Profile of gastrointestinal involvement in patients with systemic sclerosis

Schmeiser, T ; Saar, P ; Jin, D ; Noethe, M ; Müller, A ; Soydan, N ; Hardt, P D ; Jaeger, C ; Distler, O ; Roeb, E ; Bretzel, R G ; Müller-Ladner, U

Abstract: Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease. Of the numerous organ manifestations, involvement of the upper and lower gastrointestinal tract (GIT) appears to be the most frequent with regard to the clinical symptoms. However, as the frequency and clinical relevance of GI involvement in patients with SSc are not known in detail, the German network of the systemic sclerosis (DNSS) has developed a detailed questionnaire to evaluate the extent and profile of gastrointestinal involvement in SSc patients. The multi-symptom questionnaire was used at baseline and after 1 year in registered patients of the DNSS. In addition, the results were compared with gastrointestinal disorders in patients with SSc and other rheumatic diseases, as well as with the medical history of the patients. In total, 90 patients were included in the study. The results of the study show that in reality, a much higher (nearly all) percentage of (98,9%) patients than expected suffer from GI-symptoms, regardless of the stage of their disease. Of these, meteorism (87,8%) was the most common followed by coughing/sore voice (77,8%), heartburn (daytime 68,9%, nighttime 53,3%), diarrhea (67,8%), stomach ache (68,9%) and nausea (61,1%). Although SSc patients were treated according to the respective recommendations, only limited improvements with regard to GI-symptoms could be achieved after 1 year of follow-up. In addition, the study revealed that the multi-symptom questionnaire is a useful tool to contribute to identify the gastrointestinal sequelae in systemic sclerosis.

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Corresponding Author: Tim Schmeiser

Corresponding Author's Institution: Kerckhoff-Klinik Bad Nauheim

First Author: Tim Schmeiser

Order of Authors: Tim Schmeiser;Petra Saar;Daniela Jin;Matthias Noethe;Adelheid Müller;Nedim Soydan;Clemens Jaeger;Philip D. Hardt;Oliver Distler;Elke Roeb;Rheinhard G. Bretzel;Ulf Müller-Ladner

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[1] Department of Rheumatology and Immunology, Kerckhoff-Clinic Bad Nauheim
[2] Department of Cardiology, Clinic of Hanau
[3] Department of Internal Medicine and Rheumatology, Justus-Liebig-University Gießen
[4] Department of Endocrinology and Gastroenterology, Justus-Liebig-University Gießen
[5] Department of Internal Medicine, University Regensburg
[6] Department of Internal Medicine, Main Taunus Clinic Bad Soden
[7] Department of Rheumatology and Institute of Physical Medicine, University Hospital Zürich, Switzerland
[8] Department of Pneumology and Gastroenterology, Justus-Liebig-University Gießen


Tim Schmeiser
Department for Rheumatology and
Immunology Kerckhoff- Clinic Bad Nauheim
Benekestr. 2- 8
61231 Bad Nauheim
+49-6032- 9960
t.schmeiser@kerckhoff-klinik.de

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[1] Department of Rheumatology and Immunology, Kerckhoff-Clinic Bad Nauheim
[2] Department of Cardiology, Clinic of Hanau
[3] Department of Internal Medicine and Rheumatology, Justus-Liebig-University Gießen
[4] Department of Endocrinology and Gastroenterology, Justus-Liebig-University Gießen
[5] Department of Internal Medicine, University Regensburg
[6] Department of Internal Medicine, Main Taunus Clinic Bad Soden
[7] Department of Rheumatology and Institute of Physical Medicine, University Hospital Zürich, Switzerland
[8] Department of Pneumology and Gastroenterology, Justus-Liebig-University Gießen

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Methods: The multi- symptom questionnaire was used at baseline and after one year in registered patients of the DNSS. In addition the results were compared with gastrointestinal disorders in patients with SSc and other rheumatic diseases, as well as with the medical history of the patients. In total, 90 patients were included in the study.

Results: The results of the study show that in reality a much higher (nearly all) percentage of (98,9%) patients than expected suffer from GI- symptoms, regardless of the stage of their disease. Of these, meteorism (87,8%) was the most common followed by coughing/ sore voice (77,8%), heartburn (daytime 68,9%, nighttime 53,3%), diarrhea (67,8%), stomach ache (68,9%) and nausea (61,1%).

Conclusions: Although SSc patients were treated according to the respective recommendations, only limited improvements with regard to GI- symptoms could be achieved after one year of follow up. In addition, the study revealed that the multi- symptom questionnaire is a useful tool to contribute to identify the gastrointestinal sequelae in systemic sclerosis.

Introduction

Systemic sclerosis (SSc) is a generalised chronic autoimmune connective tissue disease with a prevalence of about 20:100.000. Females are affected 4.6 times more than males [1]. The pathophysiology of SSc, especially of the GIT, is known only to a limited extent. This idea is not only based on clinical experience but on the only slowly increasing knowledge of pathways leading to increased fibrosis, altered regulation of microcirculation as well as of humoral and cellular changes similar to the alterations observed in SSc skin [2,3]. Clinically, SSc can present as diffuse (skin thickening proximal of the elbow and knee) and limited (skin thickening restricted to areas distal of elbow and knee) disease.

