

REVIEW

The Potential Role for Early Biomarker Testing as Part of a Modern, Multidisciplinary Approach to Sjögren's Syndrome Diagnosis

Kenneth A. Beckman · Jodi Luchs · Mark S. Milner ·
Julian L. Ambrus Jr.

Received: January 18, 2017 / Published online: March 10, 2017
© The Author(s) 2017. This article is published with open access at Springerlink.com

ABSTRACT

Sjögren's syndrome (SS) is a chronic and progressive multisystem autoimmune disease typically managed by rheumatologists. Diagnostic delays are common, due in large part to the non-specific and variable nature of SS symptoms and the slow progression of disease. The hallmark characteristics of SS are dry eye and dry mouth, but there are a broad range of other possible symptoms such as joint and muscle pain, skin rashes, chronic dry cough, vaginal dryness, extremity numbness or tingling, and disabling fatigue. Given that dry eye and dry mouth are typically the earliest presenting complaints, eye care clinicians and dental professionals are often

the first point of medical contact and can provide critical collaboration with rheumatologists to facilitate both timely diagnosis and ongoing care of patients with SS. Current diagnostic criteria advocated by the American College of Rheumatology are predicated on the presence of signs/symptoms suggestive of SS along with at least two objective factors such as traditional biomarker positivity, salivary gland biopsy findings, and/or presence of keratoconjunctivitis sicca. Traditional biomarkers for SS include the autoantibodies anti-Sjögren's syndrome-related antigen A (SS-A/Ro), anti-Sjögren's syndrome-related antigen B (SS-B/La), antinuclear antibody (ANA) titers, and rheumatoid factor (RF). While diagnostically useful, these biomarkers have low specificity for SS and are not always positive, especially in early cases of SS. Several newly-identified biomarkers for SS include autoantibodies to proteins specific to the salivary

Enhanced content To view enhanced content for this article go to <http://www.medengine.com/Redeem/0F87F060569E0A33>.

K. A. Beckman (✉)
Comprehensive EyeCare of Central Ohio,
Westerville, OH, USA
e-mail: kenbeckman22@aol.com

K. A. Beckman
Ohio State University, Columbus, OH, USA

J. Luchs
Hofstra University School of Medicine, Hempstead,
NY, USA

J. Luchs
South Shore Eye Care, Wantagh, NY, USA

M. S. Milner
The Eye Center of Southern Connecticut, PC,
Hamden, CT, USA

M. S. Milner
Yale University School of Medicine, New Haven, CT,
USA

J. L. Ambrus Jr.
Division of Allergy, Immunology and
Rheumatology, Department of Medicine, SUNY at
Buffalo School of Medicine, Buffalo, NY, USA

and lacrimal glands [SP-1 (salivary gland protein-1), PSP (parotid secretory protein), CA-6 (carbonic anhydrase VI)]. Data suggest that these novel biomarkers may appear earlier in the course of disease and are often identified in cases that test negative to traditional biomarkers. The Sjö[®] test is a commercially available diagnostic panel that incorporates testing for traditional SS biomarkers (anti-SS-A/Ro, anti-SS-B/La, ANA, and RF), as well as three novel, proprietary early biomarkers (antibodies to SP-1, PSP, and CA-6) which provide greater sensitivity and specificity than traditional biomarker testing alone. Timely diagnosis of SS requires appropriate clinical vigilance for potential SS symptoms, referral and collaborative communication among rheumatology, ophthalmology, and oral care professions, and proactive differential work-up that includes both physical and laboratory evaluations.

Keywords: Autoantibodies; Diagnosis; Keratoconjunctivitis sicca; Novel biomarkers; Salivary gland biopsy; Sjögren's syndrome; Sjö test; Traditional biomarkers

INTRODUCTION

Sjögren's syndrome (SS) is a chronic, progressive, multisystem autoimmune disease that involves primarily the lacrimal and salivary glands [1, 2]. The disease may also have widespread systemic manifestations, generally appearing years after the initial ocular and oral symptoms, and which can have major adverse effects on patient quality of life and survival. Lacrimal gland dysfunction produces dry eye symptomatology which is a non-specific, yet hallmark, feature of SS. A large study of 327 patients presenting with clinically significant aqueous-deficient dry eye (ADDE) in the US found 11.6% of the patients to have SS [3]. Salivary gland dysfunction leads to dry mouth and associated problems such as trouble swallowing dry food, dental caries, and even oral candidiasis [2].

Because of the ambiguous nature and gradual onset of SS symptoms, patients may seek medical attention from a variety of clinical

specialists. While SS is a disease typically overseen by rheumatologists, ophthalmologists, and oral medicine clinicians are often the first point of patient contact when early symptoms appear. Awareness of SS is important to facilitate diagnostic suspicion and trigger consultation with other professionals as needed. Following a review of the clinical features of SS and diagnostic considerations and challenges, this article will provide an overview of the Sjö[®] test, a non-invasive approach to diagnosis which incorporates some novel biomarkers for SS and may be a useful adjunctive tool for differential workup.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Epidemiology of SS

SS is the second most common autoimmune rheumatic disease [2], with a prevalence of approximately 1% (range 0.1–4.8%) [2, 4] and an incidence of about 7 per 100,000 person-years at risk [5, 6]. In total, up to 4 million Americans have SS [7–9].

When diagnosed in an otherwise healthy individual, SS is classified as primary SS. Primary SS typically presents with ADDE syndrome, dry mouth symptoms, evidence of reduced salivary secretion, and may show positivity for various autoantibodies [10]. About half of SS cases are the primary type [3, 9]. SS also manifests in patients with a coexisting autoimmune disease such as rheumatoid arthritis (RA) [10]. These distinctions have no bearing on the clinical management of SS.

Women constitute the vast majority of SS patients, with a female to male ratio in incidence of approximately 9:1 [6]. Onset typically occurs during the 4th or 5th decade of life, but SS may occur at any age [11]. The overall age of primary SS patients at diagnosis has been reported to be 56 years (95% CI 53–60 years) [5]. Among women, the incidence of primary SS

increases with age and peaks during the years of 55–65. In contrast, among men, primary SS is most common among individuals 65 years or older [5].

