University of Pittsburgh & UPMC Scleroderma Center

COLLAGEN CONNECTION

Winter 2018

Gastrointestinal Manifestations of Scleroderma and Their Impact on Nutrition

by David J. Levinthal, MD, PhD

The optimal function of the gastrointestinal (GI) tract requires an intricate balance of muscle contraction, secretion, and absorption, and even subtle disruption in these processes may cause GI-related symptoms. The GI tract is the most common internal organ to be impacted by scleroderma, and ~90% of patients with systemic sclerosis (Ssc) experience at least one persistent GI symptom (1). However, patients may experience GI symptoms differently due to the heterogeneity in the severity and location of GI tract involvement. Therefore, care plans for treating SSc-related GI symptoms need to be highly individualized. SSc-related GI dysfunction negatively impacts quality of life and poses a challenge to remain nutritionally replete. The following overview will highlight important aspects of the diagnosis and treatment of some common SSc-associated GI disorders, as well as strategies for maintaining nutrition in this context.

SSc and the Esophagus

SSc disrupts the timing or strength of esophageal contractions, leading to swallowing-related symptoms ("dysphagia"), as well as regurgitation, a sense of heartburn, or chest discomfort. Many SSc patients experience at least some difficulties clearing solids and sometimes liquids. In evaluation, a barium esophagram or an esophageal manometry test can be useful. The latter involves a nasally-inserted catheter equipped with pressure sensors to determine patterns of esophageal motility. About one third of symptomatic SSc patients have essentially absent motility, but most patients have some functional reserve. Additionally, reduced lower esophageal sphincter tone makes gastro-esophageal reflux disease (GERD) a common and persistent problem.

The treatment of SSc-related esophageal motility problems relates to the degree of functional motility reserve. Most patients benefit from eating slowly with smaller bites of softer foods, in a fully upright position to maximize gravity in clearing the esophagus. A few medical therapies may minimize dysphagia, such as pyridostigmine and bethanechol, and the serotonin agonist buspirone has recently been shown to boost esophageal motility and reduce dysphagia in SSc patients (2).

Continue on page 2

David J. Levinthal, MD, PhD

Dr. Levinthal serves as the Director of the Neurogastroenterology and Motility Center at the University of Pittsburgh Medical Center (UPMC). He is a graduate of the University of Pittsburgh School of Medicine's MD/PhD Program, receiving his PhD in Neuroscience. After Internal Medicine Residency training at the University of Michigan, Dr. Levinthal returned to Pittsburgh for post-doctoral research and GI Fellowship training at UPMC. Dr. Levinthal's current NIH-funded research program is focused on understanding the neural basis of brain-gut interactions and the mechanisms that link cognitive and emotional processes with changes in GI tract function. He also directs clinical research focused on uncovering the determinants of outcomes in patients with functional GI and motility disorders, and he is involved in the development of high-value clinical care models in this patient population.

IN THIS ISSUE

SSc-related GERD can be managed with proton-pump inhibitors. Lifestyle treatments include eating smaller, more frequent meals, avoiding eating within 2 hours of bedtime, and avoiding very spicy foods, caffeine, alcohol, and tobacco use. Elevating the chest relative to the abdomen is an effective measure to minimize passive reflux while sleeping, which can be accomplished by elevating the head of the bed by 2-3 inches or use of a "wedge pillow".

Scleroderma and the Stomach

Scleroderma-related fibrosis of the stomach wall impairs accommodation and contraction, leading to gastric stasis that causes "dyspepsia" – a term encompassing symptoms of meal-induced fullness, upper abdominal discomfort, and/or bloating – as well as nausea or vomiting. Many patients undergo an upper endoscopy to investigate these symptoms, and some patients have a gastric emptying test. The treatments for SSc-related dyspepsia are somewhat limited, but "prokinetic" medications such as erythromycin/azithromycin, metoclopramide, domperidone, or pyridostigmine can be used. In general, eating smaller, more frequent meals during the day may present less "work" for the stomach, and hopefully allows nutrition to be maintained while also minimizing symptoms. If nausea and/or vomiting symptoms dominate, then medications such as ondansetron, promethazine, or prochlorperazine can be helpful. Herbal remedies for persistent dyspepsia and nausea include Iberogast and ginger, respectively, and these approaches can be surprisingly effective.

