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# Exocrine pancreatic dysfunction in systemic sclerosis and primary Sjogren's syndrome patients

## Sistemik skleroz ve primer Sjögren sendromu hastalarında ekzokrin pankreas disfonksiyonu

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### Abstract

**Objective:** Gastrointestinal problems are frequently encountered in systemic sclerosis (SSc) and primary Sjogren's syndrome (pSS). It has been thought that the pancreas were affected by these diseases. It was aimed to investigate exocrine pancreatic insufficiency in SSc and pSS patients and its potential effect on patient's gastrointestinal problems.

**Methods:** Patients with a diagnosis of SSc or pSS patients, according to 2013 and 2016 American College of Rheumatology/European League Against Rheumatism criteria were consecutively examined. The gastrointestinal quality of life questionnaire was used for functional assessment. Fecal samples were taken from participants and fecal elastase level (fe), which were measured by the ELISA kit.

**Results:** Forty SSc and forty-one pSS patients were enrolled in the study. Groups had similar disease duration, age, and sex distribution. Fe levels were not different between the groups, Healthy control groups had median fe level of 516 μg/g, whereas SSc patients had 437±128 μg/g and pSS patients had 428±149 μg/g. The proportion of patients exhibiting pathological fecal elastase levels were also the same between the groups (12.2% versus 7.5% respectively). However, the functional survey score was worse in the SSc group.

**Conclusion:** Gastrointestinal problems were prevalent in connective tissue disorders, especially in SSc patients. Although pancreatic exocrine dysfunction is rare in these patient groups, its contribution to the development of these complaints is limited.

**Keywords:** Systemic sclerosis, primary Sjogren's syndrome, fecal elastase, pancreatic exocrine function, and connective tissue disease

### Öz

**Amaç:** Skleroderma (SSc) ve primer Sjögren sendromunda (pSS) gastrointestinal problemlerle sıklıkla karşılaşılır. Pankreasın bu hastalıklardan etkilendiği düşünülmektedir. Bu çalışmada, SSc ve pSS hastalarında ekzokrin pankreas yetmezliğinin ve hastanın gastrointestinal problemlerine olası etkisinin araştırılması amaçlandı.

**Yöntem:** 2013 ve 2016 Amerikan Romatoloji Birliği/Avrupa Romatoloji Birliği kriterlerine göre SSc veya pSS hastası tanısı alan hastalar incelendi. Fonksiyonel değerlendirme için gastrointestinal yaşam kalitesi anketi kullanıldı. Katılımcılardan dışkı örnekleri alındı ve ELISA kiti ile ölçülen dışkı elastaz düzeyi (fe) bakıldı.

**Bulgular:** Çalışmaya kırk SSc ve kırk bir pSS hastası alındı. Gruplar benzer hastalık süresine, yaş ve cinsiyet dağılımına sahipti. Fe düzeyleri gruplar arasında farklı değildi, SSc hastaları 437±128 μg/g ve pSS hastaları 428±149 μg/g idi. Patolojik fekal elastaz seviyeleri sergileyen hastaların oranı da gruplar arasında aynıydı (sırasıyla %12,2'ye karşı %7,5). Ancak, fonksiyonel anket puanları SSc grubunda daha kötüydü

**Sonuç:** Gastrointestinal problemler, SSc hastalarında daha çok olmak üzere, bağ dokusu romatizması olan bireylerde yaygın olarak görülmektedir. Pankreatik ekzokrin disfonksiyonu bu hasta gruplarında nadir görülmekle beraber, bu şikayetlerin gelişmesine katkısı sınırlıdır.

**Anahtar Kelimeler:** Sistemik skleroz, primer Sjögren sendromu, fekal elastaz, pankreas ekzokrin fonksiyonu, bağ dokusu hastalığı

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## Introduction

Scleroderma (SSc) and primary Sjögren's syndrome (pSS) are the two main connective tissue disorders. SSc can be seen approximately one in 10.000 people,[1] whereas pSS prevalence is much higher, around to be 4 per 1.000 patients per year.[2] Although the pathogenic mechanisms and severity of the disease are not identical, gastrointestinal system (GIS) problems are frequently seen in both patient groups, particularly in patients with SSC patients. Approximately 90% of SSc patients had esophagus and anorectal involvement following GIS involvement, specifically fibrosis, muscle atrophy, and sphincter dysfunction.[3] In the literature, studies focus primarily on these two parts of the gastrointestinal tract, although little is known about the pancreatic implication of SSc. On the other hand, being a partial exocrine gland structure, it is supposed that pSS also affects pancreatic anatomy and function. Pancreatic involvement can be seen in 24-100% of pSS patients.[4] Although the clinical effect is less commonly seen due to possible organ capacity to overcome the disease effect. Several studies have examined exocrine pancreatic insufficiency (EPI) in SSc or pSS patients.[5-14] Only a minority of those studies[12-14] used fe levels to detect EPI and none of them compared two connective tissue diseases in terms of both GIS symptoms and exocrine pancreatic function.