Clinical Manifestations of SS

The cardinal complaints of SS are dry eyes (xerophthalmia) and dry mouth (xerostomia) [7, 12]. The dry eye symptoms of SS may include a variety of sensations, including itching, grittiness, and soreness with a normal appearing eye [4, 7]. Other ocular symptoms are complaints of eye fatigue, reduced visual acuity, photosensitivity, ocular discharge, erythema, and the sensation of a film across the visual field [7]. Patients who previously wore contact lenses may report that they cannot continue to wear them and need to use tear substitutes [4]. Patients may also report accumulation of sticky mucus overnight that makes opening their eyes difficult in the morning [4]. The patient's ocular symptoms may be aggravated by various external factors, such as low humidity levels and exposure to cigarette smoke, as well as anticholinergic drugs [7].

On examination, patients with SS can exhibit a variety of ocular findings [4, 7]. These include accumulation of mucus secretions along the inner canthus and decreased tear secretion, although there is no correlation between tear flow rates and ocular discomfort. Desiccation may cause superficial/shallow erosions of the corneal epithelium, and filamentary keratitis, which can be seen on slit lamp examination, may occur in more severe cases. In some patients, conjunctivitis may occur due to *Staphylococcus aureus* infection. Rare ocular manifestations include lacrimal gland enlargement and other complications, such as corneal ulceration, vascularization, opacification, and, very rarely, perforation.

Dry mouth, the other hallmark symptom of SS, is associated with an inability to swallow dry food without liquid, dried and fissured tongue, cheilitis, aphthae, chronic oral candidiasis, and dental caries [4, 13]. Involvement of other exocrine glands may produce complaints of dry

skin and hair, vaginal dryness, and gastrointestinal symptoms due to impaired secretion of protective mucus [4].

SS is a systemic disease with a range of systemic symptoms such as fatigue and arthralgia, along with a number of more serious complications (Table 1). Data from the Sjögren's International Collaborative Clinical Alliance (SICCA) registry suggest that primary SS is characterized by immunologic and hematologic abnormalities that may affect multiple organ systems [14]. Patients with SS have an increased risk of cerebrovascular events and myocardial infarction [15], and are more than twice as likely as age- and sex-matched controls to have hypertension and hypertriglyceridemia. Other systemic developments include arthritis (often misdiagnosed as RA), interstitial cystitis, neuropathy, and vasculopathies, including anti-phospholipid antibody syndrome. Renal involvement is rare, occurring in less than 10% of cases [16] and most commonly involving renal tubular acidosis. Autonomic symptoms may affect 50% of individuals with SS [17]. Clinical pulmonary involvement occurs in 20–30% of patients with SS and is associated with a four-fold increase in 10-year mortality [18]. A standardized tool for measuring SS disease activity, the European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index or ESSDAI [19], was introduced in 2010 and is increasingly used in clinical practice and clinical trials.

The risk of lymphoma in individuals with SS has been estimated to be 16–37.5 times higher than that in the general population [20, 21]. A meta-analysis of 14 primary SS studies found an increased risk of non-Hodgkin lymphoma (pooled RR 13.76; 95% CI 8.53–18.99) and thyroid cancer (pooled RR 2.58, 95% CI 1.14–4.03) [22].

Due to the range of medical complications associated with SS, it is not surprising that the disease is associated with significant impairments in quality of life [23–27] and functioning [25, 28]. Patients with SS also have a high rate of depression [26]. These factors result in a high burden of illness and high health care costs for patients with SS [29].

Table 1 Clinical and laboratory abnormalities in primary Sjögren's syndrome; adapted with permission from Rischmueller et al. [5]

Sicca Syndrome	Cutaneous
Constitutional symptoms	- annular erythema
- fever	- leukocytoclastic vasculitis/cryoglobulinemic vasculitis
- night sweats	
- fatigue	Renal
- weight loss	- tubulointerstitial nephritis, associated with renal tubular acidosis type I
Laboratory	- glomerulonephritis, secondary to cryoglobulinemia
- antinuclear antibodies	Genitourinary
- anti-SS-A/Ro antibodies	- dyspareunia
- anti-SS-B/La antibodies	- interstitial cystitis, urinary urgency, frequency, nocturia
- rheumatoid factor	Hematologic
- increased erythrocyte sedimentation rate	- leukopenia
- hypergammaglobulinemia	- neutropenia
- monoclonal gammopathy	- lymphopenia
- cryoglobulinemia	- thrombocytopenia
- low C3, C4	- lymphoma
Glandular	Neurologic
- parotid, submandibular, or lacrimal gland enlargement	- peripheral: axonal polyneuropathy, mononeuritis multiplex, pure sensory neuropathy, small-fiber neuropathy
Arthralgia/nonerosive inflammatory arthritis	- central: pachymeningitis, meningoencephalitis
Raynaud's phenomenon	- autonomic dysfunction
Pulmonary	Perinatal
- dry cough	- Neonatal lupus
- rhinosinusitis	- Congenital heart block
- follicular bronchiolitis	
- chronic obstructive pulmonary disease	
- interstitial lung disease	
- organizing pneumonia	
- cystic lung disease	
- amyloidosis	

DIAGNOSTIC ASPECTS AND CHALLENGES

One of the major challenges of SS is that it can be difficult to diagnose. Data show that patients have symptoms for an average of 3.9 years before being diagnosed with SS [9], and it has been estimated that more than half of adults with SS are undiagnosed [7, 10, 30]. There are many factors that add to the difficulty of diagnosing SS, including variable expression of

ocular and non-ocular symptoms, symptoms that do not always present at the same time, and slow disease progression [7, 10, 31, 32].

On average, systemic and/or extraglandular ocular complications develop about 10 years after the initial onset of dry eye symptoms in patients with SS [33], underscoring the diagnostic importance of dry eye symptoms as an early manifestation of the disease, especially if dry mouth symptoms are also present. Early diagnosis and treatment of SS can be an

important step to help prevent or decrease the complications of SS, facilitate early treatment of existing complications, and identify patients at risk for systemic complications of SS for which monitoring is needed [10, 15, 26, 31, 33, 34]. Delayed diagnosis can also lead to psychological distress associated with unexplained symptoms [26].

