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INVITED REVIEW

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GASTROINTESTINAL INVOLVEMENT IN SJÖGREN'S DISEASE

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Abstract

Sjögren's disease (SjD) is a chronic autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands, which can also affect the gastrointestinal (GI) tract, hepatobiliary system, and pancreatic exocrine tissues. Approximately one-third of patients experience GI-related symptoms, with xerostomia, dysphagia, dyspepsia, and atrophic gastritis being the most commonly reported manifestations. SjD is also associated with autoimmune liver diseases, including autoimmune hepatitis and primary biliary cholangitis. Pancreatic involvement is less frequent, but may present as autoimmune pancreatitis or exocrine pancreatic insufficiency. The complexity of SjD and the variety of its manifestations underscore the importance of a multidisciplinary management approach, where collaboration among healthcare professionals is crucial for optimising patient outcomes.

Keywords: Sjögren's disease, gastrointestinal tract, autoimmune hepatitis, primary biliary cholangitis, pancreatitis

INTRODUCTION

Sjögren's disease (SjD) is an autoimmune exocrinopathy that can affect the entire gastrointestinal (GI) system, including the intestinal lumen, hepatobiliary tract, and pancreas. Given that the GI tract encompasses numerous exocrine functions, its involvement in SjD is expected. Over the course of the disease, approximately one-third of patients develop GI symptoms. Among the most bothersome manifestations is xerostomia, which results from lymphocytic infiltration of, and subsequent damage to, the salivary glands (1,2).

In addition, several other GI and hepatopancreatic manifestations have been reported, including dysphagia, esophageal dysmotility, chronic atrophic gastritis, irritable bowel syndrome, celiac disease (CD), primary biliary cholangitis (PBC), pancreatitis, exocrine pancreatic insufficiency, autonomic nervous system dysfunction, and liver disease (Table 1) (3-6).

General management aligns with the 2020 European Alliance of Associations for Rheumatology (EULAR) recommendations for SjD: evaluate systemic activity (e.g., EULAR SjD disease activity index); treat sicca symptoms (topical therapies; secretagogues such as pilocarpine or cevimeline when appropriate); screen for extraglandular involvement (hepatobiliary or pancreatic involvement where indicated); manage comorbidities; and monitor lymphoma risk in highrisk phenotypes. Co-ordinate care with gastroenterology or hepatology for abnormal liver tests or suspected biliary disease (7).

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Table 1. Anatomical distribution and clinical features of gastrointestinal involvement in Sjögren's disease (adapted from reference 6)

Organ	Type of involvement and clinical features
Oral cavity/salivary glands	Xerostomia, atypical dental caries, glossitis, taste disturbances, difficulty chewing, gingival problems, difficulty speaking, hoarseness, dysphagia, oral ulcers/aphthae, atypical angular cheilitis, lip dryness, oral candidiasis
Esophagus	Dysphagia, dysmotility, esophageal atrophy, Candida esophagitis
Stomach	Chronic atrophic gastritis, dyspepsia, delayed gastric emptying
Small intestine	Duodenal ulcers, celiac disease, pseudo-obstruction, pneumatosis cystoides intestinalis, protein-losing enteropathy, secondary vasculitic findings, increased risk of B-cell lymphoma, vitamin B12 deficiency/ pernicious anemia
Colon	Increased risk of colorectal cancer
Liver	Increased risk of complications from hepatitis C, primary biliary cholangitis, autoimmune hepatitis, and other autoimmune liver diseases
Pancreas	Autoimmune pancreatitis, chronic pancreatitis (weight loss, diarrhea, steatorrhea), exocrine pancreatic insufficiency
Gallbladder	Primary biliary cholangitis

MATERIAL AND METHODS

We conducted a narrative review to synthesize clinically relevant evidence on GI, hepatobiliary, and pancreatic involvement in primary SjD. Databases: Medline/PubMed and Scopus. Timeframe: inception to September 2025. Keywords (Boolean examples): ["Sjögren*" and (gastrointestinal or hepatobiliary or liver or biliary or pancreas or pancreatitis or dysphagia or gastritis or PBC or autoimmune hepatitis (AIH) or "exocrine pancreatic insufficiency" or microbiome)]. Study selection: English-language human studies prioritizing systematic reviews/ meta-analyses, large cohorts, guidelines/consensus statements, and clinically illustrative case series; single-case reports were used only to highlight rare entities. Statements reflect the level of available evidence. Abbreviations are defined at first mention in the text.

Gastrointestinal Tract Involvement in Sjögren's Disease

Oral involvement in SjD is primarily characterized by xerostomia (dry mouth), which affects approximately 80% of patients. Xerostomia may lead to a broad spectrum of secondary oral manifestations, either as a consequence of reduced salivary secretion or as direct effects of the disease. These include atypical angular cheilitis, lip dryness, non-classical dental caries, gingival disease, glossitis, taste disturbances, difficulty speaking, hoarseness, dysphagia, and oral ulcers (aphthae). On physical examination, the oral mucosa often appears dull and parchment-like and tends to adhere to the examiner's finger on palpation. Additionally, there may be reduced salivary pooling in the sublingual region and recurrent swelling of one or both of the parotid and submandibular glands. Furthermore, patients with SjD exhibit an increased susceptibility to oral candidiasis (1,5). Abnormalities in parasympathetic neurotransmission contribute to glandular dysfunction in SjD. Consequently, the management of xerostomia may involve the use of topical agents and secretagogues that stimulate muscarinic receptors, such as pilocarpine and cevimeline (1,4,7).

Autonomic neuropathy, a condition in which the nerves that control involuntary bodily functions are damaged, is associated with SjD and may contribute to GI dysmotility. This condition, along with impairment of muscarinic receptors by SjD-related autoantibodies, can lead to reduced salivary gland function and potentially altered intestinal motility, including peristalsis (4,8). Understanding these mechanisms is important for the comprehensive management of SjD patients. Studies evaluating dysphagia in patients with SjD have reported a prevalence as high as 80%. Reduced salivary secretion and esophageal dysmotility have been identified as major contributing factors to dysphagia in these patients. Since saliva is essential for pharyngo-esophageal bolus transfer, its deficiency may significantly exacerbate swallowing difficulties. Several studies have demonstrated that patients with SjD exhibit an increased frequency of non-specific motility abnormalities, including aperistalsis, tertiary contractions, non-peristaltic contractions, and reduced contraction amplitude, all of which may play a role in dysphagia (1,9,10). These abnormalities most commonly involve the cervical esophagus, the pharynx, or the mid-thoracic region, and, in advanced cases, esophageal atrophy may develop.

Patients with SjD may present with delayed gastric emptying; dyspepsia has been reported in approximately 20% of individuals with primary SjD. Among those undergoing upper

endoscopy, chronic atrophic gastritis has been reported in up to approximately 60% of patients in hospital-based series (age and selection-dependent), with its prevalence increasing with age. Although gastric parietal cell antibodies are detected in approximately 30% of patients, low serum vitamin B12 levels and pernicious anemia are rarely observed (4,11). Patients with SjD also have an increased risk of duodenal ulcers, and the likelihood of CD in primary SjD is approximately tenfold higher, with an estimated prevalence of 4.5%. Furthermore, the risk of lymphoma is increased; evidence for solid tumors (e.g., colorectal cancer) is inconsistent and should be interpreted cautiously in this population. Additional GI complications reported in SjD include intestinal pseudo-obstruction, pneumatosis cystoides intestinalis, and protein-losing enteropathy (12,13). Predictors reported in SjD include persistent parotid enlargement, palpable purpura or vasculitis, lymphadenopathy, cryoglobulinemia, low C4 levels, and monoclonal gammopathy of undetermined significance; composite risk scores have been proposed in cohorts (14,15).

Isolated case reports have also described the coexistence of ulcerative colitis and Crohn's disease in patients with SjD. GI vasculitis is uncommon, but, when present, is often associated with hypocomplementemia and cryoglobulinemia. In severe cases, vasculitis may lead to intestinal ischemia, necrosis, or gangrene, potentially resulting in an acute abdomen (14,15). Reported GI symptoms in patients with SjD affecting the small and large intestines include abdominal discomfort (37%), nausea (5%), constipation (23%), diarrhea (9%), and iron-deficiency anemia secondary to malabsorption (5%). However, data from extensive cohort studies indicate that direct intestinal involvement in SjD is either rare or absent (1,3). The prevalence of CD in SjD, as assessed by small-bowel biopsies, has been reported to range from 4.5% to 14.7%. Evidence supporting the benefit of a gluten-free diet in improving sicca symptoms remains limited. When SjD coexists with CD, celiac-type enamel defects may be observed, potentially contributing to an increased risk of dental caries. The coexistence of SjD and inflammatory bowel disease has rarely been reported in the literature. Although uncommon, serious GI complications have been described in SjD, including pneumatosis cystoides intestinalis, colorectal cancer, and intestinal pseudo-obstruction (1,12).

Hepatic and Biliary Tract Involvement in Sjögren's Disease

Hepatic involvement is observed in approximately 30% of patients with SjD and is associated with the systemic clinical features of the disease, autoimmunity, and inflammatory markers. After excluding patients with chronic liver diseases and hepatotoxic drug use, the primary etiologies include chronic viral hepatitis [hepatitis C virus (HCV), hepatitis B virus] in approximately 50% of cases and autoimmune liver diseases, such as PBC and AIH, in approximately 20%. Among these, chronic viral liver disease—most commonly HCV-related—is the leading cause of hepatic involvement in SjD, with a prevalence of approximately 13%, roughly three times as frequent as autoimmune liver involvement. Immunologic abnormalities can be observed in viral infections—including elevated cryoglobulin levels and low complement levels—and in autoimmune liver diseases such as AIH, with an increased frequency of autoantibodies. Mild elevations in liver enzymes are reported in 5-49% of patients with SjD; however, the majority of patients remain asymptomatic, and clinically significant liver disease is uncommon (1,3). Abnormal liver function tests typically show a cholestatic pattern but may also present as hepatocellular or mixed patterns (1). Idiopathic granulomatous hepatitis has also been associated with SjD. Although the overall risk of lymphoma within the liver is not increased, cases of pseudolymphoma secondary to dense lymphocytic infiltration have been described (16,17). Additionally, hepatomegaly is observed in approximately 15% of patients with SjD (1).

SjD is among the systemic rheumatic diseases (SRDs) most frequently associated with autoimmune liver diseases. In heterogeneous cohorts of patients with primary SjD, the reported prevalence of AIH ranges from 0.4% to 4% (2). Although AIH occurs relatively frequently in patients with rheumatoid arthritis (RA) or systemic lupus erythematosus, PBC is more common in patients with SjD, RA, or systemic sclerosis (18-20).

