

## Primary Sjögren's syndrome in patients with celiac disease

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**Background/aim:** Many autoimmune diseases occur concomitantly with celiac disease (CD). We aimed to determine the frequency of Sjögren's syndrome (SS) in CD patients based on SS-specific serology verified by minor labial salivary biopsy.

**Materials and methods:** Eight-two patients with CD were included in the study. After examination for objective evidence of sicca complex, all patients were tested for serological presence of rheumatoid factor (RF) and antinuclear antibodies (ANAs) and for ANA profile. Minor labial salivary biopsy was performed for patients with positive serology and/or clinical signs of SS.

**Results:** Of the patients included, 24 (29.3%) had dry eye symptoms while 20 (24.4%) had dry mouth symptoms. Dry eye was detected by Schirmer test in 10 patients (12.2%) and by ocular staining score in only 2 patients (2.4%). All samples were negative for RF while 12 (14.6%) samples were positive for ANAs. Of 82 patients with CD, the diagnosis of SS was established in only one patient (1.2%), while one patient (1.2%) was diagnosed with morphea and 4 patients (4.9%) were classified as having undifferentiated connective tissue disease.

**Conclusion:** The prevalence of SS in CD is low, so there is no need for serologic screening of all patients with CD for SS.

**Key words:** Celiac disease, Sjögren's syndrome, antinuclear antibodies, connective tissue disorders

### 1. Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by circulating autoantibodies against intracellular autoantigens and destruction of the exocrine glands due to lymphocytic infiltration (1,2). In addition to the exocrine glands, many other organs such as the lungs, kidneys, peripheral nervous system, and joints can be involved in patients with SS. Gastrointestinal symptoms such as dysphagia due to diminished saliva and esophageal dysmotility, epigastric pain, and chronic atrophic gastritis can also be seen in SS (3).

Celiac disease (CD) is an autoimmune enteropathy induced by dietary glutens such as gliadin found in wheat. This enteropathy is characterized by a wide spectrum of clinical symptoms including chronic diarrhea, weight loss, abdominal distension, and less commonly extraintestinal manifestations such as anemia, edema, recurrent oral aphthae, and arthritis (4).

Many autoimmune diseases such as dermatitis herpetiformis, type 1 diabetes, autoimmune thyroiditis, primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, and Addison's disease have been previously reported in patients with CD (5). The association of CD with SS was first described by Pittman and Holub in 1965 (6). Since then, a few reports have confirmed this association and have suggested the frequency of SS in CD to be as high as 15% (7). The association between SS and CD can be at least partly explained by a similar genetic involvement, namely the DQ2 heterodimer coded by the DQA1\*0501 and DQB1\*0201 alleles (8,9).

In this study, we aimed to determine the frequency of SS in CD patients based on SS-specific serology verified by minor salivary gland biopsy. We think that this study can provide additional information about the need for investigation of SS in patients with CD.

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## 2. Materials and methods

### 2.1. Patients

The study cohort included patients with CD who were followed at the Department of Gastroenterology of Antalya Training and Research Hospital between 2010 and 2014. The diagnosis of CD was made according to positive celiac autoantibodies (antiendomysial antibodies and/or antitissue transglutaminase antibodies) and pathognomonic changes in the histopathological examination of the small intestine. The diagnosis of Sjögren's syndrome was made according to the 2012 American College of Rheumatology (ACR) classification criteria for SS (10). The study protocol was approved by the Ethics Committee of Antalya Training and Research Hospital (2014 - 36/4). All patients gave written informed consent before participation.

All patients were questioned about other systemic diseases and drugs that can affect the salivary and lacrimal glands. The exclusion criteria were history of hepatitis C, human immunodeficiency virus, graft-versus-host disease, sarcoidosis, active tuberculosis, amyloidosis, and radiotherapy to the head and neck area. After a systemic examination in the rheumatology department, all patients underwent an examination for dry eye. In all patients, Schirmer test, tear film tear break-up time (TBUT), corneal epithelial staining using fluorescein, and conjunctival epithelial staining using lissamine green were performed. The eyes were graded separately and the ocular staining score (OSS) was recorded. Schirmer score of <5 mm (without anesthesia), TBUT of ≤10 s, and OSS of ≥3 were considered as abnormal and signs of dry eye.

### 2.2. Laboratory tests

A volume of 10 mL of venous blood was taken from each patient. After centrifugation, all serum samples were maintained at -80 °C until use. Antinuclear antibodies (ANAs) were detected by indirect immunofluorescence on HEp-2 cells (Euroimmun, Lubeck, Germany) at a screening dilution of 1:100 for every patient and control. Preparations stained according to the manufacturer's recommendations were evaluated by fluorescence microscope (EurostarII, Euroimmun) with 40× lenses. Fluorescent acuity was determined semiquantitatively based on negative control (-) and positive control (+4) ranging from +1 to +5. Besides nuclear patterns reported as granular, homogeneous, cytoplasmic membrane, nuclear speckled and DFS70, centromere, and nucleolar patterns were also identified. A subgroup of patients and controls was further tested at dilutions of 1:320 and 1:1000.