SSc and the Small Intestine

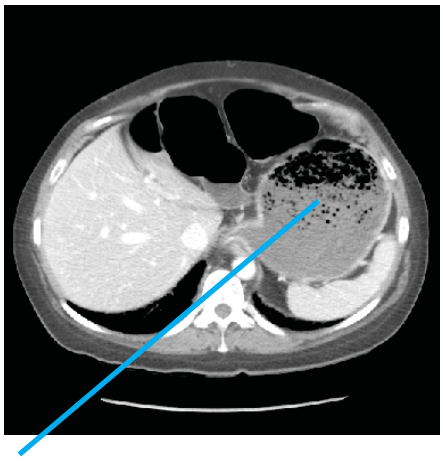
Ssc-associated small intestinal dysmotility leads to stasis of material and symptoms of nausea, bloating, gassiness, and abdominal pain all worsened if small intestinal bacterial overgrowth (SIBO) occurs. SIBO can lead to macro- and micronutrient deficiencies and is characterized by progressive weight loss despite eating with diarrhea that is worsened by eating. SIBO can be confirmed by culturing intestinal fluid (via enteroscopy) or breath testing (which detects gas products from gut bacterial fermentation), but often the diagnosis is made clinically. Antibiotics treat SIBO, but unfortunately SIBO often recurs, requiring treatment with scheduled "cycles" of antibiotics over the long term. Prokinetic medications such as pyridostigmine and erythromycin/azithromycin may improve small intestinal motility and decrease the risk of recurrent SIBO, but most patients do not have major improvements with these approaches.

Nutritional Support Strategies

SSc can have a major nutritional impact via its effects on esophageal, stomach, or small intestinal function. In those with mild to moderate SSc-related GI symptoms, nutrition can typically be maintained by eating smaller volume, calorically dense meals more frequently throughout the day. Liquid nutritional supplements can help maintain total caloric intake and come in a variety of forms. Some shake-like supplements have >500 kcal per ~8 ounce serving. Thinner liquids and gels with high protein content can also be useful to boost protein and calorie intake in smaller volumes. Finally, juice-like supplements contain protein and supply 200-250 kcal in ~7 ounces servings. A dietician can be invaluable to identify nutritional deficiencies and develop individualized strategies to combat them.

For those with severe GI symptoms that hinder oral intake, liquid nutritional support via a feeding tube may be required. Feeding tubes can be temporary (such as a naso-gastric or naso-duodenal tube), or more durable (such as a gastrostomy tube or jejunostomy tube). The more permanent feeding tubes can be placed by gastroenterologists, interventional radiologists, or surgeons.

Finally, those with the most severe forms of SSc-related GI dysfunction often cannot meet nutritional goals via the enteral route. In these cases, intravenous (parenteral) nutrition may be indicated, but this is typically viewed as a therapy of last resort. Total parenteral nutrition (TPN) is complete nutrition delivered via a catheter in a large vein, but can have long term complications including an increased risk of catheter-associated infections, blood clots, and liver dysfunction. Thus, the decision to initiate TPN needs to be carefully weighed against these potential risks.



Distended Stomach full of solid food >12 hours after last meal

References:

1. Emmanuel A. (2016) Current management of the gastrointestinal complications of systemic sclerosis. Nat Rev Gastro & Hepatol 13:461-472.

2. Karamanolis GP, Panopoulos S, Denaxas K, Karlaftis A, Zorbala A, Kamberoglou D, Ladas SD, Sfikakis PP. (2016) The 5-HT1A receptor agonist buspirone improves esophageal motor function and symptoms in systemic sclerosis: a 4-week, open-label trial. Arthritis Res Ther. 2016 Sep 1;18:195.