In literature, the Raynaud- phenomenon and skin thickening are the most common and prominent characteristics in patients with SSc, but some data [4] supported also the hypothesis that involvement of the GI- tract might be more frequent than expected. Fibrotic changes due to increased deposition of collagen and other extracellular matrix components in the upper and lower GIT lead to dysmotility, malabsorption, malnutrition and dilation of the intestine. Main symptoms are meteorism, dysmotility of the esophagus, heartburn and dysphagia. In addition coughing and a sore voice can occur. Furthermore, constipation and diarrhea have been reported. In severe cases, gastrointestinal manifestations can result in lethal complications such as pseodoobstruction similar to severe cardiopulmonary or renal involvement. Therefore, the aim of the study was to elucidate a detailed profile of gastrointestinal involvement in patients with SSc using a newly designed questionnaire.

Methods and Patients

Based on the research plan of the German network for systemic sclerosis (DNSS), we developed a multi- symptom questionnaire which consisted of 12 main items (symptoms) addressing the activity and frequency of known and potential GI- symptoms. Each of these items was subdivided in time and frequency (scaled in continuously, daily, several times, a few days in the month, rare, never [Figure 1]).

Another subitem was the consumption of alcohol and tobacco.

Patients with the clinical diagnosis of SSc with regard to the classification criteria of the American College of Rheumatology [5] or MCTD [6] were included into the study.

SSc patients were subclassified into the group of diffuse cutaneous SSc (dcSSc), of limited cutaneous SSc (lcSSc) and of mixed connective tissue disease (MCTD) patients with dominant SSc features. In addition, the patients had to be able to understand and answer the questionnaire completely. The

recruitment period was between 2005- 2007 and to illustrate a real- life situation, the inclusion of patients was based on patient- need and not on order or patients- call. 90 patients, 75 females and 15 males, with a mean age of 57,4 years were included into the study. 55 patients with lcSSc, 16 with dcSSc, 16 with MCTD and 3 with an undifferentiated connective tissue disease (mixed connective tissue disease and undifferentiated – with allotments of systemic sclerosis) could be enclosed.
Until present, 34 patients could be included in the follow up after one year. Of these 31 female patients (91,2%) and 3 males (8,8%) were included with a mean age of 55,6 years. 4 patients suffered from a diffuse and 19 from the limited subtype of SSc. Enclosed were also 8 patients with a mixed connective tissue disease (MCTD) and 3 with an undifferentiated connective tissue disease. For the comparison with the 34 SSc follow up patients, 34 patients with another inflammatory rheumatic disease such as rheumatoid arthritis, systemic lupus erythematosus and psoriatic arthritis were included. 82,4% of these patients with another rheumatologic disease were female and 17,6% male. The patients that were enrolled in the control group had a mean age of 60,9 years.

Results

Gastrointestinal involvement in patients with SSc

Although earlier investigations had reported that GI- symptoms are a significant problem for patients with SSc, the results of our study indicate that when examining GI- symptoms on a detailed basis nearly all of these patients with SSc suffer from GI- symptoms. When applying the multi- symptom questionnaire to these patients (83,3% were female and the mean age was 57,4 years) 98,9% reported to suffer from any kind of gastrointestinal complications. Only one SSc patient (1,1%) did not report any gastrointestinal symptom. Nutritive effects did not appear to contribute significantly to this high frequency of GI- symptoms as only 15 patients consumed alcohol occasionally and none regularly. Similarly, only 9 patients smoked on a regular basis, 5 occasionally.
The most frequent symptom of gastrointestinal involvement was meteorism (87,8%) followed by coughing/ sore voice (77,8%), heartburn (daytime 68,9%, nighttime 53,3%), diarrhea (67,8%), stomach ache (68,9%) and nausea (61,1%). Almost every second patient (48,9%) suffered from constipation. Less frequent symptoms were vomiting (36,7%) and weight loss (27,8%). Fecal incontinence was reported by 22,2%. The main manifestations are summarized in Figure 2.

Differences in GI- symptoms in patients with limited SSc, diffuse SSc and MCTD

When evaluating the different SSc subsets, distinct differences could be revealed (Figure 3). The most frequent and prominent symptoms in patients with dcSSc were meteorism (80,0%), daytime heartburn

(80,0%), coughing/ sore voice (80,0%) and stomach ache (80,0%). Nighttime heartburn (73,3%), diarrhea (73,3%) and nausea (60,0%) were reported also very often. Less frequent symptoms were constipation (46,7%), vomiting (33,3%), weight loss <=9 kg (26,7%) and fecal incontinence (13,3 %).

