



# GASTROINTESTINAL INVOLVEMENT IN SYSTEMIC SCLEROSIS

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## WHO IS AT RISK OF DEVELOPING GASTROINTESTINAL DISEASE IN SYSTEMIC SCLEROSIS?

The digestive tract is involved in nearly all systemic sclerosis patients and can be present even in the absence of symptoms in half of patients. The frequency is similar in diffuse and limited forms of systemic sclerosis. However, severe manifestations are uncommon, occurring in less than 10% of patients.



## WHAT CAUSES DIGESTIVE TRACT ABNORMALITIES IN SYSTEMIC SCLEROSIS?

Abnormalities of the digestive tract are caused by the same pathophysiological mechanisms that affect all other organs in systemic sclerosis: there are early abnormalities in the small blood vessels, in the nervous system that controls the propulsive movements of the gut after a meal (peristalsis), and in the immune system (white blood cells and autoantibodies), eventually leading to weakening of the muscles of the digestive tract and fibrosis. The latter stage is often associated with more pronounced symptoms.

## WHAT ARE THE GASTROINTESTINAL MANIFESTATIONS IN SYSTEMIC SCLEROSIS?

The earliest and most common gastrointestinal manifestation is the malfunction (dysfunction) of the esophagus (the digestive tube that connects the mouth to the stomach). However, a dysfunction can affect the digestive tract at any level, from the mouth to the anus.

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# OROPHARYNGEAL INVOLVEMENT (MOUTH AND THROAT)



Fibrosis of the tissues of the mouth, including the tongue, soft palate (back of the palate) and larynx, as well as of the surrounding skin often leads to a narrowing of the mouth opening and can cause several problems due to stiffness and thinning of these structures. This leads to difficulties in chewing and swallowing food, especially when accompanied by a lack of saliva production due to salivary gland disease (sicca syndrome or Sjögren's syndrome). These problems may occur in up to 25% of patients.

Patients may be inconvenienced during meals, with a variety of symptoms: pain in the mouth, feeling that food sticks in the throat, retention of food in the mouth or throat, coughing after swallowing, small leakage of saliva and/or food at the corners of the mouth, and, rarely, aspiration of food into the lungs. Some patients may also have some difficulty speaking. Teething problems may also occur, such as malalignment of the teeth or abnormal wear (resorption) of the jaw bone and gums due to excessive pressure caused by tight facial skin.

The treatment of oropharyngeal problems remains mainly focused on prevention and support. It is important to maintain the flexibility of the facial skin through regular exercise. A physiotherapy consultation can be helpful for learning the most appropriate exercises and, in some cases, how to use stretching devices. Good dental hygiene and regular visits (at least twice a year) to the dentist can go a long way in preventing tooth decay. There are several models of toothbrushes and floss applicators that are suitable for patients with reduced hand mobility, and the advice of a dentist or occupational therapist may be helpful. The dentist can also suggest specialized mouthwashes and toothpastes that offer increased protection against cavities. It is important to contact the dentist when there is persistent abnormal pain or ulceration in the mouth, or when teeth become too loose.

To improve dryness of the mouth, one should drink water at regular intervals, eat soft foods, and use ice cubes, sugar-free gum or sugar-free candy. Also avoid tobacco, alcohol and dry foods. Severe rigidity of the mouth can make it difficult to drink from a regular glass. In this case, the use of a straw or specialized glass can be useful. If these measures are insufficient, the use of artificial saliva or certain medications that stimulate saliva production (Salagen®) may be considered, if indicated according to the treating physician. In more severe and advanced cases, local injections to increase the volume of the lips, as well as certain highly specialized surgical procedures, may be used to improve mouth closure and chewing.