In patients with primary SjD, the prevalence of PBC varies between 1% and 9% across different studies (21,22). Among anti-mitochondrial antibody-positive (AMA+) patients with primary SjD, histopathological examination of liver biopsies reveals features characteristic of PBC in up to 95% of cases. Importantly, AMA+, asymptomatic patients should be closely monitored for potential development of PBC. Early diagnosis of PBC and timely initiation of ursodeoxycholic acid therapy are critical for optimizing disease management and improving long-term outcomes (22,23).

Among SRDs, SjD is most frequently associated with PBC, with a reported prevalence ranging from 3.5% to 38%. In addition to their clinical coexistence and comparable epidemiologic characteristics, SjD and PBC share overlapping pathogenetic mechanisms and genetic susceptibility factors (22,24). One notable example is the E2 subunit of the pyruvate dehydrogenase complex, a major PBC-specific autoantigen, which has also been detected on the surface of salivary epithelial cells in SjD.

Furthermore, human leukocyte antigen (HLA)-DR2 and HLA-DR3 alleles have been identified as shared genetic susceptibility markers for both conditions (22,24). Although the prevalence of anti-smooth muscle antibodies in SjD is generally higher than that of AMA, the occurrence of co-existing AIH among SjD patients is less frequent than the occurrence of coexisting PBC. Small-scale studies and case series have described SjD-PBC overlap syndromes, suggesting that these associations may represent a causal relationship rather than sporadic coexistence. Importantly, clinicians should consider the coexistence of immunoglobulin G4-related disease (IgG4-RD) in patients who present with autoimmune pancreatitis in the context of SjD-PBC overlap disease (22,24).

Pancreatic Involvement in Sjögren's Disease

Pancreatitis has been reported infrequently (generally ≤7% across heterogeneous series; overlap and selection likely contribute) in patients with SjD (1). It may present as either autoimmune pancreatitis or chronic pancreatitis. Notably, in nearly all reported cases of overlap between SjD and primary sclerosing cholangitis, patients exhibit chronic pancreatitis, characterized by the triad of weight loss, diarrhea, and steatorrhea (2,25,26).

Several distinct pancreatic findings have been described in SjD, including isolated pancreatic calcifications, enlargement of the pancreatic head mimicking a neoplasm, and elevated serum cancer antigen 19-9 levels in benign pancreatic conditions (1). Furthermore, abnormal exocrine pancreatic function has been detected in approximately 18-37.5% of asymptomatic SjD patients, but steatorrhea remains an uncommon clinical finding in this population (2,27,28).

Chronic pancreatitis has also been reported in association with other autoimmune diseases, including SjD, PBC, and primary sclerosing cholangitis (28-30).

When autoimmune pancreatitis is suspected, apply the international consensus diagnostic criteria and histology, imaging, serology, other organ involvement, response to therapy diagnostic frameworks and distinguish type 1 (IgG4-RD) from type 2 (idiopathic ductcentric). Include malignancy in the differential diagnosis when focal enlargement mimics a neoplasm (31).

CONCLUSION

GI, hepatobiliary, and pancreatic involvement represents a clinically relevant yet often under-recognized component of SjD. Sicca-related oral and esophageal symptoms remain the most frequent manifestations, but a subset of patients experiences broader GI dysfunction, including dysmotility, chronic atrophic gastritis, CD, and rare but significant complications such as pseudo-obstruction or protein-losing enteropathy. Hepatobiliary disease—most notably PBC and, less commonly, AIH—constitutes an important extra-glandular domain with implications for long-term monitoring. Pancreatic involvement, although uncommon, encompasses autoimmune pancreatitis and exocrine dysfunction and should be considered in patients with unexplained abdominal symptoms or malabsorption. These findings emphasize the importance of systematic evaluation of GI and hepatopancreatic systems in SjD. Multidisciplinary collaboration is essential to ensure timely diagnosis, tailored management, and improved patient outcomes.

Footnotes

Authorship Contributions

Concept: F.A., Design: F.A., E.İ., S.Y., Data Collection or Processing: E.İ., S.Y., Y.A., Analysis or Interpretation: F.A., E.İ., S.Y., Literature Search: E.İ., S.Y., Y.A., Writing: F.A., Y.A.

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ORIGINAL ARTICLE

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ANTI-RO ANTIBODY POSITIVITY AND ITS RELATIONSHIP WITH PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Abstract

Aim: Pulmonary involvement is a major contributor to both morbidity and mortality in systemic sclerosis (SSc). While specific autoantibodies, such as anti-Scl-70 and anti-centromere, have been linked to distinct disease subtypes and organ complications, the role of anti-Ro antibodies in SSc—particularly in relation to pulmonary manifestations—has not been fully elucidated. Understanding this relationship may provide insights into disease stratification and risk assessment for lung involvement in SSc patients. This study aimed to determine the prevalence of anti-Ro antibodies in patients with SSc and to investigate their potential association with pulmonary complications, including interstitial lung disease and pulmonary arterial hypertension.

Material and Methods: We retrospectively reviewed 73 patients with SSc who underwent anti-Ro antibody testing, chest X-rays, and high-resolution computed tomography (HRCT). Serum levels of anti-Scl-70, anti-centromere, anti-Ro, and anti-La antibodies were measured using enzyme-linked immunosorbent assay, with a positivity threshold of ≥21 IU/mL, while antinuclear antibodies (ANA) were assessed via indirect immunofluorescence. Pulmonary changes were evaluated by imaging, with particular attention to reticular patterns, ground-glass opacities, and honeycombing.

Results: ANA positivity was observed in 94.5% of patients. Anti-Scl-70 and anti-centromere antibodies were detected in 52.8% and 18.8% of patients, respectively. Anti-Ro antibodies were positive in six patients (8.2% of the cohort); all were also ANA-positive. Two patients (2.7% of the cohort) were positive for anti-Scl-70, while none exhibited anti-centromere antibodies. Pulmonary abnormalities were more frequently observed in anti-Ro-positive patients on both chest radiographs and HRCT, although these differences did not reach statistical significance.

Conclusion: Anti-Ro antibodies were uncommon in SSc, but were associated with a non-significant trend toward increased pulmonary involvement. Larger prospective studies, especially evaluating anti-Ro52, are needed to clarify their clinical relevance.

Keywords: Systemic sclerosis, anti-Ro antibodies, interstitial lung disease, pulmonary involvement, autoantibodies

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INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease characterized by microvascular injury, immune activation, and fibrosis of the skin and internal organs (1). While cutaneous thickening is often the most apparent manifestation, internal organ involvement—particularly of the lungs—plays a decisive role in disease progression and patient prognosis. Among pulmonary manifestations, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) represent two of the most frequent and clinically significant complications (2,3).

ILD is associated with SSc affects approximately 40-60% of patients and typically develops insidiously, often progressing to pulmonary fibrosis and, ultimately, respiratory failure (4). PAH may initially present without symptoms but can advance to exertional dyspnea, right ventricular dysfunction, and reduced survival. Given their substantial impact on morbidity and mortality, early detection of pulmonary involvement and identification of predictive biomarkers are crucial components of effective disease management.

Autoantibodies not only aid in the diagnosis of SSc but also provide valuable insights into disease subsets, prognosis, and organ-specific involvement. Antinuclear antibodies (ANA) are present in the vast majority of patients, while more specific autoantibodies—such as anti-Scl-70, anti-centromere, and anti-RNA polymerase III—are strongly associated with distinct clinical phenotypes and organ complications (5). Among these, anti-Ro [Sjögren's disease antigen A (SSA)] antibodies are detected in a subset of SSc patients and have gained increasing attention for their potential association with particular clinical manifestations, including pulmonary involvement.

Although anti-Ro antibodies are most commonly associated with Sjögren's disease and systemic lupus erythematosus, they have been reported in roughly 10-20% of SSc patients (6,7). Their presence has been linked to earlier disease onset, increased systemic inflammation, musculoskeletal symptoms, digital ulcers, and involvement of certain internal organs (8,9). However, the connection between anti-Ro positivity and pulmonary complications—particularly ILD and PAH—remains uncertain, with previous studies reporting inconsistent findings (10).

This study aims to assess the prevalence of anti-Ro antibodies in patients with SSc and to examine whether their presence correlates with an increased risk of pulmonary involvement, especially ILD and PAH, thereby informing their potential role as predictive markers for lung complications.

MATERIAL AND METHODS

Study Design and Participants

Baseline demographic and clinical data, including age, sex, disease duration, time interval between SSc diagnosis and ILD onset, and pulmonary artery pressure (PAP) values, were collected from medical records. ILD subtypes were classified based on high-resolution computed tomography (HRCT) patterns (ground-glass opacity, reticular pattern, honeycombing) according to international guidelines.

Anti-Ro-positive patients were systematically assessed for overlap with Sjögren's disease using a combination of clinical history (sicca symptoms), serological testing (anti-La/Sjögren's disease antigen B), and salivary gland evaluation, when available. Patients meeting established Sjögren's criteria were excluded from the anti-Ro-positive SSc subgroup analysis. Data were extracted retrospectively from hospital charts and patient files. The study protocol was approved by the Fırat University Non-Invasive Research Ethics Committee (approval number: 39433, date: 24.09.2025) and was conducted in accordance with the principles of the Declaration of Helsinki.

Laboratory Assessments

Serum levels of anti-Scl-70, anti-centromere, anti-Ro, and anti-La antibodies had been measured previously under standardized laboratory conditions using enzyme-linked immunosorbent assay, with values ≥21 IU/mL considered positive according to reference ranges. ANA were evaluated using the indirect immunofluorescence technique.

Pulmonary Assessment

Pulmonary involvement was evaluated by reviewing chest radiographs and thoracic HRCT scans. Radiographs were assessed for changes in hilar prominence, lung parenchymal density, and contour. HRCT scans were analyzed for features suggestive of ILD, including ground-glass opacities, reticular patterns, and honeycombing. Two experienced radiologists, blinded to serological results, independently assessed the extent and severity of abnormalities using a semiquantitative scoring system as described by Goh et al. (11).

