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Investigating the Correlation between Fecal Calprotectin and Gastrointestinal Involvement in Systemic Sclerosis Patients

Leila Azizi[1]*, Bahareh Ebrahimi[2], Mohammadali Nazarinia[3]

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Abstract

Background: Systemic sclerosis (SSc) is a systemic autoimmune disease that is associated with gastrointestinal involvement. Calprotectin, as a heterodimer protein (S100A8/S100A9), is a good marker for active inflammatory bowel disease; this marker is a non-invasive and reproducible test. It is believed that fecal calprotectin (FC) increases in several inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, and SSc. In this study, we tried to measure the correlation between gastrointestinal involvement and FC level in SSc patients.

Methods: This study is cross-sectional; 31 SSC patients were evaluated using the UCLA.SCTC 2.0, and then they were referred to the laboratory to assess their blood malnutrition biomarkers and stool sample to check FC. The quantitative data were analyzed using the T-test and the qualitative data using Chi-Square test.

Results: The mean (SD) was 50.8 (4.2) for age and 15.0 (8.3) for ESR. Assessing the malnutrition markers showed that all assessed factors were in the normal range; the range of FC was higher than that of normal people (10-60). There was no correlation between FC and malnutrition markers, but a significant relationship between FC level and gastrointestinal symptoms such as diarrhea (74%), Constipation (74%), and bloating and abdominal distension (87 %) was detected.

Conclusion: due to the high prevalence of gastrointestinal involvement in SSc patients, diagnosing gastrointestinal symptoms is an important step in ensuring patients' health. This study suggests that higher fecal calprotectin is an alarm for gastrointestinal involvement.

Keywords: Fecal Calprotectin, Gastrointestinal, Systemic Sclerosis

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Introduction

Systemic sclerosis (SSc) is a systemic inflammatory disorder affecting patients' different organs, particularly skin and gastrointestinal tract [1-4]. Gastrointestinal involvement occurs in up to 90% of patients with SSc, and GI dysfunction is a major cause of mortality and morbidity in them [4, 5].

In SSC, almost any part of the gastrointestinal system can be affected, which can be life-threatening in severe cases [4-6]. The lower gastrointestinal tract is commonly involved in SSC; bloating, abdominal distension, diarrhea, and constipation are its common complaints [7, 8]. According to the conducted studies, Small intestinal bacterial overgrowth (SIBO) can be seen in 40% of SSc patients. SIBO often presents with gastrointestinal symptoms such as bloating, nausea, abdominal pain, discomfort, and intermittent constipation [9, 10]; this disease diagnosis is based on jejunum aspirate and fluid culture with more than 100,000 colonies or hydrogen and methane breath test [11-13]. Usual tests are often invasive or expensive; for example, a colonoscopy is used to investigate lower gastrointestinal involvement, which is an invasive test and a hydrogen breath test, that used to investigate small intestinal bacterial overgrowth, is an expensive test [11-14]. Therefore, it is very beneficial to find a non-invasive and cost-effective

Corresponding author: Dr Leila Azizi, azizi.l@iums.ac.ir

1. Department of Rheumatology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
2. Shiraz Geriatric Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
3. Department of Internal Medicine, Division o Rheumatology, Geriatric Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

↑What is "already known" in this topic:
Fecal calprotectin (FC) increases in inflammatory bowel disease. Other researchers believed that FC increases in several inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, and Systemic sclerosis (SSc).

→What this article adds:
Due to the high prevalence of gastrointestinal involvement in SSc patients, diagnosing gastrointestinal symptoms is an important step in ensuring patients' health. Our study suggests that higher FC is an alarm for gastrointestinal involvement in SSc.

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method to evaluate gastrointestinal involvement, particularly SIBO in SSc patients.

Calprotectin, as a heterodimer protein (S100A8/S100A9), is mainly found in neutrophils, monocytes, and macrophages and stimulates the innate immune system [15, 16]. Studies have shown fecal calprotectin (FC) as a good marker for active inflammatory bowel disease; this marker is a non-invasive and reproducible test [17, 18]. The authors believe that FC increases in several inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, and SSc [15, 17, 19]. In this study, we tried to measure the correlation between gastrointestinal involvement and fecal calprotectin level in SSc patients.

Methods

This study is a cross-sectional study which was conducted at the Scleroderma clinic of Hafez Hospital, affiliated to Shiraz University of Medical Science, Iran. The study was conducted from December 2022 to January 2022. For assessing the patients' SSc, we used the 2013 ACR/EULAR classification criteria for Scleroderma [20].