The ANA profile test was performed using the ANA profile 3 kit (Euroline, Euroimmun) at 1:100 dilution in accordance with the manufacturer's recommendations. This kit provides a quantitative in vitro assay for human autoantibodies of the IgG class to 14 different antigens:

uridine 1-low-molecular-weight ribonuclear protein (nRNP), Smith antigen (Sm), soluble substance A (SS-A native and Ro 52), soluble substance B (SS-B), DNA topoisomerase I (Scl-70), cytoplasmic histidyl-tRNA synthetase (Jo-1), centromeres (CENP B), proliferating cell nuclear antigen (PCNA), double stranded DNA (dsDNA), nucleosomes, histones, ribosomal P-protein (RibPP), and pyruvate dehydrogenase complex including antimitochondrial M2 antigens (AMA-M2) in serum or plasma. Rheumatoid factor (RF) was detected with a commercially available kit (N Latex RF kit, Siemens Diagnostics, Marburg, Germany).

When clinically indicated, minor salivary gland biopsy was taken just after receiving the patient's permission. Biopsy samples were immediately fixed in 10% formaldehyde and embedded in paraffin and then 4-µm-thick sections were obtained from paraffin blocks and stained with hematoxylin-eosin for conventional histopathological examination. The focus score was defined as the group of inflammatory cell aggregates containing at least 50 mononuclear cells per 4 mm<sup>2</sup> of tissue area (11).

### 2.3. Statistical analysis

The data were analyzed with descriptive statistics. Data are presented as mean ± SD or percentage. Statistical analyses were performed using SPSS 18.

## 3. Results

Overall 82 patients (60 women and 22 men) were included in the study. All the patients were on gluten-free diets for at least 1 year. Table 1 presents epidemiological and clinical features of the study population.

**Table 1.** Epidemiological and clinical features of the study population (n = 82).

Features	
Female/male	60/22
Age, mean years (range)	40.65 (20–62)
Dry mouth symptoms, n (%)	20 (24.4)
Dry eye symptoms, n (%)	24 (29.3)
Aphthous stomatitis, n (%)	9 (11)
Raynaud's phenomenon, n (%)	1 (1.2)
Co-morbid diseases, n (%)	
Autoimmune thyroiditis	4 (4.9)
Diabetes mellitus	6 (7.3)
Hypertension	3 (3.6)
Depression	8 (8.9)

Twenty-four patients with CD (29.3%) had dry eye symptoms but 9 patients (11%) were using systemic medications that could contribute to their dry eye symptoms. Dry eye was detected in 10 patients (12.2%) by Schirmer test, in 22 patients (26.8%) by TBUT, and in only 2 patients (2.4%) by OSS.

All samples were negative for RF. Twelve patients (14.6%), who were in serological remission for CD, were positive for ANAs; however, of these, 6 patients were asymptomatic. They were all negative for SS-A, SS-B, and the other autoantibodies analyzed. Of three patients with negative ANAs, 2 had anti-Ro52 and one had anti-SSA, all of whom had no symptoms or signs. There was history of Hashimoto thyroiditis in 2 of 6 patients.

There were 5 patients with suspicious SS. The minor salivary gland biopsies revealed that only one patient had a focus score of  $\geq 1$ , while the remaining 4 patients had focus scores of  $< 1$ . Of the 82 CD patients, a diagnosis of SS was established in only one patient (1.2%). In addition, one patient (1.2%) was diagnosed with morphea while 4 patients (4.9%) were classified as having undifferentiated connective tissue disease (UCTD). Of the

4 patients diagnosed with UCTD, there was symmetrical polyarthralgia and prolonged morning stiffness in 3 patients and erythematous skin lesion in one patient. Of these, no patient fulfilled the criteria for rheumatoid disorder. Table 2 presents the clinical details of these patients.

**4. Discussion**

Currently, it is known that CD may be associated with other autoimmune diseases. Several studies have revealed a high prevalence of CD among patients with SS. Iltanen et al. found that 5 patients (14.7%) had CD among 34 patients with primary SS (7). This high prevalence was confirmed by Szodoray et al., who observed a CD prevalence of 4.5% in a population of 111 patients with SS, whereas the prevalence of CD is estimated to be 0.45% in the general population (12).