Most interestingly, symptoms originating from the upper GI were named less frequently by patients with lcSSc than patients with dcSSc. The most prominent differences between dcSSc and lcSSc were nighttime heartburn (-24,2%), daytime heartburn (-14,5%) and stomach ache (-14,5%). Also diarrhea (-6,0%) was reported less frequent from patients with lcSSc. In contrast, fecal incontinence and (+14,0%) meteorism (+7,3%) were reported more frequently by patients with lcSSc.
No differences between the SSc subsets could be found for coughing/ sore voice (-1,8%), nausea (-1,8%), vomiting (+3,1%), constipation (+4,2%) and weight loss <=9 kg (+4,2%).
The frequency of distinct symptoms of the upper GIT appeared also to be more similar between dcSSc and MCTD. In patients with MCTD, daytime heartburn (+1,3%) and coughing/ sore voice (+1,3%) were named as frequent as in dcSSC patients. No differences for the lower GIT could be found for: fecal incontinence (-0,8%), diarrhea (+1,7%), constipation (+3,3%) and weight loss <= 9kg (+4,6%).
In contrast, differences were reported for meteorism (+13,8%), nighttime heartburn (-10,8%), vomiting (+10,5%), nausea (+8,8%) and stomach ache (-5,0%).

Follow up of gastrointestinal involvement after one year

As it could be expected that evaluation and adequate treatment of GI- symptoms by a rheumatologist and/ or gastroenterologist might result in an alteration and/ or improvement of GI- symptoms, the SSc patients were re- evaluated on a routine basis after one year. The results of the baseline visit and the data of the follow up visit could be evaluated for 34 patients until present as shown in Figure 4. When compared to the initial examination, the profile of the patients was similar and only 3 were still consuming tobacco regularly and 1 occasionally. The patient without any symptoms at the baseline visit did not present again in the outpatient clinic. Interestingly another patient with GI-disorders in the first year did report no GI-symptoms in the follow up visit any more.
The most prominent changes (Table 1) in the pattern of GI- symptoms after one year of follow up were the decrease in nausea (-14,7%) and nighttime heartburn (-11,8%), followed by a decrease of weight loss (-8,4%), daytime heartburn (-5,9%), vomiting (-5,9%) and coughing/ sore voice (-5,9%).

Disorders	baseline visit (%)	Change rate*	follow up visit (%)
Meteorism	**82,4**	+	**88,2**
Coughing/ sore voice	**82,4**	-	**76,5**
Diarrhea	**79,4**	~	**79,4**
Stomach ache	**73,5**	~	**76,5**
Heartburn (day)	**73,5**	-	**67,6**
Nausea	**67,6**	--	**52,9**
Heartburn (night)	**61,8**	--	**50**
Constipation	**50**	++	**67,6**
Vomiting	**44,1**	-	**38,2**
Weight loss <=9 kg	**29**	-	**20,6**
Fecal incontinence	**23,5**	~	**23,5**
Treatment with PPI	**82,4**	~	**84,5**

* ~ = +/- 5%
+/- = +/- 5-10%
++/-- = +/- >10%

Table 1 Results of baseline visit and follow up visit shown in percent (+/-).

In contrast, constipation (+17,6%) and meteorism (+5,8%) increased considerably. Without significant change were the frequency for diarrhea (0,0%) fecal incontinence (0,0%) and stomach ache (+3,0%). Of note, this development could not be associated with a change in reflux therapy as at baseline 82,4% of the patients received already a treatment with proton pump inhibitors (PPI) and at time of follow up 84,5% received this treatment.

Comparison of the DNSS questionnaire and medical history

Owing to the lower frequency of GI- symptoms in literature and our study, we also compared the differences between the medical history of the 90 patients performed by the respective physicians and the results of the questionnaire (Figure 5). Of note, gastrointestinal symptoms were documented much less frequently by physicians who evaluated the medical history on a routine basis, i.e. heartburn (49,4%), stomach ache (29,9%), nausea (9,2%), constipation (25,3%), diarrhoea (26,4%), meteorism (37,9%) and weight loss (18,4%) underlining the need for a more thorough GI- evaluation in daily routine clinical practice.

Differences in gastrointestinal involvement between SSc patients and patients with other rheumatic diseases

To evaluate whether GI- symptoms are of a more general nature in patients with rheumatic diseases versus being specific for SSc, we applied the questionnaire also to patients with other rheumatic diseases (Figure 6). The data (Table 2) show that patients with other rheumatic diseases also suffer

from gastrointestinal disorders. They also reported some symptoms with a similar frequency: meteorism (79,4%), diarrhea (79,4%), constipation (55,9%) and fecal incontinence (23,5%).

Disorders	SSc baseline (%)	Change rate*	Patients with other rheumatic diseases (%)
Meteorism	82,4	~	79,4
Coughing/ sore voice	82,4	-	73,5
Diarrhoea	79,4	~	79,4
Stomach ache	73,5	~	70,6
Heartburn (day)	73,5	--	55,9
Nausea	67,6	--	55,9
Heartburn (night)	61,8	--	32,4
Constipation	50	+	55,9
Vomiting	44,1	-	38,2
Weight loss <=9 kg	29	--	14,7
Fecal incontinence	23,5	~	23,5
Medical treatment	82,4	--	55,9

* ~ = +/- 5%
+/- = +/- 5-10%
++/-- = +/- >10%

Table 2: Patients with other rheumatic diseases

In contrast, symptoms associated with the upper GIT were noted less frequently in non- SSc rheumatologic patients than in patients with SSc with weight loss 14,7% being the most prominent difference followed by heartburn (daytime: 55,9%, nighttime: 32,4%), coughing/ sore voice 73,5%, stomach ache 70,6%, vomiting 38,2% and nausea 55,9%.
This spectrum of sequelae was not age and gender related as also 82% were female and the mean age of this group was 60,9 years.