The detection of pancreatic exocrine deficiency is important because it can be treated with enzyme replacement therapy; thus it can alleviate symptoms efficiently.[15] Gold standards for the diagnosis of EPI non-invasively via 24-h stool collection and invasively via secretin - cerulein test.[16,17] However, they are not suitable for patients and laboratory staff and are not a practical test for screening. In contrast, fecal elastase (fe) can be a useful tool for detect pancreatic exocrine dysfunction.[17] However, the clinical picture of the patients is not solely affected by fecal elastase level, patients' concomitant diseases and drug usage, as well as organ involvement, can contribute to the symptoms and quality of life of the patients. EPI can be seen above the levels of fe levels of 200 ng/m; it has shown that the 200 ng/mL level is a good cut-off point for screening purposes.[18] Gastrointestinal quality of life (GIQLE) is one of the most widely used questionnaires for objective measurement of QoL in gastrointestinal disease and wide separately has been used since 1993.[19] It consists of five domains and investigates the effect on the physical, social, and psychosocial life of the patients, related to gastrointestinal symptoms. The Turkish validation of this GIQLE was previously performed in pSS patients.[20]

The aim of this study, to evaluate the possible exocrine pancreatic dysfunction of SSc and pSS, by measuring the levels. Also, the patients' GIQLE score was calculated and investigated whether exocrine pancreatic function contribute patients complaints.

## Materials and Methods

This study was conducted in a tertiary rheumatology clinic between June 2019 and December 2019. Patients having diagnosed with SSc or pSS[21,22] for at least one year and attending regularly to policlinic control were included in the study. Sex- and age-matched control subjects were recruited from the stuff of our clinics. Patients and controls with concomitant chronic pancreatitis or other rheumatic disease other than SSc or pSS, a history of pancreatic surgery, alcohol abuse, diabetes mellitus, and taking pancreatic enzyme extracts were excluded from the study. Demographic and laboratory information of the patient was obtained from the registered electronic system. The functional assessment was carried through the GIQLE form. It is aimed to achieve harmony between the clinical and biochemical findings of patient group. Informed consent was obtained from patients and ethical approval was provided by the local committee (approval number: 817, date: 12.11.2018).

### Fecal Elastase Measurement

Stool samples were collected and instantly stored at -80 °C until analyzing time. Fecal elastase concentrations of all stool samples were measured on the same day with a commercially available enzyme-linked immunosorbent assay (ELISA) kit (BIOSERVE DiagnosticsGmbH, Rostock, Germany) according to the manufacturer's instructions. The intra-assay and inter-assay variation coefficients were 2.7% and 5.6%, respectively. Measurements were defined as Fecal Elastase per gram stool. Each 10 mg stool sample was homogenized with 1 mL extraction buffer using a vortex mixer. Homogenate was kept at 2-8 ° temperature overnight and the supernatant was obtained. Next day, the supernatants were diluted 1/201 with the wash solution. These diluted samples were used for the analysis. Fecal Elastase-1 levels >200 µg/g were defined as possible normal exocrine pancreatic function, and Fecal Elastase-1 levels <200 µg/g were defined as possible EPI.[18]

### Statistical Analysis

Categorical variables were given as number and percentages. Continuous data were as mean ± standard deviation or median (interquartile range). The conformity of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical

methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). If variables were normally distributed Student t-test was used, if not the Mann-Whitney U test was used for comparison of data sets. Comparison of categorical variables was made with chi-square or Fisher's exact tests. A two-sided p-value of 0.05 or less was considered statistically significant in all analysis. Correlation analysis was performed using the Spearman correlation coefficient and interpreted as a poor agreement (0.0-0.2), fair (0.2-0.4), moderate (0.4-0.6), good (0.6-0.8), or excellent (0.8-1.0).[23]

## Results

Between June 2019 and December 2019, 47 SSc patients and 45 pSS patients accepted to participate in the study. Stool samples which could be neither studied nor transferred to storage within 2 h, in four SSc patients and three pSS patients were excluded from the measurement of fecal elastase level. Two patients in the SSc group a one patient in pSS had acute gastroenteritis, whereas one patient in SSc had already taken pancreatic enzyme extracts. Forty patients in SSc and 41 patients in pSS were included in the final analysis. As a control group, there were age and sex-matched 23 patients.

