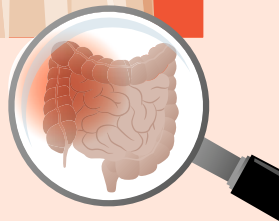
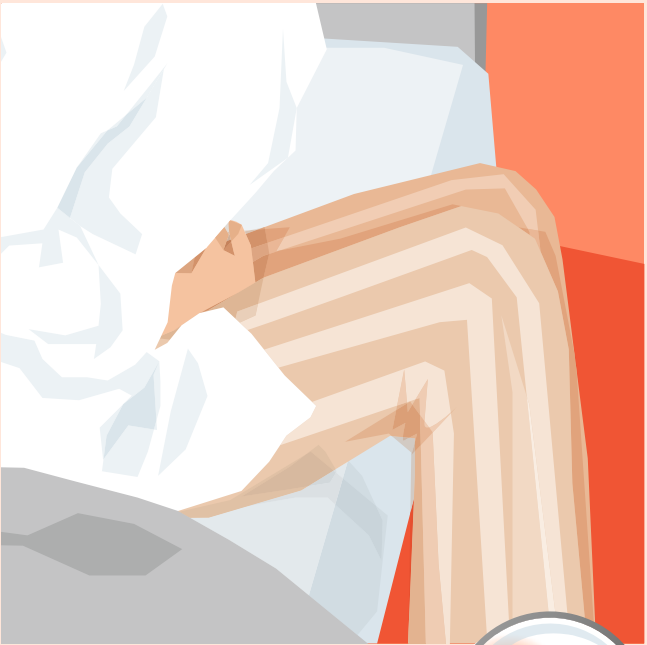


Microscopic colitis

Collagenous and
lymphocytic colitis



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Microscopic colitis

Collagenous and lymphocytic colitis

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Introduction

The term *microscopic colitis* encompasses two different disorders of the colon known as *collagenous colitis* and *lymphocytic colitis*.

Both disorders are characterized by non-bloody watery diarrhea and are sometimes referred to as watery diarrhea syndromes (Fig. 1).

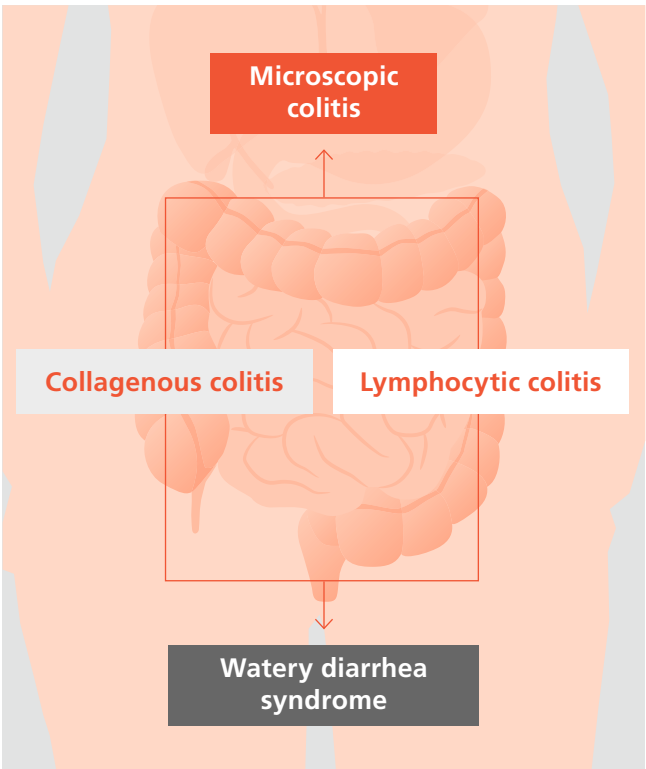


Fig. 1: Definition of microscopic colitis.

The term *microscopic colitis* describes a chronic inflammatory disease of the colon (“colitis” comes from the Latin term “colon” and the ending “-itis”, which is used in medicine to refer to inflammation) that a doctor cannot identify by colonoscopy with the naked eye because the mucosa of the colon appears normal. In order for the disease to be diagnosed, the doctor must therefore remove a small tissue sample and examine it under a microscope. This is the only way to diagnose *microscopic colitis*.