In 1994, Collin et al. showed that patients with CD have an increased prevalence of autoimmune diseases, especially insulin-dependent diabetes and SS (13). Based on California criteria, SS was diagnosed in 3.3% of celiac patients (13). We found the prevalence of SS to be 1.2%,

**Table 2.** Clinical characteristics and laboratory findings of patients with CTD.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Diagnosis	SS	Morphea	UCTD	UCTD	UCTD	UCTD
Sex	Female	Female	Female	Female	Female	Male
Age	50	57	51	52	55	48
Dry eye symptoms	+	-	+	+	-	-
Dry mouth symptoms	+	-	+	+	+	+
Arthralgia	+	-	+	+	+	-
Cutaneous lesions/sclerosis	-	-	-	-	-	+/-
RP	-	-	-	-	-	-
OSS	8;8	0;0	2;2	2;2	1;1	0;0
ESR	89	83	48	14	21	12
RF	-	-	-	-	-	-
ANA	Speckled	Homogeneous	Centromere	Speckled	Speckled	Homogeneous
ANA titer	1/100	1/320	1/100	1/100	1/320	1/1000
ENAA	SSA/SSB	-	ACA	SSA	SSA	-
MSGB(FS)	One	-	Zero	Zero	Zero	Zero
Capillaroscopy	-	Normal	Normal	-	-	-

CTD: Connective tissue disease, SS: Sjögren's syndrome, UCTD: undifferentiated connective tissue diseases, RP: Raynaud's phenomenon, OSS: ocular staining score, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, ANA: antinuclear antibody, ENAA: extractable nuclear antigen antibodies, ACA: anticentromere antibody, MSGB: minor salivary gland biopsy, FS: focus score.

which is similar to the rate of the general population. The incidence and the prevalence of SS vary widely depending on the specific classification criteria, study design, and population examined. In our study, we used the ACR classification criteria for SS diagnosis. The reason for this difference in prevalence rates may be due to different classification criteria used. Iqbal et al. reported that the SS prevalence was 0.8%, but that was a survey-based study and the criteria used were not specified (14).

Arthritis involving both the peripheral and axial joints has been reported in as many as 26% of patients presenting with CD (15). More recent reports suggest a lower proportion of subjects with CD presenting with arthritis (1%) (16). In our study, 13% of CD patients had symptoms of arthralgia while no arthritis was seen in these patients. The arthritis in CD is acute and nonerosive and generally resolves with the institution of a gluten-free diet. In our study, all patients were on a gluten-free diet, which may explain lack of arthritis. Furthermore, the differences in the arthritis prevalence may depend on the diet compliance of patients screened for arthritis.

Dental enamel defects in permanent and mucosal inflammatory lesions such as recurrent aphthous ulcers and angular cheilitis are common in CD (17–19). Moreover, dental caries due to the decreased salivary flow can be seen frequently in SS. Thus, patients who have concomitant CD and SS are at risk of mucosal and dental abnormalities. In our study, the frequency of dry mouth was 24.4% in the individuals with CD, which is lower than the rate reported (40%) in the study of Patinen et al. (20). They found that the median salivary gland focus score of patients with CD was 2.1 (1.0–3.1) and they reported that patients with CD can develop sialadenitis without accompanying SS (20). However, in our study, except for the SS patient, the salivary gland focus scores obtained from the 4 patients diagnosed with UCTD were zero. Thus, we disagree with the opinion that celiac patients without SS could have subclinical autoimmune focal sialadenitis. However, to be able to comment better on this subject, more extensive studies should be done.

Mollazadegan et al. found a moderately increased risk of uveitis and cataracts in patients with biopsy-verified CD

(21,22). However, in the literature, there are no data about dry eye syndrome in CD patients. While dry eye symptoms were found in 24 patients, only 9 (10.9%) patients had clinically significant dry eye that was not due to a systemic disease or drug. In this study, dry eye was detected at a high rate in CD patients, but it is unclear whether there is a causal relationship between these two situations.

In the literature, a high rate of ANA positivity has been reported in individuals with CD. Utiyama et al. detected ANA positivity to be significantly high in CD with a frequency of 8.9% (23). In the study by Caglar et al., ANA frequency in the patients with CD was 12.9%, but there was no significant difference between the patients and healthy controls (13.8%) (24). In our study, the ANA test was positive in 12 (14.6%) patients. Of these, 8 (9.8%) had another autoimmune disease, including connective tissue disease in 6 patients and Hashimoto thyroiditis in 2 patients. The ANA rate in our study was similar to those previously detected. Previously, the SS-A/SS-B antibody was detected in 6.4% (2/31) of patients with CD who had systemic lupus erythematosus and SS (24). We found SS-A in one patient and Ro52 in 2 patients without any other autoimmune disease. These patients were on a gluten-free diet when examined for autoantibody frequency and no analysis was done before switching to a gluten-free diet. It is known that all celiac-related antibodies decline after a period of a gluten-free diet. Similarly, gluten-free diets can lead to negativity in the ANA test.

In our cohort study, the prevalence of SS in CD was approximately similar to the value reported in the general population. However, our study has some limitations. We used a cross-sectional approach and evaluated only patients who were on a gluten-free diet. The effect of a gluten-free diet on the development of autoimmune disease and ANA positivity is still under debate. Therefore, examination of SS and ANA prevalence might be more accurate before the beginning of a gluten-free diet.

In conclusion, contrary to the previously published studies, despite the high frequency of positive ANAs, we found the prevalence of SS low in CD. There is no need for routine screening of SS in patients with CD.

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