Digestive involvement in primary Sjögren's syndrome: analysis from the Sjögrenser registry

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ABSTRACT

Objective. *Digestive involvement (DI) has been reported in 10–30% of primary Sjögren's syndrome (pSS) patients, and few studies have systematically analysed the prevalence of DI in pSS patients. The aim of this study was to describe DI prevalence in pSS patients from the Sjögrenser Study, and to analyse its clinical associations.*

Methods. *All patients included in the Sjögrenser study, a Spanish multicentre randomised cohort, containing demographic, clinical and histologic data, have been analysed retrospectively. Patients were classified according to the presence of DI (oesophageal, gastric, intestinal, hepatic and pancreatic), and we have performed DI clinical associations, descriptive statistics, Student t or χ^2 test, and uni and multivariate logistic regression.*

Results. *From 437 included patients, 95% were women, with a median age of 58 years, 71 (16.2%) presented DI: 21 (29.5%) chronic atrophic gastritis, 12 (16.9%) oesophageal motility dysfunction, 3 (4.2%) lymphocytic colitis, 18 (25.3%) primary biliary cholangitis, 15 (21.1%) autoimmune hepatitis, 7 (9.8%) pancreatic involvement and 5 (7%) coeliac disease. Half of them developed DI at the same time or after pSS diagnosis. Patients with DI were significantly older at pSS diagnosis (p=0.032), more frequently women (p=0.009), presented more autoimmune hypothyroidism and C3 hypocomplementaemia (p=0.040), and were treated more frequently with glucocorticoids, immunosuppressant and biologic therapies. Patients with pancreatic involvement presented more central nervous system and renal involvement, Raynaud's phenomenon, lymphoma and C3/C4 hypocomplementaemia.*

Conclusion. *DI is frequent in Sjögrenser patients, mainly in the form of autoimmune disorders, and seem to be associated with a more severe phenotype. Our results suggest that DI should be evaluated in pSS patients, especially those with more severe disease.*

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by lymphocytic infiltration of exocrine glands, mainly salivary and lacrimal glands. It is a very heterogeneous disease, and may present extraglandular involvement in any internal organ (1). Systemic involvement is frequent, occurs in more than half of the patients with long standing disease (2), is associated with anti-Ro/La antibodies (3), and usually determines patient prognosis and quality of life. Extraglandular involvement of any part of the digestive system, including the hepatobiliary system, or digestive involvement (DI) has been described in up to 10–30% of pSS patients (4). Although this is a rather high prevalence, few studies have specifically analysed in detail DI globally in pSS cohorts.

Some studies have analysed specific subtypes of DI, such as upper dysphagia, secondary to the lack of saliva, (5, 6), oesophageal motility (7), gastroesophageal reflux (8), and atrophic or chronic gastritis (6, 9, 10, 11). Non-

specific bowel symptoms (12, 13), coeliac disease (14), inflammatory bowel disease (12), lymphocytic colitis (15), or severe intestinal dysbiosis (16) have been found in selected pSS patients. Liver involvement, such as enzymatic abnormalities (17, 18), primary biliary cholangitis (19), or autoimmune hepatitis (20), have also been described, and pancreatitis has been found in up to 0.6% pSS patients (6, 21, 22). Although some of these DI manifestations have been studied in large cohorts of patients (6, 8, 11, 22), the majority have been described in small, selected groups, or symptomatic patients. Many of these types of DI have been associated with other extraglandular involvement, or signs of disease activity. All in all, these findings might suggest that DI involvement could be also a marker for a more severe disease. In this regard, it would be important to specifically describe the full picture of DI in unselected pSS patients, including the different clinical manifestations, disease associations and need for systemic therapies.

Sjögrenser is a multicentric cohort, containing data from 437 pSS Spanish patients from 33 Rheumatology centres in Spain (23). Twenty patients from each centre were randomly selected before the inclusion, enabling us to establish a cohort of unselected pSS patients from daily clinical practice. Sjögrenser included detailed information on epidemiological, clinical, serological and therapeutic features from a large group of pSS patients, and constitutes an adequate setting to thoroughly study DI involvement in this disease.

In order to test the hypothesis that DI involvement in pSS appears associated with a more severe disease, the aim of our study is to describe the prevalence of the different subtypes of DI in the Sjögrenser registry, and to analyse the associations of DI, globally and by the main subtypes, with other clinical, serological, or therapeutic characteristics of the disease.