For *collagenous colitis*, a thickened collagen layer becomes visible when the tissue samples are stained using special methods, whereas *lymphocytic colitis* is detected as an increased number of a specific type of white blood cells called lymphocytes (see page 12).

Our understanding of *microscopic colitis* has expanded greatly since it was first described in the 1970s. Because the disease is so difficult to diagnose, it is not well known, even though it is thought to occur about as often as the inflammatory bowel diseases of Crohn’s disease and ulcerative colitis. The number of undiagnosed cases is likely high.

The standard of care is budesonide (taken orally as capsules or granules), a locally-acting corticosteroid drug that inhibits inflammation in the gut. Depending on the form of *microscopic colitis*, budesonide can be used to treat the symptoms of acute disease or in case of chronic disease it can also be used to prevent the recurrence of diarrhea.

Clinical presentation

Microscopic colitis primarily affects older women. The defining symptom of *microscopic colitis* is watery diarrhea, which can occur suddenly and may mimic an infection. A large study in Sweden also reported the following symptoms:

- In almost 30% of patients: nocturnal diarrhea
- In over 40% of patients: weight loss
- In over 40% of patients: abdominal pain
- In over 20% of patients: nausea
- In over 10% of patients: flatulence

Although the precise cause of weight loss remains unclear, it appears likely that patients eat fewer calories due to well-intentioned dietary restrictions which cause them to lose weight. Patients rarely have issues with dehydration despite the frequent diarrhea.

Fecal incontinence and fatigue are other symptoms that occur with *microscopic colitis* and greatly impair patients' quality of life.

30–50% of patients with *microscopic colitis* may also experience symptoms or conditions in other organs outside of the gut, for example rheumatoid arthritis of the joints, psoriasis of the skin, or even thyroid gland dysfunction (Fig. 2). These issues require additional treatment.



