Increased intestinal permeability in ankylosing spondylitis – primary lesion or drug effect?

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Abstract

We have found increased small intestinal permeability to ^{51}Cr-ethylenediaminetetra acetate in patients with ankylosing spondylitis compared with controls. There is no significant difference between patients with ankylosing spondylitis and patients with rheumatoid arthritis taking non-steroidal anti-inflammatory drugs (NSAID). The increased intestinal permeability in ankylosing spondylitis is independent of disease activity. These findings suggest that the increased permeability is caused by NSAID treatment and is probably not a primary lesion of small bowel mucosa.

The link between seronegative arthropathy and small bowel disease is well established.[1][2] Recent work has suggested a high incidence of both microscopic and macroscopic changes in the terminal ileum of patients with seronegative spondylarthropathy at ileocolonoscopy.[3] These findings were not observed in patients with rheumatoid arthritis or the urogenital form of reactive arthritis, raising the possibility of a primary small bowel lesion in the other patients with seronegative spondylarthropathy. The concept of intestinal permeability refers to the passive permeation of low molecular weight molecules across the intestinal mucosa. Increased permeability has been previously documented in those with inflammatory bowel disease,[4] alcoholics,[5] and in patients with untreated coeliac disease.[6] It has also been found in patients with inflammatory joint disease taking non-steroidal anti-inflammatory drugs (NSAIDs).[7] It has been suggested that increased intestinal permeability is the triggering factor in NSAID induced small bowel damage.[8] There is currently little data on intestinal permeability to sugars and on disaccharide/monosaccharide ratios in patients receiving NSAIDs.

We have therefore measured intestinal permeability in patients with ankylosing spondylitis taking NSAIDs and compared these results with those of a control group of healthy volunteers and a similar group of rheumatoid arthritis patients on NSAID therapy. We also studied the effect of disease activity on intestinal permeability in ankylosing spondylitis.

Patients and methods

PATIENTS

Seventeen patients with ankylosing spondylitis taking NSAIDs who were attending our rheumatology outpatient clinic were studied. They were compared with two control groups, the first comprising 16 healthy volunteers and the second

19 patients with rheumatoid arthritis being treated with NSAIDs. In our clinical practice we had insufficient patients with ankylosing spondylitis who were not taking NSAIDs to form a separate control group. In these groups, coeliac disease, inflammatory bowel disease, alcohol abuse, and, in the volunteers, NSAID therapy were excluded on the basis of history and clinical examination. The ankylosing spondylitis patients were all men aged 29–63 years, healthy volunteers (eight men and eight women) were aged 24–63 years, and the rheumatoid group (10 men and nine women) were aged 37–82 years. All tests were performed on an outpatient basis and informed consent was obtained before each procedure.

METHODS

After an overnight fast, patients and controls received 150 ml of solution containing 2 g mannitol, 5 g lactulose, 1 g L-rhamnose, 20 g sucrose, 20 g lactose, and 4 MBq of ^{51}Cr-EDTA. The patients' urine was collected for 24 hours after taking the test solution. The collection period was divided into 0–6 hours and 6–24 hours. One ml of thiomersol (10% w/v) was added to the containers as preservative. The addition of sugars (sucrose and lactose) to the test solution rendered the final solution hyperosmolar at 1200 mOsmol/l.

Estimation of urinary recovery of ^{51}Cr-EDTA used the methods described by Bjarnason.[5][6] Urinary L-rhamnose, mannitol, and lactulose were estimated by modification of two gas liquid chromatography methods.[9][10]

Statistical tests were performed using the Wilcoxon rank sum test, Mann-Whitney U test, and Pearson's correlation test.

Results

We found that intestinal permeability to ^{51}Cr-EDTA in the 0–6 hours collection was median 0·35% (range 0·09–0·70) in controls, 0·61% (range 0·15–1·29) in ankylosing spondylitis and 0·54% (range 0·12–1·27) in rheumatoid arthritis. In the 6–24 hours collection values were: median 1·23% (range 0·4–3·21) control; 1·31% (0·3–2·28) ankylosing spondylitis, and 2·12 (0·12–11·40) rheumatoid arthritis. The sugar permeability results were: lactulose 0·25% (0·05–1·1), rhamnose 8·6% (4·9–24·9), and lactulose/rhamnose (L/R) ratio 0·02 (0·01–0·05) in controls; lactulose 0·26% (0·04–0·59), rhamnose 8·8% (1·2–11·6), and L/R ratio 0·03 (0·01–0·27) in ankylosing spondylitis; and lactulose 0·29% (0·1–0·95), rhamnose 9·0% (2·9–20·3), and L/R ratio 0·03 (0·01–0·07) in rheumatoid arthritis. The L/R ratios and lactulose/mannitol (L/M)

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Median (range) % excretion of ^{51}Cr-EDTA in urine

Group	0–6 hours	6–24 hours
Control	0·35 (0·09–0·70)	1·23 (0·4–3·21)
Rheumatoid arthritis	0·54 (0·12–1·27)	2·12 (0·12–11·40)
Ankylosing spondylitis	0·61 (0·15–1·29)	1·31 (0·3–2·28)

ratios measure the same pathways and only L/R ratios are presented here. There was a correlation (r=0·65) between lactulose and ^{51}Cr-EDTA permeability in the 0–6 hours collection.