At the beginning of the visit, with respect to inclusion and exclusion after filling out the informed consent form by patients, the cases diagnosed with scleroderma according to the ACR and EULAR classification of 2013, were diagnosed using the UCLA questionnaire. SCTC20 was evaluated, and the patients who were eligible for the study were referred to the laboratory. After obtaining informed consent from the patients, 10 ml blood samples were taken along with stool samples for calprotectin analysis.

Participants were randomly selected among patients who were referred to the rheumatology clinic of Hafez Hospital with a 95% confidence level to reach a significant difference, 80% test capacity, and considering SD=25, and according to the evidence in similar studies [21], 31 patients were selected and investigated in the study.

Inclusion criteria included all patients with systemic sclerosis who have gastrointestinal symptoms. But patients who were treated with non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), or antibiotic drugs were excluded; we also omitted patients with IBD, GI malignancy, and patients with overlap syndrome or other rheumatic diseases.

The patients' demographic data, including age, sex, and disease duration, and medical histories, were collected. Patients' GI problems were scored using a standardized questionnaire (UCLA Scleroderma Clinical Trial Consortium GIT 2.0 [UCLA SCTC 2.0]) [22]. This is a 34-item questionnaire to evaluate GI symptoms in irritable bowel syndrome. The scale includes seven dimensions: reflux, distention/bloating, diarrhea, constipation, emotional well-being, and social functioning.

In all patients, biochemical factors including vitamin B12, folic acid, Zinc, Magnesium, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, ferritin, Iron, and transferrin iron-binding capacity (TIBC) will be done. As the primary outcome, fecal calprotectin was assessed using a commercially available enzyme-linked immunosorbent assay (ELISA kit).

Data analysis

Data were analyzed using SPSS Statistics 22.0 software; quantitative data were analyzed using the T-test and qualitative data using Chi-Square test. A p-value less than 0.05 was considered statistically significant.

Results

Demographic data showed that all participating SSc patients were women and the mean age of them was 50.78±4.2 years. The mean (SD) of ESR was equal to 15.0±8.3. Assessing the Inflammatory markers showed that CRP and ESR of these patients did not have a higher mean level of inflammatory markers.

Assessing the malnutrition markers in patients' serum showed that all assessed factors were in the normal range. However, the ferritin and Vitamin B12 levels in these patients were near their lower limits. FC demonstration in SSc patients showed that in these patients, the range of calprotectin was higher than that of normal people. Data analysis did not show any correlation between FC and malnutrition markers (Table 1). Among 31 systemic sclerosis patients who had gastrointestinal symptoms, the level of serum folate in systemic sclerosis patients who had gastrointestinal symptoms was in the upper range of normal, although it was at a normal level.

According to UCLA data, among 31 SSc patients, 18 patients (58%) had reflux, 27 (87%), 23 (74%), 17 (54%), and 17 (54%) patients had distention/bloating, diarrhea, loss of social function, and loss of emotional well-being; data demonstrated constipation in 23 patients (74%) (Table 2).

Table 1. Malnutrition markers and fecal calprotectin assessment in 31 SSc patients

Variable	Normal range	Patients' Mean ± SD	Correlation with Fecal calprotectin (*P*)	Variable	Normal range	Patients' Mean ± SD	Correlation with Fecal calprotectin (*P*)
serum iron (sFe) (µg/dL)	60 -140	88.31 ±27.26	-0.09 (0.671)	ZINC (µg/dL)	60-120	81.97 ± 19.99	-0.07 (0.770)
Total Iron-Binding Capacity (TIBC) (mcg/dL)	240 - 450	332.3 ± 61.53	-0.04 (0.972)	Magnesium (mg/dL)	1.7 to 2.3	2.056 ± 0.26	0.18 (0.300)
Ferritin (ng/mL)	12 - 150	44.69 ± 49.52	-0.17 (0.420)	Vitamin B12 (pmol/L)	118 to 701	213.4±55.32	0.20 (0.410)
Folic acid (nmol/L)	6.12 - 38.52	16.42±5.81	0.22 (0.501)	Fecal calprotectin (µg/mg)	10 - 60	74.52±85.74	-

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Investigating the correlation between GI problems and patients' FC data showed that there is a significant relationship between FC levels and diarrhea in SSc patients. In this way, the FC level was higher in patients who had diarrhea (*P*=0.001), bloating and intestinal distention (*P*=0.001). The higher the degree of abdominal bloating, diarrhea, and distention, the higher the fecal calprotectin level was reported. Assessing the correlation between the FC and patients' reflux rate did not show any significant relationship (*P*=0.324), although the FC level in SSc patients with reflux was higher than the normal level. Constipation analysis showed an opposite, though non-significant, relationship with FC (*P*=0.412). According to Figure 1, there is no significant relationship between FC and emotional health and social dysfunction in scleroderma patients (*P*=0.211 and 0.198).