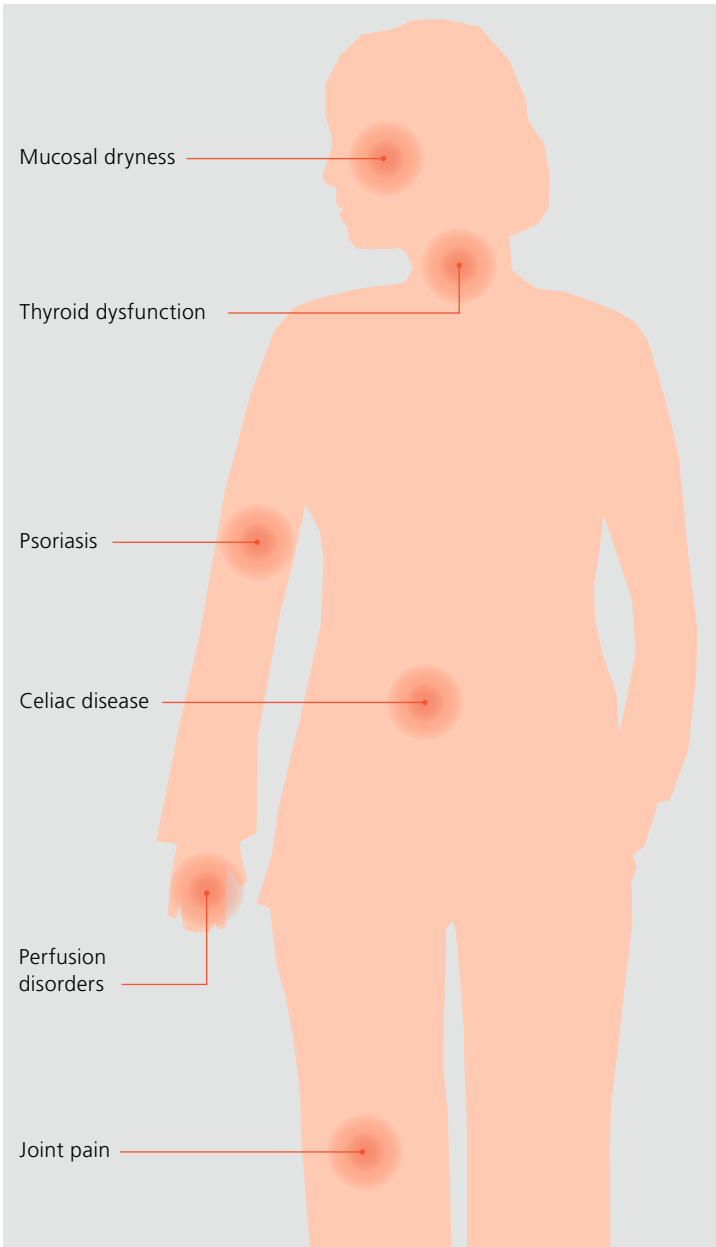


Fig. 2: Conditions that may accompany microscopic colitis.

Several studies have shown that patients with *microscopic colitis* also frequently have celiac disease (or gluten intolerance) and vice versa.

Therefore, patients should be checked for both conditions. A recent study reported that 12.9% of patients with *collagenous colitis* also have celiac disease.

Microscopic colitis generally has a benign outcome, although about 40% of patients complain of chronic (meaning permanent or continuously recurring) watery diarrhea. However, this diarrhea does not increase the risk of developing colorectal cancer.

In order to diagnose the condition, doctors must rule out the possibility of other conditions with similar symptoms: Typical gut disorders associated with diarrhea but not with weight loss include irritable bowel syndrome (diarrhea-type) and intolerance to several different types of foods, such as the very common lactose intolerance.

Microscopic colitis can usually be clearly distinguished from Crohn's disease and ulcerative colitis (together known as inflammatory bowel disease), since a colonoscopy reveals a typical pattern of intestinal mucosa pathology with ulcers in inflammatory bowel disease. When inflammatory bowel disease spreads to the colon, as is often the case, diarrhea is usually bloody.

Causes and development of microscopic colitis

Although the exact causes of *microscopic colitis* remain unknown, several theories have been proposed.

Several studies have proposed that *microscopic colitis* may be caused by the increased use of certain medications, typically those used to manage joint pain. These include drugs called “non-steroidal anti-inflammatory drugs” as well as drugs used to treat high cholesterol levels or to stop blood clotting.

Case reports have suggested that proton-pump inhibitors may play a role in the development of *microscopic colitis*, but this link has not been thoroughly investigated.

A retrospective study showed that the percentage of smokers is higher among *collagenous colitis* patients than among the population as a whole. This study was the first to demonstrate a potential effect of nicotine on the development of *microscopic colitis*. This effect might be based on the fact that nicotine increases the permeability of the intestinal mucosa. Continued nicotine consumption also reduces a patient’s response to budesonide treatment.



It is theoretically possible that increasing the permeability of the intestinal mucosa (the cause of which remains unknown) may allow digested food to migrate into the intestinal wall and disrupt the function of the gut. A recent study reported that the microbial flora of the gut has a different composition in patients with *microscopic colitis* than in healthy controls.

Antibodies targeting parts of the body itself have been detected in about half of all patients with *lymphocytic colitis*. These antibodies are directed at the gut, and as a result this disease might need to be classified as an “autoimmune disorder”.

In contrast, antibodies are frequently found in *collagenous colitis* patients that target bacteria – bacteria which themselves cannot be detected in the body. This may be a sign of a prior infection by these bacteria. Alternatively, it might reflect the increased permeability of the intestinal wall, which could lead to the production of antibodies against microbes located in the wall (e.g. *Yersinia* species).

It is still unknown how these phenomena result in a thickening of the collagen layer in *collagenous colitis* or lead to an accumulation of immune cells (lymphocytes) in the intestinal mucosa in *lymphocytic colitis*. However, we do know that the collagen deposits found in *collagenous colitis* patients do not result from the overproduction of collagen, but rather from reduced degradation of collagen.

