Pancreatic function in Crohn's disease

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Abstract

We investigated exocrine pancreatic function in a population of patients with Crohn's disease in order to correlate the pancreatic function with clinical and laboratory variables. A total of 143 patients affected by Crohn's disease and 115 control subjects were studied. All had a Lundh meal test. As a group patients with Crohn's disease had significantly decreased activity of both amylase ($p < 0.02$) and lipase ($p < 0.001$) in duodenal aspirates. In patients with Crohn's disease enzyme activities were not correlated to duration of disease or to extent or localisation of previous bowel resection. The lowest enzyme values were found in patients with the most extensive bowel involvement, and they were significantly lower ($p < 0.05$) than in patients with disease confined to the terminal ileum. The differences between enzyme values in other subgroups of patients were not significant. For the patient group as a whole no correlation was found between disease activity and enzyme values, but for the most uniform group of patients, those with terminal ileitis, pancreatic function was significantly lower ($p < 0.05$) in patients with moderate and severe disease compared with patients with mild disease. Thus at least two factors seem to be responsible for impaired pancreatic function in Crohn's disease: firstly disease activity and secondly localisation or extent of disease.

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Decreased function of the exocrine pancreas has been reported in 20–30% of patients with various intestinal disorders.^{1,2} In 1953 Dreiling³ found impaired pancreatic function in five of 21 patients with regional enteritis or diffuse jejunoileitis. Others have reported impaired exocrine pancreatic function in about 50% of patients with Crohn's disease,^{2,4} though the numbers were small (four and 17 patients).

It has been suggested that decreased pancreatic function in patients with Crohn's disease is a non-specific effect of protein deficiency secondary to malabsorption. In a small series of patients the decrease in pancreatic function was

related to the duration of disease,⁴ but otherwise the groups of patients have been too small to draw any conclusion concerning possible relations between clinical parameters and pancreatic function.

The present study was performed to investigate exocrine pancreatic function in a population of patients with Crohn's disease and to correlate pancreatic function with clinical and laboratory variables.

Patients and methods

During a four year period every patient admitted to the department with known or suspected Crohn's disease had a Lundh meal test.⁵ Crohn's disease was diagnosed in 143 patients (59 males, 84 females, mean age 37, range 15–80 years). Diagnostic criteria were based on radiological, endoscopic, and histological findings and clinical history. Eighteen patients were treated with prednisolone, 29 with salazosulfapyridine, and 10 with both drugs. Two patients had a jejunostomy; none had an ileostomy or colostomy; and none had a history of previous pancreatic disease or alcohol abuse. The mean duration of disease was 76 months (range 1–684 months). Table I gives the site of disease.

As control subjects, 115 patients (65 females, 50 males, mean age 46 years, range 13–77 years) were investigated during the same period for other causes or preoperatively before ileal bypass operation for obesity. None had pancreatic or biliary disease, presently or previously, or previous gastrointestinal surgery except for simple appendectomy. None had diabetes mellitus or a history of alcohol abuse. Table II lists the diagnoses.

In patients with Crohn's disease activity was divided into three grades (mild, moderate, severe) on the basis of clinical criteria used in the Harvey Bradshaw index⁶: *mild* 0–2, *moderate* 3–8, *severe* >8.

All patients and control subjects had a Lundh test.⁵ After an overnight fast a duodenal tube was placed with the tip in the horizontal part of duodenum under fluoroscopic control. A standardised meal was given. The meal (Nutrizon standard, Nutricia Nordica A/S Denmark) consisted of 12 g protein, 4 g fat, and 36 g carbohydrate mixed with water to a total volume of 300 ml. Collection of duodenal aspirate was performed by simple siphonage (0–60 minutes). The samples were put on ice and stored at -20°C until analysed for amylase and lipase. Volume and pH were measured. The median volume in patients was 66 ml (range 20–242 ml) and in control subjects 54 ml (range 20–230 ml). The median pH in patients was 6.22 (range 5.50–6.86) and in control subjects 6.23 (range 5.50–7.44).

Lipase was assayed by the method described

TABLE I Lundh test results in 143 patients with Crohn's disease grouped according to localisation of disease. Median values (ranges)

Localisation of Crohn's disease	No.	Lipase (KU/l)	Amylase (KU/l)
Terminal ileum	43	740 (184–1732)*	199 (33–933)
Colon (including rectum)	15	751 (49–1412)*	175 (26–727)
Ileum	11	682 (126–2095)	205 (51–408)
Terminal ileum+colon	59	600 (5–1542)*†	166 (3–538)*
Extensive (ileum+jejunum 4, colon+ileum+ jejunum 8, extensive ileum+colon 3)	15	496 (65–1584)*†	123 (26–447)*†

*Activity lower than in control subjects ($p < 0.05$). †Activity lower than in patients with lesions of the terminal ileum ($p < 0.05$).

