Small intestinal structure and passive permeability in systemic sclerosis

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SUMMARY Seventeen patients with proven systemic sclerosis had a peroral jejunal biopsy performed. Four biopsies were regarded as showing abnormalities, which were mostly confined to the deeper structures, although in two there was a minimal degree of villous atrophy without epithelial cell changes. Passive intestinal permeability, as assessed by the cellobiose/mannitol test, was normal in all patients. In contrast, seven patients had a low xylose test result, which in five of them could be accounted for by impaired renal function, small intestinal bacterial contamination, or altered gastrointestinal transit. These results indicate that passive intestinal permeability is unaltered in systemic sclerosis, and that malabsorption, when it occurs, is caused by other factors.

Malabsorption of nutrients in one form or another is a recognised complication of systemic sclerosis, occurring in from 10% to 30% of patients. Among the aetiological factors which have been documented are pancreatic dysfunction and small intestinal bacterial overgrowth, but other suggested causes include impaired intestinal motility, relative intestinal ischaemia, lymphatic obstruction, and altered permeability due to involvement of the intestinal wall by fibrosis.

Biopsies of the jejunum have usually been reported as showing either no abnormality or a minimal inflammatory infiltrate, although one series of selected cases described fibrosis of Brunner’s glands in six out of eight specimens.

It is generally accepted that malabsorption in systemic sclerosis is unlikely to be due to a direct decrease in intestinal mucosal permeability. This has been difficult to demonstrate, however, as most tests of absorption are affected by other factors. Abnormal xylose test results have frequently been documented, but the significance of these in terms of permeability is doubtful, as excretion is known to be abnormal in the presence of small bowel bacterial overgrowth, altered intestinal transit, or when there is renal impairment.

We have described recently the use of a test of intestinal permeability based on the simultaneous administration of two test substances, cellobiose, a disaccharide, and mannitol, a polyhydric alcohol, both molecules being passively absorbed by the small intestinal mucosa. The test studies two aspects of altered permeability—namely, the decreased absorption of small molecules (mannitol), and the increased permeability to larger molecules (cellobiose) which are known to occur in mucosal diseases such as coeliac disease. By expressing the result as a ratio, cellobiose/mannitol, we have shown good separation between histologically normal and abnormal mucosae. Moreover, as the effects of non-mucosal factors such as renal failure or small bowel contamination tend to be similar for both molecules, we have found that the cellobiose/mannitol ratio is not affected by such disturbances (unpublished). For this reason it is a particularly appropriate test of intestinal permeability for the investigation of patients with systemic sclerosis, who are liable to develop such complications as a result of the disease process.

This study presents the jejunal biopsy findings in 17 unselected patients with systemic sclerosis, together with the results for the cellobiose/mannitol, and routine xylose tests. The results are correlated with general disease severity, gastrointestinal symptoms, the presence or absence of bacterial overgrowth, and the findings of small bowel radiology.

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Methods

Successful biopsies were obtained from the small bowel in 17 unselected patients with systemic sclerosis. In five cases, samples were obtained from the jejunum and duodenal loop using a Quinton hydraulic biopsy capsule. In one case, biopsies from the second part of the duodenum were obtained at fibreoptic endoscopy. In the remainder, a Crosby capsule (Watson model) was used to obtain samples from the distal duodenum or proximal jejunum.

The seventeen patients comprised 15 women and two men, with ages ranging from 15 to 67 years. All of the patients had Raynaud's phenomenon and typical acrosclerotic cutaneous features of systemic sclerosis, although there was considerable variation in the degree of clinical severity of the disease in this unselected group of patients.

The degree of visceral involvement, and hence general disease severity, was quantitatively assessed in each patient using the criteria described by Hughes et al.12 This index makes use of a scoring system, with points allotted on the basis of involvement of skin, lungs, gastrointestinal tract (in particular radiological involvement of oesophagus and/or colon), heart, kidneys, or the presence of other abnormalities—for example, Sjögren's syndrome. The higher the 'score' for a given patient, the greater the degree of visceral involvement.

Biopsies were sectioned at three levels and stained by haematoxylin and eosin. A further section of level 2 was stained by the periodic acid-Schiff method. The following changes were sought and if present graded as mild, moderate or severe: (1) villous atrophy; (2) lamina propria fibrosis; (3) thickening of the muscularis mucosa; (4) submucosa fibrosis; and (5) fibrosis of Brunner's glands.

