

Review

Ophthalmological Approach for the Diagnosis of Dry Eye Disease in Patients with Sjögren's Syndrome

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Abstract: Dry eye has two basic subdivisions: aqueous deficient dry eye (ADDE), with SS a major cause; and evaporative dry eye (EDE), due to either intrinsic or extrinsic factors. SS is a chronic inflammatory disorder defined by dysfunction of the exocrine glands leading to dry eye and dry mouth. The objective of this article was to carry out a systematic and critical review of several scientific publications on dry eye disease, with the aim of providing general recommendations to distinguish dry eye and its different variants in patients with SS, during the period 1979 to 2020, using search engines for articles indexed in Scopus, Latindex, Scielo, Clinical Trials, Medline, Embase, and Cochrane, allowing the analysis of 132 articles published in indexed journals on the subject of dry eye disease and SS, evidencing its conceptualization, prevalence, risk factors, etiopathogenesis, clinical manifestations, diagnosis, and treatment.

Keywords: dry eye; Sjögren's syndrome; evaporative dry eye; water deficiency dry eye; questionnaires; Schirmer I test; Schirmer II test; invasive tear film rupture time; tear meniscus height

1. Introduction

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disease that causes the dysfunction of the exocrine glands. It includes immune-mediated damage to the lacrimal and salivary glands, destroyed by infiltrating lymphocytes [1,2]. Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis and accompanied by ocular symptoms in which the instability and hyperosmolarity of the tear film, inflammation and ocular surface damage, and neurosensory abnormalities play an etiological role [3–6]. Symptoms can vary from itching or sandy to burning and stinging sensation. Diagnosis begins with determining the dry eye essential nature: aqueous deficient dry eye (ADDE), or evaporative dry eye (EDE) [1]. SS depends on the ADDE division, furthermore ADDE cases need to be investigated as potential SS associated dry eye. In Figure 1, the leading etiological causes of DED are represented [3–6].

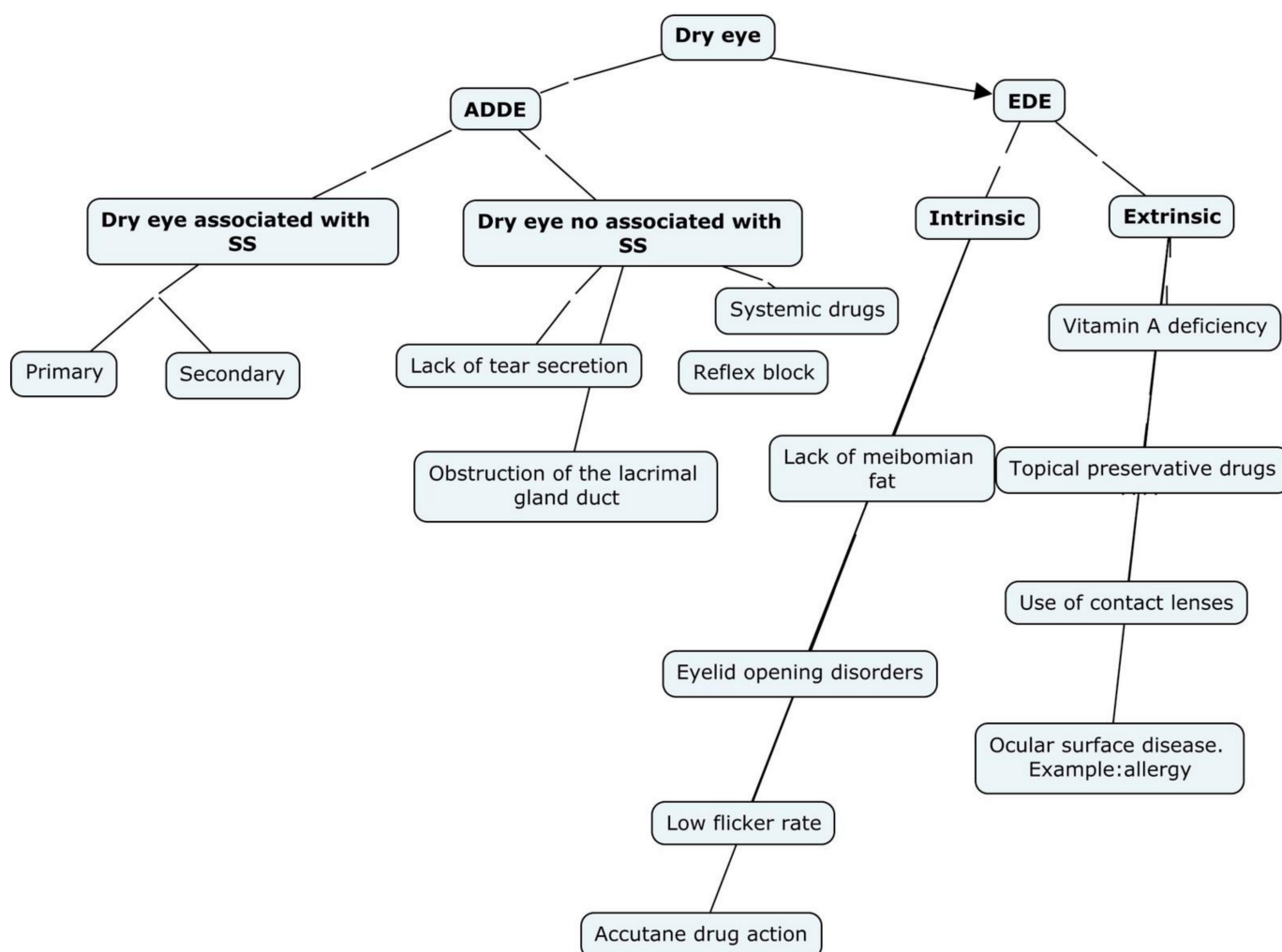


Figure 1. Main etiological causes of dry eye. Dry eye due to lack of aqueous secretion has two main groups: dry eye associated with SS and dry eye not associated with SS. ADDE: Aqueous deficient dry eye. EDE: Evaporative dry eye. SS: Sjögren Syndrome.

Since the 2017 TFOS DEWS II report, additional risk factors for SS have been identified, associating it with age, female gender, poor health, use of contact lenses, smoking, use of oral steroids or antidepressants, poorly managed thyroid disease and a greater extent of medical comorbidities, occupational risk factors (prolonged screen time), and environment factors (air conditioning and heaters) [5,7]. Factors that lowered the risk include a sedentary lifestyle and the use of angiotensin-converting enzyme inhibitors [8,9].

The human eye is usually protected from evaporation and desiccation by tear film homeostasis, which regulates the secretion of tears and distribution in the ocular surface in response to the blinking reflex. DED is characterized by a low quantity or quality of tears, destabilizing this microenvironment. The principal mechanism in DED is evaporative loss of water that leads to tearing hyperosmolarity. These mechanisms are thought to drive inflammation of the ocular surface and cell apoptosis in both the epithelial cells of the cornea and conjunctiva and the goblet cells of the conjunctiva [10]. In the case of SS, the etiology is not entirely clear. The presence of salivary gland epithelial cells expressing primary histocompatibility complex class II molecules and the identification of specific markers such as HLA-DR15 and HLA-DR3 imply that there are environmental antigens that trigger an inflammatory response [11]. The following is the recommended sequence (Table 1) of the diagnostic workup for DED:

Table 1. Sequence of diagnostic tests for DED.

