The Journal of Rheumatology 2021;48:1422–6
doi:10.3899/jrheum.201283
First Release June 1 2021

The Journal of Rheumatology

UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract (GIT) 2.0 Reflux Scale Correlates With Impaired Esophageal Scintigraphy Findings in Systemic Sclerosis

Giuseppina Abignano[1], Gianna Angela Mennillo[2], Giovanni Lettieri[3], Duygu Temiz Karadag[4], Antonio Carriero[2], Angela Anna Padula[2], Francesco Del Galdo[5], Dinesh Khanna[6], and Salvatore D'Angelo[2]

ABSTRACT. ***Objective.*** The University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0) instrument is a self-report tool measuring gastrointestinal (GI) quality of life in patients with systemic sclerosis (SSc). Scarce data are available on the correlation between patient-reported GI symptoms and motility dysfunction as assessed by esophageal transit scintigraphy (ETS).

Methods. We evaluated the GIT 2.0 reflux scale in patients with SSc admitted to our clinic and undergoing ETS, and correlated their findings.

Results. Thirty-one patients with SSc undergoing ETS were included. Twenty-seven were female, and 9 had diffuse cutaneous SSc. Twenty-six of 31 (84%) patients had a delayed transit and an abnormal esophageal emptying activity (EA); they also had a higher GIT 2.0 reflux score ($P = 0.04$). Mean EA percentage was higher in patients with none to mild GIT 2.0 reflux score (81.1 [SD 11.5]) than in those with moderate (55.7 [SD 17.8], $P = 0.003$) and severe to very severe scores (55.8 [SD 19.7], $P = 0.002$). The percentage of esophageal EA negatively correlated with the GIT 2.0 reflux score ($r = -0.68$, $P < 0.0001$), but it did not correlate with the other GIT 2.0 scales and the total GIT 2.0 score.

Conclusion. SSc patients with impaired ETS findings have a higher GIT 2.0 reflux score. The GIT 2.0 is a complementary tool for objective measurement of esophageal involvement that can be easily administered in day-to-day clinical assessment.

Key Indexing Terms: gastroesophageal reflux disease, gastrointestinal tract, outcome assessment, scleroderma, scintigraphy, systemic sclerosis

Systemic sclerosis (SSc) is a complex disease characterized by early microvascular abnormalities, immune dysregulation and chronic inflammation, as well as subsequent fibrosis of the skin and internal organs.[1] The esophago-gastrointestinal tract is the most frequently involved internal organ in SSc, affecting up to 90% of patients. The esophagus is the most commonly affected

DK is supported by the National Institutes of Health (NIH; AR063120: Outcomes Research in Rheumatic Diseases [K24]).

[1]G. Abignano, Clinical Researcher and Honorary Consultant Rheumatologist, MD, PhD, Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital, Potenza, Italy, and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]G.A. Mennillo, Consultant Rheumatologist, MD, A. Carriero, PhD Fellow, MD, A.A. Padula, Consultant Rheumatologist, MD, S. D'Angelo, Consultant Rheumatologist, MD, PhD, Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital, Potenza, Italy; [3]G. Lettieri, Consultant Radiologist, MD, Radiology Department, San Carlo Hospital, Potenza, Italy; [4]D. Temiz Karadag, Consultant Rheumatologist, MD, Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital, Potenza, Italy, and Department of Rheumatology, Kocaeli University, Kocaeli, Turkey; [5]F. Del Galdo, Associate Professor, MD, PhD, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [6]D. Khanna, Professor, MD, MS, University of Michigan Scleroderma Program, University of Michigan, Ann Arbor, Michigan, USA.

FDG receives research grants and honoraria not relevant to the topic of the article from GSK, AstraZeneca, Capella Biosciences, Kymab, Chemomab, Mitsubishi Tanabe, Actelion, and Boehringer Ingelheim. DK receives grant support from the NIH, Immune Tolerance Network, Bayer, BMS, Horizon, Pfizer; is a consultant for Acceleron, Actelion, AbbVie, Amgen, Bayer, Boehringer Ingelheim, CSL Behring, Corbus, Galapagos, Genentech/Roche, GSK, Horizon, Merck, Mitsubishi Tanabe Pharma, Sanofi-Aventis, and United Therapeutics; participates in Continuing Medical Education programs for Impact PH; holds stocks in Eicos Sciences, Inc (< 5%); and has a leadership/equity position as Chief Medical Officer for CiviBioPharma/Eicos Sciences, Inc. The other authors declare no conflicts of interests.