Statistical Analysis

Descriptive statistics were reported as mean ± standard deviation for normally distributed continuous variables and median with interquartile range (IQR) for non-normally distributed variables. Categorical variables were presented as frequencies and percentages. Fisher's exact test was used to compare categorical variables, and the Mann-Whitney U test was used for continuous

variables that were not normally distributed. Associations between anti-Ro positivity and clinical or imaging findings were initially examined using univariable logistic regression. Variables with $p<0.10$ in univariable analysis (including age, sex, disease duration, and anti-Scl-70 positivity) were entered into a multivariable logistic regression model. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for univariable analyses in Table 1. Statistical significance was defined as $p<0.05$. All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 73 patients with SSc were included in the analysis. The mean age was 48.6±12.4 years, and 63% of the patients were female. The median disease duration was 7 years (IQR: 4-12). The median time interval between SSc diagnosis and ILD onset was 3 years (IQR: 2-6). PAP measurements were available for 60 patients; the median systolic PAP was 28 mmHg (IQR: 25-34 mmHg).

ANA positivity was detected in 94.5% of participants. Regarding disease-specific autoantibodies, anti-Scl-70 antibodies were present in 52.8% (n=38), anti-centromere antibodies in 18.8% (n=13), anti-Ro antibodies in 8.2% (n=6), and anti-La antibodies in 1.4% (n=1). Among the six anti-Ro positive patients, two (2.7%) were also positive for anti-Scl-70, and none had anti-centromere antibodies. Importantly, none of the anti-Ro-positive patients met criteria for Sjögren's disease overlap based on clinical assessment, anti-La testing, and salivary gland evaluation.

Pulmonary involvement was observed more frequently among patients with anti-Ro antibodies compared to those without. Chest radiographs of anti-Ro-positive patients showed findings, including prominent pulmonary hilar, reticular opacities, and basal parenchymal irregularities. HRCT scans revealed ground-glass opacities, reticular patterns, and, in some cases, honeycombing, suggestive of fibrotic ILD.

Overall, 83.3% (n=5) of anti-Ro-positive patients exhibited pulmonary abnormalities, compared with 63.2% (n=42) of anti-Ro-negative patients. Chest X-ray findings included pulmonary conus prominence in 2 (25%) anti-Ro positive patients versus 10 (15%) anti-Ro negative patients (OR: 2.8, 95% CI: 0.5-17.7, p=0.26), and a reticular pattern in 3 (50%) anti-Ro positive patients versus 19 (28%) anti-Ro negative patients (OR: 2.5, 95% CI: 0.5-13.6, p=0.28). HRCT findings included ground-glass opacity in 4 (75%) anti-Ro positive patients versus 28 (42%) anti-Ro negative patients (OR: 2.8, 95% CI: 0.5-16.3, p=0.26) and honeycombing in 3 (50%) anti-Ro positive patients versus 11 (16%) anti-Ro negative patients (OR: 5.1, 95% CI: 0.9-28.6, p=0.065). Although none of these differences reached statistical significance, a trend toward increased pulmonary involvement in anti-Ro positive patients was observed (Table 1).

Regarding respiratory symptoms, including dyspnea, dry cough, and reduced exercise tolerance, 66.7% of anti-Ro positive patients reported these symptoms compared with 40.3% in the anti-Ro negative group (p=0.12), suggesting a higher symptom burden in the anti-Ro positive subgroup.

Univariable logistic regression analyses were performed to examine associations between anti-Ro antibody positivity and individual pulmonary findings. Variables with $p<0.10$ in univariable analysis (age, sex, disease duration, and anti-Scl-70 positivity) were included in a multivariable logistic regression model. The Hosmer-Lemeshow test indicated a good model fit (p=0.72). The OR presented in Table 1 reflect the univariable associations between anti-Ro positivity and each pulmonary finding.

Table 1. Pulmonary findings according to anti-Ro antibody status in patients with systemic sclerosis

Variable	Anti-Ro positive (n=6)	Anti-Ro negative (n=67)	OR (95% CI)	p-value
Baseline characteristics				
Age, mean ± SD	49.2±11.6	48.5±12.6	-	0.81
Female sex, n (%)	4 (66.7%)	42 (66.7%)	1.1 (0.3-4.1)	0.89
Disease duration, median (IQR)	7 (5-11)	7 (4-12)	-	0.76
Pulmonary findings				
Pulmonary conus prominence, n (%)	2 (33.3%)	10 (14.9%)	2.8 (0.5-17.7)	0.26
Reticular pattern, n (%)	3 (50.0%)	19 (28.4%)	2.5 (0.5-13.6)	0.28
Ground-glass opacity, n (%)	4 (66.7%)	28 (41.8%)	2.8 (0.5-16.3)	0.26
Honeycombing, n (%)	3 (50.0%)	11 (16.4%)	5.1 (0.9-28.6)	0.065

OR: Odds ratio, CI: Confidence interval, SD: Standard deviation, IQR: Interquartile range

Collectively, these findings indicate a potential association between anti-Ro antibody positivity and an elevated risk of pulmonary manifestations in patients with SSc, emphasizing the importance of close monitoring and early imaging in this subgroup.

DISCUSSION

In this study, we aimed to evaluate the prevalence of anti-Ro antibodies and their association with pulmonary involvement in patients with SSc. Anti-Ro antibodies were present in a minority of patients (8.2%). Their presence was associated with a trend toward increased pulmonary abnormalities on both chest X-ray and HRCT, as well as more pronounced respiratory symptoms, although this association was not statistically significant. These findings suggest that anti-Ro positivity may identify a subgroup of SSc patients at higher risk for lung involvement. To our knowledge, this study contributes to the limited literature on the clinical relevance of anti-Ro antibodies in SSc, indicating a potential link with ILD and underscoring the importance of vigilant pulmonary monitoring in this subset of patients.

Several studies have investigated the prevalence and pulmonary implications of anti-Ro antibodies, particularly the anti-Ro52 (TRIM21) subtype, in autoimmune diseases (12). Anti-Ro52 antibodies have been frequently associated with ILD in conditions such as idiopathic inflammatory myopathies, mixed connective tissue disease, and Sjögren's disease, suggesting a potential pathogenic role in fibrotic lung involvement (13,14). In SSc, data are more limited, but emerging evidence indicates that anti-Ro52 positivity may identify patients at higher risk of ILD or progressive pulmonary manifestations (15).

For instance, a meta-analysis of 59 observational studies reported that anti-Ro52/SSA positivity in SSc was associated with ILD (OR: 1.71; 95% CI: 1.04-2.83; p=0.036) (12). A large multicenter cohort of 963 patients identified anti-Ro52/TRIM21 antibodies in approximately 20% of patients and suggested a potential association between these antibodies and ILD and overlap syndromes (16). In a longitudinal study of 43 early SSc ILD patients, 23% were anti-Ro52 positive, and these patients exhibited a significantly faster decline in vital capacity (VC) (-2.41% predicted VC per year; 95% CI: -4.28 to -0.54; p=0.013), with anti-Ro52 levels showing a dose-response relationship with lung function decline (-0.03% predicted VC per arbitrary unit per mL per year; 95% CI: -0.05 to -0.02; p<0.001) (14). More recently, dual positivity for anti-Ro52 and anti-Ro60 was shown to substantially increase the risk of ILD (adjusted OR: 2.27; 95% CI: 1.02-5.14) and disease progression (adjusted hazard ratio: 2.20; 95% CI: 1.36-3.57) compared with double-negative patients (17). Together, these findings suggest that anti-Ro52 positivity may serve as a biomarker to identify a subgroup of SSc patients at higher risk for pulmonary complications (14). Clinically, this could inform closer monitoring, earlier imaging, and potentially more proactive management strategies for ILD (12). Nevertheless, the observed associations should be interpreted cautiously, given the heterogeneity in assays, cohort sizes, and follow-up durations. Future large-scale prospective studies are needed to validate these observations and to clarify whether anti-Ro52 positivity has predictive value for disease progression or response to therapy in SSc (11,14).

The potential mechanisms linking anti-Ro antibodies, particularly anti-Ro52, to pulmonary involvement in SSc remain incompletely understood, but several hypotheses have been proposed (16). Anti-Ro52 is known to target the TRIM21 protein, which plays a role in regulating innate immune responses, including type I interferon pathways, cytokine production, and antiviral defense (18). Dysregulation of these pathways may contribute to chronic inflammation, endothelial injury, and fibroblast activation, which are central to the development of ILD in SSc (18,19). Furthermore, anti-Ro52 positivity has been associated with more severe pulmonary phenotypes in other connective tissue diseases, suggesting a potential shared pathogenic mechanism underlying autoimmune-related lung fibrosis (20). Clinically, these findings highlight the value of serologic profiling in risk stratification, as anti-Ro positive patients may benefit from closer pulmonary surveillance, including regular imaging and pulmonary function testing, even in the absence of overt respiratory symptoms (12). Early identification of at-risk patients could facilitate timely intervention, potentially mitigating disease progression and improving long-term outcomes (15).

In our cohort, anti-Ro positivity was associated with higher rates of radiographic and HRCT abnormalities, suggesting that these patients may represent a subgroup with an intermediate or overlapping risk of pulmonary complications, warranting vigilant monitoring and timely imaging (21).

Study Limitations

Despite the insights gained from our study, several limitations should be acknowledged. First, the retrospective design and relatively small sample size, particularly the low number of anti-Ro positive patients, limit the statistical power to detect significant associations and may contribute to type II errors. Second, the study did not distinguish anti-Ro52 from anti-Ro60 subtypes in all patients, which may have diluted potential subtype-specific associations with pulmonary involvement. Third, although imaging and clinical assessments were systematically reviewed,

the absence of longitudinal follow-up for pulmonary function and ILD progression constrains our ability to evaluate temporal relationships and draw causal inferences. Finally, single-center data may limit the generalizability of our findings to broader SSc populations with different demographic or ethnic characteristics. Future research should focus on prospective, multicenter studies with larger cohorts, detailed anti-Ro subtyping, serial HRCT scans, and standardized pulmonary function testing to clarify the prognostic value of anti-Ro52 antibodies and inform risk stratification and early intervention strategies in SSc-associated ILD.

CONCLUSION

In this study, anti-Ro antibodies were detected in 8.2% of patients with SSc. Individuals with these antibodies had a higher frequency of pulmonary abnormalities on imaging and more frequent respiratory symptoms than those without anti-Ro positivity, although the differences were not statistically significant. These results indicate a possible association between the presence of anti-Ro antibodies and increased pulmonary risk in SSc.

Ethics

Ethics Committee Approval: The study protocol was approved by the Fırat University Non-Invasive Research Ethics Committee (approval number: 39433, date: 24.09.2025) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.A., Z.A.A., A.K., B.Ö., Concept: Z.A.A., Design: Z.A.A., A.K., B.Ö., Data Collection or Processing: U.A., Z.A.A., B.Ö., Analysis or Interpretation: Z.A.A., A.K., B.Ö., Literature Search: U.A., Z.A.A., A.K., B.Ö., Writing: Z.A.A., A.K.

