Role of bile acids and bile acid binding agents in patients with collagenous colitis

K-A Ung, R Gillberg, A Kilander, H Abrahamsson

Abstract

Background—In a retrospective study bile acid malabsorption was observed in patients with collagenous colitis. Aims—To study the occurrence of bile acid malabsorption and the effect of bile acid binders prospectively in patients with chronic diarrhoea and collagenous colitis.

Methods—Over 36 months all patients referred because of chronic diarrhoea completed a diagnostic programme, including gastroscopy with duodenal biopsy, colonoscopy with biopsies, and the 75Se-homocholic acid taurine (75SeHCAT) test for bile acid malabsorption. Treatment with a bile acid binder (cholestyramine in 24, colestipol in three) was given, irrespective of the results of the 75SeHCAT test.

Results—Collagenous colitis was found in 28 patients (six men, 22 women), 27 of whom had persistent symptoms and completed the programme. Four patients had had a previous cholecystectomy or a distal gastric resection. The 75SeHCAT test was abnormal in 12/27 (44%) of the collagenous colitis patients with 75SeHCAT values 0.5–9.7%, and normal in 15 patients (56%).

Bile acid binding treatment was followed by a rapid, marked, or complete improvement in 21/27 (78%) of the collagenous colitis patients. Rapid improvement occurred in 11/12 (92%) of the patients with bile acid malabsorption compared with 10/15 (67%) of the patients with normal 75SeHCAT tests.

Conclusion—Bile acid malabsorption is common in patients with collagenous colitis and is probably an important pathophysiological factor. Because of a high response rate without serious side effects, bile acid binding treatment should be considered for collagenous colitis, particularly patients with bile acid malabsorption.

Methods

Over a period of 36 months all patients (n=404) referred to our Gastroenterology Unit because of severe chronic diarrhoea without blood and with negative faecal culture for bacteria, completed a diagnostic programme which included gastroscopy with duodenal biopsy, colonoscopy with biopsy, and the 75SeHCAT test for bile acid malabsorption. Some of the patients included had been referred to our hospital because of persistent symptoms and a previous, incomplete diagnostic evaluation. In total 28 patients with collagenous colitis were registered during the three year period. Twenty seven of the patients had persistent severe diarrhoea. In one male patient the symptoms decreased spontaneously after the colonoscopy; this patient declined the 75SeHCAT test and further treatment.

During colonoscopy, biopsy specimens were obtained from the left colon in all patients.
from the proximal colon in 22 patients, and from the distal ileum in nine patients. Conventional criteria for collagenous colitis were typical microscopic inflammation including an increased number of intraepithelial lymphocytes, and a subepithelial collagen layer of at least 10 μm. Gastroscopy was performed on all patients and a duodenal biopsy sample was taken for histological evaluation, including a coeliac disease test. In two of three patients with a history of coeliac disease, normalisation of the duodenal mucosa with a gluten free diet had been shown before this study.

**Statistical Analysis**

The results for stool frequency are presented as medians, interquartile range, and 10th and 90th percentiles. A comparison between groups with and without bile acid malabsorption was performed using the Mann-Whitney U test for unpaired data.

**Results**

**Bile Acid Absorption**

Bile acid malabsorption, defined as a $^{75}$SeHCAT retention less than 10% on day 7, occurred in 12 of 27 (44%) patients with collagenous colitis. Figure 1 shows the results of the $^{75}$SeHCAT test in relation to age and sex. The occurrence of bile acid malabsorption was not significantly related to age or sex.

**Stool Frequency**

Figure 2A shows the mean number of stools per day for individual patients during the week of symptom registration. There was a significant negative correlation between the mean number of stools and the $^{75}$SeHCAT retention on day 7 ($p=0.02$). Figure 2B shows that stool frequency was significantly higher in patients with collagenous colitis and bile acid malabsorption than in those without bile acid malabsorption.