1.	History
2.	Use of symptom questionnaires.
3.	Determine functional VA and contrast sensitivity
4.	Measure the invasive tear film break-up time (BUT)
5.	Ocular surface staining with fluorescein sodium
6.	Ocular surface staining with lissamine green
7.	Evaluation of tear flow using the Schirmer I–II test
8.	Perform an ocular surface examination
9.	Meibometrics
10.	Measurement of tear osmolarity

BUT: invasive tear film breakup time; Schirmer I test; Schirmer test. (Adapted from Merayo L, J. Spanish guidelines for the treatment of eye disease. Consensus document. Spanish Society of Ocular Surface and Cornea. 2017; 4 (1): 33).

1.1. Anamnesis

The patient should be asked about symptoms suggestive of dry eye. These include eye irritation, burning, stinging, foreign body sensation, blurred vision, improved vision when blinking, photophobia, or pain. The patient should also be asked about possible risk factors such as a history of collagen diseases, refractive surgery, stem cell transplantation, hepatitis, vitamin A deficiency, antihistamines, selective serotonin reuptake inhibitors, tricyclic antidepressants, and beta-blockers [9,12]. If the patient already has a diagnosis of SS, it is crucial to learn if this diagnosis was confirmed through gland biopsy or laboratory markers, Table 2.

Table 2. Directed interrogation of ocular and medical history.

Ocular
• Use of topical treatments: frequency, duration, effects, and whether or not they contain preservatives (artificial tears, glaucoma treatments, corticosteroids, antihistamines, vasoconstrictors and phytotherapy preparations, etc.). • Use of contact lenses: frequency, and care. • Allergic conjunctivitis. • History of eye or eyelid surgery. • History of ocular surface diseases. • Facial paralysis.
Medical history
• Smoking (including passive smoking). • Facial and eyelid hygiene (products, techniques, and frequency). • Dry mouth sensation. • Fatigue. • Joint and muscle pain. • Use of systemic drugs (diuretics, antihistamines, hormonal treatments, antidepressants, antineoplastics and any anticholinergic drug, etc.). • History of systemic inflammatory diseases (Sjögren's syndrome, rheumatoid arthritis and systemic lupus erythematosus, etc.). • Menopause. • Trauma (mechanical, thermal, and chemical). • Atopy. • Head and neck surgeries or transplants. • Chronic viral infections. • Neurological disorders (Parkinson's disease and trigeminal neuralgia, among others).

(Adapted from Merayo L, J. Spanish guidelines for the treatment of eye disease. Consensus document. Spanish Society of Ocular Surface and Cornea. 2017; 4 (1): 34).

1.2. Questionnaires on Symptoms

Numerous questionnaires are available for the assessment of symptoms in patients with DED, the TFOS DEWS II report recommends OSDI and DEQ-5 questionnaires. These questionnaires are both completed by the patient [7,9].

1.3. Determination of the Functional Visual Acuity (FVA)

The FVA is the continuous VA of the patient when performing activities such as reading or driving. However, standard VA tests may be normal [13].

1.4. Measurement of the Invasive Tear Film Breakdown Time (BUT)

The measurement of the invasive tear film breakdown time (BUT) is defined as the time between a complete blink and the appearance of the first tear film rupture. The average value is 10 s or more [14–16].

1.5. Lacrimal Osmolarity

Tear osmolarity was performed using TearLab® (TearLab Corporation, San Diego, CA, USA). The cutoff suggestion ranges were 300–320 mOsm/L in mild DED, and 320–340 mOsm/L in moderate DED [17–20]. This test must be taken before the instillation of any drops or dyes on the ocular surface so it is the first thing that should be completed, with a differential value between eyes of > 8 mOsm/L as a reference of positivity to specify dry eye [21–23].

It should be noted that the frequency of meibomian gland dysfunction (MGD) is higher in patients with SS than in the average population, which contributes to the worsening clinical picture. The complete diagnostic analysis for SS is used based on the European–American criteria (ACR/EULAR) proposed in 2016 for the classification of primary SS (Table 3) [24–26]. The more recent criteria are considered more refined and emphasize objective measures, including biopsy samples, as opposed to older criteria that were more exhaustive [25]. The biopsy sample study improves SS diagnosis but needs an interdisciplinary consultant with a rheumatologist [27–29]. When SS is suspected in a patient with dry eye, knowledge of the extraocular signs and symptoms of SS can aid in making the diagnosis [30–32].

Table 3. European–American criteria (ACR/EULAR) proposed in 2016 for the classification of primary SS.

Item	Score
Focal lymphocytic sialadenitis in minor salivary gland with ≥ 1 lymphocytic focus/4 mm ² of glandular tissue	3
Anti-SSA/Ro positive	3
Ocular staining score ≥ 5 (or ≥ 4 according to the Bjsterveld scale) in at least one eye	1
Schirmer test ≤ 5 mm/5 min, in at least one eye	1
Unstimulated salivary flow ≤ 0.1 mL/minute	1
Diagnosis > 4 points	

(Adapted from Shiboski CH, et al. Ann Rheum Dis 2017; 76: 9–16. doi:10.1136/annrheumdis-2016-210571).

1.6. Measurement of Matrix Metalloproteinases (MMP-9)

In recent years the technology has allowed clinical ophthalmologists, and other health-care staff to measure MMP-9 levels in the tear film with a simple device, the InflammaDry assay (Rapid Pathogen Screening, Inc., Sarasota, FL, USA) [33,34]. The test is a rapid (<10 min) and noninvasive test that measures MMP-9 levels above 40 ng/mL. The results depend on two lines, one blue and one pink. Only the blue line on the test windows indicates a level under 40 ng/mL and two lines indicate levels above this mark [35].

1.7. Measurement of the Ocular Surface Sodium Fluorescein Staining

Following Sjögren's international collaborative clinical alliance (SICCA) registry ocular examination protocol, the cornea staining score was determined [36]. Fluorescein stains areas of the ocular surface with corneal epithelial defects; its application allows for a better appreciation of the size of the tear meniscus. This technique should be performed before

positioning the patient for evaluation and without lighting to avoid the lacrimation reflex and the formation of mucous filaments [37].

1.8. Dye Staining (Lissamine Green and Rose Bengal) of the Ocular Surface

Damage to the ocular surface can be examined with specific stains where defects of the corneal epithelium (rose bengal) and cell damage of the cornea and conjunctiva (lissamine green) can be seen and both must be performed separately [38]. In Table 4 the characteristics of the different colorants are compared [39].

Table 4. Comparison of the dyes fluorescein, rose bengal and lissamine green.

	Fluorescein	Bengal Rose	Lissamine Green
Healthy cell staining	No	Yes	No
Dead cell staining	No	Yes	Yes
Stain significance	Cell disruption and increase membrane permeability	Loss or insufficient protection of ocular surface mucin	Cell degeneration and death
Staining best seen with	Yellow barrier filter	Green barrier filter	Red barrier filter

(Adapted from Tseng SCG. Evaluation of the ocular surface in dry-eye conditions. *Int Clin Ophthalmol* 1994; 34: 57–69).

The classification system first proposed by van Bijsterveld, on which current diagnostic criteria are based, qualifies three areas in each eye: the nasal and temporal bulbar conjunctiva and the cornea. The intensity of rose bengal staining is rated on a scale of 0 (no staining) to 3 (confluent staining) for each area (Figure 2). The maximum staining value for each eye is nine. Staining values of three or more are considered abnormal [8,40,41].