Patients and methods

Study design

This is a secondary data analysis of the Sjögrenser, a randomised multicentre retrospective study, carried out in 33 rheumatology centres in Spain in the period 2013-2014, and including pSS patients fulfilling the 2002 European-American consensus criteria for pSS (24). To ensure unbiased inclusion in Sjögrenser, prior to inclusion 20 patients were randomly selected from existing databases in each centre (23). This study was conducted in accordance with Good Clinical Practice and the current version of the revised Declaration of Helsinki (World Medical Association Declaration of Helsinki), and was approved by the ethics committee of all participating centres. All patients gave their informed consent before being included in Sjögrenser.

Patient selection and data acquisition

All patients from Sjögrenser Study were included. The data were obtained through a protocolised medical interview with the patients the day of the inclusion, and from chart review. The data were then included in a database, specifically created for the study, and kept by the Spanish Society for Rheumatology (SER) (23).

Variables

298 variables had been included in Sjögrenser, grouped in epidemiological, clinical, serological, histological, therapeutic, and outcome characteristics. ESSDAI activity index was also included. Definitions of these variables have been previously published (23). As part of the study protocol, all Sjögrenser participants answered specific questions included in the interview to evaluate DI involvement. The types of DI included were: the presence of chronic atrophic gastritis; oesophageal motility dysfunction, lymphocytic colitis, primary biliary cholangitis, autoimmune hepatitis, pancreatic involvement and coeliac disease. Patient's answers were confirmed in electronic charts. Oesophageal motility dysfunction was diagnosed by oesophageal manometry and pancreatic involvement by clinical and radiological criteria. All the others were diagnosed by typical histologic changes of the affected organ. Hypocomplementaemia was defined as C3 or C4 levels below normal, according to the method used in each centre.

Statistical analysis

Patients were divided according to the presence of DI, globally and by the predefined DI subtypes. Descriptive analysis and comparison between groups were carried out by parametric or non-parametric test, based on the distribution of the variables. Quantitative variables were described by mean and standard deviation (SD) or median and interquartile range, and qualitative variables by frequencies and percentages. The association between DI with demographic, clinical, serological and therapeutic characteristics was assessed calculating crude association measures (OR) with its 95% confidence interval (CI). Clinical associations of DI were analysed following multivariate logistic regression model. In this model, independent factors associated with DI in the bivariate analysis with a p-value <0.20 were included, and the effect of age and sex was controlled. In order to identify possible differences in clinical determinants of the different subtypes of DI, bivariate and multivariate association analysis were conducted independently for every subgroup (stratified analysis).

Results

Sjögrenser cohort includes 437 patients with pSS, 95% women, with median age of 58 years at inclusion. Seventy-one (16.2%) presented DI: 21 (29.5%) chronic atrophic gastritis; 12 (16.9%) altered oesophageal motility; 3 (4.2%) lymphocytic colitis; 18 (25.3%) primary biliary cholangitis (PBC); 15 (21.1%) autoimmune hepatitis (AIH); 7 (9.8%) pancreatic involvement and 5 (7%) celiac disease. Nine patients presented more than one type of DI (7 patients 2 types and 2 patients 3 types). More than half (54%) developed DI at pSS diagnosis or after, whereas 46% had already DI at pSS diagnosis.

Differences between patients with and without DI are presented in Table I. Age was significantly higher in patients with DI. Clinically, patients with DI presented more frequently thyroid involvement (autoimmune hypothyroidism), C3 hypocomplementaemia, and had been treated more frequently with glucocorticoids, immunosuppres-

Table I. Clinical, serological and therapeutic differences between patients with and without digestive involvement in Sjögrenser cohort.