Patients and disease characteristics are shown in Table 1. Groups were similar in terms of age, sex, and disease duration. The median disease activity score was one in the pSS group, the median modified rodnan score was 12 in SSc patients. Healthy control groups had a median fe level of 516 µg/g, whereas in pSS and SSc patients were 489 µg/g and 459 µg/g respectively (p>0.05). The percentage of patients with fe level <200 µg/g, which was related to possible pancreatic exocrine dysfunction was 5% in the control groups and not significantly different in the pSS and SSc groups. Contrary quality of life score was compared between groups and shown in Table 1. Both GIQLE total score and sub-domains score was higher in SSc patients, and healthy controls had the best results both in total and subgroup score.

**Table 1.** Disease and patient characteristics of the disease groups

| | pSS (n=41) | SSc (n=40) | Control (n=23) | p |
|---|---|---|---|---|
| Age (IQR) | 45 (11) | 44.5 (9.5) | 45 (10) | 0.879 |
| Female | 38 (92) | 38 (95) | 20 (86) | 0.768 |
| Disease duration (year) (IQR) | 5 (4) | 6 (2.75) | - | 0.405 |
| ESSDAI (IQR) | 1 (2) | - | - | - |
| mRSS score (IQR) | - | 12 (8) | - | - |
| Fecal elastase (IQR)<br><200 mg/mL n (%) | 489 (226)<br>5 (12) | 459 (189)<br>3 (7.5) | 516 (172)<br>3 (13) | 0.867<br>0.712 |
| GIQLE score total (IQR) | 78 | 40 | 82 | **<0.001***/>0.05** |
| Main | 28 (15) | 12 (12) | 29 (14) | <**0.001***/>0.05** |
| Physical | 12 (4) | 8 (8) | 13 (4) | **0.001***/>0.05** |
| Physiological | 14 (16) | 8 (10) | 14 (10) | **0.001***/>0.05** |
| Social | 12 (12) | 4 (8) | 12 (10) | **0.002***/>0.05** |
| Disease-related | 12 (7) | 4 (4) | 14 (6) | **0.001***/>0.05** |

*ESSDAI: The EULAR Sjögren's syndrome (SS) disease activity index, GIQLE: Gastrointestinal quality of life, mRSS: Modified rodnan skin score. *: p values for comparison between pSS and SSc patients. **: p values for comparison of pSS and healthy control groups, pSS: Primary Sjogren's syndrome, IQR: Interquartile range*

The fecal elastase level was correlated with patient characteristics. Fe levels had a negative moderate correlation with the disease duration of the patients in both disease groups (Table 2). The disease activity of pSS also had a fair negative correlation in pSS patient; however, however mMMRS score did not. On the other hand, the levels had a negative fair correlation with the GIQLE total score in only pSS patients significantly but not in SSc patients. A similar fair negative correlation also in the subdomain scores of GIQLE for pSS groups but again not in SSc (data not shown).

## Discussion

Gastrointestinal disorders were commonly seen in patients with pSS and SSc. In this study, fecal elastase levels were shown to be preserved in pSS and SSc patients. Levels of fe <200 µg/g, suggestive of personal protective equipment (PPE), were similar to those in a healthy population. The GIQLE score was directly related to gastrointestinal disorders and was significantly higher among patients with SSc patients. There was a moderate negative correlation between disease levels and duration in the two groups and a fair correlation with disease activity in the pSS groups. This was the first time in the literature, comparing the two connective diseases, which had the most prevalent gastrointestinal complaints in terms of fecal elastase levels and gastrointestinal quality life assessment. These data demonstrate that EPI did not have a major role in the underlying reason for gastrointestinal symptoms of pSS and SSc. However, levels of fe may be reduced as the disease progresses.