Discussion

Although there have been several publications addressing the frequency and intensity of GI-symptoms in SSc patients, the most important result of the detailed evaluation by a disease- specific questionnaire is the much higher frequency (up to 99%) of GI- symptoms in a rheumatology GI- center setting.
As the frequency of GI involvement is very high - similar or even higher than others such as Raynaud-phenomenon and skin thickening - the data underline the need for a detailed GI evaluation early in the course of the disease, also because the involvement of the GIT in patients with SSc influences significantly the morbidity and mortality of these patients [7]. There is also a correlation between the

intensity of symptoms and their well being [8]. In contrast to the most published studies addressing gastrointestinal involvement [4, 8, 9], meteorism is the most frequent symptom (87,4%) in our cohort. But also coughing/ sore voice (77,0%) and heartburn (daytime 69,0%, nighttime 55,2%) were mentioned by patients with systemic sclerosis very often.

Cohen et al. [10] postulated a concept of the underlying pathomechanisms with regard to these symptoms: neural lesions may occur early and can cause an irreversible disruption of the esophageal motor function followed by development of significant smooth muscle atrophy. The associated reduced esophageal motility thereafter contributes to gastroesophageal reflux [11], heartburn, esophageal strictures, sore throat and even continuous microaspiration followed by pneumonia. Whether this dysfunction might also lead to a bronchospasmic reaction, restrictive lung disease and a pulmonary fibrosis, is not known yet [12].

Of note, Weber et al. found that gastrointestinal symptoms do not always correlate with the results of GI examinations [13].

Our patients also reported frequently stomach ache (67,8%) and vomiting (60,9%). An explanation for the pathomechanism of gastric dysmotility that could lead to these symptoms was developed by Sjögren et al.: Replacement of normal smooth muscles by fibrous connective tissue based on vascular damage (grade 0), neurogenic impairment (grade 1) and finally myogenic dysfunction (grade 2) [12,14] have been suggested as underlying causes.

In a similar way, stomach dysmotility and dysfunction of the small intestine may be the underlying causes for gastroparesis, malnutrition and weight loss [12].

Recently, Czirjak et al. [9] described gastrointestinal tract- related lethal cases due to bleeding from watermelon stomach (gastric vascular ectasia), dysmotility and malabsorption. Another complication of vascular ectasia and incessant hemorrhages is chronic anemia and even death [15].

Our real- life SSc outpatient results of a very frequent involvement of the upper GIT differ also in some patients from the regression model of Chung et al. [15]. In their study esophageal dysfunction was not identified as a dominant symptom for SSc patients admitted to hospital or for those who died in hospital. They also reported that aspiration pneumonitis as a complication of esophageal dysfunction was more common. This leads to the assumption that the effects of esophageal dysmotility in SSc patients may be higher than estimated by the regression models. Similarly, there are distinct differences with regard to the involvement of the lower GIT when compared to other studies [8,14].

Almost every second patient (48,9%) reported to suffer from constipation in our questionnaire.

Usually this is based on dysmotility with a delayed colonic transit [16] and increased intestinal permeabilities [18] and a feeling of bloating and meteorism, which was also the most prominent symptom in our cohort (87,8%).

Impairment of the anorectum leads to symptoms such as fecal incontinence. According to the data obtained from our patients the prevalence (22,2%) of fecal incontinence is lower than expected. In this aspect our results are similar to those of the studies mentioned above [8,9].

However it needs to be considered that fecal incontinence might not have been mentioned by sensitive patients even if it existed as revealed by the questionnaire [11].
In summary the increase of fibrosis and the disturbed regulation of microcirculation as well as humoral and cellular changes is most likely the underlying cause for the impairment of the GIT in patients with systemic sclerosis [3].
After one year distinct alterations in symptoms could be observed. The most prominent changes could be found with regard to decrease of nausea (-14,7%) and nighttime heartburn (-11,8%). In contrast, symptoms such as constipation (+17,6%) and meteorism (+5,8%) were reported more frequently.
When comparing SSc subsets, distinct differences could be revealed. The majority of the symptoms listed in our questionnaire were reported with a higher frequency in patients with either dcSSc or MCTD in contrast to patients with lcSCC. Most prominent differences were found for nighttime heartburn (-24,2%), daytime heartburn (-14,5%) and stomach ache (-14,5%). The result of the comparison of the subsets points out that MCTD and dcSSc are more alike in development of GI-symptoms than lcSSc. In addition, Walker et al. [17] reported particular organ manifestations in the subsets of SSc which are associated with distinct clinical disorders. Nevertheless the data of our SSc patients illustrate the more diffuse/ systemic character of the dcSSc subset.
As recent studies [17,19] suggested that there might not be distinct differences between gastrointestinal disorders in the subtypes of connective tissue disease, our questionnaire revealed the few but distinct differences in the individual occurrence of symptoms between the subtypes, with nighttime heartburn being the most prominent [73,3% (dcSSc); 49,1% (lcSSC); 62,5% (MCTD)].