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# ESOPHAGEAL INVOLVEMENT (TUBE BETWEEN THE MOUTH AND STOMACH)



Involvement of the esophagus is the earliest and most common gastrointestinal involvement in systemic sclerosis. It may occur in 90% of patients. It is characterized by a dysfunction in the motility of the esophagus (reduced or absent contraction movements) and by a reduction in the tightness of the closure between the esophagus and the stomach (lower esophageal sphincter). These abnormalities can be demonstrated by a barium meal, an esophageal transit scintigraphy and/or by esophageal manometry.

The symptoms most frequently associated with esophageal involvement are due to the following problems:

### GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is caused by incompetence of the lower esophageal sphincter, which normally closes after food passes from the esophagus to the stomach. As mentioned above, this incompetence is one of the first abnormalities of systemic sclerosis and may be the reason that prompts someone to consult their doctor for the first time. The resulting loss of tightness allows the very acidic contents of the stomach to rise up into the esophagus and can lead to several symptoms: sensations of burning or pain (spasms) in the chest or stomach cavity after eating, which can also occur during the night.

Treatment for GERD is primarily based on lifestyle changes:

- ▶ establishing and maintaining a normal weight because excess weight promotes GERD;
- ▶ raising the head of the bed with blocks under the legs (pillows are ineffective);
- ▶ eating several small meals at regular intervals, instead of 3 meals a day;
- ▶ avoiding acidic, spicy, high-fat foods and some foods that are more difficult to digest (e.g., cabbage, onions, broccoli);
- ▶ avoiding going to bed less than three hours after a meal;
- ▶ quitting smoking or other tobacco products;
- ▶ minimizing alcohol and caffeine intake.

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It is worth noting that some medications used to treat other manifestations of systemic sclerosis, such as calcium channel blockers, (e.g., Adalat®) for Raynaud's phenomenon, can sometimes make GERD worse. If lifestyle modification is not enough, the most effective medications to treat GERD are proton pump inhibitors, or PPIs, e.g., pantoprazole (Pantoloc®), dexlansoprazole (Dexilant®), omeprazole (Losec®), esomeprazole (Nexium®), lansoprazole (Prevacid®) or rabeprazole (Pariet®). These medications are taken once a day and can be increased up to twice a day.

If GERD symptoms persist despite the treatments listed above, a gastroscopy (direct visualization of the esophagus and stomach through the passage of a tube by a gastroenterologist) is then indicated to rule out alternative causes of pain.

Surgery to correct GERD is reserved for patients with severe reflux that is refractory to any treatment, as it can sometimes worsen some digestive symptoms, and the benefits may not always be long-lasting.

### **HYPOMOTILITY**

Decreased normal movement of the esophagus (hypomotility) may result in difficulty swallowing or a feeling that food sticks in the throat.

Unlike GERD, the treatment of hypomotility is mostly pharmaceutical, with agents that increase esophageal motility (contractions occurring in the esophagus), thus facilitating the propulsion of food through the tract (prokinetic drugs). The most commonly used medications are domperidone and metoclopramide (Metonia®) in the order of 10 mg four times a day, taken thirty minutes before meals. Erythromycin (250 mg three times a day, thirty minutes before meals) can sometimes be useful if the other medications have failed. However, because of the possibility of side effects and undesirable interactions with some other medications, these treatments should be prescribed and monitored with caution.

It is also important to avoid, if possible, or use with caution, certain medications that may increase the risk of esophageal ulceration in systemic sclerosis patients, such as tablet bisphosphonates used in the treatment of osteoporosis, such as alendronate (Fosamax®) or risedronate (Actonel®).

### **STENOSIS**

Narrowing of the esophagus (stenosis) may occur if GERD is prolonged and left untreated. This can lead to significant difficulty swallowing food (a feeling of food blockage in the chest or stomach) and regurgitation of fluid through the mouth. The treatment of stenosis involves the dilation of the stricture after a tube is passed through the esophagus (gastroscopy) by a gastroenterologist.

