Assessment of gastrointestinal involvement

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ABSTRACT
The purpose of this paper is to identify a list of clinical, laboratory and instrumental tools suitable to assess the presence of gastrointestinal involvement in SSc patients to be included in clinical investigational studies. The pertinent literature was reviewed to select those variables which have been demonstrated to be valid, reliable and feasible. A minimal core set of variables has been identified to be used in clinical investigation for the assessment of esophagus, stomach, small intestine, colon and anorectum involvement in scleroderma patients.

Introduction
Involvement of the gastrointestinal (GI) tract in systemic sclerosis (SSc) is second in frequency only to the skin: esophageal dysmotility and its problems occur in 75-90% of SSc patients, stomach involvement in at least 50%, small bowel involvement in 40-70%, colon involvement in 20-50%, and anorectal involvement in 50-70% (1). Since there is often a disparity between the frequency of symptoms in contrast to the frequency of objective signs of organ involvement, patient symptoms alone cannot be relied upon to accurately and objectively document GI involvement.

Pathophysiology
Although the manifestations of involvement in the different GI organ systems may vary considerably, the underlying pathophysiology for the gastrointestinal tract is the same. The primary abnormality involves dysmotility of smooth muscles of the entire gastrointestinal tract. In this respect, relevant information has been provided by manometry, which measures pressure changes inside the gastrointestinal tube. These pressure changes are thought to reflect the state of muscle tone and peristalsis (i.e., increased pressure is thought to represent increased tone). When a normal subject swallows a wet meal, there is migration of increased pressure as the esophagus attempts to propel the bolus down into the stomach. Also at the time of the swallow, there is relaxation of the lower esophageal sphincter (LES) pressure in anticipation of the arrival of the bolus. Once the bolus arrives, the pressure in the sphincter rises back to its baseline (usually 20-30 mm Hg) to close off the stomach from the esophagus, preventing reflux.

When a scleroderma subject with esophageal involvement swallows a wet meal, there is an abnormal pressure response. Because the pharynx, which is composed of skeletal muscle, usually remains functional, manometry registers the swallow in the pharynx. Conversely manometry registers a reduced pressure response from the smooth muscle of the body of the esophagus and a lack of relaxation of the lower esophageal sphincter (LES) pressure. In many instances the LES pressure remains reduced or low most of the time. Similar dysmotility problems occur throughout the stomach and intestines and with increasing frequency and severity, the longer the duration of SSc. In the fasting state, antr duodenal motility recordings show that there is spontaneous peristalsis in the form of migrating myoelectric complexes (MMC). Activity (increases in pressure) begins in the antrum of the stomach. The activity slowly migrates into and down the duodenum. Within 10-15 minutes after eating, the normal MMCs (which are seen during fasting) are replaced by irregular contractile activity (which at times can be quite intense). This irregular contractility is designed to move foods and liquids out of the stomach and into the intestine. In scleroderma, the MMCs are reduced or absent at rest. In their place high-amplitude, uncoordinated contractions are seen in the antrum and small intestine. After eating, the uncoordinated...
activity may persist but there may be no contractile response of the stomach or intestine to a meal. In advanced intestinal scleroderma, dramatic hypomotility of the stomach and small intestine can occur, which at times gives rise to pseudo-obstruction. In 1971 Cohen et al. published a report that greatly advanced our understanding of the pathophysiology of gut problems in scleroderma (2). Using esophageal manometry, they studied LES pressures in normal subjects, healthy subjects who had an incompetent LES, subjects with Raynaud’s phenomenon, and two groups of scleroderma patients (one with normal peristalsis in the body of the esophagus and the second with abnormal peristalsis). Cohen found that LES pressure was lower in scleroderma populations than in normals. More importantly, they studied the response of LES pressures to stimulation by several different pharmacologic agents: one agent which directly stimulated smooth muscle (methacholine) and two agents which stimulated smooth muscle indirectly through stimulation of cholinergic nerves (edrophonium and Gastrin I). The studies showed that esophageal muscle could and did respond to direct stimulation with methacholine. On the other hand stimulation of cholinergic nerves by edrophonium and gastrin failed to lead to stimulation of the LES. The conclusion was that the cholinergic nerves were not transmitting the message to the smooth muscle. A further conclusion was that the earliest defect in the dismotility disorder of scleroderma is in the cholinergic nerves which supply the muscle rather than a process primary to the muscle itself. Pathologic studies support this observation. Early in scleroderma, the smooth muscle of the esophagus may appear normal structurally but its function may be decreased. Later, progressive atrophy develops and what remains of the muscle fails to respond to drugs. In addition the mucosal surfaces may become atrophic and the muscle and adventitial layers become fibrotic. These data have given rise to a 3-phase hypothesis that has practical implications for the evaluation and management of GI tract problems in SSc.