It needs to be noted that our study has some limitations due to the lack of a full- range comparison of the sequelae with technical procedures such as 24- pH monitoring, gastroesophageal endoscopy, radionuclide assays but in our experience in a routine setting the patients are more than hesitant to undergo all of these strenuous procedures if not urgently needed.

In summary this is the first study applying and evaluating a detailed GI- questionnaire on patients with SSc in Western Europe including a follow up reexamination.
Our results support the hypothesis that besides the well known Raynaud- phenomenon and skin thickening, gastrointestinal disorders in patients with SSc are more frequent than expected and their evaluation should be done at the first time of presentation of the patient. The results also illustrate the need for a detailed interview of the patient as standard medical records do not match the results of the questionnaire.
This may be based on the fact that patients (and physicians) often do not realize the correlation between the gastrointestinal symptoms and their autoimmune disease.
Therefore, the presented questionnaire is a useful tool to contribute to the timely evaluation of gastrointestinal involvement in systemic sclerosis and thereby to optimize life quality of patients.

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Figure legends:

Figure 1: Detailed multi- symptom questionnaire (Original in German, trade names of drugs according to the German market).

Figure 2: Gastrointestinal symptoms of SSc patients at time of first presentation. Drugs were taken by approximately 70% of these patients.

Figure 3: Differences in GI- disorders in patients that suffer from diffuse SSc, limited SSc and MCTD. Diffuse SSc patients received more frequent medication for those sequelae.

Figure 4: Gastrointestinal symptoms in patients with SSc after one year of follow up.

Figure 5: Comparison DNSS questionnaire and medical history

Figure 6: Comparison GI- disorders between SSc patients and patients with other rheumatic diseases

Figure
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Questionnaire

Expert Centre C4 Gastroenterology Giessen (Regensburg)

Gastrointestinal Involvement

Since when do you suffer from Raynauds phenomenon ?
(Coldness of the fingers, change in colour (white/ blue) _____ (month/ year)

Since when do you suffer from skin thickening? _____ (month/ year)

Since when are you treated for systemic sclerosis by your physician/rheumatologist ? _____ (month/ year)

Since when are you treated for gastrointestinal symptoms by your physician ? _____ (month/ year)

Since when are you suffering from symptoms in the gastrointestinal tract (esophagus, stomach, intestine, defecation, etc.)?

> 10 years ☐ 2-10 years ☐ 1-2 years ☐ 6-12 months ☐ 3-6 months ☐ less than 3 month ☐

How would you explain (in your own words) these symptoms?

_____

Do you smoke? ☐ yes ☐ occasionally (less than 2 cigarettes per day) ☐ no

Do you drink more than one bottle of beer or a glass of wine? ☐ yes ☐ occasionally ☐ no

How many calories do you eat/drink approximately every day? _____

How much weight did you loose or gain in the last 3 months?

increase in kg_____/ decrease in kg_____

your height _____(cm) your weight_____(kg)

How often do you suffer from....

Daytime heartburn	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Nighttime heartburn	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Coughing/ sore voice	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Stomach ache	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Nausea	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Vomiting	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Meteorism	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Diarrhea	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Fecal incontinence	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐
Constipation	continuously☐- daily☐- several times per week☐- a few days per month☐- rarely☐- never☐

Which drugs are used to treat your systemic sclerosis at present?

_____

_____

Which drugs were/are used to treat your gastrointestinal symptoms?

- Proton pump inhibitors (e.g.. Omep, Pantozol, Nexium) never☐- more than one year ago ☐ -in the last 12 months☐- currently☐
  This drug improved my symptoms.... yes☐ no☐ occasionally☐
- H2-Inhibitors (e.g.. Ranitidin) never☐- more than one year ago ☐ -in the last 12 months ☐- currently☐
  This drug improved my symptoms.... yes☐ no☐ occasionally☐
- Stomach protectors (e.g. Ulcogant,Riopan,Maalox) never☐- more than one year ago ☐ -in the last 12 months ☐- currently☐
  This drug improved my symptoms.... yes☐ no☐ occasionally☐
- Prokinetics (e.g. Paspertin, MCP) never☐- more than one year ago ☐ -in the last 12 months ☐- currently☐
  This drug improved my symptoms.... yes☐ no☐ occasionally☐
- Anticonstipation drugs (e.g.. Dulcolax, Bifiteral) never☐- more than one year ago ☐ - in the last 12 months ☐-currently☐
  This drug improved my symptoms.... yes☐ no☐ occasionally☐
- Antidiarrhea (e.g. Imodium) never☐- more than one year ago ☐ - in the last 12 months ☐-currently☐
  This drug improved my symptoms.... yes☐ no☐ occasionally☐
- Plant extracts (e.g._____) never☐- more than one year ago ☐ - in the last 12 months ☐-currently☐
  This drug improved my symptoms.... yes☐ no☐ occasionally☐
- Homoeopathics (e.g. _____) never☐- more than one year ago ☐ - in the last 12 months ☐-currently☐
  This drug improved my symptoms.... yes☐ no☐ occasionally☐
- Relaxation techniques (e.g. biofeedback,_____) never☐- more than one year ago ☐ -in the last 12 months ☐- currently☐
  This technique improved my symptoms.... yes☐ no☐ occasionally☐