### **INFECTION**

Some esophageal symptoms refractory to conventional treatments may be caused by a fungal infection (Candida). The diagnosis is made by gastroscopy and treatment is very effective: the drug nystatin in the form of a liquid suspension 400,000 to 600,000 units four times a day for two weeks, or fluconazole 100 mg once a day for seven days.

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### GASTRIC INVOLVEMENT (STOMACH)



Fibrosis of the stomach is often less pronounced than that of other parts of the digestive tract, which is why significant symptoms are uncommon. The main symptoms in more severe cases are slower emptying of gastric contents (gastroparesis) and, more rarely, bleeding from the stomach.

#### GASTROPARESIS

Slower emptying of gastric contents leads to a feeling of fullness soon after starting a meal, with more or less severe bloating and vomiting beginning a few hours after meals. Symptoms are often intermittent, with quiet periods that can last several months. However, this problem can lead to significant weight loss and nutritional deficiencies over time. Some tests may give indirect clues to the presence of gastroparesis (barium meal or gastroscopy), but the most reliable test is the gastric emptying scintigraphy in nuclear medicine. The treatment is similar to that for hypomotility of the esophagus (see above), but the drugs are less effective. During periods of vomiting, it is preferable to use certain medications that reduce nausea (such as Graval® 50-100 mg or Stemetil® 10 mg three times daily) and to avoid solid foods.



#### BLEEDING

Abnormal dilations of small blood vessels (telangiectasia) or veins (venous ectasia) are sometimes present in the stomach. These abnormalities can lead to more or less severe bleeding, resulting in anemia and new fatigue. If the bleeding is heavy, black stools or vomiting of blood may occur. But most often the bleeding occurs slowly and the only symptoms will be the progressive development of new fatigue and sometimes shortness of breath. Diagnosis and treatment (coagulation of the abnormal vessels by laser beam) require direct visualization by gastroscopy. These treatments are generally very effective, but usually need to be repeated periodically (e.g., several months apart). Surgical resection of part of the stomach is very rarely performed nowadays.

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### INVOLVEMENT OF THE SMALL INTESTINE (SMALL BOWEL)



Abnormalities in the function of the small bowel are reported in 20 to 60% of patients with systemic sclerosis. The symptoms most frequently associated with these abnormalities are due to the following problems:

#### **MALABSORPTION**

About 10-30% of systemic sclerosis patients suffer from malabsorption. Normally, the absorption of nutrients from ingested food is carried out specifically from the small intestine into the bloodstream. It should be pointed out that ordinarily bacteria residing in the small intestine, called the normal bacterial flora, play an important role in the digestion and absorption of food. However, in systemic sclerosis patients, the ability of the small intestine to contract effectively and, therefore, to propel food through the digestive tract may be reduced. This slowed intestinal transit promotes excessive development of the normal bacterial flora of the small intestine (bacterial overgrowth), leading to nutrient absorption problems.

Malabsorption is manifested by several symptoms that are usually intermittent: abdominal bloating, abdominal pain and constipation (stoppage of stool). When the problem becomes more serious and prolonged, diarrhea and weight loss may occur, eventually leading to more or less severe malnutrition. Malabsorption is often suspected by the doctor because of the typical symptoms reported by the patient. An examination in radiology ("small bowel study" or "small bowel transit") may then show abnormalities suggestive of small bowel involvement (dilated intestinal loops, slowed transit time and other abnormalities). This test may be falsely negative in the earlier

stages. The best test to detect malabsorption is the "breath test". This test is done in nuclear medicine and consists of administering a predetermined load of sugar contained in a drink with subsequent measurement of the sugar degradation products in the air exhaled by the patient. An endoscopic investigation (introduction of a small tube through the mouth to the small intestine) by a gastroenterologist may sometimes be necessary for patients not responding to treatment, or when an alternative diagnosis is sought.