Interestingly, in patients with an artificial outlet to the gut, known as a stoma, the collagen layer in the gut segments downstream of the stoma returns completely to normal, resulting in a cure of the disease. This suggests that the contents of the gut are important for developing the disease.

Diagnosis

In order to confirm the diagnosis of *microscopic colitis*, experience has shown that patients with watery diarrhea lasting longer than 4 weeks should be examined by colonoscopy. If the results of the colonoscopy are normal, meaning the doctor cannot detect any changes to the mucosa with the naked eye, small tissue samples should be collected from the intestinal mucosa (using biopsy forceps) (Fig. 3). The diagnosis is based on an assessment of this samples under the microscope. About 10% of patients with watery diarrhea lasting longer than 4 weeks and normal colonoscopy results are diagnosed with *microscopic colitis*. It is important to collect samples from different segments of the colon in all patients, since *collagenous colitis* is limited only to the ascending segment of the colon in about one-quarter of patients, to give one example.

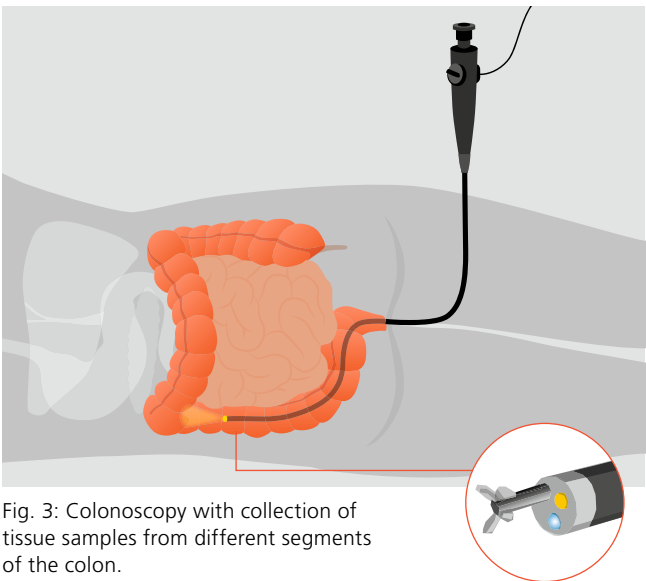


Fig. 3: Colonoscopy with collection of tissue samples from different segments of the colon.

Biopsy forceps,
approx. 3 mm

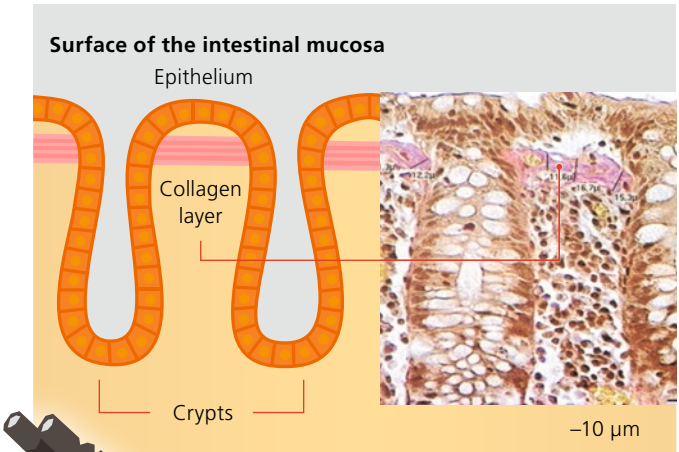


Fig. 4a: Diagram (left) and microscopic image (right) of the intestinal mucosa in a patient with **collagenous colitis**. The thickened collagen layer, which is stained pink, is clearly visible.