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INVESTIGATION OF THE ROLE OF HISTOGRAM ANALYSIS IN THE DIFFERENTIAL DIAGNOSIS OF INFECTIOUS AND AXIAL SPONDYLOARTHRITIS-RELATED SACROILIITIS

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Abstract

Aim: It is not easy to differentiate *Brucella* sacroiliitis from axial spondyloarthritis (axSpA)-related sacroiliitis using conventional magnetic resonance imaging (MRI). Histogram analysis, a new technique, is considered useful for differential diagnosis. This study aimed to investigate the role of MRI histogram analysis in the differential diagnosis of *Brucella* sacroiliitis and axSpA-related sacroiliitis.

Material and Methods: This study included 25 patients with axSpA-related sacroiliitis and 25 patients with sacroiliitis secondary to brucellosis. Histogram analysis of the sacroiliac MRI images of the patients was performed on inflammatory areas detected on the T2 fat-suppressed sequence. Ten percent, 90 percent, entropy, kurtosis, maximum, mean, median, minimum, skewness uniformity, and variance values were measured. The values obtained were compared between the groups.

Results: There was a statistically significant difference between the 10 percent, median, and minimum values ($p=0.018$, $p=0.029$, $p=0.002$, respectively) and no difference between the other values ($p>0.05$ for all).

Conclusion: MRI histogram analysis appears promising as a potential complementary tool for differentiating *Brucella* sacroiliitis from sacroiliitis associated with axSpA; however, these findings are preliminary and require confirmation in larger studies.

Keywords: *Brucella* sacroiliitis, axial spondyloarthritis, sacroiliitis, histogram analysis

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INTRODUCTION

The sacroiliac joint (SIJ) is the largest joint of the axial skeleton and plays a key role in transferring loads between the lumbar spine and lower extremities (1). Sacroiliitis, defined as inflammation of the SIJ, may result from infectious, rheumatic, neoplastic, or metabolic causes (2). Acute sacroiliitis is most often infectious, whereas chronic sacroiliitis is usually associated with spondyloarthropathies, in which it represents an early and characteristic feature (3,4). Infectious sacroiliitis is uncommon, accounting for 1-4% of all bone and joint infections (5). While *Staphylococcus aureus* is the predominant pathogen, other agents such as *Salmonella, Brucella, Streptococcus pyogenes*, and *Mycobacterium tuberculosis* may also be responsible (6-10). *Brucellosis*, in particular, frequently involves the SIJ (11).

Magnetic resonance imaging (MRI) is the gold standard for diagnosing sacroiliitis, as it can detect early inflammatory changes in the SIJ (12). However, findings such as bone marrow edema (BME), enthesitis, capsulitis, and synovitis are not specific to axial spondyloarthritis (axSpA) and may also occur in infectious sacroiliitis (13). Distinguishing between infectious and axSpA-related sacroiliitis is crucial because their treatment approaches differ, and delayed diagnosis of infection may lead to morbidity (14). MRI characteristics, including extensive bone erosions, pronounced capsulitis, extracapsular fluid accumulation, and periarticular muscle edema are typically suggestive of infectious processes, while iliac-sided BME and enhancement of the joint space are more commonly associated with axSpA (15).

Digital images are employed in clinical practice for diagnostic purposes. Pixels make up a two-dimensional digital image, and each pixel's gray-level intensity is represented by a value (16). By assessing signal heterogeneity that is invisible to the human eye, histogram analysis of pictures can provide quantitative information about texture-based tissue features (17). The gray-level intensity histogram offers a straightforward and compact representation of the statistical characteristics within an image. It is derived from individual pixel values, which reflect first-order statistical properties of the image (15). Parameters such as the 10^{th} and 90^{th} percentiles, entropy, kurtosis, maximum, mean, median, minimum, skewness, uniformity, and variance are included in this analysis (17,18). This method enables a more objective evaluation and provides dependable data for distinguishing and classifying benign and malignant tumors (19).

Conventional MRI sequences provide important anatomical and structural information, but their interpretation often relies on subjective assessment and visual identification of inflammatory changes. This can make it challenging to differentiate between infectious and axSpA-related causes of sacroiliitis, particularly in early or ambiguous cases. Histogram analysis is a novel, quantitative imaging method that evaluates signal heterogeneity within a region of interest (ROI) by analyzing pixel intensity distribution. Unlike conventional interpretation, this method provides objective numerical values that may reflect underlying tissue characteristics not readily visible to the human eye. While histogram analysis has been explored in other musculoskeletal and oncologic conditions, to our knowledge, it has not yet been applied to the evaluation of sacroiliitis. In this study, we aimed to investigate whether histogram-based MRI analysis can contribute to the differential diagnosis of *Brucella* and axSpA-related sacroiliitis.

MATERIAL AND METHODS

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki after obtaining approval from the Fırat University Non-Interventional Research Ethics Committee (approval no: 17285, date: 20.07.2023). Informed consent was obtained from all participants.

Patient Selection

Medical records from January 2021 to January 2023 were reviewed. Twenty-five patients diagnosed with axSpA according to the Assessment of SpondyloArthritis International Society criteria, and 25 patients diagnosed with *Brucella* sacroiliitis based on positive serology (standard tube agglutination ≥1:160 or enzyme-linked immunosorbent assay positivity) and compatible clinical findings, were included. The inclusion was irrespective of whether *Brucella* species were isolated from blood culture.

Inclusion criteria were: age >18 years, Presence of sacroiliitis confirmed on MRI, diagnosis of axSpA or brucellosis according to the above criteria.

Exclusion criteria were: history of pelvic or spinal trauma, other causes of sacroiliitis (e.g., neoplasm, tuberculosis), inadequate image quality precluding histogram analysis.

To minimize bias related to inactive disease, only patients with active BME on T2 fat-suppressed (T2-FatSat) images were included. Patients with axSpA who had only chronic structural changes without active BME were excluded.

MRI Acquisition Protocol

All MRI scans were conducted on a 1.5 Tesla system using a dedicated pelvic phased-array coil (Philips Achieva, Philips Healthcare, Best, the Netherlands). The SIJ imaging protocol consisted of semi-oblique coronal T1-weighted sequences (TR/TE: 500/12 ms), semi-oblique coronal T2-weighted fat-suppressed

sequences (TR/TE: 3500/60 ms), and axial T2-FatSat sequences (TR/TE: 3500/60 ms). Images were obtained with a slice thickness of 4-mm, an interslice gap of 0.4-mm, a field of view of 320×320 mm, and a matrix of 320×256.

ROI Placement and Histogram Analysis

A musculoskeletal radiologist with five years of experience, musculoskeletal radiologist blind to the clinical diagnosis, performed histogram analysis on the semi-oblique coronal T2-FatSat images.

Anatomical boundaries: The ROI, was drawn freehand within the BME area for each patient, eliminating cortical bone, joint space, and periarticular soft tissue, and was rigidly limited to the subchondral bone marrow space. To preserve comparability with axSpA patients, the ROI was nevertheless limited to the subchondral region in *Brucella* sacroiliitis, even if edema occasionally went beyond the usual anatomical boundaries.

Changes in axSpA structure: The ROI was positioned to cover only the edematous bone marrow and to avoid chronic lesions while taking into account the presence of erosions, fat metaplasia, or bony buds next to BME.

Participation of multiple quadrants: The ROI was positioned on the slice displaying the largest confluent BME region, if BME was found in more than one quadrant of the SIJ. To prevent intra-patient duplication bias, only one ROI per subject was examined. OsiriX V.4.9 (Pixmeo, Switzerland) was used to extract the following histogram parameters: variance, skewness uniformity, entropy, kurtosis, maximum, mean, median, minimum, and the 10th and 90th percentiles. An internal MATLAB script (version R2017a, MathWorks, Natick, MA, USA) was used to process the ROI data.

Statistical Analysis

The study data were analyzed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to assess the normality of continuous variables. Parametric numerical data with a normal distribution were expressed as mean ± standard deviation, while qualitative variables were presented as percentages. Independent group comparisons were performed using the Student's t-test, and categorical variables were compared using the chi-square test. A p-value of <0.005 was considered statistically significant in all analyses.

RESULTS

The mean age of the axSpA-related sacroiliitis group was 34.24±12.66 years, and the mean age of the *Brucella* sacroiliitis group was 41.00±14.77 years (p=0.088). The male-to-female ratios were similar between the two groups (p=0.777).

Histogram analysis parameters, including the 10th percentile, 90th percentile, entropy, kurtosis, maximum, mean, median, minimum, skewness uniformity, and variance, were compared between groups (Table 1).

A statistically significant difference was observed in the 10th percentile, median, and minimum values between the groups:

- **10th percentile:** The mean 10th percentile value was significantly lower in the *Brucella* sacroiliitis group compared with the axSpA group (p=0.018), indicating reduced signal intensity in the lowest-intensity voxels within the ROI.
- **Median:** The median gray level measurement also decreased in the *Brucella* sacroiliitis group (p=0.029), reflecting an overall shift of the intensity distribution toward lower values in infection-related sacroiliitis.
- **Minimum:** The lowest gray-level value was markedly reduced in the *Brucella* group (p=0.002), suggesting the presence of very low-intensity voxels, potentially corresponding to areas of necrosis or pronounced BME.

No statistically significant differences were found for the 90th percentile, entropy, kurtosis, maximum, mean, skewness uniformity, or variance (p>0.05 for all). The large numerical values observed for skewness and kurtosis reflect the non-normal, highly heterogeneous intensity distribution of bone marrow signal on MRI, rather than unit or calculation errors.

Although formal box-plot visualizations were not available, descriptive analysis showed that the *Brucella* sacroiliitis group consistently demonstrated a narrower range of high-intensity values and a downward shift in central tendency measures (median and 10th percentile), while the axSpA group displayed a relatively balanced distribution with higher central intensity values.

DISCUSSION

Our study showed a statistically significant difference between the two groups in the median, minimum, and 10th percentile values. According to our study, MRI histogram analysis may be promising for use in the differential diagnosis of axSpA-related sacroiliitis and *Brucella* sacroiliitis.