Address correspondence to Dr. G. Abignano, Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital, Via Potito Petrone snc, 85100 Potenza, Italy.
Email: g.abignano@hotmail.com.

Accepted for publication December 17, 2020.

tract.[2] Esophageal dysfunction involves the lower two-thirds of the organ and is characterized by a hypotensive lower esophageal sphincter (LES) pressure and a weak or absent distal esophageal peristalsis with subsequent gastroesophageal reflux disease (GERD).[3]

Several standardized techniques may be used to assess the esophageal involvement in SSc, including pH monitoring, manometry, barium swallow, upper gastrointestinal (GI) endoscopy, and esophageal transit scintigraphy (ETS). The last technique is an old and reliable methodology,[4] with the ability to assess the motor function of the esophagus and its emptying activity (EA).[3]

Despite providing objective information on measuring reflux, esophageal motility, or morphology, all the mentioned techniques are invasive or use radiation; thus, they are not applicable for monitoring the esophageal involvement and symptoms at each follow-up visit. Therefore, patient-reported outcomes have been developed for guiding patient care for GERD management.[5] They also have the potential to be more practical and cost-effective outcome measures for randomized, placebo-controlled clinical studies.[5] Within this group, the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0) instrument is a self-report tool, with 7 multiitem scales measuring GI quality of life.[6]

With regard to the reflux scale, GIT 2.0 has been shown to be sensitive to change following therapeutic intervention in a recent multicenter study.[5] Association of the GIT 2.0 reflux scale with objective tests such as manometry, barium swallow, and upper GI endoscopy has been investigated in previous studies, showing its complementary value as a tool for objective measurement of esophageal involvement,[7,8] whereas no data are available with ETS.

The aim of this study was to evaluate patient-reported GI symptoms by GIT 2.0 in patients with SSc undergoing ETS and to correlate the findings.

METHODS

Patients. Inclusion criteria were subjects admitted for the first time to the inpatient rheumatology clinic of San Carlo Hospital (Potenza, Italy) from September 1, 2017, to December 31, 2019, for suspected or confirmed diagnosis of SSc, who underwent ETS for the assessment of internal organ involvement. All patients fulfilled the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc.[9] The study was conducted according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of Basilicata (n. 705/2017). Informed consent was obtained from all patients. Clinical data were collected during admission and included a wide set of variables, as previously described.[10]

Questionnaires. All participants were invited to fill the Italian version[11] of GIT 2.0 and the Health Assessment Questionnaire (HAQ)[12] with the 5 SSc-related visual analog scales (VAS).[13]

The GIT 2.0 includes 34 items with 7 multiitem scales (reflux, distention/bloating, fecal soilage, diarrhea, social functioning, emotional well-being, and constipation).[6] All scales are scored 0.00–3.00, except diarrhea and constipation (0.00–2.00 and 0.00–2.50, respectively). The total GIT 2.0 score averages 6 of 7 scales (excluding constipation) and is scored from 0 (no GI problems) to 2.83 (most severe).[14] The GIT 2.0 was found to have acceptable validity in different observational studies.[5,7,14–18]

The HAQ is a self-report questionnaire, scored 0.00–3.00,[15] and extended to form the Scleroderma HAQ (SHAQ) that incorporates the pain VAS and 5 SSc-related 0–100 VAS (intestinal problems, breathing, Raynaud phenomenon, finger ulcers, and overall disease severity from the patient's perspective).[13]

ETS. Patients undergoing ETS were requested to fast for at least 4 hours. The test consisted of swallowing a small amount of radiotracer (technetium-99m-labeled liquid), followed by immediate image acquisition by a gamma camera. ETS was performed in an upright position. Data were analyzed using standard nuclear medicine software for generating time/activity curves from dynamic studies. Regions of interest were drawn for the upper, middle, and lower thirds of the esophagus. Time/activity curves derived from the middle and distal thirds were evaluated and interpreted by a nuclear medicine physician. Qualitatively, the esophageal transit was classified as normal or delayed. Quantitatively, the EA was considered abnormal if < 90% of bolus was cleared in 10 seconds, and the percentage number of the EA (0–100%) was calculated.

