Oftalmología
clínica y experimental

Scientific publication of the Argentinian Council of Ophthalmology · Volume 17 · Supplement 1 · March 2024 · ISSNe 2718-7446

LATIN AMERICAN CONSENSUS ON OCULAR LUBRICANTS AND DRY EYE (LUBOS)

LUBOS
Latin American Consensus on Dry Eye

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Asociación Colombiana de Catarata y Refractiva

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LUBOS would like to thank the Dry Eye &
Ocular Health and Contact Lenses Division
of Alcon Laboratories for their collaboration
in the development of this consensus.

Latin American Consensus on Ocular Lubricants and Dry Eye (LUBOS)

General direction
María Ximena Núñez

Co-investigators
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Oftalmol Clin Exp (ISSNe 1851-2658)
2024, 17 (S1): eS1-eS103

Oftalmología
clínica y experimental

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Intellectual property number
69974236.

www.revistaoce.com

ISSN 1851-2658 (in print, 2007-2021)
ISSNe 2718-7446 (online)

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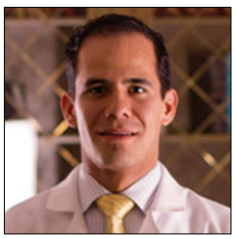

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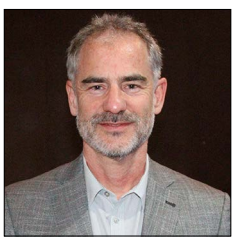

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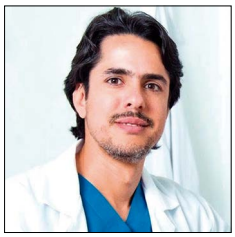

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Scientific publication of the Argentinian Council of Ophthalmology ISSN 2718-7446

Oftalmología
clínica y experimental

Volume 17 • Supplement 1 • March 2024

LATIN AMERICAN CONSENSUS ON OCULAR LUBRICANTS AND DRY EYE (LUBOS)

Sumário

LUBOS
Latin American Consensus
on Dry Eye

Latin American Consensus on Ocular Lubricants and Dry Eye (LUBOS)

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Acknowledgments
LUBOS would like to thank the Dry Eye & Ocular Health and Contact Lenses Division of Alcon Laboratories for their collaboration in the development of this consensus.

Abstract

The tear film has a complex composition allowing it fulfill multiple functions, such as optical, lubrication, immunological, endocrine, and neurotrophic, which are relevant for visual health. Alterations in its components, both in quality and quantity, will affect its homeostasis, also impacting the ocular surface, leading to a condition known as "dry eye". Dry eye has a high global prevalence, which is further increasing due to environmental factors (mainly screen mainly) and the overall rise in life expectancy. Several products are available for its treatment, but lubricants, generally referred to as "artificial tears", continue to be crucial. There is a wide variety of lubricant formulations with different indications, which, when used appropriately according to the type and severity of dry eye, allow for effective customized treatment. Considering the complexity and relevance of this issue, the Latin American Study Group on Lubricants and Dry Eye (LUBOS) was formed. This work represents a consensus with the aim of creating a diagnostic and therapeutic algorithm for dry eye, focused on the proper use of lubricants, providing practical guidance for general ophthalmologists.

Keywords: tear film, ocular surface, dry eye, artificial tears, ocular lubricants, consensus, Latin America.

* see page S2 a S4

Introduction

To say that ocular surface problems are frequent around the world, that they are influenced by environment, diet and lifestyle, and that there are many different therapeutic approaches, does not really say much, and offers little from a practical and care-based standpoint. Setting aside globalization, there are also regional medical differences that can affect pathology expression and therapeutic approach.

Latin America is a vast geographical region with social, cultural, ethnic, political, geographic, and environmental differences that justify reaching expert medical consensus with the purpose of evaluating if the concepts created in other parts of the world can be successfully applied in their communities. Sometimes they may require adaptations or even the development of different strategic options to solve local health problems. Reaching a medical-scientific consensus and using the right methodology allows us to employ the experience of experts in a topic to review published scientific evidence and build practical knowledge that can assist the medical community's decision-making.

This work will approach the topic of dry eye and artificial tears, considering it is a frequent, complex, and multifactor pathology that can manifest itself in an abrupt and intense fashion, but that generally appears as a pathological, chronic, and evolving pathology, for which artificial tears are used. It is logical to say that hydration therapies are used to correct ocular surface "dryness", given that the latter is the key foundation of artificial tears. But in reality, there currently are no artificial tears capable of replacing the natural lubricant our eyes produce: tear film. It is a substance made up of elements that undergo physiological dynamic changes in order to maintain ocular surface homeostasis. Modification of this homeostasis leads to different degrees of dry eye. This does not necessarily mean a lack of tears, but rather that their components might be suffering some pathologic alteration, meaning we are dealing with an illness that requires a therapeutic solution based on more than "wetting, moistening, or lubricating" the eye with a drop.