It is very difficult to diagnose infectious sacroiliitis because it presents similar findings as other lumbar and hip pathologies (20). Blood culture is positive in approximately 40-50% of cases, and SIJ biopsy may be required to identify the causative agent (21). It is known that 24% of patients with *Brucella* sacroiliitis are clinically asymptomatic (22). In the absence of other signs

Table 1. Comparison of histogram analysis results of groups

	Brucella sacroiliitis (mean ± standard deviation)	Inflammatory sacroiliitis (mean ± standard deviation)	p-value
10 percent	87.19±27.82	109.01±31.07	**0.018**
90 percent	154.84±43.12	179.12±49.83	0.132
Entropy	13.836±97.031	12.407±10.374	0.854
Kurtosis	17.518±16.145	16.776±13.145	0.528
Maximum	184.64±44.27	204.36±45.85	0.096
Mean	13.335±11.354	12.000±66.954	0.691
Median	115.14±31.89	143.32±45.62	**0.029**
Minimum	37.32±29.40	65.92±30.42	**0.002**
Skewness	97.688±35.708	-713.121±35.656	0.455
Uniformity	0.29343±0.07733	0.27320±0.08811	0.282
Variance	10.186±10.362	12.866±13.157	0.516

of infection, it may be difficult to differentiate between *Brucella* sacroiliitis and axSpA-related sacroiliitis. Clinical findings and laboratory tests are usually non-specific and provide limited diagnostic information. The causative bacteria may not be easily detected in blood tests and patients may be misdiagnosed with axSpA-related sacroiliitis, leading to inappropriate treatment. While early stage, changes on MRI can be important for diagnosis, they may not always provide enough information to make a definitive distinction between these conditions. Therefore, additional diagnostic tools are required for differentiation. Karayol and Karayol (23) investigated the role of diffusion-weighted MRI in the differential diagnosis of *Brucella* sacroiliitis and seronegative spondyloarthropathy but found no statistically significant difference between the measurements. In contrast to diffusion-weighted MRI, histogram analysis offers voxel-based quantification of intensity distributions and may detect subtle signal differences invisible to the naked eye, which may explain the significant findings in our study.

Histogram analysis has been applied in various radiologic contexts to quantify tissue characteristics and improve diagnostic accuracy. For instance, Ağlamış and Baykara (24) demonstrated its utility in differentiating malignant from benign breast lesions, showing significantly lower minimum and low-percentile values, along with higher skewness and lower uniformity in malignant cases. Similarly, Baykara et al. (25) found that histogram-derived parameters such as entropy, variance, and skewness were significantly lower in the affected median nerves of patients with carpal tunnel syndrome, despite normal-appearing signal intensity. Colombi et al. (26) used histogram-based quantitative computed tomography assessments to monitor disease progression in idiopathic pulmonary fibrosis. In another study, Yildirim and Baykara (18) observed significantly higher minimum, median, and maximum values in lytic bone metastases compared to multiple myeloma. These studies collectively show that histogram parameters can reveal microstructural alterations and tissue heterogeneity not visible on conventional MRI. Similarly, in sacroiliitis, the distribution of voxel intensities may correspond to variations in marrow perfusion, inflammatory infiltration, and edema. Such pathophysiological changes differ between infection-related and axSpA-related sacroiliitis, explaining the distinct histogram profiles observed in our study.

Our findings align with recent quantitative imaging studies in axSpA. Xie et al. (27) performed whole-joint histogram analysis using mono- and bi-exponential diffusion-weighted imaging (DWI) and diffusion kurtosis imaging in 82 patients with axSpA and 17 with non-specific low back pain. Parameters such as perfusion fraction, mean kurtosis, and mean diffusivity were analyzed. While these metrics showed limited ability to distinguish active from inactive axSpA, they successfully differentiated both groups from controls. Mean diffusivity correlated with high-sensitivity C-reactive protein, and most parameters correlated with bath ankylosing spondylitis disease activity index, whereas the Spondyloarthritis Research Consortium of Canada score did not differentiate disease activity. Although our study differed by using T2-FatSat sequences and lacking a control group, both studies support the idea that quantitative histogram-derived parameters can provide diagnostic information beyond conventional MRI.

From a methodological perspective, *Brucella* sacroiliitis often presents with edema extending beyond typical anatomical boundaries and may occasionally form abscesses. In our study,

ROIs were restricted to the subchondral bone marrow to maintain comparability with axSpA cases, potentially excluding some peripheral infection-related changes. This restriction may have also led to the omission of perilesional edema or small abscess formations, commonly seen in *Brucella* sacroiliitis, which could have resulted in underestimation of signal heterogeneity in these cases. The lower minimum and median histogram values observed in the *Brucella* group likely reflect the underlying pathophysiology of infection, characterized by diffuse marrow edema, inflammatory infiltration, and micro-necrotic changes that reduce signal homogeneity. In contrast, sacroiliitis associated with axSpA tends to show localized inflammation with relatively preserved marrow architecture, resulting in higher median intensity values. Conversely, axSpA often presents with coexisting structural changes (erosions, fat metaplasia) near active lesions, although these were avoided during ROI placement, subtle overlap could still influence histogram values. Furthermore, the radiologist performing ROI placement was blinded to diagnosis, but could not be entirely unaware of certain typical patterns, introducing potential observer bias.

Compared with other advanced quantitative MRI techniques such as DWI and radiomics, histogram analysis provides a simpler and sequence-independent method that can be implemented on standard MRI data without additional scanning time. While DWI and radiomics yield more complex diffusion or texture-based metrics, they often require specialized acquisition protocols and post-processing software. In contrast, histogram analysis allows rapid voxel-based quantification of tissue heterogeneity using routinely acquired images. Therefore, it may serve as a practical complementary technique, and its integration with diffusion or radiomic parameters could further enhance diagnostic accuracy in distinguishing infectious and inflammatory sacroiliitis.

To our knowledge, this is the first study to evaluate histogram analysis in the differential diagnosis of sacroiliitis. The significant differences in median, minimum, and 10th percentile values between groups indicate that histogram parameters can quantitatively reflect disease etiology and assist in diagnosis. Larger multicenter, prospective studies with control groups and blinded multi-reader analysis are required to validate these preliminary findings. Integrating histogram analysis with other advanced imaging techniques, such as radiomics or diffusion metrics, may further improve diagnostic accuracy.

Study Limitations

This study has several limitations that should be acknowledged. First, the retrospective and single-center design may introduce selection bias and limit the generalizability of the findings. Second, the relatively small sample size (25 patients per group) reduces statistical power and precludes robust subgroup analyses. Third, the absence of a healthy control or non-specific low back pain group prevented the assessment of diagnostic accuracy parameters such as sensitivity, specificity, and ROC analysis. Fourth, although the radiologist performing the ROI analysis was blinded to the clinical diagnosis, subtle imaging patterns could still have introduced observer bias. In addition, the restriction of the ROI to subchondral bone areas in *Brucella* cases may have excluded peripheral edema or abscess formations, potentially influencing the histogram parameters. Because multiple histogram variables were analyzed, the possibility of type I error due to multiple comparisons cannot be excluded. Furthermore, the relatively large numerical values observed for skewness and kurtosis reflect non-normal intensity distributions rather than calculation errors; however, this heterogeneity may complicate direct comparison across cases. Finally, the results should be interpreted as preliminary and exploratory; larger, multicenter, prospective studies incorporating control groups and advanced quantitative MRI techniques are needed to validate and expand upon these findings.

CONCLUSION

MRI histogram analysis of T2-FatSat images provides objective and quantitative information that may potentially assist in differentiating *Brucella* sacroiliitis from sacroiliitis associated with axSpA. The lower minimum, median, and 10th percentile values observed in the *Brucella* group suggest characteristic signal intensity patterns related to infection. However, these findings should be regarded as preliminary and exploratory. Histogram-derived parameters may serve as supportive tools in differential diagnosis, but larger, multicenter, prospective studies are required to validate their diagnostic value.

Ethics

Ethics Committee Approval: This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki after obtaining approval from the Fırat University Non-Interventional Research Ethics Committee (approval no: 17285, date: 20.07.2023).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Y.U., Concept: E.Y.U., G.A., M.F.U., Design: E.Y.U., A.G., M.F.U., Data Collection or Processing:

E.Y.U., M.Y., Ş.Ö.B., Gü.A., Analysis or Interpretation: E.Y.U., M.Y., Ş.Ö.B., A.G., Gü.A., Literature Search: E.Y.U., M.Y., Gü.A., Writing: E.Y.U., M.F.U.

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INCREASED PREVALENCE OF SCOLIOSIS IN PSORIATIC ARTHRITIS: A CROSS-SECTIONAL CASE-CONTROL STUDY

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Abstract

Aim: Psoriatic arthritis (PsA) is expected to cause an increased risk of scoliosis because it affects the axial skeleton asymmetrically. In this study, we compared the frequency of scoliosis in PsA patients with that in healthy controls (HC) and axial spondyloarthritis (axSpA) patients. Thus, we aimed to explore whether scoliosis might be a clinical feature of PsA and to assess its potential role in differentiating PsA from axSpA.

Material and Methods: The study included 60 PsA patients, 60 axSpA patients and 40 HC. All individuals in the study were assessed for the presence of scoliosis by physical examination. Scoliosis radiography was performed in those with a positive scoliosis test on physical examination. The Cobb angle was measured using the appropriate method. A two-tailed significance level of 0.05 was considered in all analyses.

Results: Within this research, the frequency of scoliosis in PsA patients was compared with the axSpA and HC groups. The Cobb angle value was notably higher in the PsA group compared to axSpA and HC ($p=0.006$ and $p=0.007$, respectively). On physical examination, scoliosis findings and coronal spinal curvature, were observed at elevated rates in the PsA group relative to the other two groups ($p>0.05$ for all, indicating no statistical significance). Scoliosis was more frequent in the PsA group than in the axSpA group ($p=0.046$). All scoliosis cases in PsA were in mild or moderate severity.

Conclusion: Both the frequency of scoliosis and Cobb angle values were greater in PsA than those in axSpA. This outcome may be associated with the asymmetric involvement of lateral spinal structures typical of PsA. Overall, these results indicate that scoliosis could serve as a supportive marker for PsA and may aid in differentiating PsA from axSpA.

Keywords: Psoriatic arthritis, axial spondyloarthritis, scoliosis

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disorder that presents with a heterogeneous clinical spectrum and is associated with psoriasis (Pso) (1). The worldwide prevalence of PsA is estimated at 112 cases per 100,000 adults, affecting both men and women equally. It most frequently occurs in individuals aged 30-60 years. PsA develops in approximately 30% of patients with Pso (1,2), and can result in widely varying clinical manifestations, which often contributes to delays in diagnosis and management (3).

PsA may lead to peripheral and axial involvement. Axial involvement, which is 5-28% at the time of diagnosis, may increase up to 70% in the later stages (1). In addition to sacroiliac joints and spines, inflammation findings have been demonstrated in facet joints, ligaments, capsules, costovertebral and costotransverse joints, and entheses (3). In axial PsA, active inflammatory and structural changes, including asymmetric inflammation, erosion and osteoproliferation, may be observed in the sacroiliac joints and spine (3-7). Unlike ankylosing spondylitis, axial involvement in PsA is frequently asymmetric (3-6).

