or global functional impairment, and could be used to distinguish between normal and abnormal duct morphology without exception. A significant differentiation between equivocal and mild to moderate pancreatitis was possible on the basis of mean lipase output, while mild to moderate and considerable pancreatitis could not be distinguished (Table V, Figure). Mean amylase output could not distinguish significantly between patients with normal and those with equivocal findings, or between abnormal pancreatograms of various degree of severity (Table V). Mean volume secretion could differentiate significantly only between normal and Cambridge I findings and between Cambridge II and III pancreatitis, but not between equivocal and mild to moderate pancreatitis (Table V, Figure). Mean bicarbonate output could differentiate significantly between normal and abnormal duct changes of all degrees of severity (Table V, Figure).

tively (Table III). On the other hand, in 50% of patients with pancreatograms of Cambridge I findings, no abnormal changes were shown using computed tomography and ultrasound (Table III). Eight (67%) patients with Cambridge II changes on pancreatograms, had two or more abnormal signs on ultrasound and computed tomography, while four (23%) subjects were classified as Cambridge I on the basis of ultrasound and computed tomography findings. In all patients with Cambridge III findings shown by ERP, considerable morphological changes were confirmed in 100% and 94% of cases using ultrasound and computed tomography, respectively (Table III). In none of the groups were any significant discrepancies found between ultrasound and computed tomography findings.

Overall, 38 of 48 patients had an impairment of pancreatic function as shown by

Cambridge classification

Distribution of individual parameters in patients with normal pancreatograms (0) and chronic pancreatitis (I-III).

Discussion

Irreversible morphological changes resulting from chronic pancreatitis may lead to a

TABLE V *Pancreatic function in patients with normal pancreatograms and chronic pancreatitis*

Cambridge classification		Volume (ml/h)	HCO₃ (mmol/h)	Amylase (IU/h)	Lipase (IU/h)
Normal	(n = 10)	417 (84)	42 (10)	8183 (2088)	176079 (44431)
Cambridge I	(n = 10)	345 (93)*	34 (12)*	6011 (4670)	64024 (24781)*
Cambridge II	(n = 12)	293 (91)	24 (17)*	3662 (3615)	39559 (20765)*
Cambridge III	(n = 16)	160 (69)*	11 (5)*	2332 (2334)	34705 (19253)

*p<0·05 when compared with previous grade of severity. Data shown as mean (SEM).

permanent loss of endocrine and exocrine function.[1] In a case of suspected chronic pancreatic disease with recurrent epigastric pain, weight loss or steatorrhea, or both, ultrasound, computed tomography, secretin-caerulein test, and endoscopic retrograde cholangiopancreatography are current diagnostic procedures.[1 2] The correlation between pancreatic function and morphological changes has been investigated in a number of studies.[3–12 17–19] Most previous analyses, however, comparing pancreatic function and ERP used different and non-standardised criteria or variations of a classification described by Kasugai without ultrasound and computed tomography as complementary imaging methods.[3–12 20] The Cambridge classification of chronic pancreatitis is now widely accepted as a standard grading system.[21 22] To date, only a single previous study correlating exocrine function of pancreas and morphological changes using the Cambridge classification including ERP, ultrasound, and computed tomography has been done.[17] The aim of the present analysis was to prospectively compare pancreatic exocrine function and morphology by currently available techniques such as ultrasound, computed tomography, and ERP using the same Cambridge classification.

Most previous studies attempted to differentiate only normal from abnormal pancreas using ultrasound or computed tomography, or both, without regard for the severity of chronic pancreatitis.[23 32] The sensitivity of ultrasound in chronic pancreatitis was found to be 52–90% and the specificity 90–100%.[13 23 28 31 32] Meta analysis of 700 patients with chronic pancreatitis confirmed a sensitivity of 67% for ultrasound.[33] At 74–84% and up to 98%, respectively, the sensitivity and specificity of computed tomography are somewhat better than for ultrasound.[23 24 28 32] Evaluation of the data of 592 patients with chronic pancreatitis showed a sensitivity of 74% and a specificity of 85% for computed tomography.[33] Our results show that, compared with ERP, computed tomography and ultrasound may overestimate normal pancreatic morphology in 40–50% of patients by showing equivocal changes not found by ERP. Moreover, computed tomography and ultrasound can underestimate morphological changes in 50% of patients with Cambridge I ductal findings on pancreatograms. The main reason for this over or underestimation of pancreatic morphology is the fact that accurate interpretation of focal reductions in parenchymal echogenicity or an irregular contour of the gland by ultrasound or computed tomography is difficult. The recent data of Malfertheiner *et al* suggest also that