Discussion

Gastrointestinal involvement in SSc patients is an important factor in their mortality and morbidity. High Prevalence of SIBO in these made evaluating in the early stages

Table 2. UCLA assessed gastrointestinal problems in 31 SSc patients

Gastrointestinal symptoms	Patients number	Percent
Reflux	18	58
Distention/bloating	27	87
Diarrhea	23	74
Loss of Social function	17	54
Loss of Emotional Well-being	17	54
Constipation	23	74

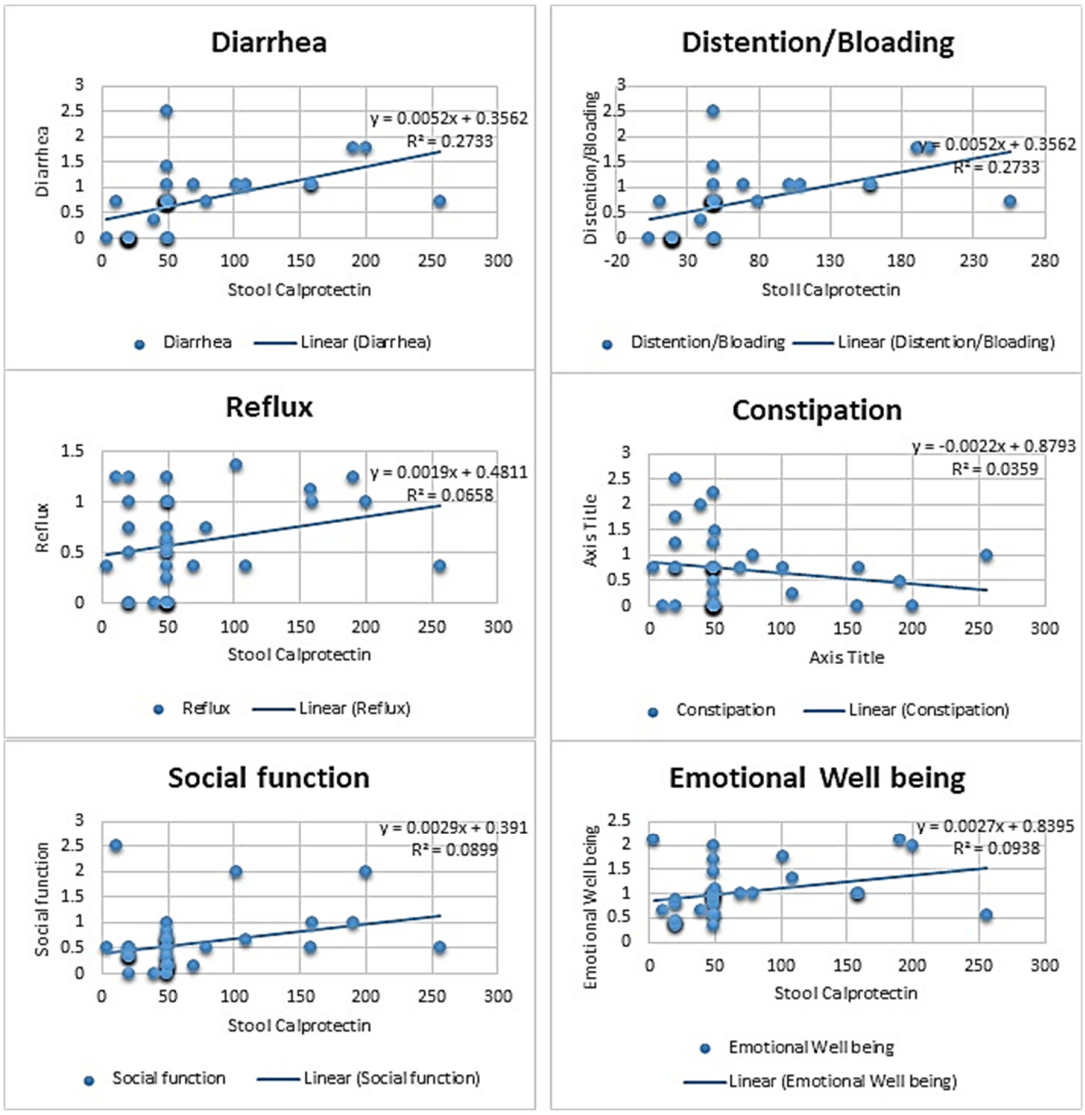

Figure 1. The correlation between GI problems and patients' Fecal Calprotectin

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necessary [1-4]. In this cross-sectional study, we showed that FC levels were higher in SSc patients with gastrointestinal symptoms such as diarrhea and abdominal distention than in patients who lacked these symptoms. In this study, we presented FC as a desirable, inexpensive, and repetitive marker in SSC patients with SIBO symptoms.