Using ^{51}Cr-EDTA, we found a significantly increased small bowel permeability in ankylosing spondylitis patients compared with controls (p=0·008 (0–6 hours)) and between rheumatoid arthritis patients, and controls (p=0·03 (0–6 hours)). There was no significant difference in ankylosing spondylitis compared with rheumatoid arthritis (p=0·84 (0–6 hours)). All other comparisons, including 6–24 hours collection periods, ^{51}Cr-EDTA, lactulose, rhamnose, and L/R ratios showed no significant differences between groups. The Table shows the results for all groups in the 0–6 hours collection period for ^{51}Cr-EDTA. There was no correlation between intestinal permeability in the 0–6 hours collection and the markers of activity measured in ankylosing spondylitis (haemoglobin (r=0·14, p=0·73), erythrocyte sedimentation rate (r= 0·53, p=0·07), white cell count (r=0·51, p=0·08), platelets (r=0·24, p=0·442).

Discussion

Bjarnason et al have postulated that absorption of an otherwise excluded antigen may be responsible for both the aetiology and propagation of diseases associated with increased intestinal permeability.[5] Furthermore, it has been speculated that increased intestinal permeability is central to the development of NSAID induced small bowel damage.[8]

In ankylosing spondylitis this theory of antigen absorption has certain attractions as it has been shown that there are increased antibodies to Klebsiella pneumoniae in the serum of patients with this disease.[11] Previous reports of fluctuating antibody concentrations to faecal Klebsiella[12] in relation to activity of the joint disease were not confirmed by these workers. In the former study increased antibody values were also found in patients with rheumatoid arthritis and Crohn's disease. It is interesting that these conditions have also been reported to be associated with increased intestinal permeability. The antibody concentrations may therefore reflect a non-specific antigen absorption secondary to inflammation of gut mucosa.

In this study we have documented increased intestinal permeability in the first six hours of collection in patients with ankylosing spondylitis. This period is thought to correspond to the absorption of the marker through the small intestine. In the 6–24 hour period there was no significant difference in permeability between ankylosing spondylitis and control. This finding suggests that the lesion causing increased permeability is localised to the small bowel. In a previous letter Wendling et al reported the

finding of increasing intestinal permeability to ^{51}Cr-EDTA in a 24 hour urine collection in patients with ankylosing spondylitis and inflammatory rheumatic diseases.[13] They studied patients with these conditions who were not taking NSAIDs and concluded that NSAIDs were a major factor in increasing intestinal permeability. Whereas untreated patients with ankylosing spondylitis in this study had increased intestinal permeability, this was also the case in untreated inflammatory rheumatic diseases, a finding which is at variance with previous reports.[7] In our study we have confirmed the results of a previous study which reported increased intestinal permeability in 0–6 hours collection in ankylosing spondylitis using the marker polyethylene glycol 400.[14] These authors did not, however, comment on the latter part of the urine collection or indicate the possible site of increased permeability.

In our study we have found no statistical significance in L/R ratios between controls and patients with rheumatoid arthritis or ankylosing spondylitis taking NSAIDs. There was, however, a correlation between ^{51}Cr-EDTA and lactulose permeability suggesting that the lesion here is of intercellular permeability rather than at a cellular level.

Our test solution had a final osmolality of 1200 mOsmol/kg which has led to seemingly reduced permeability to ^{51}Cr-EDTA in controls and patients compared with previous studies. However, the lower osmolality enhances the permeability to L-rhamnose and is therefore likely to enhance sensitivity of the monosaccharide data.[15] In this paper all patients and controls received an identical test solution and therefore statistical comparisons remain valid.

In previous studies De Vos et al found macroscopic and microscopic evidence of inflammation in the terminal ileum of patients with seronegative arthropathy. This raised the possibility of either a primary small intestinal abnormality or a drug induced lesion probably extending more diffusely through the small intestine. In these studies inflammation of the terminal ileum was found in patients not taking NSAIDs and therefore the possibility of a primary small bowel abnormality is raised. The histology of these lesions, however, particularly in the peripheral joint ankylosing spondylitis group, closely resembled subclinical Crohn's disease and this may in fact explain fully the distribution of the lesions. More recently, the same group failed to identify increased intestinal permeability, using methods similar to our own, in patients with seronegative arthropathy irrespective of the presence or absence of inflammation at ileocolonoscopy.[16] This finding seems difficult to interpret in the knowledge that an inflammatory process affecting intestinal mucosa is associated with increased intestinal permeability. We have recently described small bowel lesions identified by small bowel enteroscopy in patients with rheumatoid arthritis on NSAID therapy.[17] We concluded that these macroscopic findings were the result of NSAID induced small bowel damage. We feel a more likely explanation of these results is that NSAID therapy is responsible for the increased permeability in both

ankylosing spondylitis and rheumatoid arthritis and that the changes previously observed at ileocolonoscopy in patients with seronegative arthropathy may be partly NSAID induced. Our finding of increased intestinal permeability in patients with rheumatoid arthritis taking NSAIDs is in keeping with previous studies.[7]

In this present study small intestinal permeability in ankylosing spondylitis is independent of disease activity using the parameters measured. This further suggests that a primary small bowel lesion is unlikely as the severity of disease would be expected to mirror gut inflammatory changes if this were the primary or triggering event for joint disease.

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