Treatment of malabsorption involves taking antibiotics by mouth to restore normal intestinal flora. This antibiotic therapy is typically administered cyclically, i.e., the antibiotic is taken intermittently (e.g., for 3 weeks at a time) with antibiotic-free intervals (e.g., for one week) since continued use of the same antibiotic is associated with poorer results. Also, there is usually a rotation in the antibiotics used. Thus, for example, the patient takes a first antibiotic during the first week, a second during the second week and a third during the third week, and then takes a break (no antibiotic) during the fourth week. The antibiotics most often used in this cyclic manner are amoxicillin with clavulanate, trimethoprim, cephalosporin, ciprofloxacin, metronidazole, and tetracycline. The previous examples are provided for general information purposes only, as the selection of antibiotics, their duration of administration, and the sequence of rotation necessary to achieve good symptom control must be tailored to each patient.

It is encouraging to know that, in our experience, cyclic antibiotic therapy is usually effective in stopping malabsorption and its symptoms. Some patients may even have a prolonged remission (several months) of malabsorption after a certain period of cyclic treatment.

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### DYSMOTILITY

The abnormal movements of contraction and propulsion of food (dysmotility) that are so often present in the esophagus can also occur in the small intestine. Symptoms of small bowel dysmotility include abdominal pain, bloating, constipation, and in more severe cases, malabsorption as discussed in the previous section. The treatment of small bowel dysmotility is the same as for hypomotility of the esophagus, including agents that stimulate contractions of the gastrointestinal tract and thus the propulsion of food (prokinetic drugs, see above). Unfortunately, dysmotility of the small intestine sometimes responds less well to treatment than dysmotility of the esophagus.

Some patients with malabsorption may have extremely bothersome chronic diarrhea. In these cases, in addition to cyclic antibiotic therapy, administering octreotide (Sandostatin®) as a subcutaneous injection at bedtime can often greatly improve the diarrhea.

### PSEUDO-OCCLUSIONS

Intestinal pseudo-occlusions are prolonged episodes of significant decrease in the contraction of the small intestine (severe dysmotility), with complete cessation of the progression of food through the gastrointestinal tract. These episodes are associated with severe abdominal pain, significant bloating, and even vomiting. The treatment of pseudo-occlusions in the acute phase involves stopping the intake of food or liquids through the mouth until the crisis is resolved, as improvement may occur spontaneously in several cases. When episodes of pseudo-occlusion are frequent and/or severe, prokinetic drugs may be tried with caution.

In more severe cases of pseudo-occlusion, a short hospital stay may be necessary to ensure proper hydration (administration of fluid through a vein). Abdominal surgery should generally be avoided in pseudo-occlusions related to systemic sclerosis.

### MALNUTRITION

Malnutrition can occur in the context of multiple types of gastrointestinal involvement in systemic sclerosis. Between episodes of pseudo-occlusion, the patient should adhere to a lactose-free, low-fiber diet, and fats should be replaced by medium-chain triglycerides. Some patients require vitamin B12 injections, as well as calcium, iron and vitamin supplements. A consultation with a clinical nutrition specialist is often helpful.

If the various treatments available fail, including cyclic antibiotic therapy, a state of malnutrition may set in, gradually causing loss of muscle mass and weight loss. This condition is life-threatening. In a patient with partially preserved bowel function, a percutaneous gastrostomy tube (creation of an opening from the stomach to the skin) or jejunostomy tube (creation of an opening from the small intestine to the skin) may be placed to deliver nutrients directly into the digestive tract.

However, if the gastrointestinal tract is barely functioning, total parenteral nutrition (administration of essential nutrients through a permanent intravenous catheter) may be required. Total parenteral nutrition is an extreme measure of last resort for systemic sclerosis patients whose small intestine is so severely affected that nutrients are no longer absorbed. This requires a great deal of discipline on the part of patients as they must self-administer nutrients intravenously. On the other hand, total parenteral nutrition can be done at home and is a very effective measure to maintain a normal state of nutrition.