	With DI (n=71; 16.2%)	Without DI (n=366; 83.8%)	Total pSS (n=437)	*p*-value
Age at onset pSS symptoms	49 ± 13	46 ± 14	46 ± 14	0.089
Age at pSS diagnosis	53 ± 13	50 ± 13	50 ± 13	**0.032**
Age at inclusion in the cohort	62 ± 11	58 ± 13	59 ± 13	**0.02**
Gender	69 F (97%), 2M	347 F (95%), 19M	416 F (95%), 21M	0.392
ESSDAI	5 ± 6	5 ± 6	5 ± 6	0.279
ESSDAI >5	25 (35.7%)	108 (29.5%)	133 (30.5%)	0.301
High ESSDAI at least in one domain	88 (24.04)	107 (24.49%)	19 (26.76%)	0.626
Glandular involvement	27 (38%)	115 (31.4%)	142 (32.5%)	0.277
Central nervous system involvement	8 (11.4%)	26 (7.1%)	34 (7.8%)	0.216
Peripheral nervous system involvement	6 (8.6%)	33 (9%)	39 (8.9%)	0.905
Lung involvement	11 (15.7%)	32 (8.7%)	43 (9.9%)	0.073
Thyroid involvement (autoinmune hypothyroidism)	16 (22.5%)	63 (17.2%)	79 (18%)	**0.034**
Leukocytoclastic vasculitis	6 (8.6%)	34 (9.3%)	40 (9.2%)	0.849
Articular involvement	55 (77.5%)	298 (81.4%)	353 (80.8%)	0.439
Kidney involvement	9 (12.9%)	30 (8.2%)	39 (8.9%)	0.211
Raynaud	19 (26.8%)	73 (19.9%)	92 (21.1%)	0.197
Lymphoma	1 (1.4%)	6 (1.6%)	7 (1.6%)	0.887
ANA	67 (94.4%)	357 (97.5%)	424 (97%)	0.150
anti-Ro antibodies	64 (90.1%)	345 (94.3%)	409 (93.6%)	0.194
anti-La antibodies	50 (70.4%)	243 (66.4%)	293 (67%)	0.509
Rheumatoid factor	47 (68.1%)	237 (66.2%)	284 (66.5%)	0.758
Hypocomplementaemia C3	16 (24.2%)	49 (14.2%)	65 (15.8%)	**0.040**
Hypocomplementaemia C4	15 (22.7%)	47 (13.6%)	62 (15%)	0.057
Hypergammaglobulinaemia	41 (60.3%)	189 (53.7%)	230 (54.8%)	0.317
Glucocorticoid treatment	42 (60.9%)	171 (47.2%)	213 (49.4%)	**0.038**
DMARD treatment	43 (64.2%)	173 (48.7%)	216 (51.2%)	**0.02**
Biologic treatment	10 (14.1%)	39 (10.7%)	49 (11.2%)	**0.040**

DI: digestive involvement; pSS: primary Sjögren's syndrome; ESSDAI: EULAR Sjögren's syndrome disease activity index; ANA: antinuclear antibodies; DMARDs: disease modify antirheumatic drugs.

sants and biologic therapies. ESSDAI was similar between patients with and without DI.

Association of DI (all types) with other clinical and serological characteristics, adjusted by age and sex, is expressed in Table II. Patients with DI are more frequently women, older at pSS diagnosis, and presented significantly more C3 hypocomplementaemia.

DI subgroup analysis is presented in Table III. Patients with chronic atrophic gastritis were older, both at diagnosis and at disease onset, presented more frequently AIH and had been treated more frequently with hydroxychloroquine. Patients with PBC were also older, presented more frequently autoimmune hypothyroidism and antimitochondrial antibodies and had been treated more frequently with glucocorticoids and immunosuppressants. Patients with AIH presented more frequently lung involvement, and had received more frequently glucocorticoids and immunosuppressants. Finally, patients with pancreatic involvement presented more central nervous system and renal involvement, lymphoma, Raynaud, C3 and C4 hypocomplementaemia, and had been treated more frequently with rituximab.

Discussion

In the Spanish Sjögrenser cohort, the prevalence of DI is 16.2%. Most frequent DI appears as other autoimmune conditions, as chronic atrophic gastritis, PBC or AIH. We are confident that our study population of unselected pSS patients, is suitable to analyse the prevalence of less frequent disease clinical characteristics, as DI. In Sjögrenser, although most data have been collected retrospectively, all patients agreed to participate and were contacted through personal interview, including clinical evaluation and complete physical exam. Specifically, all data regarding clinical digestive involvement were included in the personal interview (23).