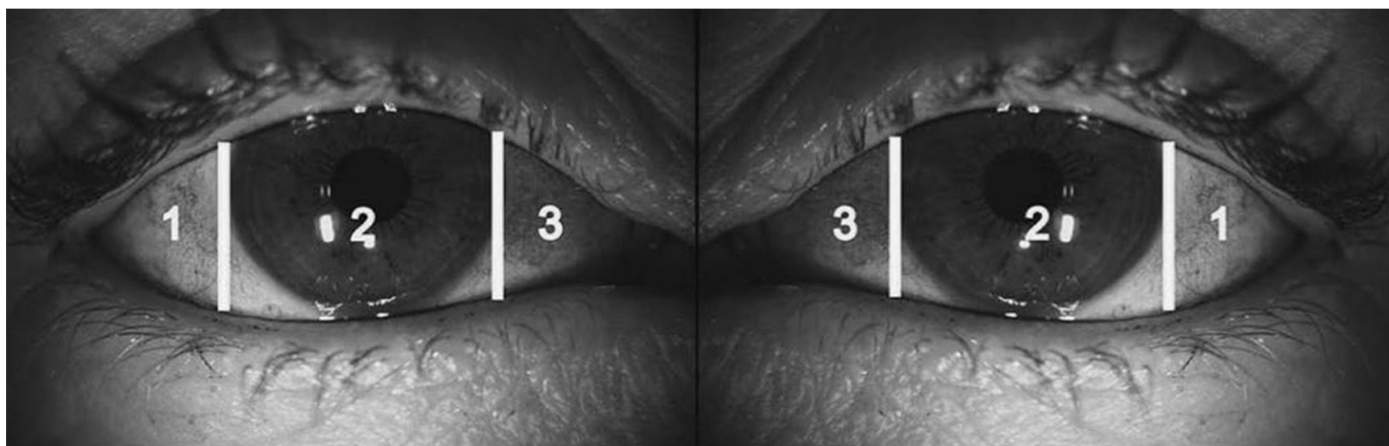


Figure 2. The exposed interpalpebral portions of the nasal and temporal conjunctiva and cornea are graded on a scale of 0 (no staining) to 3 (confluent staining). The maximum possible total score for each eye is nine. A score greater than three is considered abnormal.

1.9. Tear Flow Evaluation Using the Schirmer I–II Test

The Schirmer test measures the basal and reflex tear secretion from the primary and accessory lacrimal glands and the volume of the marginal tear film. It is performed by placing a strip of special millimeter paper between the outer half of the lower eyelid and the bulbar conjunctiva of each eye, and then the patient keeps his eyes closed for 5 min. Then the strips of paper are removed, and it is observed how wet the paper is. Various cut-off values have been proposed for the diagnosis of DED, between ≤ 5 mm and ≤ 10 mm [7,42]. The test can be performed under topical anesthesia or without anesthesia.

1.10. Perform an Examination of the Ocular Surface

It is advisable to thoroughly inspect the external surface and evaluate the ease of expression of the meibomian glands and permeability of the glandular orifices in search of MGD. Patients with mild SS can present with a normal eye examination and preserved tear function. Severe SS can present with cicatricial conjunctivitis leading to fibrosis and scarring [1,3,5,6].

1.11. Evaluation of the Meibomian Glands (Meibometry)

The meibomian glands should be assessed for the volume, quality, and ease of expression of secretions. To assess the quality of secretion, it is measured with meibometry where each gland in the central zone of the lower lid is gently pressed, and the secretion of each gland is scored as 0 (clear or normal), 1 (cloudy), 2 (granular), and 3 (pasty, similar to toothpaste) [43]. The meiboscore is the assessment of the expressibility of the glands, it is studied by pressing five glands of the lower or upper eyelid with a cotton swab [44]. The score for the number of squeezable glands is 0 (all glands), 1 (three or four glands), 2 (one or two glands), and 3 (no glands) [43,45,46].

2. Treatment of DED

TFOS DEWS II recommends individualized management of DED due to lack of aqueous and evaporative secretion, as well as the overall severity of the disease [3,5]. A dry eye can indicate the presence of SS, particularly when it is associated with inflammation, difficulty in medical management, or dry mouth. A patient with suspected SS should have an interdisciplinary assessment and follow up. The first step to diagnosing and managing this disease is referring to a rheumatologist for systemic treatment. The patient should also be referred to a dentist for the prevention and management of oral diseases [47]. Treatment for DED progresses gradually, beginning with education, diet modification, eyelid hygiene, lubricating eye drops, environmental factors modification, and nonpharmacological, and pharmacological management (Table 5) [48–50].

Diet modifications to treat DED [51,52] include supplementation with essential fatty acids (i.e., omega-3, omega-6/gamma-linolenic acid, or both) [25]. In addition, increasing fluid intake to ensure adequate general hydration [5] and avoiding alcohol intake have been recommended [53].

Table 5. Treatment schedule for DED.

Step	Treatment
Step 1	Education of the patient about:
	• Management
	• Possible dietary modifications
	• Treatment
	• Forecast
	• Modifications of the local environment.
	• Identification and modifications or elimination of systemic problems and topical medications
	• Administration of warm compresses
	• Perform eyelid hygiene and hot compresses
	• Administration of eye lubricants

Table 5. Cont.

Step	Treatment
Step 2	If the options in Step one are inadequate:
	• Manage
	○ Unpreserved eye lubricants
	○ Tea tree oil treatment for Demodex (if present)
	○ Night treatments
	○ Humidity chamber device
	○ Ointments
	○ Prescription drugs: doxycycline and tetracycline
	○ Topical antibiotics or antibiotics and steroid combination
	○ Topical corticosteroid
	○ Nonglucocorticoid topical immunomodulatory-type drugs (such as cyclosporine)
	○ Topical LFA-1 antagonist medication (such as Lifitegrast)
	○ Oral macrolide or tetracycline antibiotics
	• Preserve tears with punctal occlusion or moisture, camera glasses
	• Complete therapies in the office
Step 3	○ Intense Pulsed Light (IPL) therapy. Five sessions, with an interval of 3–4 weeks. Maintenance every 6–12 months.
	○ Meibomian gland expression
	If the options in steps one and two are inadequate:
	• Administer oral secretagogues
	• Autologous or allogeneic serum eye drops
Step 4	• Use of therapeutic contact lenses
	• Soft bandage lenses
	• Rigid scleral lenses
	If the options in the previous steps are inadequate:
	• Administer topical corticosteroids for longer duration.
	• Perform surgical options
	• Amniotic membrane graft
	• Surgical punctal occlusion
	• Tarsorrhaphy
	• Salivary gland transplant

Abbreviations: DEWS II, Dry Eye Workshop II; LFA-1, lymphocyte function-associated antigen 1; IPL, intense pulsed light. (Adapted from Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf.* 2017; 15: 575–628. Copyright © 2017 Elsevier Inc. All rights reserved).

With regard to complementary medicine, there is some evidence from clinical trials supporting the use of traditional Chinese herbs and acupuncture [51–53]. Using over-the-counter hot compresses, artificial tears, or other eye lubricants can be used as first-line treatments [4]. Measures for eyelid hygiene include detergent-based cleaning products and microblepharon-exfoliation procedures to help remove residue from the eyelid margin. Hygienic saline containing 0.01% pure hypochlorous acid has been shown to reduce biofilm, and hot compresses for eyelid hyperthermia are commonly used to soften the meibum and facilitate its exit from the ducts. Alternative options include topical corticosteroids for a limited duration, topical cyclosporine 0.05%, tacrolimus 0.03%, and lifitegrast 5%. Antibiotics such as oral doxycycline can also be given for two to three months [51,54–56].