computed tomography is not suitable in the search for early stages of chronic pancreatitis.[17] In accordance with the results of the study of Malfertheiner *et al*, in our patient group too, computed tomography and ultrasound provided better results with more pronounced abnormal morphological changes, as in the case of Cambridge II findings identified by ERP.[17] Chronic pancreatitis with considerable Cambridge III changes could readily be diagnosed in our patients by computed tomography and ultrasound in almost all cases. Similar results have shown a severity dependent diagnostic accuracy of endoscopic ultrasonography.[34] On the basis of our results, transabdominal sonography – which is a heavily operator dependent modality – used as a diagnostic tool in chronic pancreatitis may be an inexpensive and easy to perform alternative to computed tomography that may provide results of similar reliability.

Meta analysis of patients with chronic pancreatitis investigated by ERP showed a sensitivity and specificity of 86% and 90%, respectively, for this technique.[33] Our data have confirmed that, compared with ERP, ultrasound and computed tomography are less sensitive methods, especially in the case of equivocal and mild to moderate morphological changes. Previous studies suggested that pancreatic functional impairment may be present in the case of normal pancreatograms, and that a normal pancreatic duct on ERP does not exclude exocrine pancreatic insufficiency.[3 4 10 17–19 35] In a study entailing a large number of patients, almost all of a subgroup of patients with normal pancreatic duct morphology and functional impairment were found to have only slight pancreatic insufficiency.[19] In our patients, normal pancreatograms always correlated with normal exocrine function. In contrast, morphological duct changes were always associated with impaired pancreatic function, and the extent of pancreatic insufficiency depended on the severity of the morphological changes. Some previous studies, however, have also shown that pancreatic function may be normal in patients with pancreatic duct changes on ERP.[18 19 36] In a large subgroup of patients with normal pancreatic function and abnormal duct changes on ERP, almost all pancreatograms showed only equivocal findings.[19] Factors such as the use of different equipment, quality of radiographs, experience in interpreting the images, in homogeneous patient groups, the type of function test used, different definitions of normal pancreatic function and grades of functional impairment may explain in part the discrepancies between previous results and our findings.

Pancreatic function tests are of benefit if grading of exocrine pancreatic insufficiency is necessary to identify a need for enzyme substitution treatment. A comparison of ERP with functional and histological changes in chronic pancreatitis showed better correlations between the secretin-caerulein test and histological changes than between ERP and histology.[12] Moreover, recent findings suggest that the secretin test may identify patients with

chronic pancreatitis earlier than ERP.[37] In our patients, a normal pancreatogram excluded clinically relevant functional impairment of the pancreas. In the case of Cambridge I and II changes on ERP, pancreatic function tests, and pancreatograms proved to be complementary for establishing an accurate grading of exocrine insufficiency. In all these cases, either a dissociated or global exocrine dysfunction of varying severity was present. Additionally, our results emphasise a close correlation between ERP findings with considerable Cambridge III ductal changes and pancreatic function, as all patients without exception were shown to have global exocrine insufficiency. A significant correlation between duct morphology and degree of functional impairment, as found in our study, has previously been shown using other scoring systems.[17 18] In our patient group, only lipase output was found to distinguish between normal and abnormal duct morphology in all cases. Mean volume secretion, bicarbonate, and amylase outputs were all within the normal ranges in patients with equivocal duct findings. In accordance with previous results, the parameter most reliably correlating with normal and abnormal ductal findings at all grades of severity was the mean bicarbonate output.[6 17 18]

In conclusion, our data show that using the Cambridge classification, a close correlation between ERP findings and pancreatic function can be shown. In comparison with ERP, computed tomography and ultrasound are less reliable in distinguishing between normal gland and equivocal or mild to moderate morphological changes in chronic pancreatitis. Considerable morphological changes, however, can be shown equally as sensitively as with ERP. In the case of a normal pancreatogram or when considerable changes in ultrasound, computed tomography, and ERP images are found, a close correlation exists between pancreatic function and morphology, which possibly makes the need for complementary function testing unnecessary.

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