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### INVOLVEMENT OF THE LARGE INTESTINE (COLON)



Involvement of the large intestine or colon occurs in 10-50% of systemic sclerosis patients and can also occur early. The most common manifestation is dysmotility of the last part of the colon, particularly the rectum and anus. These abnormalities often come with very uncomfortable symptoms, such as constipation (less than two bowel movements per week) and fecal incontinence (involuntary loss of stool).



#### DIARRHEA AND FECAL INCONTINENCE

When incontinence is accompanied by diarrhea, the treatment is that of malabsorption (the cyclic regimen of oral antibiotics discussed above), a low-residue diet, medications for diarrhea (e.g., loperamide), and resins to conjugate bile acids (e.g., cholestyramine). Patients who do not respond to these treatments may sometimes benefit from specialized techniques, such as bio-feedback or the use of an electro-stimulator for the anal sphincter.

#### CONSTIPATION

Prokinetic drugs could be tried to treat constipation, but unfortunately they are not very effective. Medications to soften stools (e.g., docusate) or to stimulate intestinal contraction (e.g., lactulose or polyethylene glycol) may also be used.

Much rarer problems are prolapse of the rectum and perforation of the colon, both of which require prompt surgical consultation.



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# INVOLVEMENT OF THE LIVER, BILE DUCTS, AND PANCREAS



Problems affecting the liver and bile ducts are uncommon in systemic sclerosis. The most common liver involvement is primary biliary cholangitis (an autoimmune chronic inflammatory disease of the liver), which occurs mainly in patients with the limited form of systemic sclerosis and those with the presence of anti-centromere (CENP-B) autoantibodies in the blood. This disease typically causes few symptoms initially and it is prudent to screen for it with blood tests when systemic sclerosis is diagnosed. Treatment of primary biliary cirrhosis associated with systemic sclerosis is usually effective but requires regular follow-up with a hepatologist (doctor who specializes in liver disease) or gastroenterologist.

Exocrine pancreatic insufficiency (a condition in which the pancreas is unable to produce enough digestive enzymes to break down food in the intestine) due to fibrosis is rarely reported in systemic sclerosis. However, it should be sought when symptoms of malabsorption persist despite adequate treatment. If pancreatic insufficiency is confirmed by specific tests, treatment with pancreatic enzyme supplements may be beneficial.



## CONCLUSION

Systemic sclerosis affects the gastrointestinal tract in the majority of patients, although severe manifestations are uncommon. The earliest and most common involvement is esophageal dysfunction. However, a dysfunction can affect the digestive tract at any level from the mouth to the anus. Despite the complexity of the various symptoms related to gastrointestinal involvement in systemic sclerosis patients, it should be noted that the majority of patients lead a relatively normal life by following the treatments recommended by their doctors and having appropriate medical follow-up.