To our knowledge, this is the first study to analyse the global prevalence of DI in a large cohort of unselected pSS patients. Other groups have investigated specific subtypes of DI, generally in selected cases or small series of patients, making difficult to compare our results with those described by others. DI involvement is associated in our cohort with female sex, older age at pSS diagnosis, and more C3 hypocomplementaemia. Our patients with DI had received also more systemic therapy, as glucocorticoids, DMARDS and biologics. These characteristics (hypocomplementaemia, older age and systemic therapy) have been associated with some severe phenotypes of pSS, having high ESSDAI in at least one domain, who also present elevated mortality (25). We did not find any differences in global ESSDAI, or in the number of patients with at least one ESSDAI domain qualified as high, between patients with or without DI. However, our results suggest that patients with DI could also present a more severe phenotype. Since DI is not included in ESSDAI score, and our study lack longitudinal data on mortality, we cannot confirm or rule out this possibility.

Chronic atrophic gastritis has been described in up to 36% of selected symp-

Table II. Association of digestive involvement with other clinical and serological characteristics in Sjögrenser cohort.

	Univariate		Multivariate	
	OR (IC 95%)	*p*	OR (IC 95%)	*p*
Older at pSS diagnosis	1.022 (1.002 -1.043)	**0.033**	1.030 (1.007 - 1.054)	**0.009**
Gender female	1.889 (0.430 -8.296)	0.400	1.030 (1.007 - 1.054)	**0.009**
ESSDAI >5	1.327 (0.775 -2.273)	0.303	-	-
Glandular involvement	1.339 (0.790 -2.270)	0.278	-	-
Central nervous system	1.687 (0.730 -3.898)	0.221	-	-
Peripheral nervous system	0.946 (0.381 -2.350)	0.905	-	-
Lung involvement	1.946 (0.930 -4.074)	**0.077**	1.801 (0.792 - 4.096)	0.161
Leukocytoclastic vasculitis	0.915 (0.369 -2.270)	0.849	-	-
Articular involvement	0.784 (0.424 -1.452)	0.440	-	-
Kidney involvement	1.652 (0.748 -3.653)	0.215	-	-
Raynaud	1.467 (0.817 -2.631)	0.199	1.374 (0.71 - 2.660)	0.346
Lymphoma	0.857 (0.102 -7.230)	0.887	-	-
ANA	0.422 (0.126 -1.411)	0.161	0.497 (0.105 - 2.353)	0.379
anti-Ro antibodies	0.557 (0.227 -1.363)	0.200	0.654 (0.208 - 2.053)	0.467
anti-La antibodies	1.205 (0.693 -2.097)	0.509	-	-
Rheumatoid factor	1.091 (0.628 -1.894)	0.758	-	-
Hypocomplementaemia C3	1.940 (1.024 -3.675)	**0.042**	2.328 (1.095 - 4.947)	**0.028**
Hypocomplementaemia C4	1.871 (0.974 -3.594)	0.060	1.371 (0.631 - 2.977)	0.425
Hypergammaglobulinaemia	1.310 (0.772 -2.223)	0.318	-	-
Glucocorticoid treatment	1.737 (1.027 -2.939)	**0.039**	0.429 (0.088 - 2.087)	0.294
DMARD treatment	1.885 (1.097 -3.238)	**0.022**	4.134 (0.825 - 20.711)	0.084
Biologic treatment	1.375 (0.652 -2.900)	0.404	-	-

pSS: primary Sjögren's syndrome; ESSDAI: EULAR Sjögren's syndrome disease activity index; ANA: antinuclear antibodies; DMARDs: disease modify antirheumatic drugs.

tomatic patients in earlier studies (9, 10). In the largest study to date, analysing the presence of different nuclear and non-nuclear autoantibodies in a cohort of 335 patients, the presence of anti-parietal cell antibodies was as high as 27% (11). Nevertheless, pernicious anaemia or chronic atrophic gastritis was present only in 2 of 90 patients positive for these antibodies (11). Anti-parietal cell antibodies have not been specifically analysed in our cohort. The prevalence of chronic atrophic gastritis is higher in our cohort (4.5%), probably due to the different selection of patients in both studies. The association of this complication with older age at disease onset and autoimmune hepatitis has not been previously described, but it is well known than chronic atrophic gastritis is associated with other autoimmune diseases (26).