Because of the systemic nature of SS and the non-specific symptomatology of the disease, a multidisciplinary team approach with input from relevant specialists is often needed to both diagnose SS and manage the variety of possible manifestations of the disease.

Diagnostic Workup

Historically, there have been a number of published diagnostic guidelines for SS, mainly for the purpose of standardizing inclusion criteria for clinical trials, but there has been a notable lack of universal acceptance of any one set of guidelines. The American European Consensus Group (AECG) criteria, published in 2002, was considered the first “gold standard” for Sjögren’s diagnosis and combined subjective findings of dry eye and dry mouth complaints with objective test results such as dry eye test, minor salivary gland biopsy, salivary gland tests, and traditional biomarker positivity [(anti-Sjögren’s syndrome-related antigen A (SS-A/Ro) and/or anti-Sjögren’s syndrome-related antigen B (SS-B/La) positivity] [35]. Presence of at least three of the four objective criteria confirms diagnosis. Diagnostic threshold was achieved by the presence of at least four

of the six items, as long as one of the items was either positive biopsy histopathology or biomarker positivity. In 2012, a new set of criteria based on the National Institutes of Health-funded Sjögren’s International Collaborative Clinical Alliance (SICCA) registry were published upon receiving provisional approval by the American College of Rheumatology (ACR) [36]. These criteria are to be applied to patients with signs/symptoms suggestive of SS, with diagnosis being determined by meeting at least 2 of the following three standardized, objective measures: traditional biomarker positivity (anti-SS-A/Ro and/or anti-SS-B/La) or positive rheumatoid factor (RF) and antinuclear antigen (ANA) titer $\geq 1:320$; relevant labial salivary gland biopsy findings; and/or presence of keratoconjunctivitis sicca (KCS) (Table 2). In a comparison of these two sets of guidelines in 646 individuals with sicca symptoms, a total of 303 participants were classified as having SS by either AECG criteria ($n = 279$) or 2012 ACR criteria ($n = 268$); 244 of the 303 (81%) diagnosed cases fulfilled both the AECG and ACR criteria, implying good, but not complete, concordant diagnostic results [37].

Most recently, an international multispecialty panel of experts has produced a new classification criteria for SS which combines features of the ACR and European League Against Rheumatism (EULAR) guidelines [38]. As in the ACR guidelines, dry eye/dry mouth symptoms alone are not sufficient for SS diagnosis, but are used to identify patients who are candidates for objective workup. Classification is based on the weighted sum of five objective

Table 2 Proposed classification criteria for Sjögren’s syndrome (American College of Rheumatology 2012); adapted with permission from Shiboski et al. [36]

The classification of Sjögren’s syndrome, which applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least two of the following three objective features:

1. Positive serum anti-SS-A/Ro and/or anti-SS-B/La or (positive rheumatoid factor and ANA $\geq 1:320$)
2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥ 1 focus/4 mm²
3. Keratoconjunctivitis sicca with ocular staining score ≥ 3 (assuming that individual is not currently using daily eye drops for glaucoma, and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)

SS Sjögren’s syndrome, ANA antinuclear antibody

assessments with a total score ≥ 4 considered diagnostic for SS. In these new guidelines, two measures, focal lymphocytic sialadenitis and anti-SS-A/Ro positivity, are given the highest score of “3”; three other items are weighted with a score of “1”: Ocular Staining Score ≥ 5 (or van Bijsterveld score ≥ 4) in at least 1 eye; Schirmer’s test ≤ 5 mm/5 min in at least 1 eye, and unstimulated whole saliva flow rate ≤ 0.1 mL/min. Other traditional biomarkers (anti-SS-B/La, ANA, RF) are not included. The expert panel decided to exclude positive serology for anti-SS-B/La from these new guidelines in light of evidence that it appears to have no independent diagnostic significance.

In the workup of a patient with suspected SS, the aim is to rule out other potential diagnoses and identify the key features of SS. If a patient presents to an ophthalmologist with typical ocular symptoms and signs, a rheumatology consultation should be pursued early on in the diagnostic process [7]. Ophthalmological evaluation of dry eye symptoms is an important step to distinguish between evaporative dry eye (EDE) and ADDE, the latter being associated with SS. ADDE is primarily related to decreased lacrimal secretion and should raise suspicion of SS. However, it is not uncommon for SS patients to display characteristics of both ADDE and EDE [39]. Relevant ophthalmology findings should be communicated with the rheumatologist to aid in diagnosis.

In a large, prospective study of individuals presenting to optometry and ophthalmology centers in the US with clinically significant ADDE [3], 11.6% of patients were diagnosed with SS according to AECG 2002 revised criteria [35]. Compared to patients who did not have SS, the SS patients had significantly worse symptoms, conjunctival and corneal staining, and Schirmer’s test results [3]. These findings suggest that all patients with clinically significant ADDE should be assessed for SS.

Dental care professionals should be vigilant for dry mouth symptoms or signs of dry mouth complications in their patients. In the absence of clear pathology, based on clinical evidence or patient questioning, any suspicion of SS should prompt referral or consultation with a rheumatologist.

Tests Commonly Used in the Assessment of SS

The tests for making a diagnosis of SS are primarily focused on dry eye etiology, the salivary glands, and biomarkers. Tear function tests [40, 41] are used to distinguish between ADDE and EDE, as mentioned above. Schirmer’s test and tear meniscus assessment (tear lake) may help identify ADDE and distinguish it from EDE; the details of the differential diagnosis of dry eye have been reviewed in greater detail elsewhere [42, 43]. The tear function index (TFI) and vital dye stains (Rose Bengal; lissamine green) are also used. A recent analysis of data from the Sjögren’s Syndrome International Registry [44] suggested that corneal staining and conjunctival staining were associated with an increased likelihood of a positive labial salivary gland biopsy and should be part of the SS workup in dry eye patients; conjunctival staining was also highly associated with positive serology findings (anti-SS-A, anti-SS-B). The 5-item Dry Eye Questionnaire (DEQ-5) was validated in 2010; it was found that scores >6 indicate dry eye, and scores >12 indicate the need for further testing to rule out SS [45].

