Dynamics of mucosal permeability and inflammation in collagenous colitis before, during, and after loop ileostomy

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Collagenous colitis has become a more frequent diagnosis but the aetiology of this disease is still unknown. We describe a female patient with intractable collagenous colitis who was treated with a temporary loop ileostomy. She was followed clinically, histopathologically, and functionally by measuring mucosal permeability before surgery, after ileostomy, and after bowel reconstruction. In our case report, active collagenous colitis was combined with increased transcellular and paracellular mucosal permeability. Diversion of the faecal stream decreased inflammation of the mucosa and normalised epithelial degeneration and mucosal permeability. After restoration of bowel continuity, mucosal permeability was altered prior to the appearance of a collagenous layer.

METHODS

Histology
Biopsies were obtained endoscopically from the colon and stained with haematoxylin-eosin and van Gieson. Specimens from the sigmoid colon were more closely investigated. Two biopsies from the sigmoid colon were taken at each investigation. The degree of surface epithelial cell degeneration was assessed in three arbitrary units. The thickness of the collagenous band was measured in five different areas and the mean value was assessed. Immunohistochemical staining for CD3 was also performed according to routine procedures. The number of intraepithelial lymphocytes (IEL)/100 enterocytes (mean value of three countings) was assessed. Infiltration of mononuclear cells (lymphocytes and plasma cells) in the lamina propria was defined in three arbitrary units.

Ussing chamber
Biopsies were mounted in modified 1.5 ml Ussing chambers (Grass & Sweetana, Harvard apparatus Inc., Holliston, Massachusetts, USA) with an exposed tissue area of 1.76 mm². Continuous oxygenation was given; pH was kept at 7.4 and temperature at 37°C. After a 40 minute equilibration period, the marker solution containing chromium-51 ethylenediaminetetraacetate (51Cr-EDTA) and horseradish peroxidase type VI (HRP) 10 μM were added to the mucosal compartment. Every 30 minutes 0.3 ml samples were taken from the serosal side for analysis. 51Cr-EDTA uses the paracellular pathway and HRP permeates mainly transcellularly. Transepithelial potential difference (Pd), short circuit current (Isc), and transepithelial resistance (TER) were studied for 120 minutes in all specimens. Results were reported as mean ± SEM.

Abbreviations: CC, collagenous colitis; Cr-EDTA, chromium-ethylenediaminetetraacetate; HRP, horseradish peroxidase; IBD, inflammatory bowel disease; Isc, short circuit current; Pd, transepithelial potential difference; TER, transepithelial resistance; IEL, intraepithelial lymphocytes

INFLAMMATORY BOWEL DISEASE

Cases of collagenous colitis (CC) are documented with increasing frequency. Patients suffer from watery diarrhoea and systemic symptoms, such as arthralgia, myalgia, and malaise. The disease is characterised by a diffuse inflammatory infiltrate affecting the subepithelial collagen layer. Histopathologically, the condition is characterised by a thick subepithelial collagen band that is associated with increased transcellular and paracellular mucosal permeability. This barrier function seems to be impaired before the appearance of the collagenous layer.
from a control group of healthy volunteers were used for comparison.

RESULTS

Histology

Biopsies taken prior to surgery showed a classical picture of CC. Two months after loop ileostomy the submucosal collagenous layer was reduced in thickness but there was also a remarkable additional infiltration of CD3 lymphocytes in the collagenous layer. The layer was also indistinct at the deeper border (fig 1). The number of IEL, epithelial degeneration, and the density of the mononuclear cells in the lamina propria decreased (table 1). A further decrease in the collagenous band could be seen after four months and the border became more distinct, but there was still the same grade of density of mononuclear cells in the lamina propria. Upper gastrointestinal endoscopy at that time revealed a normal gastric and duodenal mucosa. Seven months after bowel reconstruction the sigmoid colon presented only with an increase in lymphocytes and plasma cells in the lamina propria whereas the collagenous band was still less than 10 µm in the sigmoid colon but increased in thickness in the rest of the colon (data not shown).

Ussing chamber

Cr-EDTA and HRP sigmoid mucosal permeability were substantially increased before surgery, when the patient had active colitis. Permeability decreased at two months and normalised after four months compared with the control group. Seven months after bowel reconstruction colonic mucosa permeability increased again to a level above the 95th percentile for controls (fig 2). Electrophysiological measurements (Pd, Isc, TER) were stable, indicating viability of all specimens.

DISCUSSION

Our case report corroborates the findings of Jänerot and colleagues that faecal stream diversion with a temporary loop ileostomy leads to clinical and histopathological remission in CC. Furthermore, we showed that mucosal barrier dysfunction was present during active CC by measuring permeability in endoscopic biopsies using Ussing chamber technology. During the period with a diverting stoma, repeated biopsies of the sigmoid colon showed that transcellular and paracellular permeability decreased at the same time as inflammation in the lamina propria diminished, and the subepithelial collagenous layer and epithelial degeneration disappeared. Histology after two months showed that the collagenous band was more diffuse and infiltrated by lymphocytes, which could be a result of resolution. We do not believe that this is associated with diversion colitis or an effect of the postoperative Clostridium difficile infection because typical signs of these conditions were not seen histologically.

The present case suggests that active CC may be described as a disease with increased transcellular permeability in addition to increased permeation via tight junctions. The increased permeability seemed however to parallel the degree of epithelial damage. Hypothetically, epithelial cell degeneration could possibly be associated with mucosal barrier dysfunction. Burgel et al showed that expression of tight junction proteins is diminished in CC but the mucosal architecture in their patients was not much altered compared with normal histology.

Many gastrointestinal diseases have gut barrier dysfunction although it is uncertain if disrupted gut barrier is a primary pathomechanism or secondary to inflammation. It...
has been suggested that increased mucosal permeability to macromolecules and antigens is a possible initiating event for developing intestinal inflammation in Crohn’s disease and ulcerative colitis. In both diseases however enhanced intestinal permeability is associated with clinical activity and intestinal inflammation, with tumour necrosis factor α as a possible mediator. In our case, mucosal permeability was normal four months after faecal stream diversion when histology showed only slight inflammation in the lamina propria, suggesting that the mucosal barrier defect is a consequence of an underlying inflammatory process.

After restoring bowel continuity the patient had a relapse in symptoms, despite continuous budesonide treatment. In parallel, histological findings of CC recurred. In the sigmoid colon mucosal permeability was altered prior to formation of the collagenous band which indicates that the collagenous band is not a primary factor for mucosal barrier defect.

The cause of CC is not known. As faecal stream diversion leads to remission it seems most likely that epithelial damage is caused by a hitherto unknown luminal agent(s) as a first event leading to mucosal inflammation and abnormal permeability. Experimental studies of rabbit and rat colon mucosa have shown that bile salts can alter the integrity of tight junctions. As bile acid malabsorption is common in CC, hypothetically bile acids could contribute to disturbed mucosal permeability. Bile acid binders often lead to clinical improvement but do not necessarily correlate with histological remission. Unfortunately, our patient did not improve when treated with cholestyramine.

In summary, our case of active CC was associated with increased transcellular and paracellular mucosal permeability. Diversion of the faecal stream decreased inflammation of the mucosa and normalised permeability. After restoration of bowel continuity permeability was altered prior to the appearance of a collagenous layer. Further studies are necessary to elucidate the role of increased macromolecular permeability in the pathogenesis of collagenous colitis.

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