Figure

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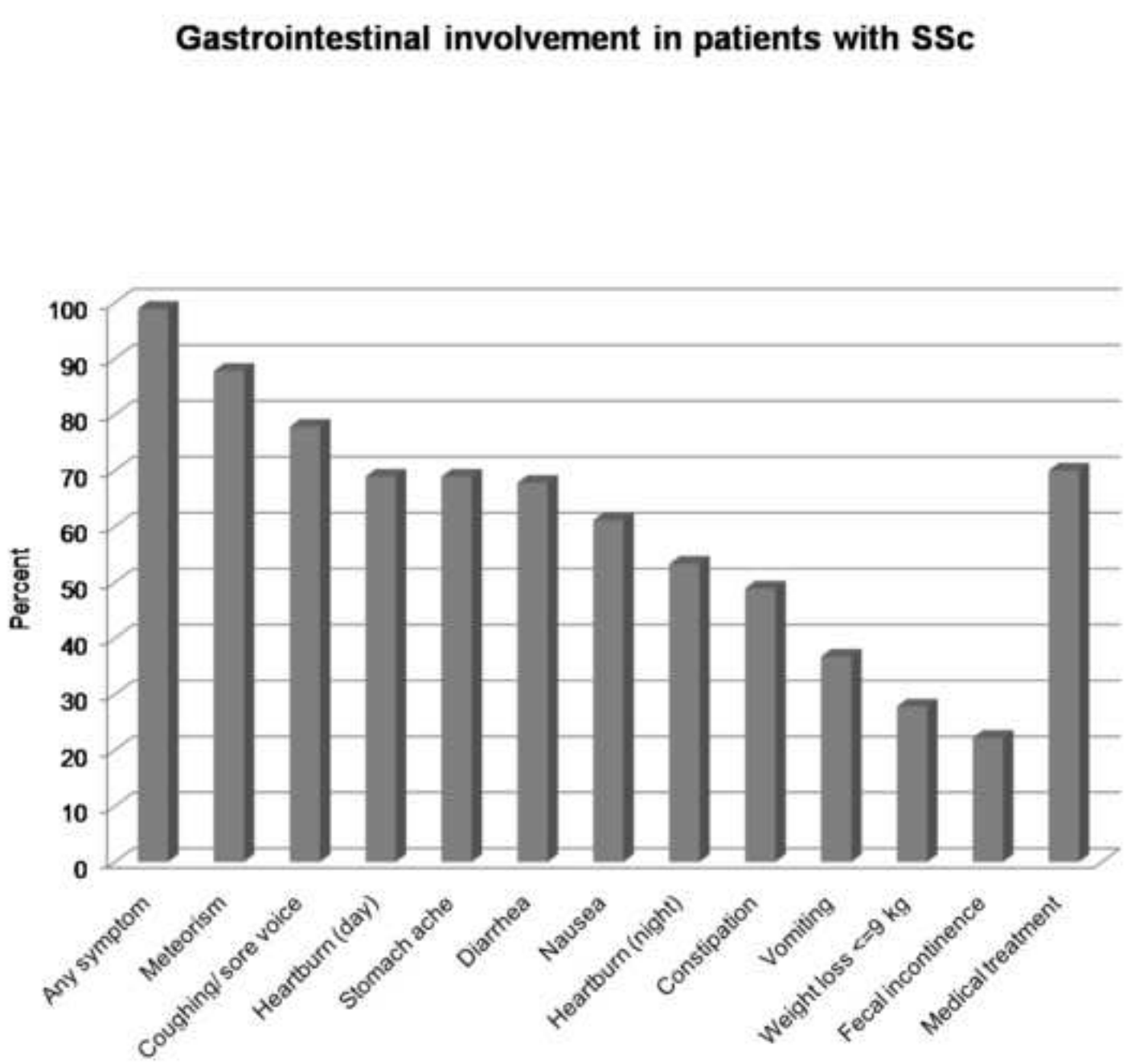

