Scleroderma and other connective tissue disorders

Asma Fikree

Abstract

Gastrointestinal symptoms are common in both inflammatory and non-inflammatory connective tissue disorders and can involve any part of the gastrointestinal tract from the mouth to the anus. Dysphagia, gastrooesophageal reflux, nausea, vomiting, abdominal pain and change in bowel habit are common symptoms and usually arise from gastrointestinal dysmotility and altered visceral sensitivity. In scleroderma, sensorimotor dysfunction is pronounced and can result in complications such as Barrett's oesophagus, gastroparesis, small intestinal bacterial overgrowth, malabsorption and malnutrition, with an associated reduction in survival. Treatment is aimed at symptom control and prevention of complications. In hypermobile Ehlers–Danlos syndrome, symptoms are often caused by functional gastrointestinal disorders such as functional dyspepsia or irritable bowel syndrome, or are secondary to associated co-morbidities (e.g. chronic pain, anxiety, postural tachycardia syndrome, opioid use). Dysmotility in the oesophagus, stomach and colon is common, so gastrointestinal physiology testing can be informative and prokinetics can be useful therapeutically. A holistic approach to management must be taken to address all contributing factors, especially anxiety and diet.

Keywords Constipation; CREST; dysmotility; Ehlers–Danlos syndrome; functional dyspepsia; functional gastrointestinal disorders; gastro-oesophageal reflux disease; gastroparesis; hypermobility; irritable bowel syndrome; MRCP; scleroderma

Key points

- Gastrointestinal symptoms, particularly dysphagia, dyspepsia and constipation, are very common in connective tissue disorders
- Symptoms are associated with alterations in sensation and motility of the gastrointestinal tract
- Treatment is symptom-based but should also focus on reducing gastrointestinal complications, for example malnutrition and gastrointestinal bleeding

Connective tissue disorders

Connective tissue is one of the four major tissue types. It is ubiquitous throughout the body, where it is thought to support, bind and enclose all the body's structures, including the gastrointestinal (GI) tract. It is therefore unsurprising that GI symptoms and dysfunction are present in connective tissue disorders, be they inflammatory or non-inflammatory. This chapter focuses on GI manifestations of systemic scleroderma and hypermobile Ehlers–Danlos syndrome (hEDS).[1]

Systemic scleroderma (SSc)

SSc (also known as systemic sclerosis) is an autoimmune inflammatory connective tissue disorder characterized by autoimmune-mediated alterations in the microvasculature and autonomic nervous system; this leads to fibrosis within the skin and internal organs. These alterations then lead to an initial neuropathy followed by a myopathy, and ultimately fibrosis secondary to collagen deposition in the mucosal and muscular layers of the GI tract. Neuromuscular dysfunction can be ameliorated in the early stages with agents such as neostigmine, but as the disease progresses and the fibrosis ensues, the dysmotility becomes irreversible.[1]

Symptoms

GI manifestations of SSc are common, and although they can affect any part of the GI tract, they are most common in the oesophageal and anorectal regions. Although 90% of patients with SSc have GI involvement, only 50% are symptomatic; in 10% the GI symptoms precede other symptoms, for example musculoskeletal. Patients with severe GI involvement have significantly decreased survival that is reported to be 15% at 9 years. About 90% of patients have upper GI involvement and 70% lower GI involvement. Lower GI symptoms are more common in those with upper GI involvement. Table 1 lists the symptoms that can arise from each area of the GI tract.

History

Ask about symptoms throughout the entire GI tract. A history of bloating ± loose stool ± an unusual (metallic) taste in mouth, excessive flatus and burping should prompt you to think about small intestinal bacterial overgrowth (SIBO). When asking about diarrhoea, remember to ask specifically about features that might suggest steatorrhoea, which can be a consequence of SIBO.

Ask also about faecal incontinence – a symptom that is not volunteered by patients, is associated with a reduction in quality of life but can be treated.

Complications of gastrointestinal involvement

The most common complications include the following:

- ***Barrett's oesophagus*** secondary to gastro-oesophageal reflux disease – this is premalignant and requires treatment with high-dose proton pump inhibitors. These should be taken twice a day (to ensure better 24-hour coverage). Regular surveillance gastroscopies with oesophageal biopsies should be undertaken to look for dysplastic changes.