WALK WITH TORI 2017

It was another beautiful day in Hagerstown, Maryland for the annual Walk With Tori! The outpouring of support is amazing every year. Tori, along with family and friends, have organized the walk to bring awareness about the disease and to raise money to support research at the Center. All monies raised at the event are used for scleroderma research. To date, Tori and her family and friends have raised over $200,000!

Thank you to all who came out to support the walk.

All photographs from the walk are courtesy of Triple-T Photography, Hagerstown, MD

CLINICAL DRUG TRIALS AND OBSERVATIONAL STUDIES

Our Center is committed to participating in clinical trials. We feel it is a vital step in working together to find a treatment for scleroderma. Without clinical trials, our field will not advance. If you would like additional information regarding ongoing clinical studies at our Center, please contact one of our scleroderma research coordinators, Dana Ivanco at des2@pitt.edu or Maureen Laffoon laffoonm@pitt.edu.

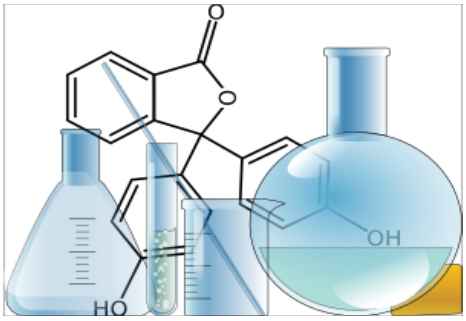
CURRENTLY ENROLLING PATIENTS:

Pilot Study To Assess The Efficacy And Safety Of Riociguat Vs. Placebo In Scleroderma-Associated Digital Ulcers (RESCUE):

This study examines the safety and effectiveness of Riociguat in scleroderma patients with digital ulcers. Riociguat is approved by the FDA for the treatment of pulmonary arterial hypertension (PAH). In this study half the patients will receive drug and half the patients will receive placebo. Patient must have an active digital fingertip ulcer at the time the trial starts. The first part of the trial is 16 weeks. After the trial all patients who participate and have digital ulcers have the opportunity to receive riociguat for an additional 8 weeks.

The Effect of Atorvastatin on Microvascular Endothelial Function and Raynauds in Early Diffuse Scleroderma (TAMER):

This is a NIH-supported single-center study (being done only in Pittsburgh). The purpose of this study is to examine the effect of atorvastatin (trade name Lipitor) on Raynaud symptoms and small blood vessel function in patients with early diffuse scleroderma. Scleroderma is characterized by blood vessel injury, immune system activation and fibrosis. The blood vessel injury is thought to be important early in the disease, and many think this may be the reason most scleroderma patients experience Raynauds as the first symptom. While atorvastatin reduces cholesterol, it is recognized to have many positive effects beyond cholesterol reduction. These include improvement of blood vessel function and reduction of fibrosis. It is believed that atorvastatin will improve blood vessel function and Raynaud symptoms in patients with early disease. Early disease means <3 years of scleroderma symptoms for this study. The trial is 16 weeks and half the patients will receive atorvastatin and half placebo. Atorvastatin (or placebo) is given as an "add-on" therapy. This means all medications can be continued while in this trial. There are only 3 visits over 16 weeks.



Evaluation of Brentuximab Vedotin for Diffuse Cutaneous Systemic Sclerosis: A Phase I/II Multicenter, Randomized, Double-Blinded Safety Study:

Brentuximab vedotin (name brand Adcetris) is a drug that was developed and has FDA approval for the treatment of lymphoma. This research is being done to evaluate the safety and tolerability of brentuximab in the treatment of diffuse skin disease in scleroderma. Patients must be early in their disease with worsening skin to participate. Two of three patients will receive brentuximab vedotin, and the other individual placebo. The study lasts 48 weeks and involves 14 visits. Patients will be able to remain on their current scleroderma medications.