**Duration of Symptoms**

Patients with bile acid malabsorption had a significantly longer history of diarrhoea than patients without bile acid malabsorption (median 8 years, range 0.5–30 years, n=12 versus median 2 years, range 0.5–15 years, n=15; $p<0.05$). There was no significant relation between the duration of symptoms and the age of the patients.
Table 1 presents the occurrence of autoimmune diseases and previous abdominal surgery. Eleven patients (41%) had at least one associated autoimmune disease. Four patients had had one or two abdominal operations, including three patients with cholecystectomy, all showing bile acid malabsorption. Fourteen patients (52%) had no history of autoimmune disease or a history of abdominal surgery. There was no statistical correlation between autoimmune disease and the occurrence of bile acid malabsorption or between autoimmune disease and sex.

**EFFECT OF TREATMENT WITH BILE ACID BINDERS**

Treatment with a bile acid binder was given to all symptomatic patients (cholestyramine to 24 patients, colestipol to three patients) with collagenous colitis. A rapid improvement with a clear cut decrease in diarrhoea within one week was noted in 21 of the 27 patients ("rapid responders" to bile acid binders). Six patients did not show this rapid response. Eleven of 12 patients with bile acid malabsorption (92%) showed a rapid response, while in patients with a normal $^{75}$SeHCAT test this response rate was 67%. Another two patients, including the non-responding patient with bile acid malabsorption, improved slowly over a period of one to two months. All the non-responders were women over 50 years old. However, there was no statistically significant relation between sex or age and the outcome of treatment with bile acid binders.

The daily dose of bile acid binder needed to control diarrhoeal symptoms ranged from 0.5 to 6 (median: 2.5) packets daily (cholestyramine 4 g or colestipol 5 g per packet). The highest dose needed was cholestyramine 24 g daily, in one particular patient. This dose could later be reduced to 16 g daily. All three patients treated with colestipol, one with and two without bile acid malabsorption, responded rapidly to treatment.

**OUTCOME OF TREATMENT STRATEGY**

Figure 3 illustrates the outcome of treatment of the 27 symptomatic patients with collagenous colitis. Twenty three of the symptomatic patients improved rapidly or slowly when treated with a bile acid binder alone. Three of the remaining four patients, with no improvement or only a slight improvement with a bile acid binder, responded to either sulphasalazine alone (two patients) or an inadvertent combination of cholestyramine and sulphasalazine (one patient). The remaining symptomatic patient responded to metronidazole within two weeks and remained asymptomatic during the long term treatment period of six months with metronidazole 0.8 g per day.

As all patients with collagenous colitis had sufficient control of the diarrhoea before the fourth optional treatment, steroids were not used in this study.

**COLLAGEN LAYER**

Ten of the patients with collagenous colitis had a collagen layer thicker than 20 µm. The remaining patients had a collagen layer thickness in the range 10–20 µm. There was no statistical difference in the $^{75}$SeHCAT test between the patients with a thick layer (median $^{75}$SeHCAT value 11%) and those with a layer 10–20 µm (median $^{75}$SeHCAT value 11%).

Eight of the nine patients who had ileal biopsies performed had normal histology. Three of these had low $^{75}$SeHCAT values. One patient with coeliac disease had atrophy of the ileal and the duodenal mucosa but had a normal $^{75}$SeHCAT value of 13%. All of the
Eleven patients (41%) had at least one autoimmune disease.

Table 1 Number of patients with associated conditions, and the individual $^{75}$SeHCAT values in 27 patients with collagenous colitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>$^{75}$SeHCAT retention (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>9.7; 21; 33</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>3</td>
<td>5.0; 13; 31</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>2</td>
<td>0.8; 15</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>2</td>
<td>2.0; 13</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Billroth I resection</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Cholecystectomy and Billroth I resection</td>
<td>1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Eleven patients (41%) had at least one autoimmune disease.

Figure 3 Resolution of diarrhoea in 28 patients with collagenous colitis.

<table>
<thead>
<tr>
<th>Status</th>
<th>Registered patients</th>
<th>Untreated</th>
<th>Bile acid binder</th>
<th>Sulphasalazine</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid improvement 1–2 weeks</td>
<td>21</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>28</td>
<td>27</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Slow improvement &gt; 1 month</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

remaining patients had a normal duodenal histopathology. Consequently, none had collagenous changes of the duodenal or the ileal mucosa.