Cellobiose/mannitol tests were carried out as previously described.10 11 Patients drank a hypertonic solution containing 2 g mannitol and 5 g cellobiose after fasting overnight, and urine was collected for five hours. The recovery of each was expressed as a percentage of the oral dose, and the ratio cellobiose (mg)/mannitol (mg) calculated.

Standard five hour urine xylose tests were performed in the fasting state using a 5 g dose. For our laboratory the lower limit of the normal range is 24% of the 5 g dose recovered in five hours.

Radiological examination was performed by small bowel meal.13 The criteria of involvement were dilatation, crowding of folds, hypomotility, saccula- tion, and stricture.14 Upper limits of normal calibre

Fig. 1 Jejunal biopsy showing focal mild villous atrophy with concomitant elongation of crypts, and mild thickening of the muscularis mucosae. At the deep margin of the muscularis, atypical multinucleate fibres project into the submucosa (arrowed). H and E, × 113.
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were taken as duodenum 35 mm, jejunum 30 mm, ileum 25 mm. Transit times vary greatly in normal subjects and depend upon the technique used. Moderate prolongation as a sole sign is not necessarily significant, although it is well recognised that patients with systemic sclerosis may have grossly prolonged times. With our technique the caecum is reached within two hours in 90% of patients and for the purpose of this study, a time in excess of 2½ hours was considered to be positive.

Results

HISTOLOGY

Villi
Two biopsies had patchy changes in villous/crypt ratio which were thought to be sufficient to be classified as partial villous atrophy of a mild degree. Figure 1 shows the histology of one of these biopsies; the changes in the other were even less marked. No epithelial cell abnormalities were found in any biopsy.

LAMINA PROPIA
Fibrosis was found in only one case, and this was considered to be of only a mild degree of severity.

Muscularis mucosae
This was identified in 16 biopsies, and was abnormal in two, showing mild thickening. One of these also showed occasional multinucleate smooth muscle cells (Fig. 1).

Submucosa
Twelve biopsies contained submucosa, but none showed increased amounts of collagen.

Brunner’s glands
These were found in only six biopsies, and two showed mild fibrosis (Fig. 2), including one of the two biopsies demonstrating thickening of the muscularis mucosae.

In all, only four biopsies showed abnormalities and these were classified as mild in all cases.

PERMEABILITY (Fig. 3, Table)
The results for the cellobiose/mannitol test are shown in Fig. 3. Although individual mannitol or cellobiose values may lie outside the normal range previously found in control subjects, all values for the ratio cellobiose/mannitol fall within the normal range21 and well below those found in untreated coeliacs.

Seven patients had values for xylose excretion below the accepted lower limit (24%) for our laboratory. Two of these had abnormal biopsies but the other five had biopsies showing no abnormality. Two patients with abnormal biopsies had a normal xylose result.

Fig. 2 In this case the central lobule of Brunner’s glands contains increased numbers of fibroblasts which, along with collagen deposition, indicate mild fibrosis. H and E, x 145.
Table Summary of clinical details of 17 systemic sclerosis patients

<table>
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<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
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<tr>
<td>1 JM</td>
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<td>41</td>
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</tr>
<tr>
<td>2 KJ</td>
<td>F</td>
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<tr>
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<td>F</td>
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<td>8 OD</td>
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<tr>
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</tr>
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</tr>
<tr>
<td>12 HS</td>
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<tr>
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<table>
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<th>Symptoms</th>
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<td>Weight loss</td>
<td>Diarrhoea</td>
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Scoring—see text.
d=dilatation, c=crowding of folds, t=prolonged transit, n=normal, v=villous atrophy, l=lp fibrosis, m=musc. mucosa thickening, b=Brunner's gland fibrosis, v=normal, v=decreased, crf=chronic renal failure, gs=gastric stasis.

Note: The table includes the scoring criteria for various symptoms and findings, along with the results for each patient.