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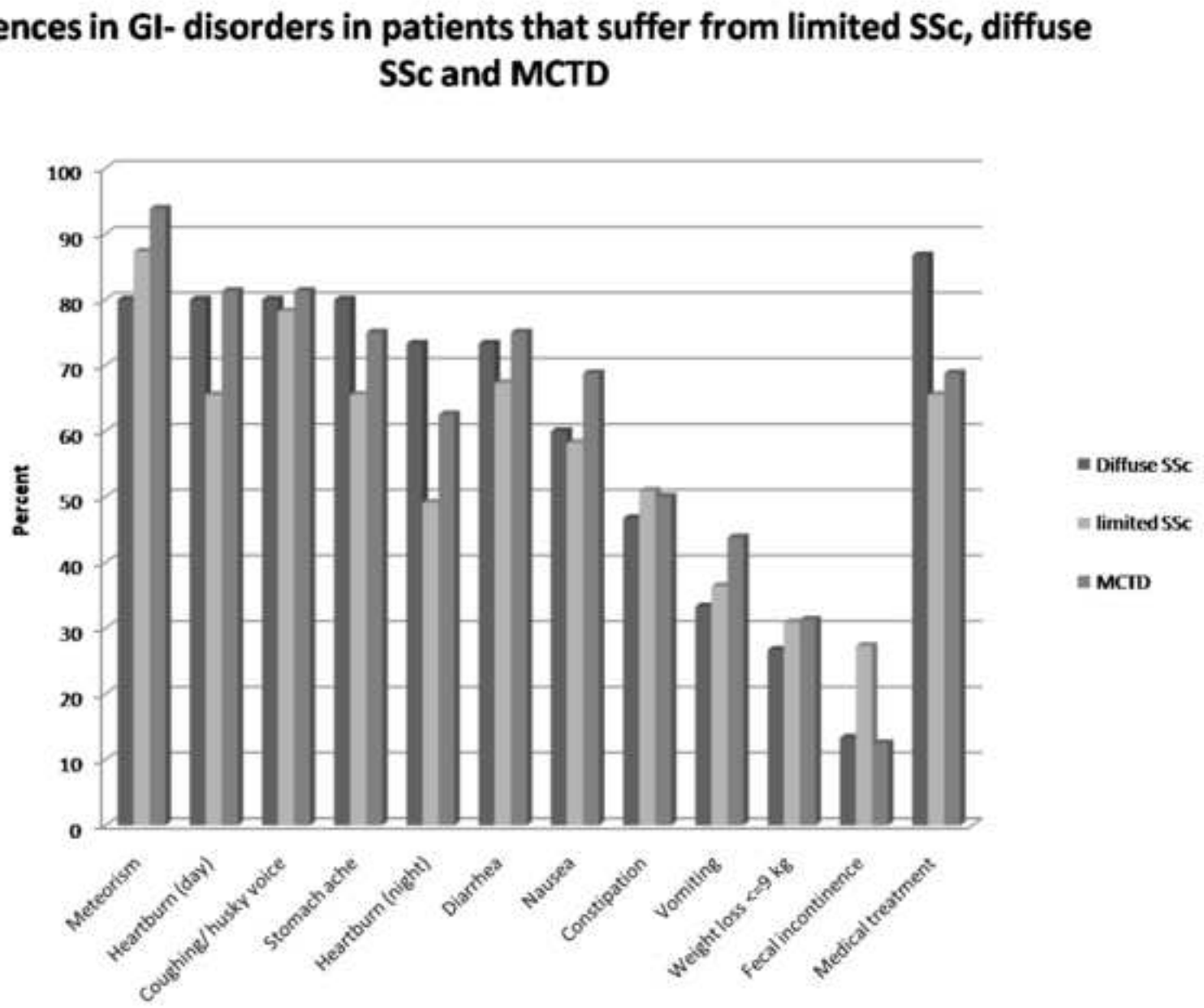

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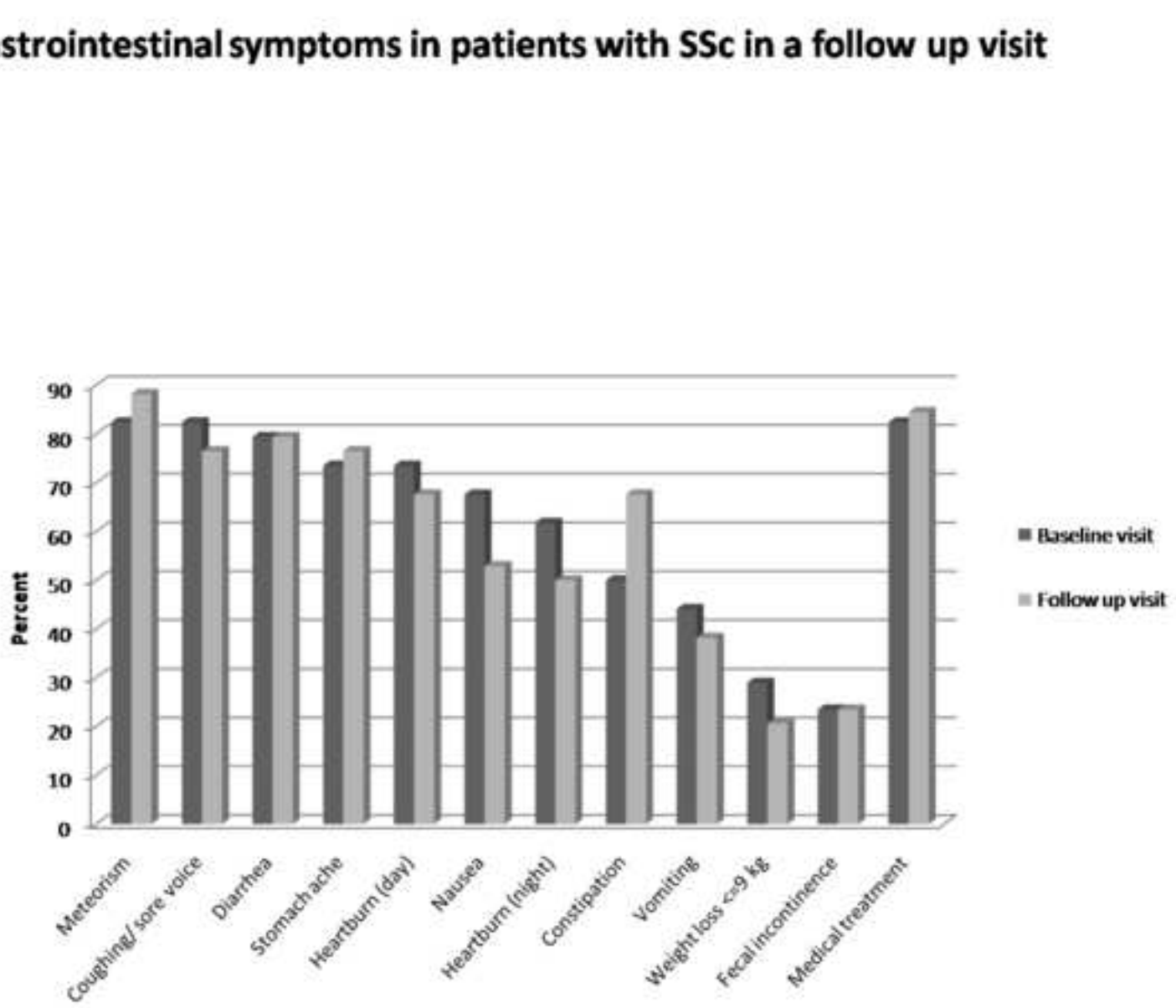