Lacrimal gland biopsy has been studied for diagnostic value in SS [46], but is rarely performed in clinical practice. This procedure is much more invasive than minor salivary gland biopsy and carries a risk of inflicting further injury to an already compromised lacrimal gland.

Minor Salivary Gland Biopsy

Although invasive, biopsy of minor salivary glands has been traditionally considered the gold standard for making the diagnosis of SS [7, 47], and is one of the objective criteria cited by the ACR [36]. While labial salivary gland histopathologic findings offer a high degree of specificity for SS [36], experience suggests that biopsy findings identify SS at more advanced stages of disease when gland damage has already occurred. Salivary gland biopsy is typically done by an oral care professional. It is important that biopsy interpretation be performed by a pathology

professional experienced with SS histology to avoid diagnostic errors. Salivary gland ultrasonography (SGUS) can aid in the differential diagnosis of primary SS [48] and has been reported to improve the diagnostic accuracy of the ACR classification criteria for SS [49–52]. However, there is a great deal of heterogeneity among SGUS scoring systems, and the procedure needs to be further standardized to increase its reproducibility [51, 53]. Another noninvasive and potentially useful test not mentioned in any SS diagnostic guidelines is acoustic radiation force impulse (ARFI) imaging of the parotid and submandibular glands; its diagnostic sensitivity is 81%, and its specificity is 67% [54].

Biomarkers

Traditional biomarkers for SS include anti-SS-A/Ro, anti-SS-B/La, ANA, and RF. Current ACR criteria include positivity for at least one or more of these biomarkers (or meeting threshold ANA titer) as partial fulfillment of SS diagnosis (Table 1) [36]. Of these traditional biomarkers, the newest joint ACR/EULAR guidelines include only anti-SS-A/Ro, but positivity for this biomarker is a major contributor to diagnosis [38]. It has been shown that autoantibodies may be present before the onset of SS symptoms. In a small study, 29/64 (66%) of patients with primary SS had detectable autoantibodies as early as 18 years before symptom onset [55], and in a larger study, 81% of sera collected up to 20 years before diagnosis were positive for one or more traditional biomarkers [56]. The presence of SS-A/Ro antibodies is associated with a higher risk of extraglandular manifestations such as anemia, cryoglobulinemia, leukopenia, vasculitis, and thrombocytopenia; such patients require close monitoring [10].

Novel Biomarkers for SS

Although the traditional biomarkers are diagnostically important, they are not always positive in SS patients, especially in early cases, nor are they specific for SS. In fact, the traditional markers anti-SS-A and anti-SS-B have been

found to be positive in only about half of SS patients who presented to ophthalmology clinics with dry eye [10]. This has prompted research into other potential biomarkers.

Based on experiments in mouse models of SS, it has been hypothesized that SS begins as an organ-specific disease initially involving the salivary and lacrimal glands, and that early diagnosis of SS might be facilitated by looking for antibodies to proteins specific to these glands [57]. In fact, three early biomarkers of SS have been identified that are specific to proteins selectively originating from the salivary and lacrimal glands, unlike SS-A and SS-B autoantibodies which are found in virtually every cell. These new biomarkers are auto-antibodies to salivary protein-1 (SP-1), parotid secretory protein (PSP), and carbonic anhydrase VI (CA-6) [58, 59]. An emerging hypothesis regarding SS pathogenesis includes a major role of the innate immune system [60]. These proteins (SP-1, PSP, CA-6) have various physiologic activities, including roles in the adherence and/or clearance of various infections [59]. High levels of mRNA for SP-1 have been found in the lacrimal and submandibular glands of mice, but its human homologue is currently unknown. It was identified as a product of one of the genes upregulated in the thymus by the autoimmune regulator gene (AIRE) to prevent development of T lymphocytes. PSP is a protein that is involved in the binding and clearance of infectious agents, while CA-6 is an enzyme that has been found to be involved in the buffering of saliva, and it is found in the cytoplasm and secretory granules of serous acinar cells in the submandibular and parotid glands [58].

A small number of studies to date have evaluated the diagnostic significance and chronological pattern of biomarker positivity in SS. In a study using an interleukin 14alpha transgenic (IL14 α TG) mouse model which develops many features of SS, Shen et al. found that only about 25% of the IL14 α TG mice developed antibodies to SS-A or SS-B [58]. Further investigations of the timing of antibody appearance found that antibodies to

SP-1 and CA-6 occurred earlier and at much higher prevalence overall compared with anti-SS-A or anti-AA-B antibodies. The same investigators also tested sera from 13 patients having SS for at least 5 years and found 69% of them positive for antibodies to SP-1 or CA-6. While 62% of the patients tested positive for the traditional biomarkers (anti-SS-A or anti-SS-B), 38% of the patients tested negative for these antibodies [58]. Finally, the investigators tested the sera from 29 patients with idiopathic xerostomia and xerophthalmia of less than 2 years' duration, all of whom met at least three diagnostic criteria for SS. Within this group of patients with apparent early SS, 76% demonstrated antibodies to SP-1 or CA-6, while only 31% had antibodies to SS-A or SS-B [58].

In another study involving 123 patients diagnosed with SS, sera from 19% of the patients tested positive for anti-SP-1 antibodies despite testing negative for anti-SS-A and anti-SS-B, suggesting that diagnosis might have been missed by relying on traditional biomarker testing alone [61]. In a study using sera from the sicca cohort, anti-SS-A and anti-SS-B positivity identified patients with more severe (or longer duration disease) SS than anti-SP-1, anti-CA-6, and anti-PSP [59]. A recent study in 37 patients with long-standing SS and high anti-SS-A/Ro titer found anti-CA-6 antibodies in 38% of patients but low positivity for antibodies to SP-1 or PSP [62]. These findings suggest that the novel biomarkers, particularly anti-SP-1 and anti-PSP, are less likely to be detected in advanced primary SS. The same authors also reported that antibodies to SP-1, CA-6, and PSP were more sensitive and specific than anti-SS-A/Ro in patients with SS in conjunction with other autoimmune diseases, which might have been an indication of earlier stage SS in these patients [62].