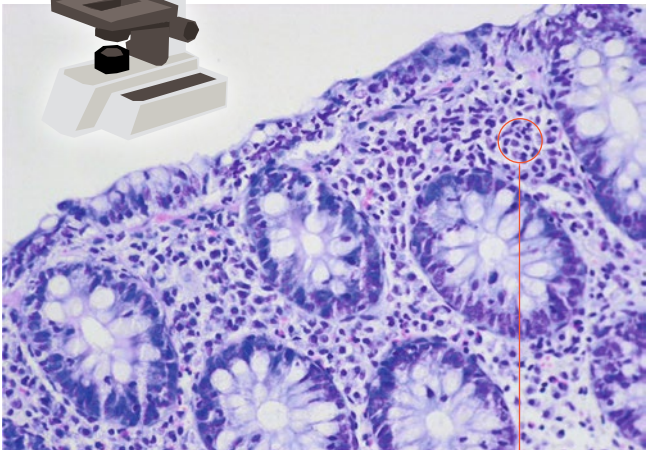
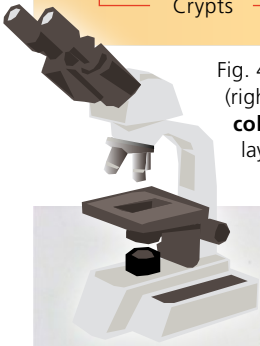


Fig. 4b: Microscopic image of the intestinal mucosa in a patient with **lymphocytic colitis** showing accumulation of lymphocytes (small purple dots).

When intestinal tissue samples are examined under the microscope, both disorders are characterized by very typical findings: Using specific staining methods, a thickened collagen layer (pink) is visible in the intestinal mucosa in patients with *collagenous colitis* (Fig. 4a).

Collagen fibers are a specific protein structure in the body that helps support tissues. While this collagen layer is less than 5 micrometers (one-millionth of a meter) wide in healthy people, it is at least 10 micrometers wide in *collagenous colitis* patients and is easily visible under the microscope after staining.

For people with *lymphocytic colitis*, doctors find an increased accumulation of immune cells (lymphocytes, a subgroup of white blood cells) in the tissue samples. The lymphocyte count is about 4- to 5-fold higher than in healthy people (Fig. 4b).

However, it is still not known what effect the thickened collagen layer or the increased accumulation of inflammatory cells has on the course of the disease.

It is currently not possible to diagnose these diseases by blood test. Levels of calprotectin, which is a marker of inflammation, may be elevated. However, this finding is not specific and does not prove somebody has *microscopic colitis*. On the other hand, it does mean that patients with persistent diarrhea and elevated calprotectin levels should always be referred to a colonoscopy for diagnostic purposes.

Treatment

The goal of treatment is to improve or completely eliminate the symptoms of the disease, which improves patients' quality of life.

Budesonide

Drug treatment using the active substance budesonide is the standard treatment option and is the treatment which has been tested the most in controlled studies. Budesonide is a modern corticosteroid drug that has very good local anti-inflammatory effects on the intestinal mucosa.

The substance was originally used as a spray to treat asthma. It has also been used to treat inflammatory bowel disease since the 1990s. Budesonide, which is given as granules or in a capsule, is not released until it reaches the border between the small intestine and the ascending colon thanks to a special manufacturing process. Once it arrives in the ascending colon, it has potent local anti-inflammatory effects on the mucosa that are stronger than the effects of classical corticosteroids. The special benefit of budesonide is the fact that over 90% of it is directly metabolized by the liver after being active in the gut. As a result, only a small percentage of the drug circulates in the bloodstream, leading to many fewer steroid-like side effects compared with classical corticosteroid drugs. Budesonide is thus an optimal choice for achieving a high degree of local effectiveness at the intestinal mucosa while keeping the rate of side effects low.

Budesonide is generally taken at a dose of 9 mg per day for 8 weeks for the treatment of acute disease. In clinical studies, this treatment was associated with clinical improvement and absence of diarrhea in about 80% of patients.



However, patients often experience a recurrence of the disease 2 months after stopping the drug. If this occurs, treatment may be resumed at a reduced dose of 4.5–6 mg budesonide per day. The doctor and the patient will need to discuss the precise length of treatment. Studies have shown that this treatment reduces the probability that symptoms will return within 6–12 months by about 60% in patients with *collagenous colitis*.