**Table 2.** Correlation of fecal elastase levels with age, disease duration, disease actitivty, and GIQLE score in the patient groups

| | | Fecal elastase | |
|---|---|---|---|
| | | Spearman rho | p |
| Age | pSS<br>SSc | -0.154<br>-0.141 | 0.304<br>0.354 |
| Disease duration (year) | pSS<br>SSc | -0.403<br>-0.526 | **0.009**<br>**<0.001** |
| GIQLE (total) | pSS<br>SSc | -0.312<br>-0.170 | **0.047**<br>0.912 |
| ESSDAI | pSS | -0.362 | **0.020** |
| mRSS | SSc | -0.079 | 0.629 |

*GIQLE: Gastrointestinal quality of life, pSS: Primary Sjogren's syndrome, SSc: systemic sclerosis*

EPI is one of the main interest points in the clinical practice of patients with dyspeptic and malnutrition patients because its treatment with orally taken enzyme replacement was easy and successful in treatment. The gold standard for PPE diagnosis relies on an invasive secretion-cerulein test procedure, which cannot be used in patient screening.[17] However, the elastase enzyme was produced from the pancreas and undigested by the intestinal enzyme. Thus, by measuring in the feces, it can provide valuable information about pancreatic exocrine function non-invasively. The EF level measured by monoclonal ELISA can detect PPE at 90% sensitivity and specificity.[17] Although gastrointestinal disturbances were widespread in patients with SSC patients in the literature, there has been only one study that investigates levels of fe in patients with SSc and pSS, the remaining studies focused on motility dysfunction, bacterial over-growthand extra-intestinal complications.[13,14] Levels of fe were retained in the patient population in the studies. However, they did not mention the potential effect of the level on the quality of life. In addition, it has not been compared with connective tissue diseases a high prevalence of gastrointestinal disorders.

The GIQLE score was first reported in 1993 in patients undergoing surgery. It objectively showed the change in the quality of life of patients in these patient groups.[19] A number of rating systems have been used in rheumatological diseases to evaluate gastrointestinal complications. However, none of them took a holistic approach to gastro-intestinal quality of life. GIQLE scoring was previosly used in several studies regarding rheumatologic disease and compared with healty populations.[20,24] Consistant with our findings, SSc patients had worse scoring, whereas pSS patients had similar results compared to the normal population.

In every domain, SSc patients had higher scores compared the pSS groups, which indicate that SSc patients were suffering from[25] GIS -related symptoms more severely. Considering the similar range of fe levels in both disease groups, the difference can not be only attributed to EPI, becasue the mechanisms of gastrointestinal involvement in SSc patients are diverse and different from pSS.[25] In accordance with the literature, we believe that PPE was not a contributory factor to these symptoms in SSS patients.[13] Studies investigating EPI in pSS patients were conducted via several methods.[14,26-28] In these studies, it was shown that fecal chymotrypsin levels and intestinal decreased in pSS patients compared to the control population, whereas $HCO_3$ levels and percentage of patients with chymotrypsin levels suggesting EPI were similar.[25-27] They had a few patients ,which limited the generability of the results.[29] Only in one study fecal elastase levels were measured and found the decreased levels with respect to the heatly population.[14] However, the fe levels <200 µg/g were similar between the groups. The relatively low level of fe levels could be attributed to pSS involvement, which did not reach clinically significance. Furthermore, in accordance with the literature, the duration of the disease impacted EPI in patients with pSS.[28,29] Our results may be an early sign of exocrine dysfunction in pSS patients, but long-term follow-up results are needed.

### Study Limitations

That study had a number of limitations. First, EPI was not diagnosed via golden standard diagnostic methods, thus not all patients with fe levels <200 might not have EPI and amongst those with >200 levels might have EPI. It was wise to use a screening method because without any symptoms, it would be unethical to conduct an invasive test for all participants. The onset time of illness cannot be readily detecte; therefore, this may obscure the power of the correlation between fe levels and disease duration, which migth have affected the FE levels.

## Conclusion

Exocrine pancreatic functions are generally well maintained and have not contributed to complaints related to gastrointestinal symptoms in patients with pSS and SSc patients. Gastrointestinal QOL scores were worse in the SSc group, indicating an alternative mechanism to EPI to explain the difference with pSS patients.

### Ethics

**Ethics Committee Approval:** Informed consent was obtained from patients and ethical approval was provided by the local committee (approval number: 817, date: 12.11.2018 - Gazi University Ethics Committee).

**Informed Consent:** Informed consent was obtained from patients.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: H.B., B.G., Ş.H., M.A.Ö., A.T., Design: R.B.S., A.A.G., H.K., B.G., Ş.H., M.A.Ö., A.T., Data Collection or Processing: R.B.S., H.B., N.A., A.A.G., H.K., Analysis or Interpretation: H.S., B.G., Ş.H., M.A.Ö., A.T., Literature Search: H.S., S.C.G., R.B.S., H.B., N.A., A.A.G., H.K., Writing: H.S., B.A., S.C.G., A.T.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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