In an analysis of 6300 dry eye patients, 1544 cases were positive for SS biomarkers. A majority (72.6%) of the positive cases were positive only for the early biomarkers, while 27.3% were positive for both the early and late biomarkers [63]. In a population of patients with idiopathic dry eye, 60%

expressed positivity for antibodies to SP-1, CA-6, or PSP, and 30% were positive for traditional SS antibodies [64]. While a number of these patients also reported dry mouth, none had been diagnosed with SS. These studies suggest that the new biomarkers may identify those patients who are early in the development of SS, though it remains to be seen if these early biomarkers are predictive of eventual development of systemic SS symptoms.

The Sjö® Test

The Sjö test (Bausch & Lomb, Bridgewater, NJ, USA) is a commercially available diagnostic panel designed for the early detection of SS using blood samples. This test assesses the presence of four traditional Sjögren's biomarkers (anti-SS-A/Ro, anti-SS-B/La, ANA, and RF) along with three novel, proprietary early biomarkers, antibodies to SP-1, PSP, and CA-6 (Table 3). Unlike tests such as ultrasound imaging, the Sjö test has the advantage of not being operator-dependent and, thus, potentially more objective. It was initially available only as an in-office finger stick test which presented certain barriers such as difficulties with the blood draw procedure and insufficient sample volumes. Currently, however, the Sjö panel can be ordered as a laboratory test, with fewer barriers other than laboratory accessibility and cost/reimbursement issues.

The combination of novel and traditional biomarkers in the Sjö diagnostic panel provides a greater sensitivity and specificity than traditional biomarker testing alone, and may facilitate early identification of patients with SS, including patients who test negative for traditional biomarkers. A recent analysis showed that the cumulative sensitivity of the complete Sjö panel was 91.8% (245/267); the sensitivity for anti-SS-A/SS-B alone was 74.9% (200/267), while the sensitivity for the novel biomarker antibodies alone was 49.8% (133/267). The cumulative specificity for the complete Sjö panel was 79.8% (151/189), and the cumulative specificity for the novel biomarkers was 83.5% (158/189) [65].

Table 3 Traditional and novel biomarkers included in the Sjögren diagnostic test; adapted with permission from Beckman et al. [42]

Diagnostic characteristics	
Traditional biomarkers [7]	
Anti-SS-A/Ro, anti-SS-B/La	Not specific for SS; occurs in other autoimmune disorders, particularly SLE
Antinuclear antibody (ANA)	Titer $\geq 1:40$ present in about two-thirds of SS patients [35]
Rheumatoid factor (RF)	Found in many rheumatic conditions but is not unique to SS
Novel biomarkers/autoantibodies [54]	
Salivary protein-1 (SP-1)	Greatest sensitivity and specificity for early SS
Carbonic anhydrase VI (CA-6)	Expressed very early in the course of SS; observed rarely in RA or normal controls
Parotid secretory protein (PSP)	Expressed early in SS; observed rarely in RA or normal controls

RA rheumatoid arthritis, SLE systemic lupus erythematosus, SS Sjögren's syndrome

A retrospective chart review collected data on 48 consecutive patients (83% female; mean age, 62 years; 83% White) with refractory dry eye who were evaluated for possible SS using the Sjögren[®] diagnostic test [66]. Inclusion criteria included cases of dry eye that had failed to respond as expected to traditional therapy as well as patients with concomitant dry eye and dry mouth symptoms. Potentially eligible cases were excluded only for lack of serological test results. Seven of the 48 cases considered to be eligible could not be evaluated because insufficient sera was collected. Of the remaining 41 cases, 11 (27%) tested positive for at least one SS biomarker (Fig. 1). Among these 11 positive cases, almost all (10/11; 91%) were positive for the early biomarkers anti-SP-1, anti-PSP-1, or anti-CA-6, while substantially fewer cases were positive for ANA (18%), RF (18%), and anti-SS-A and/or anti-SS-B (27%) [66]. The investigators acknowledged that biomarker positivity was just one step in a longer diagnostic process, but the testing provided evidence to trigger further work-up and additional evaluation by other specialists including rheumatologists.

Several case reports have highlighted the real-world utility of using the Sjögren diagnostic panel to make the diagnosis of SS [67–69]. A series of three previously published cases involved patients who had a history of dry eye

and tested negative for the classic biomarkers (anti-SS-A/SS-B), but tested positive for the early biomarkers using the Sjögren[®] diagnostic test [67]. The first case was a 50-year-old male patient who first developed dry eye symptoms following laser-assisted in situ keratomileusis surgery OD. This patient sought help from multiple ophthalmologists and was treated with an array of topical dry eye therapies, oral doxycycline, and insertion of punctal plugs. Upon presentation to the author's clinic, the patient was found to have meibomian gland dysfunction and was noted to have additional complaints of dry mouth and joint pain. These findings prompted referral to a rheumatologist for auto-immune workup, the results of which were negative except for human leukocyte antigen B27 positivity. The patient was given an initial diagnosis of fibromyalgia. The patient continued to experience severe symptoms including pain and photophobia, and was eventually tested using the Sjögren diagnostic panel when it became available. While he tested negative for the classic markers of ANA, RF, anti-SS-A, and anti-SS-B, results showed positivity for antibodies to SP-1, PSP, and CA-6. The patient was presumed to have early SS and referred back to a rheumatologist for further care. He was treated with oral hydroxychloroquine therapy and later treated

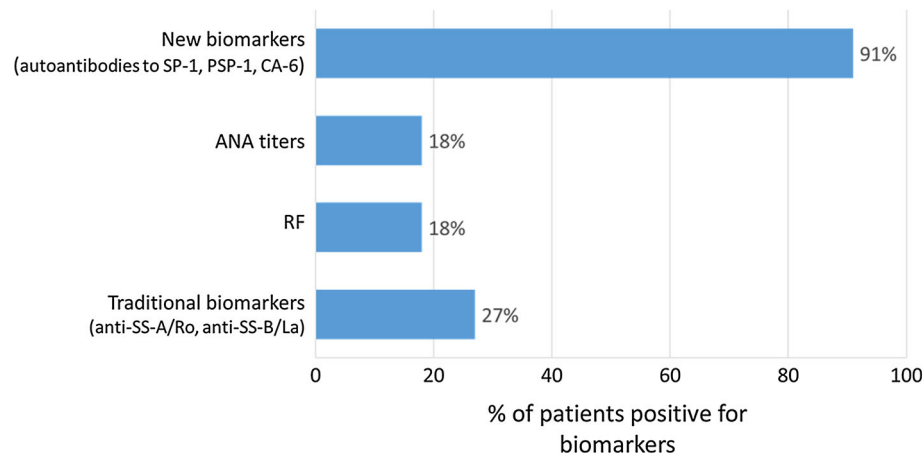


Fig. 1 Distribution of Sjögren's syndrome biomarkers among 11 cases of refractory dry eye showing positivity for at least 1 biomarker with the Sjögren diagnostic test; adapted with permission from Matossian et al. [66]. *ANA* antinuclear antibodies, *CA-6* carbonic anhydrase VI, *PSP-1* parotid secretory protein 1, *SP-1* salivary protein-1, *RF* rheumatoid factor