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Summary of GI involvement in scleroderma

Location	Symptom	Physiological abnormality/ differentials	Complications	Investigations	Treatment
Mouth	Difficulty eating	Xerostomia Decreased aperture of mouth Dry mouth (sicca overlap)			Artificial saliva Soft foods
Oeosphagus	Dysphagia Heartburn Waterbrash	Oesophageal dysmotility — aperistalsis Pathological acid reflux (GORD)	Barrett's	OGD HRM 24-hour reflux studies	Conservative measures — chew food more etc High-dose PPI given twice per day — if difficulty swallowing can use lansoprazole FasTabs Barrett's surveillance Surgical treatment avoided, complicated by dysphagia
Stomach	Nausea and vomiting Early satiety, postprandial fullness Epigastric pain Haematemesis Melaena	Gastroparesis Gastric antral vascular ectasia	Weight loss and malnutrition secondary to vomiting GI bleed Iron deficiency anaemia	Gastric emptying study Gold standard is: nuclear medicine scintigraphy study Alternative is octanoic acid breath test OGD	Reduce fat and fibre Five or six small meals per day Prokinetics — domperdione (NB Increased QT interval) — metoclopromide (NB tardive dyskinesia) — IV erythromycin (NB tachyphylaxis) Prucalopride (Also helps with constipation) Pyloric botox if pyloric spasm is present but evidence is mixed Gastric pacemaker but limited evidence in non diabetic gastropareiss GAVE: thermal therapy — APC or bipolar therapy Tends to recur so may require repeated treatments
Liver	Pruritis Jaundice	Primary biliary cirrhosis (autoimmune overlap)		Doppler ultrasound AMA MRCP	Ursodeoxycholic acid Rifampicin for pruritis
Small bowel	Bloating Pain Diarrhoea	SIBO Pseudo-obstruction (ileus)	Nutritional deficiencies secondary to malabsorption	Hydrogen breath test Jejunal aspirate though not very reliable AXR — check for dilated bowel	Antibiotics — may have to be rotating Treat nutritional deficiencies Probiotics

(*continued on next page*)

Table 1 (*continued*)

Location	Symptom	Physiological abnormality/ differentials	Complications	Investigations	Treatment
Large bowel	Constipation	Slow transit constipation	Faecal impaction	Transit study	Laxatives – softeners/stimulants
	Abdominal pain	Diverticular disease/diverticulitis	GI bleed	Colonoscopy	Avoid fibre as this causes more bloating
	Lower GI bleed	Bleeding from telengectasia in bowel	Iron deficiency anaemia	CT colonoscopy	Movicol, senna, linaclotide (risk of diarrhoea), lubiprostome, Prucalopride [a]
			Diverticulitis		Tranexamic acid to reduce bleeding
					APC therapy to treat angiodysplasia
Anorectum	Faecal incontinence	Overflow incontinence		Lower GI physiology testing	Sacral nerve stimulator
	Lump below	Atrophy of internal anal sphincter		Rectal sensitivity testing	Biofeedback treatment
		Rectal hyposensitivity		Proctogram/MR proctogram	Consider surgery for rectal prolapse
		Decreased rectal compliance		EAUSS	but surgery not without complications
		Rectal prolapse		Anal manometry	

AMA, antimitochondrial antibodies; APC, argon plasma coagulation; AXR, abdominal X-ray; GAVE, gastric antral vascular ectasia; GORD, gastrooesophageal reflux disease; HRM, high-resolution manometry; MRCP, magnetic resonance cholangiopancreatography; OGD, oesophago-gastroduodenoscopy; PPI, proton pump inhibitor; SIBO, small intestinal bowel overgrowth.

[a] Prucalopride: Increases number of bowel movements, improves symptoms, improves colonic transit time.

- ***GI bleeding*** secondary to gastric antral vascular ectasia or intestinal telangiectasias – endoscopic thermal treatments, if needed, are effective.
- ***Malabsorption*** secondary to SIBO, causing diarrhoea and bloating – treatment is with antibiotics such as doxycycline, ciprofloxacin or co-amoxiclav.
- ***Nutritional deficiencies*** or weight loss secondary to malabsorption (secondary to SIBO) and loss (e.g. GI bleeding causing iron deficiency anaemia) – this requires nutritional supplementation.
- ***Anaemia*** – iron deficiency anaemia can occur secondary to a GI bleed. Vitamin B_{12} deficiency can be secondary to malabsorption caused by SIBO.