Prednisolone

The classical corticosteroid prednisolone was frequently used in the past to treat patients with *microscopic colitis*. However, in contrast to budesonide, prednisolone is initially absorbed into the bloodstream after being ingested. As a result, it not only provides the desired therapeutic effect but also frequently leads to severe forms of the typical side effects of steroid drugs. These include “moon face” (a rounding of the face), abdominal obesity, high blood pressure, mental health disorders, and weakening of the immune system.

Bismuth

This drug has antibiotic and anti-inflammatory properties and is included in some combination drug treatment regimens when budesonide does not improve the symptoms of disease or is not tolerated by the patient. However, very few clinical studies have been performed on bismuth. Furthermore, bismuth products should not be taken for longer than 8 weeks since they may accumulate in the body.

Other treatment options

Several open-label (i.e. non-controlled) studies and case reports have investigated the effects of the probiotic (bacteria that have a beneficial or potentially beneficial effect on the gut) *E. coli* Nissle 1917 and of immunosuppressants (azathioprine, methotrexate, and different antibodies targeting inflammatory factors). Immunosuppressant therapy should be taken into consideration

for patients who do not respond to standard treatment with budesonide.

Loperamide, a drug that can stop acute diarrhea by inhibiting bowel motility, is also sometimes used for short-term symptom relief. However, it does not treat the actual cause of diarrhea, which is inflammation of the intestinal mucosa. Loperamide should be taken as briefly periods as possible and only after consulting a doctor.

Other treatment options, such as incense extract, cholestyramine, or mesalazine, have either not been adequately studied at present or did not bring about the desired treatment outcome. Therefore, these drugs should only be taken as part of any future clinical studies.

Frequently asked questions about microscopic colitis

? How common is microscopic colitis?

According to the most recent statistics (including those from the US), *microscopic colitis* is being diagnosed with increasing frequency (Fig. 5). This increase is likely due to both improvements in diagnosis as well as a real increase in the number of actual cases. The figures reveal an annual incidence (rate of new cases) of about 20 patients per 100,000 inhabitants.

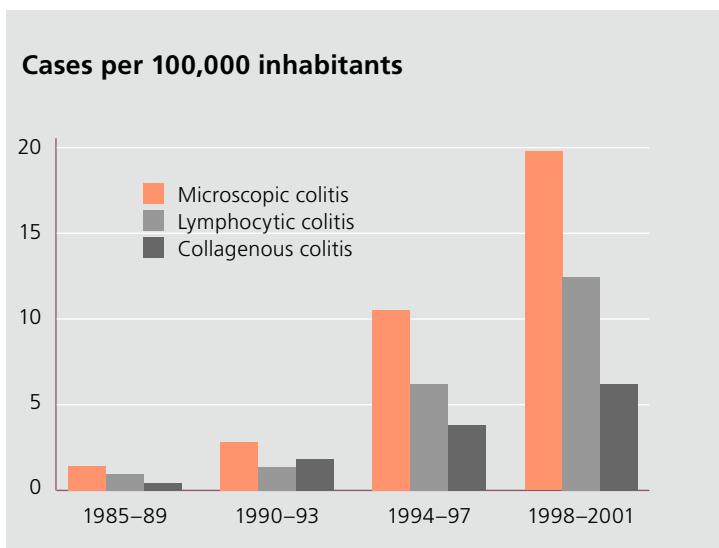


Fig. 5: Overview of the incidence of lymphocytic and collagenous colitis (from a survey in the US).

The annual incidence of *collagenous colitis* varies greatly from one country to the next, for example at 1–2 cases per 100,000 inhabitants in Spain versus 16 new cases per 100,000 inhabitants in Denmark.

Little data is available on *lymphocytic colitis*. The rate of new cases in Scandinavia is thought to be 4 per 100,000 inhabitants.

Epidemiological studies from the US and Denmark both report an increase in the rates of new cases in both countries (over the past several years).

? *Are there any factors that increase the chances of microscopic colitis?*

All of the studies conducted to date show that women develop *microscopic colitis* about 5 times as often as men. The risk increases even more greatly among women above the age of 65. This is true for both *collagenous* and *lymphocytic colitis*. The reasons for this trend are not known.