TABLE II Diagnoses in control subjects without pancreatic disease (n=115)

Chronic diarrhoea	30
Irritable bowel syndrome	67
Diverticular disease	3
Adiposity	5
Miscellaneous	10

Site and activity of disease
Duodenal lipase activity (KU/l) in 115 control subjects and 143 patients with Crohn's disease grouped according to site and activity of disease. Median values (ranges). *less than mild activity ($p < 0.05$) with identical localisation.

by Erlandson and Borgström.⁷ Amylase was determined by the method described by Dahlqvist with the modifications described by Thaysen *et al.*^{8,9}

STATISTICS

Correlation analyses and the Mann-Whitney U test for unpaired data were used for statistical analysis.

Results

As a group patients with Crohn's disease had significantly decreased activities of both amylase and lipase in duodenal aspirates. The median amylase activity for patients was 170 KU/l (range 3–933 KU/l) and for control subjects 199 KU/l (47–629 KU/l) ($p < 0.02$). The median lipase activity for patients was 702 KU/l (5–2095 KU/l) and for control subjects 880 KU/l (177–1908 KU/l) ($p < 0.001$). In both groups there was a significant correlation between amylase and lipase activities ($p < 0.001$).

Neither patients with Crohn's disease nor control subjects showed a significant correlation between age and pancreatic function. In the patients amylase and lipase activities were not correlated with the duration of disease or with the extent or localisation of previous bowel resection.

Nutritional status judged by serum albumin concentrations did not correlate with the result of the Lundh test.

Enzyme values in subgroups of patients grouped according to localisation of disease are shown in Table I. The highest values were found in patients with isolated disease of the terminal ileum, and compared with patients with extensive disease and disease confined to the terminal

ileum and colon these values were significantly higher ($p < 0.05$). Otherwise no significant differences were noted between patients with different sites of Crohn's disease.

For the patients as a whole disease activity did not correlate with enzyme activity, but in the group of patients with isolated disease of the terminal ileum the patients with moderate or severe disease activity had significantly lower enzyme activity than those with mild or severe disease (Table III, IV; Fig). Enzyme activities in patients receiving prednisolone or salazosulfapyridine, or both, were not significantly different, and furthermore were not different from activities in patients who received no medical treatment. Given the different sites of disease, enzyme activities were higher ($p < 0.05$) in patients with disease in the terminal ileum within every degree of activity.

Discussion

In the present study, which comprises the largest published number of patients with Crohn's disease who had a test of exocrine pancreatic function performed, a Lundh test showed significantly decreased exocrine pancreatic function in a group of 143 patients with Crohn's disease compared with a control group. This agrees with the trend in previous studies which included only a few patients.

In a previous study the impairment of pancreatic function was related to the duration of disease in a group of 17 patients with Crohn's disease.⁴ We could not reproduce this finding.

In contrast to the previously published studies on this subject, the large number of patients in our study allowed us to relate the enzyme activities to the localisation of Crohn's disease. The lowest enzyme values were found in patients

TABLE III Duodenal lipase and amylase activities (KU/l) in 143 patients with Crohn's disease grouped according to localisation and activity of disease. Median values (ranges)

	Disease activity		
	Mild	Moderate	Severe
Lipase:			
Terminal ileum (n=43)	979 (324-1732) (n=16)	556 (208-1152)* (n=15)	635 (184-796)* (n=12)
Colon (n=15)	768 (49-1098) (n=11)	—	880 (300-1412) (n=4)
Colon + terminal ileum (n=59)	620 (50-1542) (n=28)	446 (166-1232) (n=13)	554 (5-1060) (n=18)
Ileum (n=11)	394 (300-1504) (n=3)	1413 (730-2095) (n=2)	655 (126-1388) (n=6)
Extensive (n=15)	496 (153-1584) (n=9)	457 (65-551) (n=3)	614 (238-774) (n=3)
Total (n=143)	668 (49-1732) (n=67)	556 (65-2095) (n=33)	614 (5-1412) (n=43)
Amylase:			
Terminal ileum (n=43)	271 (101-933) (n=16)	176 (58-326)* (n=15)	168 (33-242)* (n=12)
Colon (n=15)	167 (26-390) (n=11)	—	291 (119-727) (n=4)
Colon + terminal ileum (n=59)	171 (112-488) (n=28)	136 (47-313) (n=13)	217 (3-538) (n=18)
Ileum (n=11)	132 (74-350) (n=3)	327 (243-408) (n=6)	166 (51-264) (n=3)
Extensive (n=15)	136 (29-447) (n=9)	91 (26-162) (n=3)	116 (50-194) (n=3)
Total (n=143)	178 (12-933) (n=67)	164 (26-408) (n=33)	175 (3-538) (n=43)