In studies on inflammatory bowel disease (IBD), it was proved that FC is a useful and important biomarker for evaluating and monitoring intestinal inflammatory activity [19, 23, 24]. For example, in a systematic review of 435 manuscripts for the diagnosis of IBD, it was shown that serum and fecal markers such as FC are short-term targets [23].

These results are confirmed by other studies on patients with RA diseases; according to previous studies, blood and fetal levels of calprotectin are significantly higher in RA patients compared to healthy individuals [25, 26]. On the other hand, calprotectin levels have been reported to be connected with RA patients' clinical and laboratory parameters, such as their disease activity, therapeutic reactions, and ultrasound parameters [27, 28]. In another systematic review on different calprotectin sources within SSc patients, the best source of calprotectin was FC., This review showed that FC is a good marker to detect inflammation and bacterial overgrowth in the small intestine [19]. A cross-sectional study was performed on SSc patients with digestive symptoms in Sweden. In this study, basically gastrointestinal symptoms were evaluated in these patients, and then their FC was measured. The study results had demonstrated increased FC in the patients with digestive symptoms; malnutrition also was observed as a result of severe digestive disease in these patients [21].

In our study, patients were evaluated through digestive questionnaires; our results were Consistent with the results of this study. In our study, we showed that an increase in FC level over 50 mg/dl was correlated with gastrointestinal symptoms. According to a systematic review that was conducted in 2020, gastrointestinal symptoms increase FC level above 50 mg/dl in SSc patients. There is also a strong correlation between the higher levels of FC (above 275 mg/dl) and SIBO [9]. Another study that was performed in 2014, in France, on 125 SSc patients with digestive symptoms, showed that an elevated FC level was correlated with gastrointestinal symptoms, especially in the patients with SIBO. SIBO was performed by breath test [29]. In our study, due to the cost of this test, it was not possible to do it for patients, but FC level in our patients with SIBO symptoms such as diarrhea, bloating, and abdominal distention has been completely correlated.

In a large study in Canada, it showed that CRP levels in SSc patients were correlated with severity of disease, such as lung and skin involvement, but it was not correlated with gastrointestinal involvement [30]. In our study, in agreement with this study, there was no correlation between CRP level and gastrointestinal involvement.

According to a systematic review, SIBO in SSc causes gastrointestinal symptoms such as abdominal discomfort, diarrhea, bloating, and distention [6]. SIBO causes malabsorption and malnutrition, and as a result, a lack of nutrients such as serum folate, vitamin D, iron, and fat-soluble vitamins is detected [14, 31]. In our study, in patients with gastrointestinal symptoms, a reduction in serum folate, not significant, was shown. It should be noted that in this study, recent use of folic acid supplementation was not a part of the exit criteria.

According to previous studies, common SIBO diagnosis methods, such as Jejunal aspirate and fluid culture, as the gold standard, time-consuming and aggressive tests. The breath test based on glucose or lactulose is a diagnostic test for suspected symptoms, is non-invasive, but expensive, and has false positive results due to disagreement in determining the cut-off level [11-14]. Due to being invasive, unavailability, expensive, and time-consuming, we decided to use FC as a surrogate test in all SSc patients with gastrointestinal symptoms such as diarrhea and bloating. There are different studies that agree with our conclusion. In one study, a positive correlation with the increase in the level of FC in SSc patients who were diagnosed with the glucose hydrogen breath test was shown. This study demonstrated the high titer of FC level (above 275), 93% sensitivity, and 95% specificity [32]. Our study has some limitations; first, there was no confirmatory test to diagnose our patients' SIBO, such as small intestine aspirate, fluid culture, and breath test, which leads to a decrease in diagnostic accuracy.

Limitations and Suggestions

It is recommended that other researchers complete this study in the form of a clinical trial. Due to the coronavirus pandemic, data collection was difficult. As a probable source of selection bias, obtaining the information from the patients referred to this specific research center must be considered.

Conclusion

Due to the high prevalence of gastrointestinal involvement in SSc, paying close attention to the gastrointestinal symptoms of these patients with correct and timely diagnosis is an important step in ensuring the health of these patients. In this study, special digestive complications in SSc patients, such as SIBO, have been more focused. This study suggests that patients who have high fecal calprotectin levels should be monitored for clinical response to treatment.

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

All authors have contributed equally to developing the concept, implementation, processing of results, and writing the article. We declare that this material has not been published before and is not under consideration by other publishers.

Ethical Considerations

All patients had filled out a written informed consent.

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This study was approved by the ethics code IR SUMS.MED.REC.1400.651.

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Data availability

The data are available upon requesting the corresponding author.

AI Use Statement

The authors did not use artificial intelligence or AI-assisted technologies in the preparation of this manuscript.

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