Management

The aims of management are 2-fold: first to treat symptoms, and second to prevent complications of GI dysfunction.[2] Symptom-based treatment is outlined in Table 1. Nutritional supplementation can be considered in patients who are malnourished or at risk of malnourishment, i.e. there is significant weight loss or prolonged lack of adequate oral nutrition. The Malnutrition Universal Screening Tool (MUST) can be used to assess for this. Parenteral nutrition can be indicated in patients who fail enteral nutrition or have pseudo-obstruction.

Surgery is generally contraindicated because of the heightened risk of postoperative complications such as poor wound healing, worsened by a suboptimal nutritional state by the time the patient is awaiting surgery.

Hypermobile EDS

The Ehlers–Danlos syndromes (EDS) are a group of non-inflammatory connective tissue disorders characterized by joint hypermobility, skin fragility and musculoskeletal symptoms. The 2017 EDS classification has divided these disorders into thirteen subtypes, the most common of which is hEDS. The exact prevalence of hEDS is unknown but is thought to be around one in 5000. The underlying patho-aetiology has not been elucidated but is postulated to involve changes in the structure and function of connective tissue elements such as collagen, although definitive evidence for this in the gut remains lacking.

Gastrointestinal symptoms in hEDS

Up to 90% of patients have GI symptoms, which can manifest in any part of the GI tract (Figure 1). The underlying pathophysiology appears to be that of sensorimotor dysfunction, and patients suffer with functional rather than organic GI disorders. Functional dyspepsia, irritable bowel syndrome and gastro-oesophageal reflux disease are common diagnoses.[3]

- ***Dysphagia*** – oesophageal hypomotility is common and can contribute to symptoms. Dysphagia in this context is frequently oropharyngeal in nature, and a review by a speech and language therapist can be useful.
- ***Reflux symptoms*** – regurgitation and waterbrash are more common than heartburn. Reflux hypersensitivity is more common than pathological acid reflux.
- ***Dyspepsia*** – this is the most strongly associated symptom. Alterations in gastric sensitivity and postprandial contractility, but not in compliance, have been observed. Prokinetics can be useful in patients with gastroparesis (Table 1).

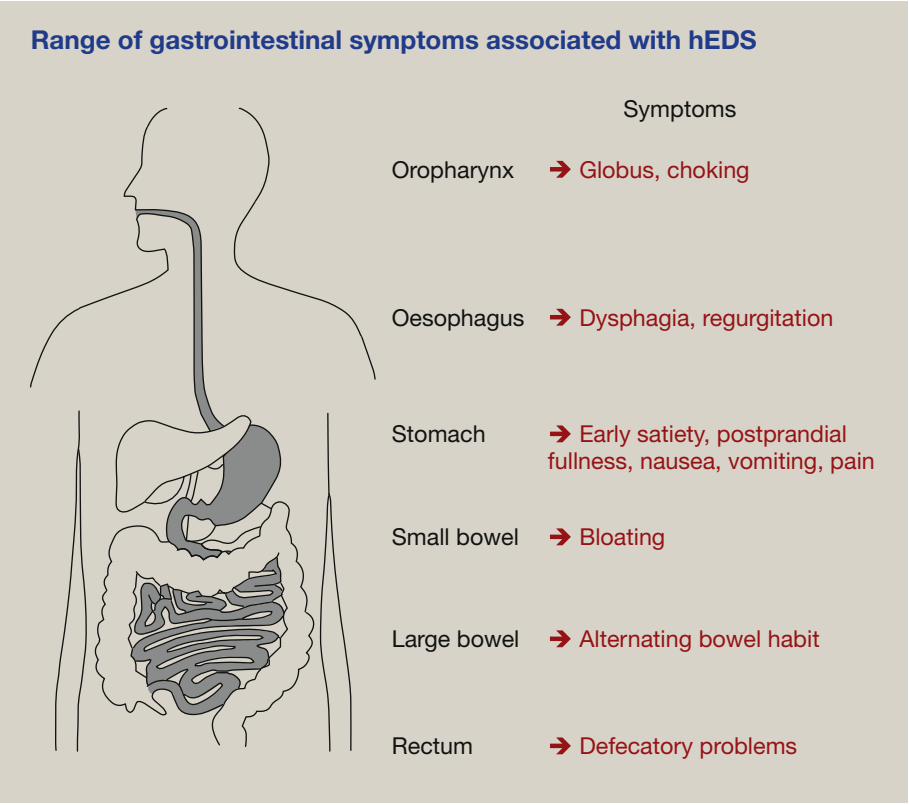

Figure 1

- ***Constipation*** – symptoms of constipation frequently begin in childhood and tend to be severe. For example, patients may only defecate once every 3–4 weeks, often needing to digitate to facilitate this. Over time, the bowel habit can adopt an alternating nature. There is an increased prevalence of rectal hyposensitivity as measured by balloon distension. Slow colonic transit is common, although this is frequently secondary to rectal evacuatory dysfunction.