Dimethyl Fumarate (Tecfidera) T, In Pulmonary Arterial Hypertension Associated With Systemic Sclerosis

Dimethyl fumarate (DMF) is a drug approved for the treatment of multiple sclerosis and psoriasis. DMF acts at multiple targets and has both anti-oxidant and anti-inflammatory properties. The NIH-funded four-center study will examine the safety of DMF in scleroderma patients, and if it improves patient function by increasing the distance scleroderma patients with pulmonary hypertension can walk. Half of the subjects will receive DMF and half placebo. Other medications can be continued throughout the study. This is a 36 week study with a total of 6 visits.

An Observational Study of the Effect of Mycophenolate Mofetil (Cellcept) in Early Diffuse Scleroderma:

This is a NIH-supported single-center study (being performed only in Pittsburgh) to observe the effect of mycophenolate for the treatment of early diffuse scleroderma. Mycophenolate is one of the most commonly used medications to treat diffuse scleroderma and scleroderma-related pulmonary fibrosis, however we know little about how to predict who will respond well to the medication. Patients whose physician recommends they should be clinically treated with mycophenolate are eligible to be in this study. When in this study your

doctor may change your medications at any time. We simply observe the effect of mycophenolate, collect data on its effect on skin, and collect blood and oral swab samples every 3 months for the first year a patient is treated with mycophenolate. This study can easily be combined with regular patient visits.

ENROLLING SOON:

A Randomized, Double-blind, Placebo-controlled Trial to Evaluate Efficacy and Safety of Anabasum in Diffuse Cutaneous Systemic Sclerosis (RESOLVE)

Corbus Pharmaceuticals is holding an Investigator's meeting in December, 2017 for their Phase 3 clinical trial on Anabasum (formerly known as JBT-101). Our center participated in the phase 2 trial of this study, and enrolled 5 patients who continue to take the therapy. This drug is being looked at in the management of early diffuse scleroderma. We hope to start enrolling in early 2018!

A Phase II double-blind, clinical trial addressing the treatment of patients with active and symptomatic scleroderma-related interstitial lung disease (SLSIII)

This study compares the safety and effectiveness of adding on pirfenidone to current mycophenolate (Cellcept) therapy for scleroderma-related lung disease. Pirfenidone is FDA approved for the treatment of pulmonary fibrosis. This research is designed to test whether combining pirfenidone and mycophenolate will result in a more rapid and possibly greater improvement in lung function than occurs when mycophenolate is used alone. There are 13 office visits and 11 phone calls over 18 months.

PATIENT EDUCATION CONFERENCE

The Pittsburgh Scleroderma Center held a Patient Education Conference on June 10th in partnership with the Scleroderma Foundation and the American Thoracic Society Public Advisory RoundTable (ATS PAR).

Many of our UPMC Scleroderma Specialists spoke at the event. The following topics were discussed:

What Type of Scleroderma Do You Have? — Thomas A. Medsger, Jr. MD

Oral Manifestations of Scleroderma —Lisa Fonas, DMD

Scleroderma Lung Involvement —Kevin Gibson, MD

The Impact of Scleroderma on Gastrointestinal Function and Nutrition—David J. Levinthal, MD, PhD

Pulmonary Hypertension — Robert Lafyatis, MD

Dr. David J. Levinthal

Dr. Robert Lafyatis

David Murad, Scleroderma Foundation Director of Chapter Relations, spoke about the desire to revitalize the Western Pennsylvania Chapter of the Scleroderma Foundation. If you are interested in participating in a support group in the Pittsburgh area for patients, caregivers and family members, please contact David at dmurad@scleroderma.org for more information.