with compounded dapsone eye drops. While he continued to experience significant symptoms, he was eventually able to discontinue the hydroxychloroquine and has done well with long-term dapsone drops. The other two cases followed similar patterns, including long-term complaints of dry eye symptoms with unsatisfactory responses to a range of interventions including artificial tears, topical cyclosporine, topical corticosteroids, punctal plugs, azithromycin ophthalmic solution, and oral omega 3 supplements. These patients had no apparent joint pain or other non-ocular complaints at the time. Both were tested using the Sjögren diagnostic panel and were found positive for antibodies to SP-1, PSP, and CA-6. Both patients were negative for anti-SS-A and anti-SS-B; one showed positivity for ANA and RF, while the other was negative for these traditional biomarkers. Both of these patients were also referred to a rheumatologist.

Several additional published cases have reported the diagnostic value of SP-1 antibody testing in patients who met the clinical criteria for SS but in whom diagnosis was delayed because of negative test findings for traditional biomarkers [68, 69]. Such cases highlight the reality that not all individuals with SS will test positive for traditional biomarkers and additional testing for additional autoantibodies may be warranted, despite the absence of these

biomarkers from current diagnostic guidelines. It would be of interest to evaluate the diagnostic correlation between novel biomarker testing and the current gold standard of salivary gland biopsy; however, such data are not presently available.

Investigational Biomarkers

A number of additional biomarkers are being investigated for potential usefulness in SS diagnosis. They include anti-kallikrein antibody, anti-LK11 antibody [70], specific antibodies against carbamate proteins [71], antibodies against TRIM38 proteins [72], lymphotoxin α , and tear cathepsin S. Further work is needed to determine the utility of these biomarkers.

CONCLUSION

Sjögren's syndrome typically presents with very non-specific symptoms, creating diagnostic challenges and delays. Timely diagnosis of SS requires appropriate clinical suspicion and diagnostic follow-up in patients with the classic symptoms of the disease, including dry mouth and dry eye, particularly ADDE. Dry eye complaints, especially if combined with dry mouth symptoms, should trigger investigative steps to rule out SS.

Collaborative efforts involving ophthalmologists, rheumatologists, dentists, and other specialists can facilitate accurate and early identification of SS using a variety of complementary diagnostic tools. Diagnostic guidelines continue to be refined, yet are not universally reliable. The Sjö[®] diagnostic test is a simple, non-invasive, operator-independent tool that can help make the diagnosis of SS by identifying both traditional and novel early-expressed SS biomarkers. This simple laboratory test can trigger additional definitive workup and improve the chances for early diagnosis and effective intervention.

ACKNOWLEDGEMENTS

Writing and editorial assistance was provided by Churchill Communications (Maplewood, NJ, USA), funded by Bausch & Lomb Inc. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Dr. Beckman discloses relationships with Allergan, Alcon, Bausch & Lomb, Shire, Sun, TearLab, and Rapid Pathogen Screening. Dr. Luchs has served as a paid consultant for Allergan, Bausch & Lomb, Shire, Sun Ophthalmics, Tear Lab; has served on a Speaker's Bureau for Allergan, Bausch & Lomb, Shire, Doctor's Allergy, Tear Lab, Sun Ophthalmics; has conducted research for Allergan, Alcon, Bausch & Lomb, Shire, Eleven, Aerie, Aven, Ocular Therapeutics, Topokine, Inotek, Kala, Refocus; and has equity in Insightful Solutions, CXLO, Rapid Pathogen Screening, Calhoun Vision, and Omega Ophthalmics. Dr. Milner has served as a paid speaker for Allergan, Shire, Bausch & Lomb, Sun Pharmaceuticals, and TearScience; has served as a paid consultant/advisory board member for Allergan, Omeros, Shire, and Sun Pharmaceuticals; has conducted research for Kala, Aldyera, and Eyegate; and is an investor in Rapid Pathogen Screening. Dr.

Ambrus holds a patent on anti-SP1, anti-CA6, and anti-PSP that is licensed to Immco/Trinity.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Anonymous. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* 2007;5(2):75–92.
2. Tincani A, Andreoli L, Cavazzana I, et al. Novel aspects of Sjögren's syndrome in 2012. *BMC Med.* 2013;11:93.
3. Liew MS, Zhang M, Kim E, Akpek EK. Prevalence and predictors of Sjögren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol.* 2012;96(12):1498–503.
4. Venables PJ. Sjögren's syndrome. *Best Pract Res Clin Rheumatol.* 2004;18(3):313–29.
5. Rischmueller M, Tieu J, Lester S. Primary Sjögren's syndrome. *Best Pract Res Clin Rheumatol.* 2016;30(1):189–220.
6. Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis.* 2015;74(11):1983–9.
7. Kassin SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med.* 2004;164(12):1275–84.

8. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* 2008;58(1):15–25.
9. Sjögren's Syndrome Foundation. About Sjögren's syndrome. <https://www.sjogrens.org/home/about-sjogrens-syndrome>. Accessed 26 May 2015.
10. Akpek EK, Klimava A, Thorne JE, Martin D, Lekhanont K, Ostrovsky A. Evaluation of patients with dry eye for presence of underlying Sjögren syndrome. *Cornea.* 2009;28(5):493–7.
11. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. *Clin Epidemiol.* 2014;6:247–55.
12. Kruszka P, O'Brian RJ. Diagnosis and management of Sjögren syndrome. *Am Fam Phys.* 2009;79(6):465–70.
13. Blochowiak K, Olewicz-Gawlik A, Polanska A, et al. Oral mucosal manifestations in primary and secondary Sjögren syndrome and dry mouth syndrome. *Adv Dermatol Allergol.* 2016;33(1):23–7.
14. Malladi AS, Sack KE, Shiboski SC, et al. Primary Sjögren's syndrome as a systemic disease: a study of participants enrolled in an international Sjögren's syndrome registry. *Arthritis Care Res (Hoboken).* 2012;64(6):911–8.
15. Bartoloni E, Baldini C, Schillaci G, et al. Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. *J Intern Med.* 2015;278(2):185–92.
16. François H, Mariette X. Renal involvement in primary Sjögren syndrome. *Nat Rev Nephrol.* 2016;12(2):82–93.
17. Newton JL, Frith J, Powell D, et al. Autonomic symptoms are common and are associated with overall symptom burden and disease activity in primary Sjögren's syndrome. *Ann Rheum Dis.* 2012;71(12):1973–9.
18. Palm O, Garen T, Berge Enger T, et al. Clinical pulmonary involvement in primary Sjögren's syndrome: prevalence, quality of life and mortality—a retrospective study based on registry data. *Rheumatology (Oxford).* 2013;52(1):173–9.
19. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's Syndrome Disease Activity Index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis.* 2010;69:1103–9.
20. Solans-Laqué R, López-Hernandez A, Bosch-Gil JA, Palacios A, Campillo M, Vilardell-Tarres M. Risks, predictors, and clinical characteristics of lymphoma development in primary Sjögren's syndrome. *Semin Arthritis Rheum.* 2011;41(3):415–23.
21. Lazarus MN, Robinson D, Mak V, Møller H, Isenberg DA. Incidence of cancer in a cohort of patients with primary Sjögren's syndrome. *Rheumatology (Oxford).* 2006;45(8):1012–5.
22. Liang Y, Yang Z, Qin B, Zhong R. Primary Sjögren's syndrome and malignancy risk: a systematic review and meta-analysis. *Ann Rheum Dis.* 2014;73:1151–6.
23. Anonymous. The epidemiology of dry eye disease: report of the epidemiology subcommittee of the international dry eye workshop (2007). *Ocul Surf.* 2007; 5(2):93–107.
24. López-Jornet P, Camacho-Alonso F. Quality of life in patients with Sjögren's syndrome and sicca complex. *J Oral Rehabil.* 2008;35(12):875–81.
25. Meijer JM, Meiners PM, Huddleston Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. *Rheumatology (Oxford).* 2009;48(9):1077–82.
26. Segal B, Bowman SJ, Fox PC, et al. Primary Sjögren's syndrome: health experiences and predictors of health quality among patients in the United States. *Health Qual Life Outcomes.* 2009;27(7):46.
27. Lendrem D, Mitchell S, McMeekin P, et al. Health-related utility values of patients with primary Sjögren's syndrome and its predictors. *Ann Rheum Dis.* 2014;73(7):1362–8.
28. Hackett KL, Newton JL, Frith J, et al. Impaired functional status in primary Sjögren's syndrome. *Arthritis Care Res (Hoboken).* 2012;64(11):1760–4.
29. Vivino FB, Carsons SE, Foulks G, et al. New treatment guidelines for Sjögren's disease. *Rheum Dis Clin North Am.* 2016;42(3):531–51.
30. Usuba FS, Lopes JB, Fuller R, et al. Sjögren's syndrome: an underdiagnosed condition in mixed connective tissue disease. *Clinics (Sao Paulo).* 2014;69(3):158–62.
31. Gomes Pde S, Juodzbaly G, Fernandes MH, Guobis Z. Diagnostic approaches to Sjögren's syndrome: a literature review and own clinical experience. *J Oral Maxillofac Res.* 2012;3(1):e3.
32. Hernández-Molina G, Sánchez-Hernández T. Clinimetric methods in Sjögren's syndrome. *Semin Arthritis Rheum.* 2013;42(6):627–39.
33. Akpek EK, Mathews P, Hahn S, et al. Ocular and systemic morbidity in a longitudinal cohort of Sjögren's syndrome. *Ophthalmology.* 2015;122(1):56–61.