**Discussion**

This study, which represents one of the largest series of intestinal biopsy findings in systemic sclerosis, confirms the results of most previous workers. Thus, in 13 biopsies (76%) no abnormality was seen, and in the other four (24%) the changes were very mild. The significance of such minor changes in villous architecture in association with skin disease has been disputed. Of the six cases in which Brunner's glands were seen, two showed mild fibrosis, and it may be that, had glands been present in all biopsies, we might have identified more cases with these mild abnormalities. The incidence is still less than that found by Rosson and Yesner (six out of eight), especially when we consider that submucosal changes were not seen in any of the 12 biopsies in which this area could be assessed. However, our series was unselected, whereas all their patients had clinical evidence of gastrointestinal involvement. In one other unselected series, there were no abnormalities found in 11 biopsies. Interestingly, the same study reported radiological changes in the small bowel in 12 out of 21 patients, a much higher incidence than in our series (two out of 17).

The radiological signs of small bowel involvement are described by Marshak and Lindner and consist mainly of hypomotility, dilatation, and crowding of mucosal folds. Sacculation and pseudo-diverticula formation may occur and pneumatosis cystoides intestinalis has been described. There are no signs of inflammation and the mucosal folds are not thickened. Transit time depends largely upon the technique of examination and the range of normal is

**Radiology (Table)**

Of the 17 patients only one had a small bowel meal which was grossly abnormal, with crowding of folds, hypomotility, and a dilated duodenum and jejunum. One other had delayed transit of barium but was otherwise normal.
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wide. However, a grossly prolonged time for the method used may occur in systemic sclerosis as a feature of hypomotility. Flocculation of contrast is not seen when modern stable media are used.

The quoted incidence of small bowel involvement varies from 22% to 57%.

Our patients being totally unselected, and our limitation of the signs of involvement to hypomotility, dilatation, crowding of folds and sacluation.

The Table summarises the clinical features and results of investigations in the 17 patients. It is interesting that intestinal involvement, as assessed by changes in radiology, biopsy, or the presence of bacterial overgrowth, appears to be independent of disease severity. Thus, of the six patients with the highest scores for visceral involvement (patients 2, 7, 9, 10, 11, 15), only one (patient 2) had an abnormal biopsy, and one (patient 9) had overgrowth.

A recent publication describes a number of patients with intestinal pseudo-obstruction, some of whom had a diagnosis of systemic sclerosis. Jejunal biopsies showed abnormalities of villous architecture, including some with subtotal villous atrophy. These patients did not respond to gluten-free diet, but a number improved clinically with antibiotic therapy. The authors could not account for the biopsy changes, but did suggest that they might be related to bacterial overgrowth in the intestine, possibly compounded by the distension of the gut wall due to the pseudo-obstruction. Of our 17 patients, only one (patient 14) had had episodes of pseudo-obstruction, and her biopsy was entirely normal. High counts (>10⁶ organisms/ml) of intestinal bacteria in jejunal aspirates were found in five patients (including the patient with pseudo-obstructions), two of whom also had a positive glucose/hydrogen breath test for intestinal bacterial overgrowth. Four of these five patients with evidence of intestinal bacterial overgrowth had normal biopsies and the other had partial villous atrophy of only very minor degree. Conversely, three patients with biopsy changes had no evidence of intestinal overgrowth. These findings would suggest that bacterial overgrowth per se is unlikely to be the cause of the abnormalities described by Schufler et al., although there may have been differences in degree of severity between their cases and our unselected group. Alternatively, changes they describe may, as they suggest, be related in some way to pseudo-obstruction, and not directly to the disease process.

The results suggest that passive permeability is unimpaired by the disease process. All patients had a normal cellobiose/mannitol ratio, which has previously been shown to be a sensitive index of permeability changes. This is confirmed by the lack of correlation between histological changes and xylose excretion, the frequency of abnormal xylose results being similar in the groups with normal (5/13) and abnormal histology (2/4). Changes in deeper structures might not be expected to alter passive permeability, but in any case only one of the two patients with villous atrophy had a low xylose result. Moreover, of the seven patients with a low xylose excretion, two had been shown to have small intestinal bacterial overgrowth, two had mild chronic renal impairment, and one was known to have a prolonged gastric emptying time.

In conclusion, we have found mild abnormalities on intestinal biopsy in four of 17 unselected systemic sclerosis patients (24%). In agreement with other workers who have shown normal absorptive function in systemic sclerosis, we would stress that malabsorption in a patient with systemic sclerosis is unlikely to be due to a change in intestinal mucosal permeability. A search for some other factor, such as small bowel bacterial overgrowth, which we have found in approximately one-third of unselected systemic sclerosis patients, is more likely to be rewarding.

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