Statistics. Continuous variables were expressed as mean and SD (if normally distributed), and as median and IQR (if not normally distributed); categorical data were expressed as number and percentage. Unpaired *t* test and ANOVA test or 2-tailed Mann-Whitney and Kruskall-Wallis tests were used for comparison between 2 or more groups, respectively. Bonferroni and Dunn tests were used for multiple comparisons. Parametric and nonparametric correlations were calculated using Pearson and Spearman rank correlation tests, respectively. Statistical analysis was performed using GraphPad Prism 7.0 (GraphPad Software).

RESULTS

Of all the patients with SSc admitted from September 1, 2017, to December 31, 2019, to our inpatient clinic, 31 underwent ETS. Clinical features, reported symptoms, and GIT 2.0 scores are shown in Table 1. Twenty-seven patients were female; 3 patients had sine scleroderma, 19 had limited cutaneous, and 9 had diffuse cutaneous SSc. At the time of admission, 24 (77.4%) patients were on proton pump inhibitors and 6 (19.4%) on prokinetic therapy. There were 26 of 31 (84%) patients who had a delayed esophageal transit and an abnormal esophageal EA. Overall, EA of the 31 patients ranged from 24% to 94%, with a mean (SD) of 68.6% (19.5). Sixteen (51.6%) patients had none to mild (0.00–0.49), 6 (19.4%) moderate (0.50–1.00), and 9 (29%) severe to very severe (1.01–3.00) GIT 2.0 reflux scores.[7] The mean EA was significantly different across those 3 groups of reflux score ($P = 0.0004$). Multiple comparison test showed that the significance was due to difference in none to mild vs other groups; specifically, mean (SD) EA was higher in patients with none to mild (81.1 [11.5]) than in those with moderate (55.7 [17.8], $P = 0.003$) and severe to very severe (55.8 [19.7], $P = 0.002$) reflux scores (Figure 1A). The 26 (84%) SSc patients with delayed esophageal transit had higher mean (SD) GIT 2.0 reflux score than the remaining 5 (16%) patients (0.9 [0.8] vs 0.1 [0.2], $P = 0.04$; Figure 1B).

EA negatively correlated with the GIT 2.0 reflux score ($r = -0.68$, $P < 0.0001$; Figure 1C), but it did not correlate with the other GIT 2.0 scales and the total GIT 2.0 score. Subanalysis showed that total GIT 2.0 score significantly correlated with HAQ ($r = 0.44$, $P = 0.014$) and VAS-GI ($r = 0.47$, $P = 0.007$), whereas GIT 2.0 reflux score correlated with HAQ ($r = 0.51$, $P = 0.004$) but did not correlate with VAS-GI. Both GIT 2.0 total and reflux scores did not correlate with VAS dyspnea.

Table 1. Clinical characteristics of the patients with SSc.

	Values
Sex, M/F	4/27
Age, yrs, mean (SD)	53.5 (13.6)
White ethnicity, n (%)	31 (100)
Clinical subset (sine scl/lcSSc/dcSSc), n	3/19/9
Disease duration, yrs, mean (SD)	7.7 (7)
ANA, n (%)	31 (100)
ACA, n (%)	10 (32.3)
ATA, n (%)	12 (38.7)
Anti-Th/To, n (%)	2 (6.5)
Anti-Pm/Scl, n (%)	1 (3.2)
Anti-U1-RNP, n (%)	1 (3.2)
mRSS, median (IQR)	3 (0–9)
Reported symptoms, n (%)	
Esophageal (reflux, dysphagia)	20 (64.5)
Gastric (early satiety, vomiting)	7 (22.6)
Intestinal (bloating, diarrhea, constipation)	15 (48.4)
Dyspnea	10 (32.3)
GIT 2.0 scales, mean (SD)	
Reflux	0.74 (0.76)
Distention/bloating	0.77 (0.65)
Fecal soiling	0.45 (0.85)
Diarrhea	0.49 (0.59)
Social functioning	0.39 (0.53)
Emotional well-being	0.45 (0.71)
Constipation	0.48 (0.57)
Total score	0.55 (0.5)
FVC% predicted, mean (SD)	89.5 (17.7)
DLCO% predicted, mean (SD)	74.1 (14.3)
Chest HRCT, n (%)	
Normal	13 (41.9)
Ground glass opacity	10 (32.3)
Fibrosis	10 (32.3)
PPI, n (%)	24 (77.4)
Prokinetics, n (%)	6 (19.4)
Immunosuppressive therapy, n (%)	11 (35.5)