Devices that can be used to preserve or stimulate tears include silicone-based punctal occlusion in thermolabile polymer and hydrogel devices, therapeutic contact lenses, and intranasal tear stimulation (e.g., TrueTear[®], Allergan, Pleasanton, CA, USA). MGD can be treated by meibomian gland expression and devices such as vectorized thermal pulsation therapy (i.e., LipiFlow[®], Johnson & Johnson Vision, Jacksonville, FL, USA), intense pulsed light (IPL, i.e., Optima IPL M22, Lumenis, Salt Lake City, UT, USA), light-based heat and compression (i.e., iLux, Alcon, Fort Worth, TX, USA), and portable thermal energy therapy (i.e., TearCare, Sight Sciences, Menlo Park, CA, USA) [4,47,57–59]. The third care step

includes oral secretagogues and autologous or allogeneic eye drops. In contrast, step four includes topical corticosteroids for longer durations, amniotic membrane grafts, surgical punctal occlusion, and more complex surgical approaches.

3. Discussion

There is a high tendency in recent times to diagnose dry eye disease worldwide due to the multifactorial nature of this entity [60]. However, the casuistry collected in much of the literature shows that Caucasian populations with a prevalence of 0.04%, individuals older than 65 years, and females tend to have a more significant association. This low-rate result was from using autoantibodies to classify patients and according to Hochberg, it was 0.6% in Greece [43]. Similar results were found in Slovenia (0.6%), Denmark (0.6–21.1%), and the United Kingdom (3–4%) using the European criteria, however in the latter using the American–European consensus, the prevalence ranged from 0.1 to 0.4% [14,58]. Using the Copenhagen criteria, the prevalence was 2.7% in Sweden and 0.7% in China [14,60,61]. In Latin America, in Brazil it was 0.17% [62], Argentina it was 0.17% [63], using the COPCORD methodology, and in Colombia it was 0.12%, with the American–European classification criteria employed in all of these [64].

There are few demographic and characterization studies of SS in Latin America, while, in other countries, important information on its management, diagnosis, and treatment is available. In a study carried out in Colombia in 2016, with 58,680 cases, they found a prevalence in people over 18 years of 0.12%. Eighty-two percent were women, with a 4.6:1 female:male ratio and there was a higher prevalence among the 65 to 69 age group. In Ecuador, Oviedo and Moya (2019), reported a prevalence of dry eye disease in a population that varied between 27 and 88% according to the OSDI, McMonnies, and DEQ5 questionnaire, estimating a range of 27–34.5% with a median age of 34 years [64–66]. These findings are accentuated by the lack of timely medical attention and failure to reach a timely diagnosis [50].

In SS, dry eye and mouth have been reported in up to 30% of people over 65 years of age, particularly in women in their perimenopausal and postmenopausal years [67]. Ocular signs include hyperemia, conjunctival keratinization, punctate or filamentous keratitis, and in some cases, involvement of the eyelids [68]. At the ocular level, the examinations focus on the objective evaluation of tear production, stability, osmolarity, and evaluation of the lid margin and the ocular surface [69]. In general, ocular treatment includes artificial tears as the first treatment alternative in order to increase the volume of the tear film and reduce friction, topical corticosteroids, immunomodulatory agents, immunosuppressants, autologous serum, and in experimental studies, new treatments with cells are proposed (mesenchymal stem cells or multipotent stem cells (MSC)) [68], in addition to systemic treatments to treat extraglandular manifestations.

The relationship between some signs and symptoms in patients with Sjögren's syndrome represents an example of "heterogeneity" associated with DED [26,70,71]. It is commonly associated with two possible etiologies: a water deficiency and excessive evaporation.

Although several studies have not reported a strong association or correlation between symptoms and signs in patients with dry eye assessed from the use of questionnaires and clinical tests [66] such as Begley et al. [45], Schein et al. [19], Hay et al. [63], Nichols et al. [32], and Lin et al. [72], most of them have found a weak or moderate association between these parameters, including a high correlation between the clinical diagnosis and the patient's symptoms, suggesting that the symptoms have a more significant influence on the diagnosis of dry eye than the results of clinical tests [53].

Many other studies have reported an association or correlation between signs and symptoms of irritation in patients with dry eye due to meibomian gland disease or aqueous lacrimal deficiency, using various clinical tests such as Schirmer, BUT, fluorescein staining, clearing test of fluorescein, and corneal sensation (Afonso et al. [31], 1999; Macri & Pflugfelder, Pflugfelder et al. [39]) [16,64,73,74]. In terms of tear osmolarity, although it shows a very close agreement between the eyes and in the same eyes over time in normal

subjects, it shows increasing variability in subjects with dry eye (Sullivan et al. [75] 2014). This is believed to be due to the instability of the tear film in affected patients and can be used as a diagnostic hallmark of DED [32,63,76]. These results advocate the clinical utility of a consensus of signs, which better captures the entire disease and discourages dependence on symptoms alone [77]. This finding differs from that reported by Schein et al. [19], who found no association between the presence of more frequent symptoms and a lower Schirmer result, regardless of whether the analysis was based on mean scores with a cut-off value of five or a cut-off value of seven [77]. Their sensitivity and specificity in the detection of symptomatic subjects was low [72,78,79].

Questionnaires are of some value for the evaluation of the etiology of dry eye [78,79]. However, alone they are insufficient to confirm a diagnosis of SS since they have no cost if they have a high value of sensitivity and specificity [13,80]. Tear function tests such as tear meniscus height and BUT play a role in the differential diagnosis of SS, the most important aspect being the difference between ADDE and EDE accompanied by the performance of the Schirmer I–II tests, as discussed above. The tear function index has been reported to be helpful in the diagnosis of SS [81–84]. In addition, vital rose bengal or lissamine green staining of the interpalpebral fissure is a noninvasive way to help diagnose SS, as conjunctival staining may be seen earlier in the course of the disease [85,86].

Regarding future lines of research, the noninvasive diagnostic tools for SS diagnosis and DED examination should be implemented in all ophthalmologist and optometrist scientific communities because of the the reliability and repeatability of the measurements. This allows the measurement of noninvasive breakup time which is more unambiguous to interpret than the one measured with fluorescein (as the FBUT might be related with local thinning of the tear film rather than with actual breakup event) and has been shown as potentially having a stronger correlation with patient discomfort. Furthermore, noninvasive techniques can be readily used by a broader range of medical personnel, such as technicians and nurses, which allows for more rapid and broadly available diagnostics of DED [87–90].

Another interesting future research line is the evaluation of the ocular surface microbiota in the pathogenesis and management of different eye diseases. Recently a larger multicenter study proposed the concept of eye community state type (ECST) with the aim of stratifying the different profiles of bacterial communities that coexist in a healthy eye. It was observed that nine different ECST could be considered within the healthy bacterial population [91]. However, the central job of the ocular surface and oral microbiota in the pathogenesis of SS is not completely understood, although microbiota changes have been distinguished [92] in these patients. Bacterial mimicry has been proposed as one of the systems by which the microbiome may take part in illness acceptance. Furthermore, microbiota dysbiosis in SS suggest that lower diversity may lead to higher disease activity [92]. Other studies have found different outcomes with greater phylogenetic diversity [93]. Therefore, commensal microbes could play a fundamental part in the pathogenesis of SS [94]. Peptides obtained from oral, stomach, and skin commensal microscopic organisms might prompt an insusceptible reaction by initiating the Ro60-receptive immune system microorganisms [94]. Likewise, it seems that an alteration of commensal bacteria in the gut caused a worsening of dry eye in SS. An improvement in microbiome health could improve the condition [93,95]. Nonetheless, the exact role of the role of the microbiota both in the management and in the diagnosis of this pathology should continue to be studied in multicenter studies with a larger number of patients.

4. Conclusions

Patient grumblings and clinical discoveries that are reminiscent of dry eye, particularly with ADDE, should always be considered possible indications of SS and a they should be given a brief further examination. Given the accessibility of new serologic indicative tests and the possibly extreme results of deferring a determination, the examination should include requests about corresponding side effects of oral dryness and a serologic assessment. Dry eye related with SS is not restricted to ADDE; associative MGD and EDE are frequently seen.