TEST FOR BACTERIAL OVERGROWTH OF THE SMALL BOWEL

Nineteen patients had a hydrogen breath test and one patient had a culture from duodenal aspirate to test for bacterial overgrowth. Nine of these patients had bile acid malabsorption and 11 patients had normal $^{75}$SeHCAT values. The bacterial culture on the duodenal aspirate was negative and the breath test showed increased hydrogen values compatible with bacterial overgrowth in only one of the patients tested. In this particular patient, bacterial overgrowth was confirmed by a positive bacterial culture on duodenal aspirate. This patient had a history of cholecystectomy and Billroth I gastrectomy due to peptic ulcer disease. As 19 of the 20 patients tested were negative, and the patient with bacterial overgrowth had a strong predisposing factor, the remaining seven patients were not tested for bacterial overgrowth.

Discussion

In this prospective study on the potential role of bile acids in collagenous colitis we found using the $^{75}$SeHCAT method that bile acid malabsorption occurred in a considerable proportion (44%) of the patients. This is in accordance with a few earlier observations in small studies, including our own initial report on the effect of cholestyramine on patients with collagenous colitis.$^3,20,21$ As in the previous series of patients with collagenous colitis, our patient group was female dominated and there was a high prevalence of autoimmune diseases, comparable to previous reports.$^3,5,27$ However, the occurrence of bile acid malabsorption in our collagenous colitis patients showed no statistical association with sex, presence of autoimmune disease, or age. The association between bile acid malabsorption and cholecystectomy or gastric resection has been described previously,$^2,28$ although the present study shows that collagenous colitis might also contribute to diarrhoea in these patients.

The simultaneous occurrence of bile acid malabsorption in patients with collagenous colitis may influence the clinical presentation of the patients. Despite similar histological findings, including the thickness of the collagen layer and similarities in other parameters between patients with and without bile acid malabsorption, patients with bile acid malabsorption had more symptoms, manifested as significantly higher stool frequency.

The patients with collagenous colitis and concomitant bile acid malabsorption had a significantly longer history of diarrhoea than patients without bile acid malabsorption. The reason for this is not obvious from the present data.

The aetiopathogenesis of bile acid malabsorption and collagenous colitis is in many aspects still obscure. The high occurrence of autoimmune disorders in the present and previous reports suggests a genetic predisposition to collagenous colitis.$^3,5,17$ The occurrence of small bowel bacteria or toxins of bacterial origin has also been suggested.$^14,20$ However, we found no obvious relation between small bowel bacterial overgrowth and collagenous colitis. Only one of 20 patients tested for bacterial overgrowth in this study showed small bowel bacterial overgrowth. This particular patient, apart from a previous cholecystectomy, had also had a previous Billroth I operation predisposing for bacterial overgrowth.$^29$ She responded to continuous cholestyramine treatment. This patient had a few later relapses of diarrhoea during cholestyramine treatment. These relapses ceased when treatment for intestinal bacteria with norfloxacin was given for periods of one to two weeks, during which she still had to maintain the ordinary dose of cholestyramine to control the diarrhoea. In this interesting case, the diarrhoea promoting factors bacterial overgrowth and bile acid malabsorption were apparently independent of each other.

Ileal biopsy specimens were available from nine patients, three of whom had bile acid malabsorption. However, ileal histology and duodenal histology were normal except in one patient, who had coeliac disease and atrophy of the ileal and the duodenal mucosa but a normal $^{75}$SeHCAT value. As in previous series of patients with microscopic colitis,$^3,8,9$ there was also an increased proportion of coeliac disease in our study. None of the patients showed signs of collagenous duodenitis or collagenous ileitis, conditions that have been previously described in a few case reports.$^{30,35}$ In the present study, small bowel factors as shown by
tests of bacterial overgrowth and by the histology of duodenal and ileal mucosa, could not explain the occurrence of collagenous colitis and the associated bile acid malabsorption.

The main pathophysiological mechanism for the occurrence of diarrhoea in collagenous colitis is suggested to be reduced permeability for electrolytes and water in the colonic mucosa, while the active absorption of bile acids occurs in the terminal ileum. Other diarrheal disorders of colonic origin have not been shown to cause abnormal $^{75}$SeHCAT values. Diarrhoea per se might reduce the $^{75}$SeHCAT value but not to an abnormal level. This suggests that the low $^{75}$SeHCAT values found in the present study correspond to a reduced capacity to absorb bile acids in the ileum and are not due to a colonic malabsorption secondary to the diarrhoea caused by collagenous colitis.