Scoliosis is usually defined as spinal curvature in the coronal plane. However, scoliosis is a more complex three-dimensional problem involving sagittal and horizontal planes (8,9). In addition to adolescent idiopathic scoliosis, adult scoliosis is an important health problem (9-12). Asymmetrical damage to the structures forming the spine, such as discs and facet joints, predisposes individuals to the development and progression of scoliosis (13,14).

Rheumatic inflammatory diseases are expected to lead to an increase in posture disorders due to their effects on the musculoskeletal (MSK) system. There are few studies investigating the presence of scoliosis in rheumatic diseases (15-22). PsA causes asymmetrical inflammatory and structural alterations in the spine and sacroiliac joints. Furthermore, it can asymmetrically involve lateral structures such as the facet joints. These observations indicate that patients with PsA might have an increased risk of developing scoliosis. To date, no studies have specifically explored the association between PsA and scoliosis in the literature.

We hypothesized that individuals with PsA are more likely to develop coronal plane-dominant postural abnormalities and scoliosis. To investigate this, we assessed the prevalence of scoliosis in PsA patients and compared the findings with those from healthy controls (HC) and patients with axial spondyloarthritis (axSpA).

MATERIAL AND METHODS

This study was approved by the İnönü University Faculty of Medicine Clinical Research Ethics Committee (approval no: 2024/08, date: 10.01.2024). All procedures were carried out in accordance with the principles of the Declaration of Helsinki (1964). Written informed consent was obtained from all participants.

Study Design and Participants

This cross-sectional case-control study was carried out to assess the presence of scoliosis in 60 consecutive patients with PsA, 60 patients with axSpA, and 40 HC who attended the Internal Medicine Rheumatology Outpatient Clinic of İnönü University, Turgut Özal Medical Centre, in 2024.

Hypothesis and Sample Size Calculation

The primary hypothesis of this research was that the prevalence of scoliosis would be markedly higher in PsA patients in comparison to both axSpA patients and HC. The alternative hypothesis suggested that there would be a meaningful difference in scoliosis prevalence between the axSpA cohort and the control group. The necessary sample size was calculated through a power analysis that was carried out according to the assumptions of the study.

Inclusion and Exclusion Criteria

Patients aged 18-65 years along with HC were enrolled in the study. PsA cases fulfilled the ClASsification criteria for Psoriatic ARthritis (CASPAR) classification criteria, while axSpA cases met the 2009 Assessment of SpondyloArthritis International Society classification criteria. Individuals with axial PsA were not considered within the axSpA group. Patients with features suggestive of axial PsA were excluded from the axSpA group. Patients diagnosed with PsA according to the CASPAR criteria were not included in the axSpA group. The differentiation was made based on peripheral joint involvement patterns and imaging findings, including asymmetric sacroiliitis and non-marginal syndesmophytes. Exclusion criteria consisted of pregnancy, as well as neurological, traumatic, or other systemic conditions that could result in spinal deformities.

Scoliosis Assessment Methods

All individuals enrolled in the study were examined for the presence of scoliosis by physical assessment. Scoliosis radiography was performed in individuals with a positive scoliosis test on physical examination. Radiological evaluation was performed with posteroanterior spine radiography and the Cobb angle was

measured with the appropriate method. Individuals with a Cobb angle of 10° and above were defined as having scoliosis. Those with Cobb angle between 10° and 20° were classified as mild scoliosis, 20-40° as moderate scoliosis, and >40° as severe scoliosis.

Statistical Analysis

The statistical procedures were conducted with IBM SPSS Statistics for Windows, version 26.0 (Armonk, NY, USA). Normality was assessed with the Shapiro-Wilk test and homogeneity of variances with Levene's test. Normally distributed variables were presented as the mean ± standard deviation and were compared using one-way ANOVA followed by Tukey's post-hoc test. Non-normally distributed variables were shown as median (minimum-maximum) and assessed using the Kruskal-Wallis test with Bonferroni-adjusted pairwise comparisons. Categorical variables were presented as counts and percentages, and compared using Pearson chi-square, continuity-corrected chi-square, or exact chi-square tests as appropriate, with Bonferroni correction for multiple comparisons. In the tables, statistically significant group differences were indicated with different superscripts (a,b) following APA style. Correlations between quantitative variables were examined using Spearman's rank correlation. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic Information or Baseline Characteristics

Demographic, clinical, and laboratory data of all study groups are summarised in Table 1.

Scoliosis Data

A marked difference was observed among the groups (PsA, axSpA, and HC) regarding scoliosis positivity on examination. The PsA group showed a higher frequency of scoliosis compared to both the axSpA and HC groups. In contrast, no clear difference was detected between the axSpA and HC groups in terms of scoliosis presence on examination (p>0.05) (Table 2).

There was a significant difference between the groups (PsA, axSpA and HC) in terms of the presence of scoliosis (Cobb angle ≥10.0) as seen on scoliosis radiograph. The presence of scoliosis on radiograph was more prevalent in the PsA group compared to the axSpA group. However, there was no significant difference between the PsA and HC groups in terms of the presence of scoliosis on radiograph (p>0.05). In addition, there was no significant difference between axSpA and HC groups in terms of the presence of scoliosis (p>0.05) (Table 2). Five (62.5%) of the scoliosis cases in the PsA group had mild scoliosis and three (37.5%) had moderate scoliosis. All scoliosis cases in the axSpA and HC groups were mild.

A clear difference was detected among the groups in terms of the median Cobb angle. The PsA group had a higher median Cobb angle compared to the axSpA and HC groups (p=0.006 and p=0.007, respectively). However, no difference was observed between the PsA and HC groups regarding median Cobb values (p=1.000) (Table 2).

Subgroup Analyses for PsA Patients

In PsA patients, scoliosis was more common in women and those with comorbidities, both clinically and radiographically (all p<0.05). Additionally, Cobb angle showed a slight but clear positive correlation with age (r=0.337, p=0.009) and Health Assessment Questionnaire score (r=0.356, p=0.005).

DISCUSSION

This study evaluated the occurrence of scoliosis among PsA patients in comparison with axSpA patients and HC. The Cobb angle was higher in the PsA group than in the axSpA group, and HC. Findings from physical examination and coronal spinal curvature were more pronounced in the PsA group compared to the other two groups. Scoliosis was also more common in the PsA group than in the axSpA group. These results indicate that scoliosis could be a helpful feature in the differential diagnosis of PsA and axSpA.

Rheumatic inflammatory diseases may have an effect on body posture and specifically on scoliosis due to their direct effect on the MSK system. While almost all rheumatic inflammatory diseases affect peripheral synovial joints, SpA group diseases directly affect the axial skeleton. Since the SpA group affects the axial skeleton, individuals in this group are expected to have more posture deficits. Different SpA subgroups may affect different MSK regions symmetrically or asymmetrically, with different severity (23-25). PsA may exacerbate scoliosis because of asymmetrical functional, inflammatory and structural changes in axial skeletal structures (3,4,6,25).

Within this study, scoliosis was more prevalent in the PsA group. Moreover, the presence of scoliosis on examination and coronal curvature of the spine were observed at relatively greater rates in this group. In addition, while there was no study directly evaluating the frequency of scoliosis in axSpA, two indirect studies provided important insights on this topic (21,22).

For example, in the DESIR cohort, 362 patients aged 18-50 years with early inflammatory back pain were evaluated for lumbar scoliosis. The mean Cobb angle was reported as 3.2°±5.0°, and lumbar scoliosis was detected in 28 patients (7.7%); all cases were grade I or II scoliosis, with no severe scoliosis observed (21). Scoliosis showed no significant association with clinical

features, radiographic or magnetic resonance imaging-detected degenerative changes, or diagnostic confidence in axSpA. Furthermore, Cobb angle was not correlated with modified stoke ankylosing spondylitis spine score or radiographic sacroiliitis scores. These findings suggest that lumbar scoliosis is uncommon in young adults with early inflammatory back pain and does not affect axSpA classification criteria or diagnostic confidence.

In contrast, Yong et al. (22) conducted a large-scale retrospective cohort study in Taiwan, investigating the incidence and risk of axSpA in patients with scoliosis. The study included 4,261 patients with scoliosis and 21,305 age- and sex-matched controls, followed for 7 years. The incidence of axSpA was significantly higher in patients with scoliosis (141 vs. 46 per 100,000 person-years). The crude and adjusted hazard ratios were reported as 2.98 [95% confidence interval (CI), 1.87-4.73; p<0.001] and

Table 1. Demographic, clinical and laboratory characteristics of the study groups

Variable		PsA (60)	AxSpA (60)	HC (40)	p-value
Age (years), mean ± SD		46.7±10.9[a]	43.7±11.1[a]	37.4±8.1[b]	<0.001
Gender (famale/male), n (%)		40 (66.7)/20 (33.3)	37 (61.7)/23 (38.3)	19 (47.5)/21 (52.5)	0.151
BMI, mean ± SD		29.5±6.1[a]	29.3±4.8[a]	26.1±4.4[b]	0.003
Smoking, n (%)		26 (43.3)	24 (40.0)	14 (35.0)	0.707
Comorbidity, n (%)		36 (60.0)[a]	25 (41.7)[ab]	9 (22.5)[b]	0.001
Time to diagnosis (years), median (min-max)		6 (0-18)	6 (0-17)	-	0.418
Symptom duration (years), median (min-max)		9 (2-35)	10 (2-28)	-	0.271
DAS28-CRP, median (min-max)		2.33 (1.3-6.3)	-	-	-
DAPSA, median (min-max)		14.00 (2.6-67.8)	-	-	-
HAQ, median (min-max)		0.35 (0-1.40)	-	-	-
PASI, median (min-max)		0.3 (0-7.0)	-	-	-
History of psoriasis in himself		46 (76.7)	0 (0)	0 (0)	-
Involved regions	Axial, n (%)	3 (5)[a]	57 (95)[b]	-	<0.001
	Peripheral, n (%)	1 (1.7)[a]	0 (0)[a]	-	
	Axial+peripheral, n (%)	56 (93.3)[a]	3 (5)[b]	-	
Dactylitis, n (%)		5 (8.3)	0 (0)	-	0.057
Uveitis, n (%)		3 (5)	3 (5)	-	1.000
Nail attachment, n (%)		42 (70.0)	0 (0)	-	<0.001
Enthesitis, n (%)		32 (53.3)[a]	0 (0)b	1 (2.5)[b]	<0.001
ESR, median (min-max)		11 (2-45)[a]	7 (1-44)[a]	5 (2-8)[b]	0.006
CRP, median (min-max)		1 (0-14)[a]	1 (0-7)[a]	0 (0-0)[b]	<0.001