*Lower than mild activity ($p < 0.05$) with identical localisation.

with the most extensive bowel involvement, and compared with values in patients with disease confined to the terminal ileum these were significantly lower. Although the difference between enzyme values in other subgroups of patients were not significant, the enzyme values given in Table I seem to indicate that the extent of bowel involvement might be an important factor in the impairment of pancreatic function in patients with Crohn's disease. The lack of significance in differences between the other subgroups might be because the extent of disease involvement in these groups was poorly defined, and therefore probably more variable, so that valid calculations are impossible to perform.

For the patient group as a whole no correlation was found between disease activity and enzyme values, but for the most uniform group of patients with well defined disease, the patients with terminal ileitis, pancreatic function was significantly lower in the patients with moderate and severe disease activity compared with patients with mild disease. In the other subgroups of patients no such relation was found. This might also be caused by the lack of precise evaluation of disease involvement in the subgroups and therefore less uniformity of patients in these groups.

The reason for the decreased pancreatic function in patients with Crohn's disease is unclear. The following factors might be responsible:

- (1) Insufficient stimulation of the pancreas on account of reduced amounts of secretory hormones or peptide in the intestinal wall due to inflammation or scarring.
- (2) Decreased pancreatic function due to changes in the exocrine pancreas caused by Crohn's disease.
- (3) Involvement of the pancreas by autoantibodies against the exocrine pancreatic tissue.
- (4) Malnutrition resulting from Crohn's disease.

Hormones involved in the stimulation of the exocrine pancreas during a meal test are most

likely secreted in the upper part of the intestine. We found the lowest enzyme values in patients with extensive disease. All of these had disease of the jejunum or ileum proximal to the terminal ileum, or both. This observation favours the hypothesis that decreased secretion of secretory hormones is a factor responsible for decreased exocrine pancreatic function in patients with Crohn's disease. This, however, is probably only one of the factors involved, since other investigators using intravenous stimulation of the pancreas, and thus bypassing this factor, also found decreased function in several patients with Crohn's disease.^{13,14} Furthermore, we also found decreased enzyme activity in some patients with colonic disease alone.

Pancreatic involvement in patients with Crohn's disease has been hypothesised from pathological and functional data, but reports of chronic pancreatitis associated with Crohn's disease are few and refer to single patients.¹⁰⁻¹² The first suggestion of a significant association between pancreatic lesions and chronic inflammatory bowel disease was reported in 1950 by Ball *et al.*,¹³ who found 14% and 53% of macroscopic and histological lesions, respectively, in a postmortem study of patients with chronic ulcerative colitis. The same group found mild to moderate pancreatic fibrosis at necropsy in 15 of 39 patients with Crohn's disease.¹⁴ Axon *et al.*¹¹ observed five cases of histologically proved chronic inflammatory bowel disease in a series of 59 abnormal pancreatograms, which was too many to be considered merely incidental. In the present study none of the patients had symptoms consistent with chronic pancreatitis, but endoscopic retrograde cholangiopancreatography was not performed and histological specimens were not available.

Crohn's disease is known to be complicated by an autoimmune involvement of other organs. Some investigators have found a high occurrence of autoantibodies against pancreatic tissue in serum from patients with Crohn's disease,¹⁵ but contradictory reports exist.⁴ We did not analyse for autoantibodies, and the question must be considered open.

In our study no correlation was found between malnutrition, judged by albumin concentrations, general nutritional status, and pancreatic function.

Our observation is in agreement with a recent study.⁴ In other studies such a correlation has been suggested,¹² but remains speculative. The result of the Lundh meal test does not necessarily provide precise information on pancreatic function. The meal test and the cholecystokinin/secretin test are, however, the only validated, although indirect, tests for this purpose. We applied the same test in our control subjects to minimise methodological errors. We cannot exclude a systematic difference in gastric emptying as a source of error, but this is not considered plausible as we found no difference between controls and patients with mild disease activity. In favour of this opinion are the results of previous studies using the cholecystokinin/secretin test.^{3,4} These papers also showed lower enzyme activities in patients with Crohn's disease.

We conclude that at least two factors seem to be responsible for impaired pancreatic function in Crohn's disease: disease activity and localisation or extent of disease.

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