The present prospective study tested whether the clinical response of patients with collagenous colitis to treatment with an open label bile acid binder is related to simultaneous bile acid malabsorption—that is, whether the result of the $^{75}$SeHCAT test could predict the outcome of treatment. All patients with bile acid malabsorption, defined as a low value with the $^{75}$SeHCAT test, responded to bile acid binders. Eleven of 12 patients showed a rapid response. The twelfth patient showed a slower but positive response, which could be a drug effect or it could represent the natural course of the disease similar to the spontaneously improved patient.

There was no statistically significant difference in the response rate in patients with and without bile acid malabsorption. This was due to the relatively high response rate (67%) in non-bile acid malabsorption patients. The results suggest that in patients with collagenous colitis and bile acid malabsorption, treatment of the observed bile acid malabsorption was sufficient to obtain a clinical response and none of the drugs used for inflammatory bowel disease was needed. It seems less likely that the rapid response, often within a few days, could correspond to a normalisation of the colonic mucosa. However, no detailed information is as yet available regarding the regression of histological inflammation during bile acid binder treatment although this issue is now under investigation (Ung et al, to be published).

The high response rate to the bile acid binders, even in patients with a normal $^{75}$SeHCAT test value, suggests that cholestyramine and colestipol may also have clinical effects on collagenous colitis through mechanisms other than pure bile acid binding. This would be in agreement with a previous case report, where the patient with collagenous colitis responded to cholestyramine. However, direct tests of bile acid malabsorption were not performed in that patient. The mechanisms of cholestyramine were suggested to be binding of toxins and other effector substances on the intraluminal contents. Alternatively, the colonic inflammation may be the result of an abnormal reaction to normal amounts of bile acids entering the colon. In this context, it is of interest that in none of our patients could the collagenous colitis related diarrhoea be linked to small bowel bacterial overgrowth.

Hitherto, there has been no generally accepted drug of choice for the treatment of patients with collagenous colitis. In the present study we had a treatment strategy with additional options based on the previously reported effects of sulphasalazine, antibiotics, and steroids. The risk of long term treatment with metronidazole, particularly neuropathy, prompted us to choose sulphasalazine as the second line drug and metronidazole as the third option, should bile acid binders fail. Remarkably, all 27 patients responded to one of the first three choices and steroids, the fourth option, were not prescribed. Further studies are needed to evaluate the histological improvement during the course of the various types of treatment. As steroids do not heal the inflammatory changes in the colonic mucosa in patients with collagenous colitis, the strategy of using a bile acid binder as the first line treatment with 5-acylsalicylic acid/sulphasalazine and antibiotics as alternative drugs, seems attractive. Apart from the taste problem and for some patients the smell, as well as the potential need for vitamin supplements, side effects from bile acid binders are rare.

In patients with collagenous colitis without bile acid malabsorption, bile acid binders may also be the first option. However, apart from bile acid binders, bismuth subsalicylate has recently been reported to have a good clinical effect on patients with microscopic colitis. In one patient with microscopic colitis, a normal $^{75}$SeHCAT value, and disabling diarrhoea, refractory to six different drugs including cholestyramine, the response to bismuth subsalicylate was excellent. Further placebo controlled studies of a variety of other drug regimen and placebo are needed to evaluate the effect of bile acid binders, bismuth, and other drugs of potential interest.

In conclusion, the present study shows that a considerable proportion of patients with collagenous colitis have bile acid malabsorption and that in these patients bile acid binders seem to be the first line treatment. Moreover, in collagenous colitis patients without bile acid malabsorption, two thirds responded to a bile acid binder (cholestyramine or colestipol). The results show that bile acids may be an important aetiopathogenetic factor, although not the only factor, in patients with collagenous colitis. This study was supported by the Swedish Medical Research Council (grant 8288) and by the Faculty of Medicine, University of Göteborg. This work was presented in part at the 1997 meeting of the American Gastroenterological Association and published in abstract form (Gastroenterology 1997;112:A1108).