Diagnosing and treating dry eye requires a high degree of personalization. More ocular lubricant topical formulations are being developed because of this. It is crucial that ophthalmologists understand they have a vast array of artificial tears at their disposal, and become familiar with their characteristics in order to use them properly. The importance of choosing an artificial tear should not be overlooked. Despite the fact that they generally have a broad security margin, they are not harmless. In addition to the active ingredient, they have other substances that could be inadequate or even toxic for the ocular surface of some patients. On the other hand, ocular lubricants are therapeutic options amply used by large swaths of the world population that patients and healthcare systems must pay for, which in turns renders them attractive for pharmaceutical companies. All this motivated us to put together a work group and form a consensus intended to provide ophthalmologists with practical knowledge, giving them up-to-date information on lubricant components and their functions considering the different needs of patients with dry eye. In order to do this, we needed to review and update other aspects, such as those related to tear film components under different conditions, prevalence issues, epidemiology, costs, current dry eye classification, and also review what other therapeutic options were available for this anomaly (pharmacological ones as well those mediated by devices). This is how we formulate the goal of achieving a diagnostic and therapeutic algorithm for dry eye based on the appropriate use of the active principles in ocular lubricants.

Materials and methods

A study based on expert consensus was designed using Delphi[1] methodology in accordance to principles established by the ACCORD[2] guide. Colombia was the host of the initial call made by the Colombian Association of Cataract and Refractive (ASOCYR, for its Spanish initials), and led by Dr. María Ximena Núñez, to develop the first study on Lubricants and Dry Eye (LUBOS, for its Spanish initials) conducted by a group of Latin American experts, with the backing of ASOCYR

Table 1. Questions upon which the LUBOS consensus group was developed.

LUBOS consensus group questions
1. What are the components of tear film and what is its function?
2. What is dry eye and how do you find tear film in a dry eye?
3. What is the impact of dry eye and how does it affect quality of life?
4. What are the consequences of having dry eye?
5. What are the etiological causes of dry eye?
6. How many dry eye severity levels are there based on etiology?
7. What is the role of artificial tear components?
8. What is the ideal tear for every type of dry eye according to etiology and severity?
9. What is the function of non-pharmaceutical dry eye treatments?
10. What pharmacological mechanisms complement dry eye treatment with lubricants?
11. What is the treatment algorithm for dry eye?

President, Dr. Ernesto Otero. Four rounds of work were scheduled and six main researchers from different Latin American countries were initially appointed (Drs. Alejandro Rodríguez García, María Ximena Núñez, Jose Pereira Gomes, Manuel Garza, Alejandro Aguilar, and María Alejandra Henríquez). These researchers worked in rounds 1 and 2, generating a series of question under the PECOT methodology (PECOT stands for patients, exposure, comparison, outcomes, and time)[3]. Briefly, the PECOT method aimes to craft specific questions related to a certain pathology, in this case, dry eye. By the end of stage 2, there were 10 questions and an 11th extra inquiry (table 1) that was resolved based on an analysis of the answers for the ten previous questions. Clinical coordinator and external methodology advisor Dr. Lisandro M. Carnielli was in charge of group coordination and task assignment.

For stage 3, we called upon expert ophthalmologists to participate voluntarily. We did a preselection based on their academic achievements and experience on the subject, and contacted them via email. The final researcher panel was complete once these experts were confirmed (February 2023), alongside the six lead researchers. We had an initial online meeting to explain the objectives, working methodology, and timeline of the study. In stage 3, we randomly divided the investigators into different subgroups and distributed the questions to allow each group to work on a specific topic. During this stage, the expert panel had access to literature provided by the coordinator, who ranked information based on its evidence level. The coordinator prioritized systemic reviews and randomized controlled trials, but also included other reports such as guides and consensus produced by relevant scientific societies (for instance, reports from the Tear Film and Ocular Surface Society)[4]. Participants could also propose new references and scientific literature sources if they deemed it necessary.

Round 4 was done during a two-day in-person meeting in the Cali Country Club, Colombia, on June 6 and 7, 2023. Every group presented their topic (one of the assigned questions) to the other participants. Following the presentation, there was a round table in which all panelists participated and offered their opinions. The final step was to obtain approval of the different topics through consensus by voting (half plus one of total votes was the required majority for approval). The answers to the questions of table 1 were therefore obtained through consensus.

During this same meeting, the answer to question 11 regarding the creation of a therapeutic algorithm for dry eye and ocular lubricants was also resolved. All participants reported no conflict of interests. Prior to the beginning of the study, it was agreed that no lubricant brand names would be used, mitigating any potential bias in favor of pharmaceutical companies that manufacture it.

Results

The results for this study will be presented in stages in the form of answers to questions 1 through 10. Discussion on the topic will be introduced in each of them in order to establish final concepts obtained via consensus.