In addition, patients already suffering from certain diseases of the immune system (called autoimmune disorders) appear to develop *microscopic colitis* more often than patients without pre-existing autoimmune disorders. This includes patients with hypothyroidism and celiac disease. Up to 40% of all patients with *microscopic colitis* also suffer from an autoimmune disorder.

Patients with *microscopic colitis* are more likely to have celiac disease and vice versa; therefore, patients with one of these conditions should be tested for the other (by transglutaminase antibodies or duodenal biopsy).

About 10% of patients also report a history of cancer. The majority of these cases involve colorectal cancer, breast cancer, prostate cancer, or lung cancer. Cancer patients are at a higher risk of developing *microscopic colitis* than the general population, especially women over the age of 65.

Patients with diabetes may also potentially be at a higher risk of *microscopic colitis*. This appears to be the case primarily for older men.

Overall, more research is needed to investigate a potential link between *microscopic colitis* and the disorders listed here, as well as their underlying causes.

? **What is known about the causes of microscopic colitis?**

The ultimate cause of *microscopic colitis* remains unknown.

It is notable that increased use of pain medicines (including ibuprofen and acetylsalicylic acid) has been identified as a potential trigger in a relevant number of patients. These medicines may increase the permeability of the intestinal mucosa, which might promote the absorption of other substances that trigger the disease which are not yet known. However, other drugs, such as simvastatin (used to lower cholesterol), ticlopidine (used to reduce blood clotting), or acarbose (used to treat diabetes), have also been reported to be potential triggers of *microscopic colitis*. The potential role of proton-pump inhibitors has not been conclusively determined.

Studies have also shown that the percentage of *collagenous colitis* patients who are smokers is significantly higher than in the population as a whole. Smoking should therefore be avoided since nicotine increases the permeability of the intestinal wall. Continued nicotine consumption also lowers a patient's response to budesonide treatment.

Several different studies have detected antibodies to *Yersinia* in about 80% of patients. *Yersinia* are bacteria that can lead to an infection of the intestinal mucosa. In contrast, *Yersinia* are only rarely detected in the stool of *microscopic colitis* patients.

These findings can be interpreted as a reflection of the increased permeability of the intestinal wall for *Yersinia* leading to secondary antibody production.

There is also evidence that *microscopic colitis* occurs more frequently within families. However, it remains unclear whether this points to a genetic component.

? How does microscopic colitis differ from irritable bowel syndrome?

The primary symptom of both *microscopic colitis* and irritable bowel syndrome is chronic, non-bloody, usually watery diarrhea.

Endoscopy findings and stool tests for microbes are typically normal in both diseases. Collection and microscopic examination of tissue samples is thus important for the diagnosis of both. These examinations clearly reveal the characteristic signs of *microscopic colitis* and allow it to be confidently differentiated from irritable bowel syndrome.

There are also other characteristics (see Table 1) that tend to point to one or the other condition. These characteristics may help confirm, yet cannot replace, a microscopic diagnosis.

Primary symptoms of irritable bowel syndrome – Microscopic colitis		
	Irritable bowel syndrome	Microscopic colitis
Initial onset of disease	often below age 50 women ≥ men	often above age 50 women >> men
Stool consistency	soft – variable – firm	watery/soft
Abdominal pain/ discomfort	obligatory	variable
Nocturnal diarrhea	very rare	possible
Sensation of in- complete evacuation	common	no
Weight loss	rare	common
Fecal incontinence	rare	common
Bloating	common	rare
Autoimmune comorbidities	no	yes

Table 1

? **What is the explanation for the thickening of the collagen layer in the intestinal mucosa?**

The increase in the size of the collagen layer in *collagenous colitis* is not due to increased collagen production but rather to decreased collagen degradation. However, the precise mechanisms leading to this reduced degradation of collagen in the intestinal mucosa have not been studied in depth. It is also not known whether and how thickening of the collagen layer triggers the typical symptoms of *collagenous colitis*.