34. Juarez M, Toms TE, de Pablo P, et al. Cardiovascular risk factors in women with primary Sjögren's syndrome: united Kingdom primary Sjögren's syndrome registry results. *Arthritis Care Res (Hoboken)*. 2014;66(5):757–64.
35. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*. 2002;61(6):554–8.
36. Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's international collaborative clinical alliance cohort. *Arthritis Care Res (Hoboken)*. 2012;64(4):475–87.
37. Rasmussen A, Ice JA, Grundahl K, et al. Comparison of the American-European consensus group Sjögren's syndrome classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully selected sicca cohort. *Ann Rheum Dis*. 2014;73(1):31–8.
38. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against rheumatism classification criteria for primary Sjögren's Syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol*. 2017;69:35–45.
39. Foulks GN, Forstot SL, Donshik PC, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. *Ocul Surf*. 2015;13(2):118–32.
40. Kaye SB, Sims G, Willoughby C, Field AE, Longman L, Brown MC. Modification of the tear function index and its use in the diagnosis of Sjögren's syndrome. *Br J Ophthalmol*. 2001;85(2):193–9.
41. Anonymous. Methodologies to diagnose and monitor dry eye disease: report of the diagnostic methodology subcommittee of the international dry eye workshop (2007). *Ocul Surf*. 2007;5(2):108–152.
42. Beckman KA, Luchs J, Milner MS. Making the diagnosis of Sjögren's syndrome in patients with dry eye. *Clin Ophthalmol*. 2016;10:43–53.
43. Cornec D, Saraux A, Jousse-Joulin S, et al. The differential diagnosis of dry eyes, dry mouth, and parotidomegaly: a comprehensive review. *Clin Rev Allergy Immunol*. 2015;49:278–87.
44. Bunya VY, Bhosai SJ, Heidenreich AM, et al. Association of dry eye tests with extraocular signs among 3514 participants in the Sjögren's Syndrome international registry. *Am J Ophthalmol*. 2016;172:87–93.
45. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Contact Lens Anter Eye*. 2010;33(2):55–60.
46. Xu KP, Katagiri S, Takeuchi T, Tsubota K. Biopsy of labial salivary gland and lacrimal glands in the diagnosis of Sjögren's syndrome. *J Rheumatol*. 1996;23:76–82.
47. Giovelli RA, Santos MC, Serrano ÉV, Valim V. Clinical characteristics and biopsy accuracy in suspected cases of Sjögren's syndrome referred to labial salivary gland biopsy. *BMC Musculoskelet Disord*. 2015;16:30.
48. Hammenfors DS, Brun JG, Jonsson R, Jonsson MV. Diagnostic utility of major salivary gland ultrasonography in primary Sjögren's syndrome. *Clin Exp Rheumatol*. 2015;33(1):56–62.
49. Baldini C, Luciano N, Mosca M, Bombardieri S. Salivary gland ultrasonography in Sjögren's Syndrome: clinical usefulness and future perspectives. *Isr Med Assoc J*. 2016;18(3–4):193–6.
50. Cornec D, Jousse-Joulin S, Marhadour T, et al. Salivary gland ultrasonography improves the diagnostic performance of the 2012 American College of Rheumatology classification criteria for Sjögren's syndrome. *Rheumatology (Oxford)*. 2014;53(9):1604–7.
51. Jousse-Joulin S, Milic V, Jonsson MV, et al. Is salivary gland ultrasonography a useful tool in Sjögren's syndrome? A systematic review. *Rheumatology (Oxford)*. 2016;55(5):789–800.
52. Jonsson MV, Baldini C. Major salivary gland ultrasonography in the diagnosis of Sjögren's Syndrome: a place in the diagnostic criteria? *Rheum Dis Clin North Am*. 2016;42(3):501–17.
53. Cornec D, Jousse-Joulin S, Saraux A, Devauchelle-Pensec V. Salivary gland ultrasound to diagnose Sjögren's syndrome: a claim to standardize the procedure. *Rheumatology*. 2015;54:199–200.
54. Knopf A, Hofauer B, Thürmel K, et al. Diagnostic utility of acoustic radiation force impulse (ARFI) imaging in primary Sjögren's syndrome. *Eur Radiol*. 2015;25(10):3027–34.
55. Jonsson R, Theander E, Sjöström B, Brokstad K, Henriksson G. Autoantibodies present before symptom onset in primary Sjögren syndrome. *JAMA*. 2013;310(17):1854–5.

56. Theander E, Jonsson R, Sjostrom B, Brokstad K, Olsson P, Henriksson G. Prediction of Sjögren's syndrome years before diagnosis and identification of patients with early onset and severe disease course by autoantibody profiling. *Arthritis Rheumatol.* 2015;67:2427–36.
57. Xuan J, Shen L, Malyavantham K, Pankewycz O, Ambrus JL Jr, Suresh L. Temporal histological changes in lacrimal and major salivary glands in mouse models of Sjögren's syndrome. *BMC Oral Health.* 2013;13:51.
58. Shen L, Suresh L, Lindemann M, et al. Novel autoantibodies in Sjögren's syndrome. *Clin Immunol.* 2012;145(3):251–5.
59. Suresh L, Malyavantham K, Shen L, Ambrus JL Jr. Investigation of novel autoantibodies in Sjögren's syndrome utilizing Sera from the Sjögren's international collaborative clinical alliance cohort. *BMC Ophthalmol.* 2015;15(1):38.
60. Low HZ, Witte T. Aspects of innate immunity in Sjögren's syndrome. *Arthritis Research & Therapy.* 2011;13:218.
61. Shen L, Kapsogeorgou EK, Yu M, et al. Evaluation of salivary gland protein 1 antibodies with primary and secondary Sjögren's syndrome. *Clin Immunol.* 2014;155(1):42–6.
62. De Langhe E, Bossuyt X, Shen L, et al. Evaluation of autoantibodies in patients with primary and secondary Sjögren's syndrome. *Open Rheumatol J.* (in press).
63. Malyavantham K, Forgnone J, Ambrus J, Suresh L. Novel comprehensive serology for detection of Sjögren's syndrome. *Scand J Immunol.* 2015;81:396.
64. Ambrus J, Everett S, Vishwanath S, et al. Analysis of novel Sjögren's syndrome autoantibodies in patients with dry eyes. *BMC Ophthalmol.* (in press).
65. Shen L, et al. Early detection of Sjögren's syndrome; sensitivity and specificity of the Sjo[®] Diagnostic test. *Investig Ophthalmol Vis Sci.* 2016;57:5681.
66. Matossian C, Micucci J. Characterization of the serological biomarkers associated with Sjögren's syndrome in patients with recalcitrant dry eye disease. *Clin Ophthalmol.* 2016;10:1329–34.
67. Beckman KA. Detection of early markers for Sjögren syndrome in dry eye patients. *Cornea.* 2014;33(12):1262–4.
68. Vishwanath S, Everett S, Shen L, Malyavantham K, Suresh L, Ambrus JL Jr. Xerophthalmia of Sjögren's syndrome diagnosed with anti-salivary gland protein 1 antibodies. *Case Rep Ophthalmol.* 2014;5(2):186–9.
69. Vishwanath S, Shen L, Suresh L, Ambrus JL Jr. Anti-salivary gland protein 1 antibodies in two patients with Sjögren's syndrome: two case reports. *J Med Case Rep.* 2014;8:145.
70. El Annan J, Jiang G, Wang D, Zhou J, Foulks GN, Shao H. Elevated immunoglobulin to tissue KLK11 in patients with Sjögren syndrome. *Cornea.* 2013;32(5):e90–3.
71. Bergum B, Koro C, Delaleu N, et al. Antibodies against carbamylated proteins are present in primary Sjögren's syndrome and are associated with disease severity. *Ann Rheum Dis.* 2016;75(8):1494–500.
72. Wolska N, Rybakowska P, Rasmussen A, et al. Primary Sjögren's syndrome patients with autoantibodies against TRIM38 show greater severity of disease. *Arthritis Rheumatol.* 2015;68:724–9.