# TABLE

## GASTROINTESTINAL MANIFESTATIONS OF SYSTEMIC SCLEROSIS

DIGESTIVE TRACT INVOLVEMENT	DESCRIPTION	SYMPTOMS/SIGNS	POSSIBLE INVESTIGATIONS	USUAL TREATMENTS
<b>OROPHARYNX</b>	<ul style="list-style-type: none"> <li>Reduced mouth opening</li> <li>Dry mouth</li> <li>Difficulty chewing and swallowing</li> <li>Teething problems</li> </ul>	<ul style="list-style-type: none"> <li>Mouth pain</li> <li>Retention of food in the mouth or throat</li> <li>Coughing after swallowing</li> <li>Leakage of saliva and/or food from the corner of the mouth</li> </ul>	<ul style="list-style-type: none"> <li>Regular visit to the dentist</li> <li>Physiotherapy</li> <li>Ergotherapy</li> </ul>	<ul style="list-style-type: none"> <li>Exercises to preserve the flexibility of the face</li> <li>Dental hygiene</li> <li>Avoid tobacco, alcohol, dry food</li> <li>Sugarless gum/candy</li> <li>Artificial saliva</li> </ul>
<b>ESOPHAGUS</b>	<ul style="list-style-type: none"> <li>Reduced or absent contraction movements</li> <li>Acid reflux from the stomach</li> <li>Irritation, ulcer, infection</li> <li>Narrowing</li> </ul>	<ul style="list-style-type: none"> <li>Bruising or pain in the chest or pit of the stomach after a meal or during the night</li> <li>Acid reflux</li> </ul>	<ul style="list-style-type: none"> <li>Gastroscopy</li> <li>Barium meal</li> <li>Esophageal transit scintigraphy</li> </ul>	<ul style="list-style-type: none"> <li>Raising the head of the bed</li> <li>Small regular meals</li> <li>Anti-reflux medications</li> <li>Prokinetic drugs</li> <li>Avoid irritating medications</li> <li>+/- Antifungal agents</li> <li>+/- Dilation (gastroscopy)</li> </ul>
<b>STOMACH</b>	<ul style="list-style-type: none"> <li>Slow emptying of stomach contents</li> <li>Bleeding from dilated small vessels or veins in the stomach</li> <li>Excessive bacterial flora overgrowth</li> <li>Malabsorption of nutrients</li> <li>Episodes of stoppage in intestinal transit</li> </ul>	<ul style="list-style-type: none"> <li>Feeling full soon after starting a meal</li> <li>Bloating</li> <li>Vomiting</li> <li>Fatigue, anemia</li> </ul>	<ul style="list-style-type: none"> <li>Gastric emptying scintigraphy</li> <li>Gastroscopy</li> </ul>	<ul style="list-style-type: none"> <li>Prokinetic drugs</li> <li>Drugs for nausea</li> </ul>
<b>SMALL INTESTINE</b>	<ul style="list-style-type: none"> <li>Slowing of intestinal transit</li> <li>Excessive bacterial flora overgrowth</li> <li>Malabsorption of nutrients</li> <li>Episodes of stoppage in intestinal transit</li> </ul>	<ul style="list-style-type: none"> <li>Bloating</li> <li>Abdominal pain</li> <li>Constipation</li> <li>Diarrhea</li> <li>Weight loss</li> <li>Vomiting</li> </ul>	<ul style="list-style-type: none"> <li>Breath test</li> <li>Endoscopy</li> </ul>	<ul style="list-style-type: none"> <li>Cyclic antibiotics</li> <li>Prokinetic drugs</li> <li>Nutritional supplements</li> </ul>
<b>LARGE INTESTINE (OR COLON)</b>	<ul style="list-style-type: none"> <li>Slowing of colonic transit time (through the colon to the rectum and anus)</li> <li>Rectal prolapse</li> </ul>	<ul style="list-style-type: none"> <li>Constipation</li> <li>Fecal incontinence</li> <li>Diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>Barium enema</li> <li>Anorectal manometry</li> </ul>	<ul style="list-style-type: none"> <li>Low-residue diet</li> <li>Medications for diarrhea or constipation</li> <li>Biofeedback, anal stimulator</li> </ul>
<b>LIVER AND BILE DUCTS</b>	<ul style="list-style-type: none"> <li>Primary biliary cholangitis</li> </ul>	<ul style="list-style-type: none"> <li>Fatigue</li> <li>Pruritus (itchy skin)</li> <li>Jaundice (yellow skin)</li> </ul>	<ul style="list-style-type: none"> <li>Blood test</li> </ul>	<ul style="list-style-type: none"> <li>Ursodiol</li> <li>Drugs for pruritus</li> </ul>
<b>PANCREAS</b>	<ul style="list-style-type: none"> <li>Insufficient production of pancreatic enzymes needed for digestion</li> </ul>	<ul style="list-style-type: none"> <li>Diarrhea, flatulence</li> <li>Bloating, cramps</li> </ul>	<ul style="list-style-type: none"> <li>Pancreatic function tests</li> </ul>	<ul style="list-style-type: none"> <li>Pancreatic enzyme supplements</li> </ul>