? **Are there any signs of microscopic colitis outside of the gut?**

Microscopic colitis may be accompanied by a number of other different conditions that indicate a reaction by the immune system to the tissues of the body. These include rheumatic joint pain, psoriasis, celiac disease, thyroid dysfunction, perfusion disorders, and mucosal dryness (see also Fig. 2).

? **Is a proctoscopy sufficient for diagnosis?**

Because *microscopic colitis* most frequently affects the ascending segment of the colon, a proctoscopy is not sufficient for diagnosis. The entire colon should be examined in every patient together with collection of tissue samples from the different segments of the colon. If this is not performed, up to 40% of patients with *microscopic colitis* may be missed.

? ***Does microscopic colitis increase the risk of colorectal cancer?***

No. There are no indications that polyps or colorectal cancer develop more often in patients with *collagenous* or *lymphocytic colitis*. In general, the diagnosis of *microscopic colitis* has a favorable prognosis, and the symptoms can be managed well with the drug budesonide.

? ***Are there any concerns about pregnancy?***

No. There are no concerns about pregnancy with regard to the disease itself. However, each drug taken should be reviewed to make sure there are no restrictions on its use during pregnancy or while breastfeeding. In any case, the disease tends to afflict older patients who have already gone through menopause.

? ***Are there any dietary factors that have a positive effect on microscopic colitis?***

There are no confirmed results about any potential effects of dietary factors that might trigger these diseases. It also remains unknown whether adding or removing specific foods from one's diet may have a positive or negative effect on the course of the disease.

However, because the primary symptom of the disease is watery diarrhea, lactose intolerance and celiac disease should be ruled out as potential causes during the pre-diagnosis phase.

For both of these disorders, there is a clear recommendation to maintain a lactose-free or gluten-free diet.



Studies have shown that fasting can lead to a major improvement in the diarrheal symptoms of *collagenous colitis*. However, prolonged fasting does not represent a long-term treatment option for *microscopic colitis*.

? **Can surgery help microscopic colitis?**

In the past, surgery has only been performed for very severe cases of *microscopic colitis*, which are very rare. However, the results from these patients have shown that when patients have an artificial intestinal opening (stoma) to empty their digestive tract, both the inflammation and the thickened collagen layer heal in the downstream segment of the gastrointestinal tract that is now absent of stool. This fact suggests that certain factors in the contents of the gut may be important triggers of *microscopic colitis*.

? **Is the disease ever improved or cured by itself?**

Studies on the long-term progression of *collagenous colitis* have shown that some patients remain symptom-free for a long time after a successful first round of treatment and have no need for any further medications. In one of these studies, 23% of patients still had no watery diarrhea after 10 years. On the other hand, symptoms returned in two-thirds of patients within 2 months of stopping treatment. If this happens, a new round of treatment or a low-dose maintenance therapy is recommended both for patients with *collagenous colitis* and with *lymphocytic colitis*.

? *Can binding or bulking agents have a positive effect on diarrhea?*

In cases of mild diarrhea, taking bulking agents or bile acid sequestrants is often sufficient to increase the consistency of stool and reduce the frequency of bowel movements. In one small study, diarrhea resolved in over 20% of patients taking a bulking agent (such as psyllium husk).

? *How long should budesonide be taken during the acute phase of the disease?*

In the treatment studies that have been performed on budesonide to date, the drug was given at a dose of 9 mg per day over a period of 6 or 8 weeks. The majority of patients were nearly completely free of symptoms within 14 days of starting this treatment plan. Budesonide is taken as a single dose in the morning.

? *Is there a maintenance therapy for microscopic colitis?*

After finishing budesonide therapy for the treatment of acute *microscopic colitis*, patients frequently start to experience diarrhea again within the first 2 months and thus require further treatment. Several placebo-controlled studies have all shown that, after achieving clinical improvement for acute disease with 9 mg budesonide, continuing treatment with 4.5–6 mg budesonide per day for 6–12 months can lead to a significant reduction in the rate of recurrence.

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