The ocular manifestations of SS are often accompanied by oral or systemic manifestations and a certain humeral profile. A severe dry eye accompanied by these systemic manifestations clarifies the diagnosis and directs a change in treatment from systemic treatment to a sequential ocular treatment.

There is no curative treatment available for SS, so a comprehensive treatment of the patient is essential: education and information, vigilance, and proactive steps by ophthalmologists and optometrists, in conjunction with rheumatology specialists, play a fundamental role and facilitate the early recognition of SS, allowing the management and timely intervention of ocular and systemic manifestations.

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References

1. The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007)—ScienceDirect. Available online: <https://www.sciencedirect.com/science/article/abs/pii/S1542012412700812?via%3Dihub> (accessed on 17 October 2022).
2. Tincani, A.; Andreoli, L.; Cavazzana, I.; Doria, A.; Favero, M.; Fenini, M.-G.; Franceschini, F.; Lojcono, A.; Nascimbeni, G.; Santoro, A.; et al. Novel Aspects of Sjögren's Syndrome in 2012. *BMC Med.* **2013**, *11*, 93. [CrossRef] [PubMed]
3. Stapleton, F.; Alves, M.; Bunya, V.Y.; Jalbert, I.; Lekhanont, K.; Malet, F.; Na, K.-S.; Schaumberg, D.; Uchino, M.; Vehof, J.; et al. TFOS DEWS II Epidemiology Report. *Ocul. Surf.* **2017**, *15*, 334–365. [CrossRef] [PubMed]
4. Jones, L.; Downie, L.E.; Korb, D.; Benitez-Del-Castillo, J.M.; Dana, R.; Deng, S.X.; Dong, P.N.; Geerling, G.; Hida, R.Y.; Liu, Y.; et al. TFOS DEWS II Management and Therapy Report. *Ocul. Surf.* **2017**, *15*, 575–628. [CrossRef] [PubMed]
5. Craig, J.P.; Nelson, J.D.; Azar, D.T.; Belmonte, C.; Bron, A.J.; Chauhan, S.K.; de Paiva, C.S.; Gomes, J.A.P.; Hammitt, K.M.; Jones, L.; et al. TFOS DEWS II Report Executive Summary. *Ocul. Surf.* **2017**, *15*, 802–812. [CrossRef] [PubMed]
6. Willcox, M.D.P.; Argüeso, P.; Georgiev, G.A.; Holopainen, J.M.; Laurie, G.W.; Millar, T.J.; Papas, E.B.; Rolland, J.P.; Schmidt, T.A.; Stahl, U.; et al. TFOS DEWS II Tear Film Report. *Ocul. Surf.* **2017**, *15*, 366–403. [CrossRef] [PubMed]
7. Brito-Zerón, P.; Retamozo, S.; Kostov, B.; Baldini, C.; Bootsma, H.; De Vita, S.; Dörner, T.; Gottenberg, J.-E.; Kruize, A.A.; Mandl, T.; et al. Efficacy and Safety of Topical and Systemic Medications: A Systematic Literature Review Informing the EULAR Recommendations for the Management of Sjögren's Syndrome. *RMD Open* **2019**, *5*, e001064. [CrossRef]
8. Schaumberg, D.A.; Sullivan, D.A.; Dana, M.R. Epidemiology of Dry Eye Syndrome. *Adv. Exp. Med. Biol.* **2002**, *506*, 989–998. [CrossRef]
9. Oden, N.L.; Lilienfeld, D.E.; Lemp, M.A.; Nelson, J.D.; Ederer, F. Sensitivity and Specificity of a Screening Questionnaire for Dry Eye. *Adv. Exp. Med. Biol.* **1998**, *438*, 807–820. [CrossRef]
10. Chia, E.-M.; Mitchell, P.; Rochtchina, E.; Lee, A.J.; Maroun, R.; Wang, J.J. Prevalence and Associations of Dry Eye Syndrome in an Older Population: The Blue Mountains Eye Study. *Clin. Exp. Ophthalmol.* **2003**, *31*, 229–232. [CrossRef]