Phase 1: There is neurological dysfunction, but the muscle can still respond to prokinetic agents.

Phase 2: As smooth muscle atrophies, the response to prokinetic agents becomes less reliable.

Phase 3: Finally, when muscle atrophies completely, the smooth muscle can no longer respond to prokinetic stimuli.

Candidate variables

Esophageal involvement

Hypomotility in the esophagus results in delayed transit down the esophagus and in a weakened lower esophageal sphincter. The repeated bathing of the distal esophagus by hydrochloric acid may result in erosive esophagitis and stricture. Esophageal involvement can be assessed by the following methods (3-5):

1. Manometry. Assessment of esophageal motility can be made directly using manometry. During manometry, wave amplitude (in mm Hg) and lower esophageal sphincter pressure (in mm Hg) can be determined on a continuous scale. Motility in the body of the esophagus, however, is usually graded qualitatively as normal or abnormal (hypomotile). When motility is abnormal, the degree of hypomotility can be further graded as mild, moderate, or severe.

2. pH monitoring of the distal esophagus. This test can produce quantitative data by assessing pH in the distal esophagus (i.e., the number of episodes of pH < 4, longest episode of pH < 4, percent of study time with pH < 4, etc.).

3. Scintigraphy. The results can be given quantitatively as the percent of radioactivity remaining in the esophagus “x” minutes after the patient (who is in the supine position) swallows a radioactive meal.

4. Endoscopy. This test gives primarily qualitative information about the structure of the esophagus and stomach.

5. Cine/video barium esophagram. This test, when performed in the supine position, gives qualitative information about motility (normal or abnormal; abnormal tracings can further be graded as mild, moderate or severe hypomotility or as spasm of gastroesophageal sphincter). It also can give qualitative information about structure (i.e., strictures, diverticulae, masses, etc.).

Gastric involvement

Gastric dysmotility occurs in a high proportion of patients with scleroderma (6), but the methods to assess it are few and mainly represented by:

1. Gastric emptying. The results can be given quantitatively as the percent of radioactivity remaining in the stomach “x” minutes after the patient (who is in the supine position) swallows a radioactive meal.

2. Endoscopy. This test gives only qualitative information about the structure of the esophagus and the stomach.

Small intestinal involvement

Hypomotility results in delayed transit of food and liquids through the small intestine. The stagnation of fluid from this hypomotility allows colonic bacteria to migrate upstream into the small intestine, where the bacteria breakdown bile acids necessary for the absorption of fats. The inability to absorb fats may lead to malabsorption, weight loss and diarrhea. In some instances the hypomotility may be so severe that it produces recurrent, persistent ileus (pseudo-obstruction). Intestinal involvement can be assessed by several methods, depending on which pathophysiologic aspect is more prevalent (1, 3, 7-9):

1. Small bowel barium follow through x-ray. The test tends to produce qualitative data (dilatation, pseudosacculations), but the duodenal diameter (at the 2nd portion of the duodenum) and transit time can be measured quantitatively.

2. 72-hour fecal fat determination. This incommodoius test requires a 100-gram fat diet during and for 5 meals prior to the 72-hour collection of feces. The entire stool sample is then homogenized and processed before a sample is tested for fat contents. It is considered by many to be the “gold standard” for evaluating malabsorption. It gives quantitative data.

3. Jejunal cultures. Obtaining these cultures requires passing a tube or capsule orally and verification that the culture device is actually in the jejunum.
The results are qualitative in nature (presence or absence of bacterial growth).

4. **Hydrogen-breath test.** This test is used as a surrogate for assessing small bowel bacterial overgrowth. The test subject swallows a non-absorbable sugar (i.e., lactulose) and the subject’s breath hydrogen levels are determined every 15 minutes for 3 hours. Early appearance of a hydrogen spike suggests that bacteria have metabolized the sugar high in the small intestine. It gives quantitative data but is subject to a plethora of technical problems, which may invalidate the results.

5. **Schilling’s test.** Usually thought of as the test for clinching the diagnosis of pernicious anemia, it also can show poor absorption of vitamin B12 in the presence of small bowel bacterial overgrowth. When the test is repeated after a course of antibiotics, the absorption of vitamin B12 may have increased.

6. **D-xylose test.** When swallowed, this non-metabolizable sugar will be absorbed and excreted unchanged into the urine and can be measured chemically. If the intestinal mucosa is not functioning properly, lesser than normal amounts of the sugar will be absorbed and excreted into the urine.

7. **Intestinal manometry.** In the intestine, manometric studies tend to give qualitative rather than quantitative data, which may or may not be reproducible. In addition, the techniques are not always readily available in the community or study centers. The test tends to be expensive and the results are often operator dependent.