ACA: anticentromere antibody; ANA: antinuclear antibody; ATA: antitopoisomerase I antibody; dcSSc: diffuse cutaneous systemic sclerosis; DLCO: diffusing lung capacity for carbon monoxide; FVC: forced vital capacity; HRCT: high-resolution computed tomography; lcSSc: limited cutaneous systemic sclerosis; mRSS: modified Rodnan skin score; PPI: proton pump inhibitors; scl: scleroderma; sine scl: sine scleroderma; SSc: systemic sclerosis; UCLA GIT 2.0: University of California Los Angeles Gastrointestinal Tract 2.0 instrument.

DISCUSSION

GI involvement is one the main causes of morbidity in SSc and the GIT 2.0 is a validated instrument to capture its symptoms and effects on social and mental well-being in SSc. Our current analysis shows that the GIT 2.0 reflux scale is valid in those with impaired ETS.

The prevalence of esophageal transit abnormalities was 84% in our patients with SSc; this is in line with results of previous studies ranging from 77 to 100%, despite methodological differences in the scintigraphy results evaluation.[19,20]

Previous studies assessed the associations between esophageal symptom (i.e., reflux) and other objective upper GI tools. In 55 patients with SSc enrolled at 2 centers, Bae, *et al* compared the GIT 2.0 reflux scale with upper GI endoscopy (n = 36), esophageal manometry (n = 30), and barium swallow (n = 22).[7] The reflux scale had moderate correlations with GI endoscopy (r = 0.46, P = 0.01) and esophageal manometry evaluations (r = 0.51 and 0.48 for decreased peristalsis and LES pressure, respectively; P = 0.01 for both). No correlation was found with barium swallow; however, patients with dysmotility or GERD on barium swallow had higher mean (SD) reflux score than those with a normal barium swallow (0.93 [0.69] vs 0.77 [0.46], P = not significant).[7]

Another study explored the association between high resolution manometry findings and GIT 2.0 in 40 Egyptian patients with SSc.[8] Distal esophageal amplitude and LES resting pressure negatively correlated with reflux score (r = −0.64, P = 0.001 and r = −0.46, P = 0.019, respectively) and total GIT score (r = −0.54, P = 0.007 and r = −0.42, P = 0.03, respectively). LES resting pressure had negative correlations with diarrhea score (r = −0.062, P = 0.002).[8]

In the present study, the lack of correlation with GIT 2.0 total score may be related to the composite nature of the score capturing overall GI disease aspects. Thus, the results of our study on ETS were *a priori* expected to correlate mostly with reflux scale of GIT 2.0.

The limitations of this study include the low number of patients analyzed. This was related to the nature of the study as it was conducted in clinical care, where ETS is not routinely done in all patients with SSc admitted to the inpatient clinic. Further, there was a high prevalence of antitopoisomerase I–positive patients, related to the fact that inpatient clinic admission is planned based on physician judgment of known or suspected specific organ involvements related to SSc. Also, some patients were receiving symptomatic treatment that might have influenced the reported symptoms. Additionally, because of its clinical nature, our study did not have a control group; thus, we are unable to comment on the screening ability for esophageal dysmotility in patients with SSc.

In conclusion, the results of our study confirm the association, previously found with other upper GI tools, of GIT 2.0 reflux scale with ETS. The GIT 2.0 reflux scale is a complementary tool for objective measurement of esophageal involvement and can be easily administered in day-to-day clinical assessment.