11. Gottenberg, J.-E.; Busson, M.; Loiseau, P.; Cohen-Solal, J.; Lepage, V.; Charron, D.; Sibilia, J.; Mariette, X. In Primary Sjögren's Syndrome, HLA Class II Is Associated Exclusively with Autoantibody Production and Spreading of the Autoimmune Response. *Arthritis Rheum.* **2003**, *48*, 2240–2245. [\[CrossRef\]](#)
12. Rieger, G. The Importance of the Precorneal Tear Film for the Quality of Optical Imaging. *Br. J. Ophthalmol.* **1992**, *76*, 157–158. [\[CrossRef\]](#)
13. Begley, C.G.; Chalmers, R.L.; Abetz, L.; Venkataraman, K.; Mertzanis, P.; Caffery, B.A.; Snyder, C.; Edrington, T.; Nelson, D.; Simpson, T. The Relationship between Habitual Patient-Reported Symptoms and Clinical Signs among Patients with Dry Eye of Varying Severity. *Investig. Ophthalmol. Vis. Sci.* **2003**, *44*, 4753–4761. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Liew, M.S.H.; Zhang, M.; Kim, E.; Akpek, E.K. Prevalence and Predictors of Sjogren's Syndrome in a Prospective Cohort of Patients with Aqueous-Deficient Dry Eye. *Br. J. Ophthalmol.* **2012**, *96*, 1498–1503. [\[CrossRef\]](#) [\[PubMed\]](#)
15. van Bijsterveld, O.P. Diagnostic Tests in the Sicca Syndrome. *Arch. Ophthalmol.* **1969**, *82*, 10–14. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Lemp, M.A.; Bron, A.J.; Baudouin, C.; Benítez Del Castillo, J.M.; Geffen, D.; Tauber, J.; Foulks, G.N.; Pepose, J.S.; Sullivan, B.D. Tear Osmolarity in the Diagnosis and Management of Dry Eye Disease. *Am. J. Ophthalmol.* **2011**, *151*, 792–798.e1. [\[CrossRef\]](#)
17. Tashbayev, B.; Utheim, T.P.; Utheim, Ø.A.; Ræder, S.; Jensen, J.L.; Yazdani, M.; Lagali, N.; Vitelli, V.; Dartt, D.A.; Chen, X. Utility of Tear Osmolarity Measurement in Diagnosis of Dry Eye Disease. *Sci. Rep.* **2020**, *10*, 5542. [\[CrossRef\]](#)
18. Onuora, S. First EULAR Recommendations for Sjögren Syndrome Published. *Nat. Rev. Rheumatol.* **2020**, *16*, 2. [\[CrossRef\]](#)
19. Schein, O.D.; Muñoz, B.; Tielsch, J.M.; Bandeen-Roche, K.; West, S. Prevalence of Dry Eye among the Elderly. *Am. J. Ophthalmol.* **1997**, *124*, 723–728. [\[CrossRef\]](#)
20. Lemp, M.A. Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes. *CLAO J.* **1995**, *21*, 221–232.
21. Ohashi, Y.; Ishida, R.; Kojima, T.; Goto, E.; Matsumoto, Y.; Watanabe, K.; Ishida, N.; Nakata, K.; Takeuchi, T.; Tsubota, K. Abnormal Protein Profiles in Tears with Dry Eye Syndrome. *Am. J. Ophthalmol.* **2003**, *136*, 291–299. [\[CrossRef\]](#)
22. Khanal, S.; Tomlinson, A.; Diaper, C.J.M. Tear Physiology of Aqueous Deficiency and Evaporative Dry Eye. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **2009**, *86*, 1235–1240. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Beckman, K.A. Detection of Early Markers for Sjögren Syndrome in Dry Eye Patients. *Cornea* **2014**, *33*, 1262–1264. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Machetta, F.; Fea, A.M.; Actis, A.G.; de Sanctis, U.; Dalmasso, P.; Grignolo, F.M. In Vivo Confocal Microscopic Evaluation of Corneal Langerhans Cells in Dry Eye Patients. *Open Ophthalmol. J.* **2014**, *8*, 51–59. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Shiboski, S.C.; Shiboski, C.H.; Criswell, L.A.; Baer, A.N.; Challacombe, S.; Lanfranchi, H.; Schiødt, M.; Umehara, H.; Vivino, F.; Zhao, Y.; 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.* **2012**, *64*, 475–487. [\[CrossRef\]](#)
26. Versura, P.; Frigato, M.; Cellini, M.; Mulè, R.; Malavolta, N.; Campos, E.C. Diagnostic Performance of Tear Function Tests in Sjogren's Syndrome Patients. *Eye Lond. Engl.* **2007**, *21*, 229–237. [\[CrossRef\]](#)
27. Kaye, S.B.; Sims, G.; Willoughby, C.; Field, A.E.; Longman, L.; Brown, M.C. Modification of the Tear Function Index and Its Use in the Diagnosis of Sjögren's Syndrome. *Br. J. Ophthalmol.* **2001**, *85*, 193–199. [\[CrossRef\]](#)
28. Xuan, J.; Shen, L.; Malyavantham, K.; Pankewycz, O.; Ambrus, J.L.; Suresh, L. Temporal Histological Changes in Lacrimal and Major Salivary Glands in Mouse Models of Sjogren's Syndrome. *BMC Oral Health* **2013**, *13*, 51. [\[CrossRef\]](#)
29. Szalai, E.; Berta, A.; Szekanecz, Z.; Szűcs, G.; Módos, L. Evaluation of Tear Osmolarity in Non-Sjögren and Sjögren Syndrome Dry Eye Patients with the TearLab System. *Cornea* **2012**, *31*, 867–871. [\[CrossRef\]](#)
30. Williamson, J.F.; Huynh, K.; Weaver, M.A.; Davis, R.M. Perceptions of Dry Eye Disease Management in Current Clinical Practice. *Eye Contact Lens* **2014**, *40*, 111–115. [\[CrossRef\]](#)
31. Afonso, A.A.; Monroy, D.; Stern, M.E.; Feuer, W.J.; Tseng, S.C.; Pflugfelder, S.C. Correlation of Tear Fluorescein Clearance and Schirmer Test Scores with Ocular Irritation Symptoms. *Ophthalmology* **1999**, *106*, 803–810. [\[CrossRef\]](#)
32. Nichols, K.K.; Nichols, J.J.; Mitchell, G.L. The Lack of Association between Signs and Symptoms in Patients with Dry Eye Disease. *Cornea* **2004**, *23*, 762–770. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Kook, K.Y.; Jin, R.; Li, L.; Yoon, H.J.; Yoon, K.C. Tear Osmolarity and Matrix Metalloproteinase-9 in Dry Eye Associated with Sjögren's Syndrome. *Korean J. Ophthalmol.* **2020**, *34*, 179–186. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Messmer, E.M.; von Lindenfels, V.; Garbe, A.; Kampik, A. Matrix Metalloproteinase 9 Testing in Dry Eye Disease Using a Commercially Available Point-of-Care Immunoassay. *Ophthalmology* **2016**, *123*, 2300–2308. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Park, J.Y.; Kim, B.G.; Kim, J.S.; Hwang, J.H. Matrix Metalloproteinase 9 Point-of-Care Immunoassay Result Predicts Response to Topical Cyclosporine Treatment in Dry Eye Disease. *Transl. Vis. Sci. Technol.* **2018**, *7*, 31. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Whitcher, J.P.; Shiboski, C.H.; Shiboski, S.C.; Heidenreich, A.M.; Kitagawa, K.; Zhang, S.; Hamann, S.; Larkin, G.; McNamara, N.A.; Greenspan, J.S.; et al. A Simplified Quantitative Method for Assessing Keratoconjunctivitis Sicca from the Sjögren's Syndrome International Registry. *Am. J. Ophthalmol.* **2010**, *149*, 405–415. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Meiners, P.M.; Vissink, A.; Kroese, F.G.M.; Spijkervet, F.K.L.; Smitt-Kamminga, N.S.; Abdulahad, W.H.; Bulthuis-Kuiper, J.; Brouwer, E.; Arends, S.; Bootsma, H. Abatacept Treatment Reduces Disease Activity in Early Primary Sjögren's Syndrome (Open-Label Proof of Concept ASAP Study). *Ann. Rheum. Dis.* **2014**, *73*, 1393–1396. [\[CrossRef\]](#)
38. Nichols, K.K.; Begley, C.G.; Caffery, B.; Jones, L.A. Symptoms of Ocular Irritation in Patients Diagnosed with Dry Eye. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **1999**, *76*, 838–844. [\[CrossRef\]](#)
39. Pflugfelder, S.C.; Tseng, S.C.; Sanabria, O.; Kell, H.; Garcia, C.G.; Felix, C.; Feuer, W.; Reis, B.L. Evaluation of Subjective Assessments and Objective Diagnostic Tests for Diagnosing Tear-Film Disorders Known to Cause Ocular Irritation. *Cornea* **1998**, *17*, 38–56. [\[CrossRef\]](#)