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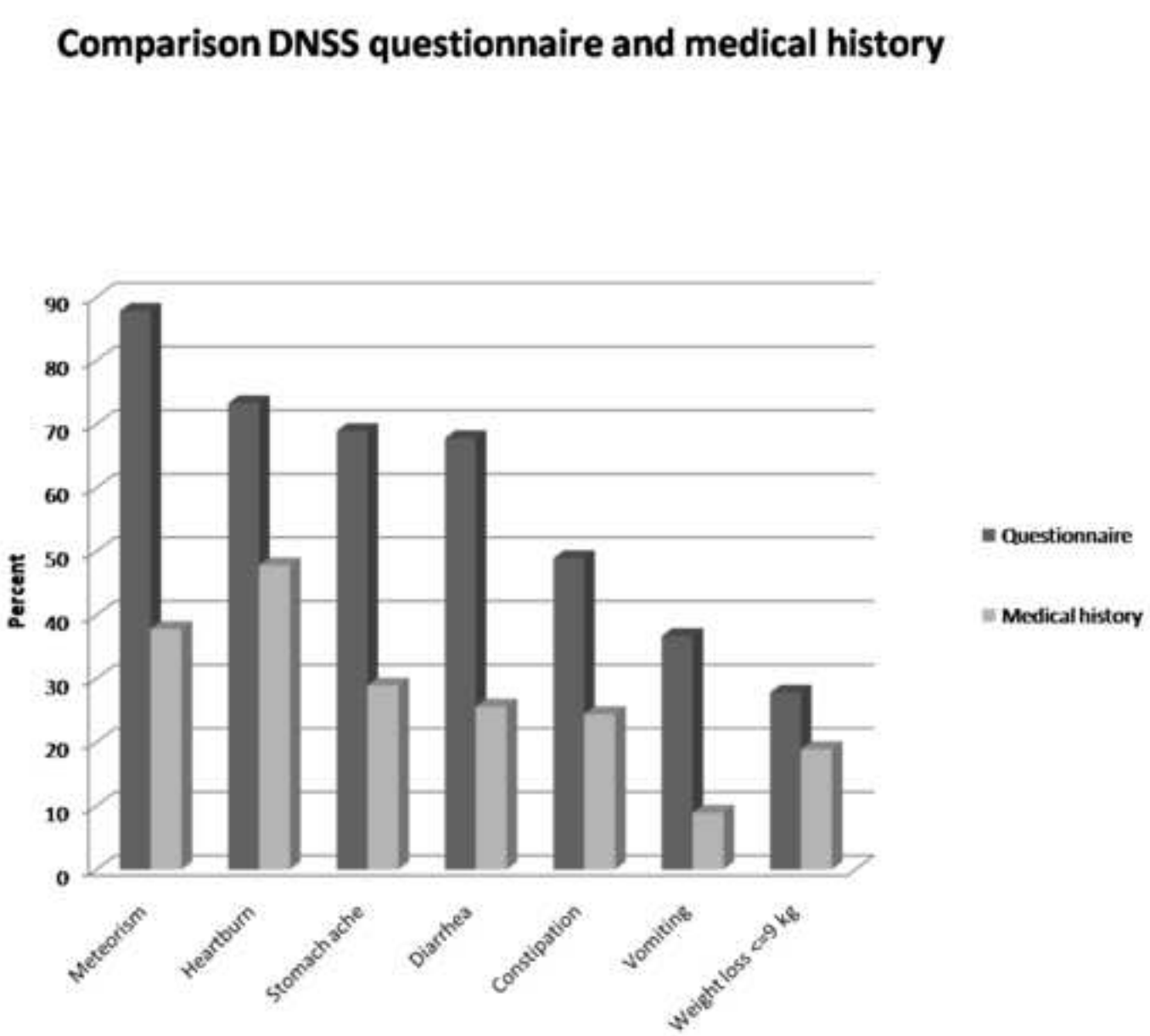

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