REFERENCES

1. Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. J Scleroderma Relat Disord 2017; 2:137-52.
2. Sjogren RW. Gastrointestinal motility disorders in scleroderma. Arthritis Rheum 1994;37:1265-82.
3. Vischio J, Saeed F, Karimeddini M, Mubashir A, Feinn R, Caldito G, et al. Progression of esophageal dysmotility in systemic sclerosis. J Rheumatol 2012;39:986-91.
4. Ziessman HA. Gastrointestinal transit assessment: role of scintigraphy: where are we now? Where are we going? Curr Treat Options Gastroenterol 2016;14:452-60.
5. McMahan ZH, Frech T, Berrocal V, Lim D, Bruni C, Matucci-Cerinic M, et al. Longitudinal assessment of

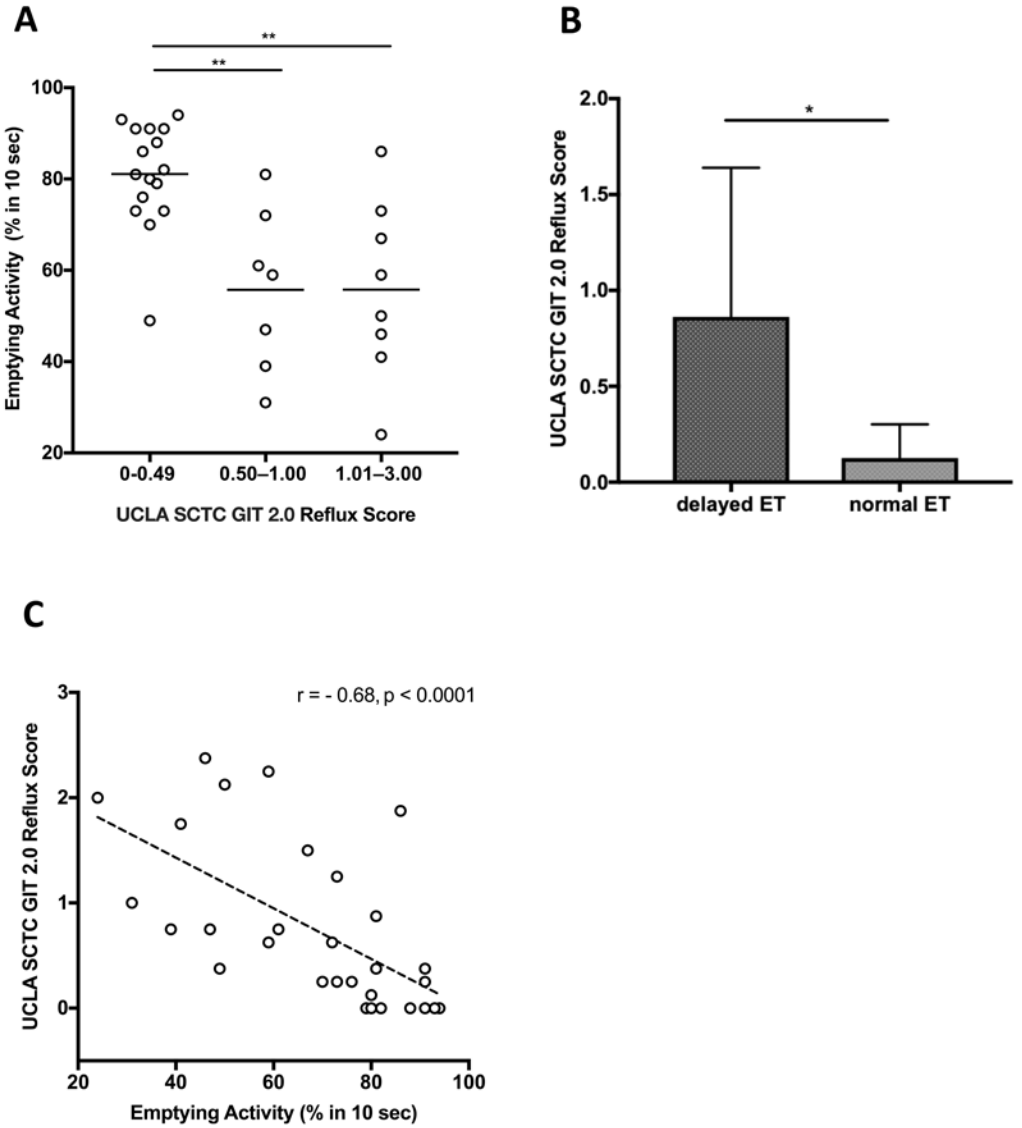

Figure 1. (A) Comparison of the esophageal EA across the 3 groups of patients classified based on none to mild (0.00–0.49), moderate (0.50–1.00), and severe to very severe (1.01–3.00) GIT 2.0 reflux score. The esophageal EA is expressed as percentage after 10 s from swallowing a small amount of radiotracer. ** $P < 0.01$. (B) Comparison of UCLA SCTC GIT 2.0 reflux score between SSc patients with delayed ET and those with normal transit as assessed by esophageal scintigraphy. * $P < 0.05$. (C) Negative significant correlation between percentage of esophageal EA and UCLA SCTC GIT 2.0 reflux score. EA: emptying activity; ET: esophageal transit; SSc: systemic sclerosis; UCLA SCTC GIT 2.0: University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 instrument.

patient-reported outcome measures in systemic sclerosis patients with gastroesophageal reflux disease - Scleroderma Clinical Trials Consortium. J Rheumatol 2019;46:78-84.
6. Khanna D, Hays RD, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Arthritis Rheum 2009;61:1257-63.
7. Bae S, Allanore Y, Furst DE, Bodukam V, Coustet B, Morgaceva O, et al. Associations between a scleroderma-specific gastrointestinal instrument and objective tests of upper gastrointestinal involvements in systemic sclerosis. Clin Exp Rheumatol 2013;2 Suppl 76:57-63.
8. Abozaid HSM, Imam HMK, Abdelaziz MM, El-Hammady DH, Fathi NA, Furst DE. High-resolution manometry compared with the University of California, Los Angeles Scleroderma Clinical Trials Consortium GIT 2.0 in systemic sclerosis. Semin Arthritis Rheum 2017;47:403-8.
9. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747-55.
10. Abignano G, Cuomo G, Buch MH, Rosenberg WM, Valentini G, Emery P, et al. The enhanced liver fibrosis test: a clinical grade, validated serum test, biomarker of overall fibrosis in systemic sclerosis. Ann Rheum Dis 2014;73:420-7.
11. Gualtierotti R, Ingegnoli F, Two R, Meroni PL, Khanna D, Adorni G, et al; VERITAS study group. Reliability and validity of the Italian version of the UCLA Scleroderma Clinical Trial Consortium

Gastrointestinal Tract Instrument in patients with systemic sclerosis. Clin Exp Rheumatol 2015;33:S55-60.
12. La Montagna G, Cuomo G, Chiarolanza I, Ruocco L, Valentini G. [HAQ-DI Italian version in systemic sclerosis.] [Article in Italian] Reumatismo 2006;58:112-5.
13. Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997;40:1984-91.
14. Khanna D, Nagaraja V, Gladue H, Chey W, Pimentel M, Frech T. Measuring response in the gastrointestinal tract in systemic sclerosis. Curr Opin Rheumatol 2013;25:700-6.
15. Pope J. Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). Arthritis Care Res 2011;63 Suppl 11:S98-111.
16. Khanna D, Furst DE, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Minimally important differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. J Rheumatol 2011;38:1920-4.
17. Bae S, Allanore Y, Coustet B, Maranian P, Khanna D. Development and validation of French version of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Clin Exp Rheumatol 2011;2 Suppl 65: S15-21.
18. Baron M, Hudson M, Steele R, Lo E. Canadian Scleroderma Research Group. Validation of the UCLA Scleroderma Clinical Trial Gastrointestinal Tract Instrument version 2.0 for systemic sclerosis. J Rheumatol 2011;38:1925-30.
19. Pitrez EH, Bredemeier M, Xavier RM, Capobianco KG, Restelli VG, Vieira MV, et al. Oesophageal dysmotility in systemic sclerosis: comparison of HRCT and scintigraphy. Br J Radiol 2006; 79:719-24.
20. Kaye SA, Siraj QH, Agnew J, Hilson A, Black CM. Detection of early asymptomatic esophageal dysfunction in systemic sclerosis using a new scintigraphic grading method. J Rheumatol 1996;23:297–301.