Values that do not share a letter (e.g., [a] vs. [b]) are significantly different at p<0.05 according to one-way ANOVA followed by Tukey's post-hoc test. A group labeled with two letters (e.g., [ab]) does not significantly differ from groups labeled with either of those individual letters ([a] or [b]).
PsA: Psoriatic arthritis, AxSpA: Axial spondyloarthritis, HC: Healthy controls, BMI: Body mass index, DAS28-CRP: Disease activity score-28 using C-reactive protein, DAPSA: Disease activity index for psoriatic arthritis, HAQ: Health Assessment Questionnaire, PASI: Psoriasis area and severity index, ESR: Erythrocyte sedimentation rate, SD: Standard deviation

Table 2. Scoliosis data of the study groups

Variable	PsA (n=60)	AxSpA (n=60)	HC (n=40)	p-value
Scoliosis on examination, n (%)	25 (41.7)[a]	11 (18.3)[b]	4 (10.0)[b]	0.001
Scoliosis (Cobb angle ≥10.0), n (%)	8 (13.3)[a]	1 (1.7)[b]	2 (5.0)[a,b]	0.039
Cobb angle, median (min-max)	0 (0-26.0)[a]	0 (0-10.0)[b]	0 (0-12.0)[b]	0.002

Values that do not share a letter (e.g., [a] vs. [b]) are significantly different at p<0.05 according to one-way ANOVA followed by Tukey's post-hoc test. A group labeled with two letters (e.g., [ab]) does not significantly differ from groups labeled with either of those individual letters ([a] or [b]).
PsA: Psoriatic arthritis, AxSpA: Axial spondyloarthritis, HC: Healthy controls

2.78 (95% CI, 1.74-4.43; p<0.001), respectively (22). These findings indicate a significant association between scoliosis and axSpA and highlight the need for further studies to clarify the underlying mechanisms.

The increased occurrence of scoliosis in PsA patients compared to axSpA may be attributed to the asymmetric involvement of spinal structures characteristic of PsA, such as cervical spine alterations, asymmetric sacroiliitis, and non-marginal syndesmophytes (3). This asymmetry may lead to uneven mechanical loading, contributing to spinal deformity, consistent with the pathophysiology of adult scoliosis. MSK pathologies that destabilize the spine—such as disc, facet joint, or ligament damage—can cause segmental instability and asymmetric degeneration, creating a vicious cycle of deformity and progression (11,12). The presence of these mechanisms in PsA supports the higher scoliosis frequency observed in our study.

The observation of relatively less scoliosis was observed in the axSpA group in our study may be due to this disease affecting the spinal structures predominantly symmetrically and causing loading in the sagittal plane. Symmetrical marginal thin syndesmophytes are frequently observed in ankylosing spondylitis (3). This suggests that axial PsA may lead to multiplanar and especially coronal posture disorders , despite the typical posture disorder (cervical flattening, increase in dorsal kyphosis, decrease in lumbar lordosis) developing in the sagittal plane expected in ankylosing spondylitis (3). The observation of fewer cases of scoliosis was observed in axSpA in our study seems to be compatible with the naturally expected progression of the disease.

All scoliosis cases in the PsA group were mild or moderate. In addition, scoliosis was not detected on radiographs in some of the patients who exhibited scoliosis symptoms on examination. Some of the patients with curvature on examination had mild scoliosis on radiographs. Although PsA affects the lateral structures of the spine asymmetrically in a way that predisposes to scoliosis, the body tries to compensate by bending the upper and lower parts of the spine to the opposite side to shift the centre of gravity to compensate for this. This may create new asymmetrical mechanical stress and inflammation points (11-14). In time, rough syndesmophytes and facet joint ankylosis may occur at these points (3-7). Although there is a predisposition to scoliosis in this process, pathological compensatory mechanisms formed in the progressive process may have contributed to scoliosis remaining at a certain level. In our study, although the frequency of scoliosis increased in PsA patients, the scoliosis remained at a mild or moderate level, which is consistent with our observations.

Our study revealed that scoliosis rates did not differ significantly between axSpA patients and HC. This may be because axSpA affects the lateral structures in the axial skeleton symmetrically. This predisposes individuals to the development of postural disorders in the axial plane rather than the coronal plane. The typical ankylosing spondylitis posture (“question mark” posture) in ankylosing spondylitis supports this (24,25). In radiographic axSpA, ossification of the ligaments around the spine, which develops in the late period, and development of symmetrical syndesmophytes between adjacent vertebrae or facet joint ankylosis, even if pathological, may limit the development of scoliosis by stabilising the spine (25).

Few studies have examined the occurrence of scoliosis in rheumatic diseases other than SpA. Among these studies, lumbar scoliosis was reported to have a relatively high prevalence, ranging from 16% to 42.6% in patients with rheumatoid arthritis (RA) (15-18). Epidemiological studies have shown that lumbar scoliosis is common in patients with and is influenced by age, disease activity, RA and treatment factors. Makino et al. (15) reported a prevalence of lumbar scoliosis of 32.0% among 241 RA patients evaluated by dual-energy X-ray absorptiometry, with an average Cobb angle of 13.6°±4.4° in patients with scoliosis. Multivariate analysis identified age as the only independent risk factor (15). Mochizuki et al. (16) conducted a larger cohort study of 411 RA patients and found a scoliosis prevalence of 30.7%, with age and vertebral fracture identified as factors associated with scoliosis. Finally, Yamada et al. (17) in a prospective longitudinal cohort study with a mean follow-up of 7 years, reported an incidence of scoliosis of 16% and identified inadequate control of RA as an independent risk factor for newly developed scoliosis. Collectively, these studies suggest that scoliosis in RA is not merely an age-related degenerative change but a complex process influenced by both disease activity and treatment factors. In a study of children with juvenile arthritis, scoliosis developed in 20% of the patients, and it was found to be particularly associated with leg length discrepancy; lower extremity joint inflammation was suggested as contributing to postural abnormalities in the axial skeleton (20). These findings suggest that in pediatric inflammatory arthritis, scoliosis may also result from a combination of systemic inflammation and mechanical factors. Overall, in both adult and pediatric inflammatory arthritis, scoliosis appears to be associated with age, disease control, and joint/lower extremity alignment. Studies in RA and juvenile idiopathic arthritis suggest that the systemic effects of these diseases, such as asymmetrical involvement of lower extremity joints, or osteoporotic vertebral

fractures, may contribute to the development or progression of scoliosis. However, unlike conditions with new bone formation observed in the SpA group, the absence of new bone formation in these conditions indicates that spinal deformities may follow a different course. This difference suggests that the development mechanisms of scoliosis may vary according to the course and pathophysiology of different inflammatory arthritides.

Our study is the first to investigate the presence of scoliosis in PsA patients. In addition, although there are indirect studies on scoliosis in the axSpA group, this was the first study to directly evaluate it. The inclusion of the axSpA group in addition to the HC group contributed to revealing the differences scoliosis across different SpA groups.

Study Limitations

There were some limitations in our study. Since our study was cross-sectional, it did not show how scoliosis changed during the course of the disease. The mean age of the PsA group was slightly higher than that of the other groups. Considering that the frequency of degenerative scoliosis may increase with age, this potential increase with age should be regarded as a limitation of the present study. In addition, the PsA group had higher body mass index (BMI) values compared to the HC. Given that a higher BMI may increase the likelihood of degenerative scoliosis, this factor should be considered as a potential limitation of our study. Since the number of subjects in the study groups was adjusted to test the hypothesis of the presence of scoliosis, there were limitations in analyses between subgroups, such as those related to age and gender. Conducting the study in a single centre limits the ability to generalise the findings. This study focused on PsA and axSpA patients, while other spondyloarthritis subgroups, including reactive arthritis and inflammatory bowel disease-associated SpA, were not included. This limits the generalizability of our findings to all forms of spondyloarthritis, and future studies should evaluate scoliosis across a broader spectrum of SpA subtypes. Multivariate analysis accounting for factors such as age, sex, BMI, and comorbidities was not performed. This represents a limitation in interpreting our results. To avoid unnecessary radiation exposure, radiographs were obtained only for subjects with positive physical findings; therefore, subclinical scoliosis cases might have been missed, potentially leading to an underestimation of scoliosis prevalence. To confirm these findings, future multicentre studies in different patient populations, with larger sample sizes, assessing the presence of scoliosis over long-term follow-up in PsA and other SpA groups, are needed.

CONCLUSION

In summary, the Cobb angle was notably higher in the PsA group compared to both the axSpA and HC groups. Examination and imaging, revealed higher rates of scoliosis in PsA patients than in those with axSpA. All scoliosis cases observed in the PsA group were classified as mild or moderate. These results suggest that the presence of scoliosis may be a supportive feature in PsA and could potentially contribute to differentiating PsA from axSpA, although further studies with formal diagnostic analyses are needed to confirm this.

Ethics

Ethics Committee Approval: This study was approved by the İnönü University Faculty of Medicine Clinical Research Ethics Committee (approval no: 2024/08, date: 10.01.2024).

Informed Consent: Written informed consent was obtained from all participants.

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Footnotes

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Concept: E.İ., S.Y., E.E., S.Z., Z.K., H.G.G.B., Design: E.İ., S.Y., E.E., S.Z., Z.K., M.S.A., Data Collection or Processing: E.İ., S.Y., E.E., S.Z., Z.K., Analysis or Interpretation: E.İ., S.Y., E.E., S.Z., Z.K., H.G.G.B., Literature Search: E.İ., S.Y., E.E., S.Z., Z.K., H.G.G.B., Writing: E.İ., S.Y., E.E., S.Z., Z.K., M.S.A., H.G.G.B.

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CASE REPORT AND LITERATURE REVIEW

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CLINICAL IMPROVEMENT IN SYSTEMIC SCLEROSIS-ASSOCIATED LOWER EXTREMITY ULCERS USING TOCILIZUMAB AND OZONE THERAPY COMBINATION: A REPORT OF TWO CASES

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Abstract

The aim of this case report was to evaluate the potential efficacy of adjunctive ozone therapy combined with tocilizumab in treating refractory lower extremity ulcers in patients with diffuse systemic sclerosis (SSc). We report two female patients with diffuse SSc who developed refractory ulcers despite prior therapies, including azathioprine, mycophenolate mofetil, cyclophosphamide, and vasodilators. Both patients were receiving weekly subcutaneous tocilizumab (162 mg) when ozone therapy was introduced. The protocol consisted of major autohemotherapy with ozone (initial dose 15 µg/mL; maintenance dose 65 µg/mL), combined with ozone bagging. Treatment included 25 daily sessions, 25 twice-weekly sessions, and subsequent weekly maintenance sessions. Both patients exhibited significant ulcer healing, pain reduction, and improved mobility, suggesting synergistic effects beyond those of tocilizumab monotherapy. Refractory SSc-associated ulcers remain a therapeutic challenge. The combination of tocilizumab and ozone therapy may provide additional benefits through anti-inflammatory and microcirculatory mechanisms. Controlled trials are warranted.