Bowel symptoms have been described in more than 50% of pSS patients in a small series (13), although lymphocytic colitis has been only rarely described (15). We found 3 cases of lymphocytic colitis in our cohort. This rather high prevalence, not previously described in larger studies (25, 27), could suggest that intestinal inflammation might be a more frequent characteristic of pSS patients than previously thought. In this regard, both elevated calprotectin (12) and severe intestinal dysbiosis (16) have been reported in pSS patients. Although this could represent merely a consequence of systemic disease affecting the gastrointestinal tract, it has been hypothesised that an imbalance in gut microbiota could drive inflammation in exocrine glands in genetically susceptible individuals (16). Associated bowel disease, as coeliac disease, has been also described in pSS patients. In a recent study including 354 pSS patients, the prevalence of celiac disease is 6.8% (14), much higher than that found in our cohort (1.14%). In the referred study, all patients were screened with serology tests for coeliac

Table III. Differences between patients with and without the distinct subgroups of digestive involvement, in the Sjögrenser cohort.

	Oesophageal motility disorder n=12 (2.7%)		Chronic atrophic gastritis n=21 (4.8%)		Primary biliary cholangitis n=18 (4.1%)		Autoimmune hepatitis n=15 (3.4%)		Pancreatic involvement n=7 (1.6%)	
	Yes / No	*p*	Yes / No	*p*	Yes / No	*p*	Yes / No	*p*	Yes / No	*p*
Female (%)	91.7/98.1	0.17	95.2/96.7	0.73	100/95.9	0.38	100/96.1	0.43	85.7/95.3	0.237
Older age (%)	14.7/12.7	0.92	12.7/12.9	**0.02**	9.7/13.3	**0.02**	14.3/12.5	0.47	13.3/12.8	0.114
CNS (%)	18.2/6.5	0.16	4.8/8.8	0.54	0/4.1	0.38	0/3.9	0.43	28.6/7.5	**0.039**
Lung (%)	27.3/10.3	0.09	14.3/12.1	0.78	22.2/9.6	0.14	26.7/9.1	0.05	14.3/9.8	0.692
Renal (%)	27.3/12.1	0.16	9.5/13.2	0.64	11.1/11	0.98	6.7/11.7	0.56	42.9/8.4	**0.002**
A.Hypothyroidism (%)	16.7/21.5	0.82	28.6/18.5	0.65	34.4/12.3	**0.004**	20/18.5	0.77	0/18.4	0.905
Raynaud (%)	33.3/24.3	0.49	33.3/22.8	0.31	16.7/23.3	0.54	33.3/19.5	0.23	57.1/20.5	**0.018**
Lymphoma (%)	0/2.8	0.55	4.8/2.2	0.50	0/1.4	0.61	0/1.3	0.65	14.3/1.4	**0.007**
AI.Hepatitis (%)	25/17.9	0.72	60/15.2	**0.01**	16.7/16.4	0.98	-	-	0/16.3	-
C3 low (%)	20/18.6	0.91	19/18.6	0.96	25/14.1	0.28	20/15.1	0.63	57.1/15.1	**0.002**
C4 low (%)	20/15.7	0.72	14.3/16.3	0.82	12.5/12.7	0.98	26.7/9.6	0.06	57.1/14.3	**0.002**
Glucocorticoids (%)	58.3/44.8	0.37	61.9/44.4	0.14	72.2/42.3	**0.02**	84.6/42.9	**0.005**	57.1/49.3	0.68
DMARDs (%)	54.5/48.1	0.68	61.9/44.7	0.23	72.2/44.3	**0.03**	91.7/44.2	**0.002**	57.1/51.1	0.75
Rituximab (%)	9.1/8.5	0.94	9.5/8.9	0.92	11.1/7	0.56	0/9.1	0.25	28.6/6.9	**0.02**

CNS: central nervous system; A. Hypothyroidism: Autoimmune hypothyroidism; AI. Hepatitis: Autoimmune Hepatitis; C3 low: hypocomplementaemia C3< 83mg/dL; C4 low: hypocomplementaemia C4<14mg/dL; DMARDs: disease modifying anti-rheumatic drugs.

disease, whereas in our cohort only those already diagnosed with the disease were considered, and no specific studies were performed in any case.