8. **Abdominal x-ray and CT.** These techniques give primarily qualitative structural data. They are also expensive.

9. **Serum carotene** can be used as a surrogate for absorption/malabsorption.

10. **Pre-albumin** can be used to assess starvation and nutrition. Low levels may result from problems with the structure, absorption and function of the gut.

11. **Body weight** (particularly changes over time) and the **body mass index** (assuming height remains constant) can be used to assess nutritional status, starvation and weight loss.

**Large intestine involvement**

Several abnormalities have been demonstrated to occur in the colon of SSc patients and the anorectum is the most affected part. Manometric studies have documented that prolonged pancolonic transit time more than functional obstruction at the anorectum is responsible for constipation (10). The internal and external sphincters may become hypotonic. Weakened sphincters may give rise to fecal incontinence. Investigation of the colon may be performed with:

1. **Sitz marker.** When swallowed, these opaque markers can be used to measure transit times in the large intestine.

2. **Intestinal manometry.** In the large intestine and rectum, manometric studies tend to give qualitative rather than quantitative data, which may or may not be reproducible. In addition, these techniques are not always readily available in the community or study centers. The test tends to be expensive and the results are often operator dependent.

3. **Sigmoidoscopy and colonoscopy.** These methods give primarily qualitative information about the structure of the colon and recto-sigmoid region.

4. **Barium enema.** This procedure can show pseudodiverticulae.

Table I summarizes the candidate variables considered above.

**Discussion**

**Identification of core set variables**

Table II lists the core set variables needed to assess the presence of GI involvement in the SSc patient enrolled in clinical investigational studies.
Rationale for the selection of the variables
Since impaired peristalsis (often appreciated as distal dysphagia for solid foods), gastroesophageal reflux, erosive esophagitis (resulting in heartburn) and esophageal strictures are likely to occur in this sequence in SSc patients (11), the presence of dysphagia and/or heartburn is to be considered sufficient to suggest esophageal involvement on clinical grounds. However, approximately 30% to 40% of SSc patients with abnormalities of esophageal function are asymptomatic. In these patients a baseline motility examination by cine-video barium esophagram is a minimal requirement to exclude or establish esophageal dysfunction.

Early satiety and/or bloating and/or vomiting can be considered suggestive of gastric dysfunction. Although we lack epidemiological data, a high frequency of gastroparesis is thought to be present in mostly asymptomatic patients.

Symptoms indicative of small bowel involvement should be one of the following: weight loss, changes of body mass index (as evidence of malabsorption), constipation, diarrhea (as evidence of motility dysfunction), and/or intestinal distension (pseudo-obstruction).

Involvement of the lower digestive tract is common and is suggested by abnormal X-ray (pseudo-obstruction), small-bowel barium follow-through study, carotene and pre-albumin (absorption/malabsorption) and, if leading to bacterial overgrowth and malabsorption, can be investigated by the hydrogen breath test, the D-xylene absorption test and the 72-hour fecal fat test. However, it is suggested by signs and symptoms. A colonic transit study could be performed in clinical practice in patients with uncertain clinical symptoms, but is unnecessary to improve comparability in clinical investigation.

Anorectal manometry, defecography and electromyography are specialized techniques and should be employed only as research tools.

Rationale for the exclusion of other variables
Other variables have been excluded because of their poor feasibility or low reliability. In particular, esophageal scintigraphy using a semi-solid bolus is both quantitative and sensitive with, however, a 20% false positive rate (12) which renders this technique inappropriate for screening. Furthermore, esophageal manometry has been shown to predict patients at risk of erosive esophagitis. It has been suggested that all patients with SSc should undergo baseline esophageal manometry and those with abnormal manometry should subsequently have endoscopy (3). However, the latter approach is to be recommended only for special studies.

Tests for gastric dysmotility including a barium study should be reserved to patients in whom gastroparesis needs to be demonstrated in the single patient in clinical practice. Evaluation of gastric emptying after a radioactive meal is more sensitive and quantitative than barium studies, but since it is less feasible it should presently be considered only for therapeutic trials.

Small bowel involvement, in dubious cases, could be assessed by abnormal X-ray (pseudo-obstruction), small-bowel barium follow-through study, carotene and pre-albumin (absorption/malabsorption) and, if leading to bacterial overgrowth and malabsorption, can be investigated by the hydrogen breath test, the D-xylene absorption test and the 72-hour fecal fat test. However, it is suggested by signs and symptoms. A colonic transit study could be performed in clinical practice in patients with uncertain clinical symptoms, but is unnecessary to improve comparability in clinical investigation.

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References