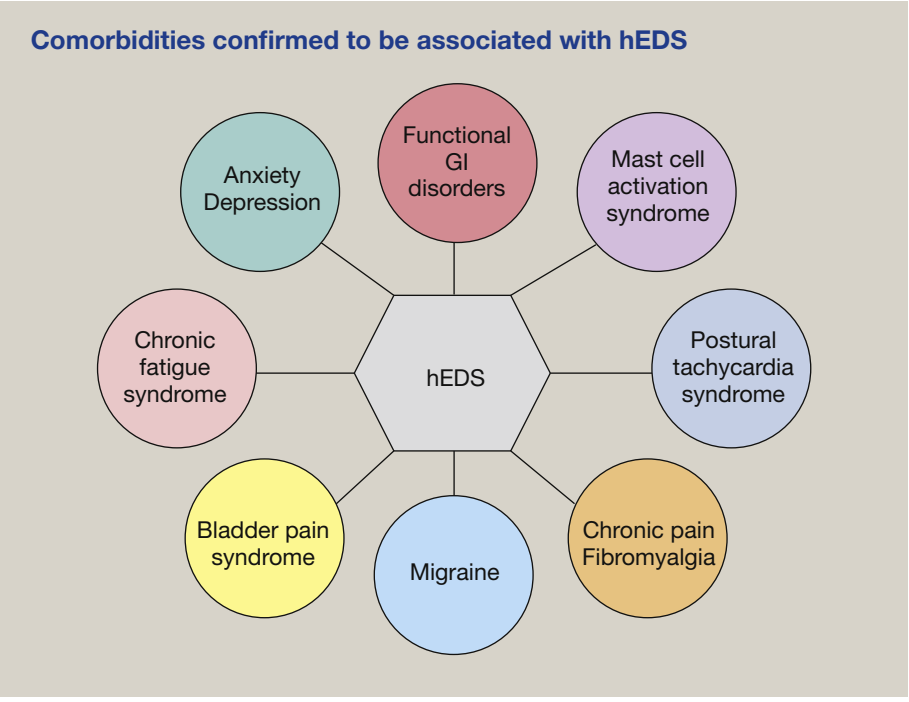

Figure 2

Associated co-morbidities that can affect gastrointestinal function

It is important to ask about the following when taking a history as they can affect GI function and therefore influence the choice of investigations and treatment.

Pain – chronic pain syndromes and opioid use are common (Figure 2). Opiates can cause GI dysmotility and symptoms.

Postural tachycardia syndrome – this presents with orthostatic syncope or presyncope. It is associated with GI dysmotility in the stomach, oesophagus and small bowel, more severe GI symptoms and a reduced quality of life.

Anxiety – this impacts on GI symptoms via the brain–gut axis, and lowers the threshold for (GI) pain.

Allergies/mast cell problems – atopy, multiple drug allergies and rashes, hypothesized to be the result of underlying mast cell dysfunction, are common in a subgroup of patients. In this context, patients often present with diarrhoea, abdominal pain and vomiting.[4]

Investigations

If symptoms remain refractory and organic conditions have been excluded, physiological investigations are most appropriate:

- high-resolution oesophageal manometry for dysphagia
- 24-hour reflux testing for reflux symptoms
- gastric emptying for nausea and vomiting: scintigraphy is more objective than breath testing
- rectal sensitivity testing, colonic transit study and proctograms for diarrhoea or constipation
- small bowel manometry if there is severe postprandial pain, vomiting and weight loss, in the absence of abnormal biochemical, endoscopic, radiological or physiological investigations. This is rarely used but can help to explain symptoms or identify patients who need enteral/parenteral nutrition.

Management

It is important in all patients to approach management holistically. These patients often need psychological therapy in parallel to medical treatment. There is currently a paucity of internationally agreed consensus management guidelines.