40. Ramos-Casals, M.; Brito-Zerón, P.; Bombardieri, S.; Bootsma, H.; De Vita, S.; Dörner, T.; Fisher, B.A.; Gottenberg, J.-E.; Hernandez-Molina, G.; Kocher, A.; et al. EULAR Recommendations for the Management of Sjögren's Syndrome with Topical and Systemic Therapies. *Ann. Rheum. Dis.* **2020**, *79*, 3–18. [\[CrossRef\]](#)
41. Posso-Osorio, I.; Méndez-Rayó, T.; Soto, D.; Nieto-Aristizábal, I.; Cañas, C.A.; Tobón, G.J. Clinimetrics in Sjögren's Syndrome. *Rev. Colomb. Reumatol. Engl. Ed.* **2019**, *26*, 260–267. [\[CrossRef\]](#)
42. Foulks, G.N.; Forstot, S.L.; Donshik, P.C.; Forstot, J.Z.; Goldstein, M.H.; Lemp, M.A.; Nelson, J.D.; Nichols, K.K.; Pflugfelder, S.C.; Tanzer, J.M.; et al. Clinical Guidelines for Management of Dry Eye Associated with Sjögren Disease. *Ocul. Surf.* **2015**, *13*, 118–132. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Nichols, K.K.; Mitchell, G.L.; Zadnik, K. The Repeatability of Clinical Measurements of Dry Eye. *Cornea* **2004**, *23*, 272–285. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Akpek, E.K.; Bunya, V.Y.; Saldanha, I.J. Sjögren's Syndrome: More Than Just Dry Eye. Available online: <https://pubmed.ncbi.nlm.nih.gov/30681523/> (accessed on 17 October 2022).
45. Begley, C.G.; Chalmers, R.L.; Mitchell, G.L.; Nichols, K.K.; Caffery, B.; Simpson, T.; DuToit, R.; Portello, J.; Davis, L. Characterization of Ocular Surface Symptoms from Optometric Practices in North America. *Cornea* **2001**, *20*, 610–618. [\[CrossRef\]](#) [\[PubMed\]](#)
46. 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*, 108–152. [\[CrossRef\]](#)
47. Tsubota, K.; Hata, S.; Okusawa, Y.; Egami, F.; Ohtsuki, T.; Nakamori, K. Quantitative Videographic Analysis of Blinking in Normal Subjects and Patients with Dry Eye. *Arch. Ophthalmol.* **1996**, *114*, 715–720. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Yoon, H.J.; Choi, W.; Yang, J.M.; Ji, Y.S.; Lee, S.-S.; Yoon, K.C. Characteristics of Dry Eye in Patients with Pre-Existing Sjögren's Syndrome According to the Revised 2016 ACR-EULAR Classification Criteria. *Medicine* **2019**, *98*, e14641. [\[CrossRef\]](#)
49. Quintana, R.; Silvestre, A.M.R.; Goñi, M.; García, V.; Mathern, N.; Jorfen, M.; Miljevic, J.; Dhair, D.; Laithe, M.; Conti, S.; et al. Prevalence of Musculoskeletal Disorders and Rheumatic Diseases in the Indigenous Qom Population of Rosario, Argentina. *Clin. Rheumatol.* **2016**, *35*, 5–14. [\[CrossRef\]](#)
50. Angeles Aguirre, M.; Alarcon, G.; Alegre, J.J.; Alperi, M.; Andreu, J.L. Manual SER de Diagnóstico y Tratamiento de las Enfermedades Reumáticas Autoinmunes Sistémicas. *Soc. Esp. Reumatol. SER* **2014**, 478.
51. Lee, A.J.; Lee, J.; Saw, S.-M.; Gazzard, G.; Koh, D.; Widjaja, D.; Tan, D.T.H. Prevalence and Risk Factors Associated with Dry Eye Symptoms: A Population Based Study in Indonesia. *Br. J. Ophthalmol.* **2002**, *86*, 1347–1351. [\[CrossRef\]](#)
52. Caffery, B.E.; Richter, D.; Simpson, T.; Fonn, D.; Doughty, M.; Gordon, K. CANDEES. The Canadian Dry Eye Epidemiology Study. *Adv. Exp. Med. Biol.* **1998**, *438*, 805–806.
53. Begley, C.G.; Caffery, B.; Nichols, K.; Mitchell, G.L.; Chalmers, R.; DREI Study Group. Results of a Dry Eye Questionnaire from Optometric Practices in North America. *Adv. Exp. Med. Biol.* **2002**, *506*, 1009–1016. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Patel, R.; Shahane, A. The Epidemiology of Sjögren's Syndrome. *Clin. Epidemiol.* **2014**, *6*, 247–255. [\[CrossRef\]](#) [\[PubMed\]](#)
55. The Epidemiology of Dry Eye Disease: Report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul. Surf.* **2007**, *5*, 93–107. [\[CrossRef\]](#)
56. Lendrem, D.; Mitchell, S.; McMeekin, P.; Bowman, S.; Price, E.; Pease, C.T.; Emery, P.; Andrews, J.; Lanyon, P.; Hunter, J.; et al. Health-Related Utility Values of Patients with Primary Sjögren's Syndrome and Its Predictors. *Ann. Rheum. Dis.* **2014**, *73*, 1362–1368. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Hackett, K.L.; Newton, J.L.; Frith, J.; Elliott, C.; Lendrem, D.; Foggo, H.; Edgar, S.; Mitchell, S.; Ng, W.-F. Impaired Functional Status in Primary Sjögren's Syndrome. *Arthritis Care Res.* **2012**, *64*, 1760–1764. [\[CrossRef\]](#) [\[PubMed\]](#)
58. Mejía, L.F.; Gil, J.C.; Jaramillo, M. Intense Pulsed Light Therapy: A Promising Complementary Treatment for Dry Eye Disease. *Arch. Soc. Espanola Oftalmol.* **2019**, *94*, 331–336. [\[CrossRef\]](#)
59. Liu, K.C.; Huynh, K.; Grubbs, J.; Davis, R.M. Autoimmunity in the Pathogenesis and Treatment of Keratoconjunctivitis Sicca. *Curr. Allergy Asthma Rep.* **2014**, *14*, 403. [\[CrossRef\]](#)
60. Zhou, L.; Wei, R.; Zhao, P.; Koh, S.K.; Beuerman, R.W.; Ding, C. Proteomic Analysis Revealed the Altered Tear Protein Profile in a Rabbit Model of Sjögren's Syndrome-Associated Dry Eye. *Proteomics* **2013**, *13*, 2469–2481. [\[CrossRef\]](#)
61. Vitali, C.; Bombardieri, S.; Jonsson, R.; Moutsopoulos, H.M.; Alexander, E.L.; Carsons, S.E.; Daniels, T.E.; Fox, P.C.; Fox, R.I.; Kassan, S.S.; 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*, 554–558. [\[CrossRef\]](#)
62. Romão, V.C.; Talarico, R.; Scirè, C.A.; Vieira, A.; Alexander, T.; Baldini, C.; Gottenberg, J.-E.; Gruner, H.; Hachulla, E.; Mouthon, L.; et al. Sjögren's Syndrome: State of the Art on Clinical Practice Guidelines. *RMD Open* **2018**, *4*, e000789. [\[CrossRef\]](#)
63. Hay, E.M.; Thomas, E.; Pal, B.; Hajeer, A.; Chambers, H.; Silman, A.J. Weak Association between Subjective Symptoms or and Objective Testing for Dry Eyes and Dry Mouth: Results from a Population Based Study. *Ann. Rheum. Dis.* **1998**, *57*, 20–24. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Tseng, S.C. Evaluation of the Ocular Surface in Dry-Eye Conditions. *Int. Ophthalmol. Clin.* **1994**, *34*, 57–69. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Begley, C.G.; Caffery, B.; Chalmers, R.L.; Mitchell, G.L.; Dry Eye Investigation (DREI) Study Group. Use of the Dry Eye Questionnaire to Measure Symptoms of Ocular Irritation in Patients with Aqueous Tear Deficient Dry Eye. *Cornea* **2002**, *21*, 664–670. [\[CrossRef\]](#)
66. McMonnies, C.W.; Ho, A. Responses to a Dry Eye Questionnaire from a Normal Population. *J. Am. Optom. Assoc.* **1987**, *58*, 588–591. [\[PubMed\]](#)