The presence of PBC has been previously investigated in 410 unselected pSS patients from a single centre in Greece, finding a prevalence of 6.6% (19) a little higher, but quite similar to that found in our cohort. The main associations of PBC in our study were the presence of anti-mitochondrial antibodies, as expected, and also older age at pSS diagnosis, and thyroid involvement. It has been suggested that both diseases, pSS and PBC, could have common pathogenic mechanisms, representing different expression of the same autoimmune mediated epithelitis (19). This could explain, at least in part, the rather high prevalence of PBC present in pSS patients, although the association of various autoimmune diseases in the same patients is a well-known feature of autoimmune patients. Regarding AIH, we found 15 patients with this complication, accounting for 3.4% of our cases. The second most frequent hepatic autoimmune disease associated with pSS, AIH has been described in 1–4% of patients in several small series (17, 18, 20, 28), similar to our findings. Patients with PBC and AIH in our study had been treated more frequently with glucocorticoids and DMARDs, suggesting a more severe disease in our pSS patients with hepatic complications.

Pancreatic involvement was found in 1.6% of our pSS patients. This prevalence is higher than the 0.6% of acute pancreatitis reported by the Big Data Sjogren Project Consortium (6) and by a large nationwide study in Taiwan (22), including nearly 9,500 pSS patients followed for more than 4 years. This difference is probably due to the fact that we include not only acute pancreatitis but also other pancreatic disorders. As an exocrine gland, pancreas shares functional and morphological similarities with salivary gland (21), and a high prevalence of pancreatic dysfunction has been described in pSS patients (29). Acute pancreatitis has been associated in pSS patients over 65 years old, gallstones, daily steroids over 5 mg every day, and use of cyclophosphamide (22), thus suggesting a more severe phenotype. In our study, pancreatic involvement is associated with kidney involvement, Raynaud's phenomenon, lymphoma development and also present more C3 and C4 hypocomplementaemia, also suggesting a more severe disease.

In our study, DI was associated with low C3, and patients with this complication required more immunosuppressant therapy. Low complement levels seem to be associated with systemic pSS features, including extraglandular involvement, and other immunological markers (25, 30). In the largest multiethnic international cohort, comprising 10,500 pSS patients, low C3 has been associated with higher ESSDAI score and higher activity in all clinical and biological ESSDAI domains (31). Low C4 levels have been previously associated with lymphoma development (30), in accordance with our findings of low C4 and lymphoma, both associated with pancreatic involvement.

Our study has some limitations. First, although all patients in Sjögrenser were included after personal interview and complete physical exam, most data were collected retrospectively from clinical charts, and since this is a multicentric study, radiological or histological studies were performed in different centres. Therefore, we cannot be absolutely sure that all types of DI were included for every patient, and that all were diagnosed with the same pre specified criteria. Second, the study was not performed specifically to investigate DI, therefore, some clinical symptoms, analytical findings or antibody presence, have not been systematically collected in all patients, which could influence, both positively and negatively, the prevalence of the different forms of DI found in our patients. Third, the number of patients in every subtype of DI is small, making it difficult to assure that the associations presented are not biased, or simply found by chance. Fourth we did not include in Sjögrenser some very frequent symptoms in general population, as dysphagia or gastroesophageal reflux, which are also very prevalent in pSS patients. Our study also has important strengths. The most important is that Sjögrenser is multicentric, including randomly selected patients from each contributing centre, making this cohort adequate to analyse the true prevalence of DI in unselected pSS. Besides, Sjögrenser patients were personally interviewed for the purpose of the study, and all were asked by protocol about the presence of all types of DI. Another strength is that, to our knowledge, this is the first study analysing specifically and globally, all possible forms of DI in a large pSS cohort. Finally, taking into account how it has been developed, SJÖGRENSER reflects daily practice in pSS patients.

In conclusion, we found that the prevalence of DI in unselected pSS patients is over 16%, mainly in the form of other autoimmune conditions. pSS patients presenting DI are older at diagnosis, have more C3 hypocomplementaemia, and are treated more frequently with glucocorticoids and immunosuppressants, suggesting a more severe phenotype of the disease. Given the rather high prevalence of DI, our results suggest that every pSS patient, especially those with more severe presentation, should be investigated for the presence of any type of digestive disease.

Take home messages

- The gastrointestinal system, including liver and pancreas, can be affected in pSS patients;
- The most common forms of DI in pSS patients are other autoimmune conditions;
- In pSS, DI seems to occur more frequently in patients with more severe diseases.

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