Dr. Lisa Fonas

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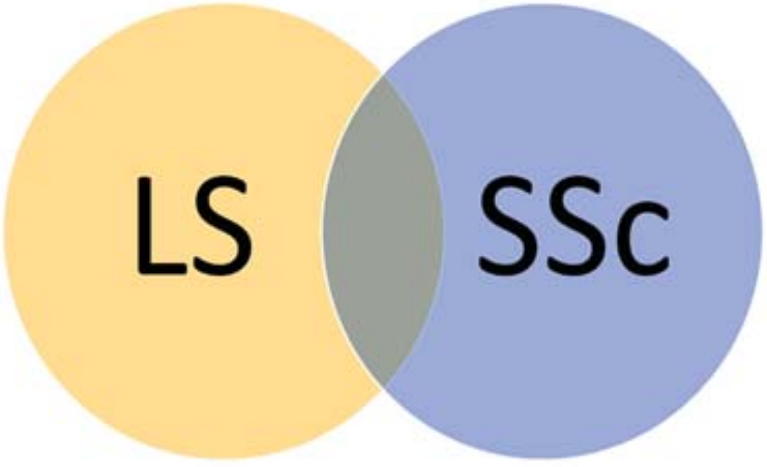
SCORE Research Study: Identifying Juvenile Scleroderma Immuno-phenotype Subsets

Dr. Kathryn (Cassie) Torok, a pediatric rheumatology faculty member of our University of Pittsburgh Scleroderma Center of UPMC was awarded a Scleroderma Foundation Multi-Center Collaborative Research (SCORE) award in 2016, titled, "Identifying Juvenile Scleroderma Immunophenotype Subsets". This award was developed by the Scleroderma Foundation to encourage multi-institutional collaboration given the rarity of scleroderma. Dr. Torok is the principal investigator, with other leading collaborators in pediatric rheumatology from across the nation, Dr. Suzanne Li from Hackensack University Medical Center, The Joseph M. Sanzari Children's Hospital in New Jersey, and Dr. Anne Stevens from Seattle the Children's Research Institute, Seattle Children's Hospital in Washington. This is the first pediatric-focused scleroderma SCORE grant awarded.

The proposed collaboration between pediatric SCORE sites (University of Pittsburgh, Seattle Children's Research Institute and Hackensack University) and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) will take advantage of the established strengths of each site and the power of the CARRA registry and biorepository to enable the feasibility of this large-scale project.

The goal of the project is to identify specific immunophenotypes (cell types, inflammatory protein profiles and antibody types circulating in the blood) of pediatric Systemic Sclerosis (SSc) and Localized Scleroderma (LS). Identifying immunophenotypes will biologically define clinical subsets of disease to help improve treatment and outcomes. Dr. Torok and her team believe there will be both shared immunological profiles between the two overall types of disease, SSc and LS, and some overlapping profiles (see Figure), which will help determine measures of clinical disease outcomes, prognosis and potentially predict response to medications.

Dr. Torok and her team intend on recruiting pediatric SSc and LS patients across the nation through different CARRA centers. At the recent CARRA conference in May, Dr. Torok and her team trained other pediatric rheumatologists at the participating CARRA sites, demonstrating different clinical tools such as skin thickness scoring, on pediatric LS and SSc subject volunteers to allow for standardized clinical measure collection across the sites. Enrollment is anticipated to begin in November. For more information, please contact the pediatric research coordinator: Kaila Schollaert-Fitch, k.fitch@pitt.edu.



Peripheral blood immunophenotype:

- **Cellular phenotype**
- **Circulating cytokines/chemokines**
- **Antibody profiles**
- **Standard laboratory evaluation**

We would like to thank the following donors for their support of scleroderma research

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Your contributions to the Scleroderma Center are greatly appreciated and help support research and patient education programs. You can remember or honor a loved one by using the envelope enclosed in this newsletter to send your donation. For additional information on giving to the Scleroderma Center, please contact Rose Jandrasits at 412-864-1958 or krj13@pitt.edu.

Four young women living with pediatric-onset scleroderma recently worked together to raise funds for ongoing pediatric scleroderma research led by Dr. Kathryn Torok at the University of Pittsburgh and Children's Hospital of Pittsburgh. Carly Bankovich, Alyssa Finney, Kiley Pesce, Sierra Pontious, and their families organized the Scleroderma 5K Run/ Walk held in Kersey, PA on June 24. A total of 63 people of all ages participated in the event, which also included a Kids Fun Run, 50/50, basket raffle, and TV raffle. A grand total of $2700 was raised for pediatric scleroderma research, and they hope to hold the event annually. Please join us in thanking them for all their work to raise awareness of pediatric scleroderma!

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