67. Baer, A.N.; Walitt, B. Update on Sjögren Syndrome and Other Causes of Sicca in Older Adults. *Rheum. Dis. Clin. N. Am.* **2018**, *44*, 419–436. [[CrossRef](#)] [[PubMed](#)]
68. Roszkowska, A.M.; Oliverio, G.W.; Aragona, E.; Inferrera, L.; Severo, A.A.; Alessandrello, F.; Spinella, R.; Postorino, E.I.; Aragona, P. Ophthalmologic Manifestations of Primary Sjögren's Syndrome. *Genes* **2021**, *12*, 365. [[CrossRef](#)]
69. Vivino, F.B.; Carsons, S.E.; Foulks, G.; Daniels, T.E.; Parke, A.; Brennan, M.T.; Forstot, S.L.; Scofield, R.H.; Hammitt, K.M. New Treatment Guidelines for Sjögren's Disease. *Rheum. Dis. Clin. N. Am.* **2016**, *42*, 531–551. [[CrossRef](#)]
70. Bron, A.J.; Evans, V.E.; Smith, J.A. Grading of Corneal and Conjunctival Staining in the Context of Other Dry Eye Tests. *Cornea* **2003**, *22*, 640–650. [[CrossRef](#)]
71. Chalmers, R.L.; Begley, C.G.; 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 Anterior Eye J. Br. Contact Lens Assoc.* **2010**, *33*, 55–60. [[CrossRef](#)]
72. Lin, P.-Y.; Cheng, C.-Y.; Hsu, W.-M.; Tsai, S.-Y.; Lin, M.-W.; Liu, J.-H.; Chou, P. Association between Symptoms and Signs of Dry Eye among an Elderly Chinese Population in Taiwan: The Shihpai Eye Study. *Investig. Ophthalmol. Vis. Sci.* **2005**, *46*, 1593–1598. [[CrossRef](#)]
73. Dogru, M.; Tsubota, K. New Insights into the Diagnosis and Treatment of Dry Eye. *Ocul. Surf.* **2004**, *2*, 59–75. [[CrossRef](#)]
74. Zeev, M.S.-B.; Miller, D.D.; Latkany, R. Diagnosis of Dry Eye Disease and Emerging Technologies. *Clin. Ophthalmol.* **2014**, *8*, 581–590. [[CrossRef](#)] [[PubMed](#)]
75. Sullivan, B.D.; Crews, L.A.; Messmer, E.M.; Foulks, G.N.; Nichols, K.K.; Baenninger, P.; Geerling, G.; Figueiredo, F.; Lemp, M.A. Correlations between Commonly Used Objective Signs and Symptoms for the Diagnosis of Dry Eye Disease: Clinical Implications. *Acta Ophthalmol.* **2014**, *92*, 161–166. [[CrossRef](#)] [[PubMed](#)]
76. Mengher, L.S.; Pandher, K.S.; Bron, A.J. Non-Invasive Tear Film Break-up Time: Sensitivity and Specificity. *Acta Ophthalmol.* **1986**, *64*, 441–444. [[CrossRef](#)]
77. Giannaccare, G.; Scoria, V. False Myths versus Medical Facts: Ten Common Misconceptions Related to Dry Eye Disease. *Biomedicine* **2020**, *8*, 172. [[CrossRef](#)] [[PubMed](#)]
78. Acs, M.; Caffery, B.; Barnett, M.; Edmonds, C.; Johnson-Tong, L.; Maharaj, R.; Pemberton, B.; Papinski, D.; Harthan, J.; Srinivasan, S. Customary Practices in the Monitoring of Dry Eye Disease in Sjogren's Syndrome. *J. Optom.* **2018**, *11*, 232–241. [[CrossRef](#)]
79. Shen Lee, B.; Kabat, A.G.; Bacharach, J.; Karpecki, P.; Luchs, J. Managing Dry Eye Disease and Facilitating Realistic Patient Expectations: A Review and Appraisal of Current Therapies. *Clin. Ophthalmol.* **2020**, *14*, 119–126. [[CrossRef](#)]
80. Solans-Laqué, R.; López-Hernandez, A.; Bosch-Gil, J.A.; Palacios, A.; Campillo, M.; Vilardell-Tarres, M. Risk, Predictors, and Clinical Characteristics of Lymphoma Development in Primary Sjögren's Syndrome. *Semin. Arthritis Rheum.* **2011**, *41*, 415–423. [[CrossRef](#)]
81. Lazarus, M.N.; Robinson, D.; Mak, V.; Möller, H.; Isenberg, D.A. Incidence of Cancer in a Cohort of Patients with Primary Sjogren's Syndrome. *Rheumatol. Oxf. Engl.* **2006**, *45*, 1012–1015. [[CrossRef](#)]
82. Suresh, L.; Malyavantham, K.; Shen, L.; Ambrus, J.L. Investigation of Novel Autoantibodies in Sjogren's Syndrome Utilizing Sera from the Sjogren's International Collaborative Clinical Alliance Cohort. *BMC Ophthalmol.* **2015**, *15*, 38. [[CrossRef](#)]
83. Barboza, M.N.C.; Barboza, G.N.C.; de Melo, G.M.; Sato, E.; Dantas, M.C.N.; Dantas, P.E.C.; Felberg, S. [Correlation between signals and symptoms of dry eye in Sjögren's syndrome patients]. *Arq. Bras. Oftalmol.* **2008**, *71*, 547–552. [[CrossRef](#)] [[PubMed](#)]
84. Figueroa-Ortiz, L.C.; Jiménez Rodríguez, E.; García-Ben, A.; García-Campos, J. [Study of tear function and the conjunctival surface in diabetic patients]. *Arch. Soc. Espanola Oftalmol.* **2011**, *86*, 107–112. [[CrossRef](#)] [[PubMed](#)]
85. Chaw, P.F.A.; del Carmen Arteaga Llor, G.; Vera, M.C.M.; Fernández, A.C.S. Los factores de riesgo para el síndrome del ojo seco en la población manabita. *Cienc. Educ. Rev. Científica* **2020**, *1*, 56–64. [[CrossRef](#)]
86. Rodríguez, A.M.; Rojas, B.A.; Mercado, M. Asociación entre los síntomas y signos en pacientes con ojo seco. *Cienc. Tecnol. Salud Vis. Ocul.* **2008**, *6*, 12.
87. Singh, S.; Srivastav, S.; Modiwala, Z.; Ali, M.H.; Basu, S. Repeatability, reproducibility and agreement between three different diagnostic imaging platforms for tear film evaluation of normal and dry eye disease. *Eye.* [[CrossRef](#)]
88. Sánchez-González, M.C.; Capote-Puente, R.; García-Romera, M.-C.; De-Hita-Cantalejo, C.; Bautista-Llamas, M.-J.; Silva-Viguera, C.; Sánchez-González, J.-M. Dry eye disease and tear film assessment through a novel non-invasive ocular surface analyzer: The OSA protocol. *Front. Med.* **2022**, *9*, 938484. [[CrossRef](#)] [[PubMed](#)]
89. Tian, L.; Qu, J.H.; Zhang, X.Y.; Sun, X.G. Repeatability and reproducibility of noninvasive keratograph 5m measurements in patients with dry eye disease. *J. Ophthalmol.* **2016**, *2016*, 8013621. [[CrossRef](#)]
90. Itokawa, T.; Suzuki, T.; Iwashita, H.; Hori, Y. Comparison and evaluation of prelens tear film stability by different noninvasive in vivo methods. *Clin. Ophthalmol.* **2020**, *14*, 4459–4468. [[CrossRef](#)]
91. Borroni, D.; Paytuví-Gallart, A.; Sanseverino, W.; Gómez-Huertas, C.; Bonci, P.; Romano, V.; Giannaccare, G.; Rechichi, M.; Meduri, A.; Oliverio, G.W.; et al. Exploring the Healthy Eye Microbiota Niche in a Multicenter Study. *Int. J. Mol. Sci.* **2022**, *23*. [[CrossRef](#)]
92. Deng, C.; Xiao, Q.; Fei, Y. A Glimpse into the Microbiome of Sjögren's Syndrome. *Front. Immunol.* **2022**, *13*, 918619. [[CrossRef](#)]
93. Watane, A.; Raolji, S.; Cavuoto, K.; Galor, A. Microbiome and immune-mediated dry eye: A review. *BMJ Open Ophthalmol.* **2022**, *7*, e000956. [[CrossRef](#)]
94. De Luca, F.; Shoenfeld, Y. The microbiome in autoimmune diseases. *Clin. Exp. Immunol.* **2019**, *195*, 74–85. [[CrossRef](#)] [[PubMed](#)]
95. Cavuoto, K.M.; Banerjee, S.; Galor, A. Relationship between the microbiome and ocular health. *Ocul. Surf.* **2019**, *17*, 384–392. [[CrossRef](#)] [[PubMed](#)]