Wean the patient off opioids to reduce opioid-related GI dysfunction. Replace them with neuromodulators such as gabapentinoids and antidepressants (amitriptyline, duloxetine), which are more effective for chronic visceral pain.

Mirtazapine is effective for dyspeptic symptoms but can cause weight gain.

Address anxiety as this also helps to manage GI symptoms – patients can be referred for cognitive behavioural therapy.

Rectal irrigation and rectal preparations of laxatives are often more useful than traditional laxatives for constipation, particularly for obstructive defecation. Avoid fibre-based preparations, such as Fybogel and lactulose, as they cause more bloating. Patients with dyspepsia often cannot tolerate large volumes of polyethylene glycol-based laxatives such as Movicol.

Prokinetics can be useful for hypomotility. The prokinetic agent prucalopride, a 5HT4 agonist, can be useful for slow-transit constipation and gastroparesis.

Nausea can be treated using a combination of various antiemetics. Consider sublingual preparations if there is vomiting.

Avoid severe dietary restrictions and consider vitamins/supplements if the patient's diet has been suboptimal. Enteral nutrition is not indicated unless they are severely underweight or have a severe upper GI dysmotility – percutaneous feeding tubes are often complicated by pain. Parenteral nutrition is very rarely indicated and is associated with an increased risk of line infections and thromboembolic complications.

Surgery is often contraindicated because of the risk of recurrence (e.g. hernias, rectal prolapses), an increased likelihood of postoperative wound complications and worsening visceral hypersensitivity.[5] ◆

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FURTHER READING

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 30-year-old woman presented with a 2-week history of severe abdominal pain, constipation and vomiting. She had hypermobile Ehlers–Danlos syndrome and a history of chronic back pain. She was taking morphine (MST) 40 mg morphine

slow release 12-hourly, cyclizine, ondansetron and stimulant and osmotic laxatives, but without relief.
On examination, she was in pain. Her heart rate was 110 beats/minute, and blood pressure 120/70 mmHg. The abdomen was generally tender on very light palpation, but there was no guarding or rigidity.

Investigations

- Haemoglobin 142 g/litre (115–165)
- White cell count 5.6×10^9/litre (4.0–11.0)
- Urea 6.5 mmol/litre (2.5–7.0)
- Creatinine 68 micromol/litre (60–110)
- CT scan of the abdomen showed no obstruction or dilated bowel.

What is the most appropriate next step in her management?

A. Add a fentanyl patch
B. Add the 5HT4 agonist prucalopride
C. Increase the dose of slow-release morphine
D. Refer her to the pain team
E. Add metoclopramide orally

Question 2

A 60-year-old woman with systemic sclerosis and longstanding gastro-oesophageal reflux disease presented with a loss of response to omeprazole 40 mg daily. She also had new-onset dysphagia and a 2 kg unintentional weight loss.
Clinical examination was unremarkable.

What is the most appropriate investigation?

A Barium swallow
B CT scan of the abdomen
C Gastroscopy
D 24-hour reflux study
E High-resolution manometry of the oesophagus

Question 3

A 49-year-old woman presented with vomiting, diarrhoea and unintentional weight loss of 10 kg despite trying to eat three meals per day and having one Fortisip drink per day. She had a long history of systemic sclerosis, gastroparesis and gastro-oesophageal reflux disease.
On clinical examination, her BMI was 16 kg/m^2.

Investigations

- Haemoglobin 95 g/litre ((115–165)
- White cell count 5.6×10^9/litre (4.0–11.0)
- Mean cell volume 89 femtolitres (80–96)
- Sodium 149 mmol/litre (133–146)
- Potassium 3.9 mmol/litre (3.5–4.9)
- Urea 12.5 mmol/litre (2.5–7.0)
- Creatinine 120 micromol/litre (60–110)
- Ferritin 10 micrograms/litre (15–300)
- Transferrin 7.1 g/litre (2.0–4.0)
- Vitamin B_{12} 90 ng/litre (160–760)
- Gastroscopy showed oesophagitis
- Colonoscopy confirmed diverticular disease
- CT scan of the abdomen revealed no neoplastic lesions but showed dilated bowel

What is the best way to manage her nutrition?

A Start parenteral nutrition
B Increase Fortisip drinks to three times per day
C Feed via an nasojejunal tube
D Feed via a percutaneous endoscopic gastrostomy tube
E Iron and electrolytes intravenously, vitamin B_{12} intramuscularly and a dietetic review