Keywords: Systemic sclerosis, ozone therapy, tocilizumab, refractory ulcers

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease characterized by immune activation, vasculopathy, and progressive fibrosis, resulting in high morbidity and mortality (1). Digital and lower-extremity ulcers are frequent complications, often refractory to conventional therapies, and have a major impact on quality of life (2). Tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, has shown efficacy in slowing the progression of SSc-related interstitial lung disease and may modulate fibrotic pathways (3). Ozone therapy, which exerts immunomodulatory, antioxidant, and microcirculatory effects, has been investigated in small trials for SSc-associated ulcers (4-6). However, its use in combination with tocilizumab has not yet been reported. We describe two cases of refractory lower-extremity ulcers in patients with diffuse SSc that improved with this combined approach.

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CASE REPORTS

Case 1

A 34-year-old woman with a 10-year history of diffuse SSc and no comorbidities presented with extensive digital and lower-extremity ulcers refractory to azathioprine, mycophenolate mofetil, cyclophosphamide, and intravenous immunoglobulin. She had been receiving tocilizumab at a dose of 162 mg subcutaneously once weekly since December 2023. Adjunctive ozone therapy began eight months earlier and consisted of major autohemotherapy starting at 15 µg/mL combined with ozone bagging: 25 daily sessions, followed by 25 twice-weekly sessions, and then weekly maintenance at 65 µg/mL. Clinical improvement of the ulcers—reduced pain, granulation tissue formation, and decreased necrotic borders—was first observed at the end of the second month of ozone therapy (Table 1).

Diagnostic Differentiation

Computed tomography/magnetic resonance (CT/MR) angiography showed no macrovascular occlusion or features of vasculitis. Laboratory evaluation, including anti-neutrophil cytoplasmic antibodies (ANCA) panel, complement levels (C3/C4), cryoglobulins, hepatitis serologies, inflammatory markers, and urinalysis, revealed no abnormalities suggestive of systemic vasculitis, which supports an SSc-related microvascular etiology. Wound and blood cultures demonstrated no bacterial growth, further excluding an infectious cause of the ulceration.

Marked ulcer healing, pain reduction, and improved mobility were observed within two months, along with decreased analgesic use (Figure 1).

Concomitant Care

No surgical debridement, topical antiseptics or antibiotics, systemic antibiotics, advanced dressings, negative-pressure therapy, or other wound-directed medications were administered during the ozone and IL-6 inhibitor treatment period.

Case 2

A 36-year-old woman with a 14-year history of diffuse SSc, with no comorbidities, who had been previously treated with mycophenolate mofetil, acetylsalicylic acid, nifedipine, and pentoxifylline, developed a refractory dorsal foot ulcer following

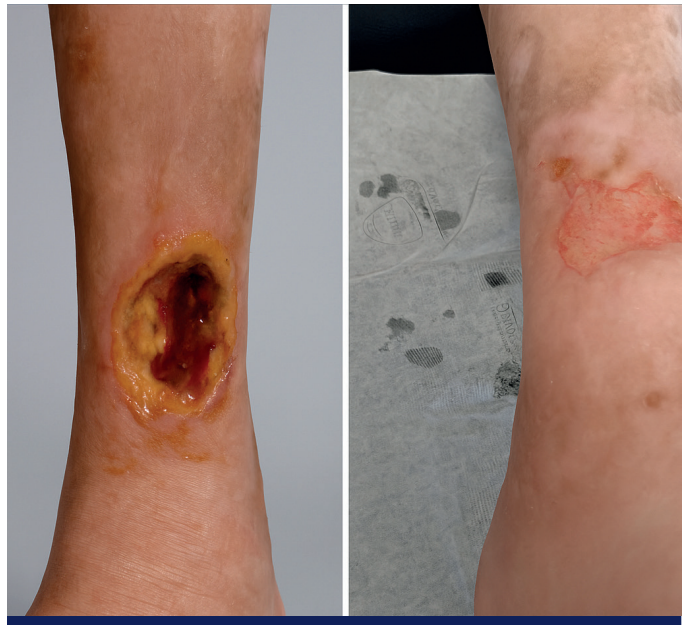

Figure 1. Marked ulcer healing in Case 1

Table 1. The protocol of ozone treatment

Component	Description
Therapeutic approach	Combined major autohemotherapy (MAH) and ozone bagging
Initial ozone concentration (MAH)	15 µg/mL
Maintenance ozone concentration (MAH)	65 µg/mL
Gas mixture	Medical-grade ozone-oxygen mixture generated immediately before administration
Volume of blood used (MAH)	Approximately 100-150 mL of patient's venous blood
Procedure (MAH)	Venous blood is withdrawn under aseptic conditions, exposed to the ozone-oxygen mixture at the specified concentration, and then reinfused intravenously over 10-15 minutes
Ozone bagging	A localized treatment in which the affected limb or ulcer area is enclosed in an airtight bag filled with ozone gas to promote local oxygenation and antiseptic effects
Treatment schedule	25 consecutive daily sessions → 25 twice-weekly sessions → Weekly maintenance sessions thereafter
Total duration	Approximately 6-8 months, depending on clinical response
Goal of therapy	To enhance tissue oxygenation, modulate inflammation, promote microcirculation, and accelerate ulcer healing

trauma. Tocilizumab 162 mg subcutaneously once weekly has been administered since September 2024; ozone therapy was introduced five months later as an adjunct therapy. A clear clinical response to ozone—decreased pain, emergence of healthy granulation tissue, and reduction in ulcer size—was first observed at the end of the third month of ozone therapy.

Diagnostic Differentiation

As in Case 1, CT/MR angiography demonstrated no large-vessel stenosis or occlusion and no vasculitic involvement. Laboratory studies likewise showed no evidence suggestive of vasculitis (ANCA negative, complement levels not depressed, no cryoglobulinemia, and unremarkable inflammatory markers and urinalysis). Wound and blood cultures demonstrated no bacterial growth (no bacterial proliferation on culture), further excluding an infectious driver of ulceration.

Concomitant Care

No surgical debridement, topical antiseptics/antibiotics, systemic antibiotics, advanced dressings, negative-pressure therapy, or other wound-directed medications were administered during the ozone/IL-6 inhibitor treatment period.

A skin biopsy was not performed in either patient. Diagnostic confidence was supported by the clinical phenotype of diffuse SSc-related ischemic ulcers, negative vascular imaging (no macrovascular disease or vasculitis), unremarkable vasculitis serology and inflammatory markers, and sterile wound and blood cultures.

The protocol mirrored that of Case 1. After one year, near-complete ulcer healing occurred, accompanied by substantial pain relief and functional improvement (Figure 2).

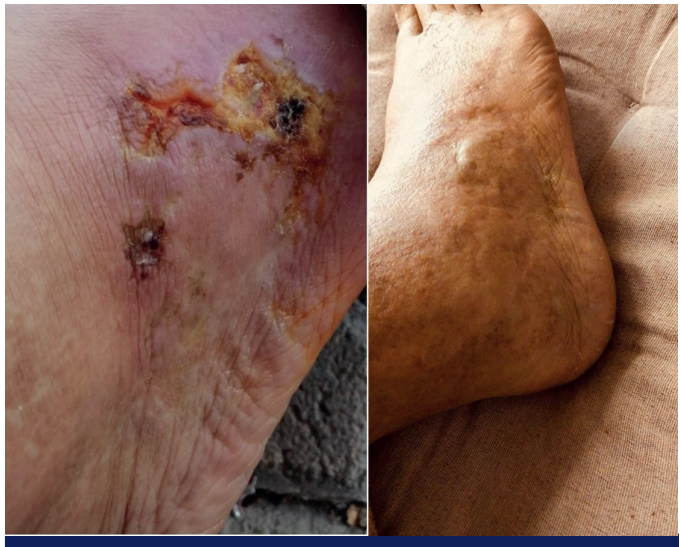

Figure 2. Near-complete ulcer healing in Case 2

Written informed consent was obtained from both patients for publication of their case details and images.

DISCUSSION

Refractory ulcers in SSc remain difficult to manage despite immunosuppressants and vasodilators. Tocilizumab targets IL-6-driven pathways, modulating inflammation and fibrosis. Its potential role in ulcer healing has been suggested in the faSScinate and focuSSced trials (7,8) and confirmed by real-world data (9).

Ozone therapy promotes wound healing through multiple mechanisms, including enhanced oxygen delivery, modulation of microcirculation, reduction of oxidative stress, and activation of growth factors. Kaymaz et al. (10) reported a 92% healing rate for refractory digital ulcers treated with ozone therapy in a randomized study.

While the combination of systemic IL-6 blockade and local ozone therapy is biologically plausible—tocilizumab may stabilize systemic inflammation whereas ozone can improve local perfusion, oxygen delivery, and antimicrobial defenses—we cannot determine whether the observed healing reflects a true synergistic effect or the non-specific wound-healing properties of ozone alone. Ozone therapy has documented efficacy in diabetic and ischemic ulcers independent of connective tissue disease; therefore, attribution of benefit to the combination (rather than to ozone itself) remains uncertain in our cases. Accordingly, these observations should be interpreted as hypothesis-generating; controlled studies are required to disentangle the relative contributions of IL-6 inhibition and ozone exposure. Limitations of our report include the small sample size, the lack of objective ulcer measurements, and the absence of a control group. Nonetheless, the rapid clinical improvement observed warrants further study.

CONCLUSION

Adjunctive ozone therapy in combination with tocilizumab facilitated healing and functional recovery in two cases of refractory SSc-associated ulcers. This novel therapeutic approach may represent a promising option for selected patients. Prospective controlled trials are needed to validate these findings.

Ethics

Informed Consent: Written informed consent was obtained from both patients for publication of their case details and images.

Footnotes

Authorship Contributions

Concept: G.Y., Design: J.K., A.K., Data Collection or Processing: G.Y., Analysis or Interpretation: J.K., Literature Search: Y.D., Writing: J.K.

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2025 Referee Index

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