Question 11 will become the practical construction of this consensus, generating a diagnostic-therapeutic algorithm. The practical aspects of the concepts we intend to share with those interested within the ophthalmology community will also be announced.

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1

WHAT ARE THE COMPONENTS OF TEAR FILM AND WHAT IS ITS FUNCTION?

General aspects of tears

Tear film (TF) is made of a complex mixture of molecules (proteins, lipids, metabolites, electrolytes, etc.) and serves multiple purposes, such as regularizing corneal surface refraction, protecting tissue through its antibacterial and immunity function, providing oxygen and nutrition, as well as removing cellular detritus and remains of metabolism waste. Together with the drainage system, eyelids, and tear duct, it also assists wound repair from surgical wounds and ocular surface trauma[1]. But tear film also dynamically generates different types of tears with unique biochemical characteristics: basal tears (which are different within the sleep-wakefulness cycle), reflex tears (released in response to stimuli), and also tears that are produced and secreted in response to our emotions. Most tear film components (such as lactoferrin, lipocalin-1, and lysozyme) remain relatively constant within the different tear types, the same as osmorality[2-3]. However, the total amount of proteins, lipids, and secretory IgA vary between different tears since, for instance, protein and lipid content is higher in basal tears[4].

Aside from different tear types, there are other non-pathological factors involved in component variation, such as age[5-7], androgen levels[8], and individual variability.[8] There are also changes due to pathological conditions, such as meibomian gland dysfunction[5-6, 10-11]; palpebral infestation by Demodex[12]; systemic diseases like Sjögren syndrome and other collagenopathies[13]; smoking; or corneal refractive surgery[6], which can change tear and, especially, lipid layer composition.

The tear film surface is between 1.5 and 2 square centimeters, with an average thickness of 3 μm. This was confirmed by King Smith *et al*., who changed the method used by Danjo until they obtained consistent thickness results, ranging from 2 to 5,5 μm on the ocular surface according to several studies[15-17]. Volume is between 2,23 ± 2,5 μl, with an approximate average of 1 μl. Secretion is considered 0,15 ± 0,12 μl/min[18], with total daily production at around 0,15 ml/day. Maximum secretion per stimuli is between 40-50 μl/min[1, 15]. Tear clearance rate is estimated to be 16 ± 5%/min[15].

Although the original tear film description made by Wolf in 1949[19] characterizing it as a well-differentiated triple layer with an inner mucin layer, an intermediate watery layer, and an outer lipid layer, is adequate for tear film conceptualization, enough evidence has been produced in recent years to suggest that in reality it is a bilayer structure made up of an outer lipid layer surrounding an aqueous-mucin layer[15, 20]. Next, we will first see the characteristics and composition of this aqueous-mucin layer, and then move on to the lipid layer[21].

Tear film aqueous-mucin layer

The aqueous-mucin layer is the largest part of the tear and is crucial in maintaining optical function by regulating, lubricating, and protecting the ocular surface.

Mucin component

Mucinous components of this layer are closer to the corneal and conjunctival epithelial that originated it. Although its main component is mucin, it is also made up of water and glycoproteins of high molecular weight. Its functions are:

maintaining tear film superficial tension, anchoring it to the apical cell microvilli of corneal-conjunctival epithelial, serving as a barrier, hydration, wetting the membranes of hydrophobic surface epithelial cells, as well as diminishing epithelial damage produced by friction during blinking[22-23].

Membrane-associated mucins (MAM) —also known as transmembrane— are produced in corneal and conjunctival epithelial cells, while secreting mucins are produced by caliciform or goblet cells. The former are classified as gel-forming and soluble mucins.

- MAM subtypes are MUC1, MUC4, MUC16, and MUC20.
- Gel-forming mucin subtypes are MUC2, MUC5AC, MUC6, and MUC19, while soluble mucin subtypes are MUC7 and MUC9.

Water molecules in tears compete for the polar attraction of mucin molecules, keeping MAM glycocalyx and secreting mucins from strongly attaching and forming a mucin concentration and dispersion gradient in the aqueous layer. This lack of adhesion allows tears to easily flow across the ocular surface and avoid blink-related microtrauma[21].

Aqueous component

The aqueous component of the aqueous-mucin layer is made up mainly of water, which contains multiple components with specific and diverse functions, as well as different concentration gradients. Among them are electrolytes produced by the lacrimal gland, the Krause and Wolfring glands[1, 24]. The components are: sodium (120-170 mM), potassium (6-42 mM), magnesium (0,3-1,1 mM), calcium (0,3-1,1 mM), chlorine (106-135 mM), bicarbonate (26 mM), and phosphate ions (0,07 mM) which are largely responsible for tear osmolarity: its value in the tear meniscus is 302 ± 6 mOsm/L[15]. Electrolytes help maintain tear pH stable: 7.45 is considered a normal value, and they range between 7.14 and 7.82. PH values vary depending on tear film exposure.

There are also different types of proteins within the aqueous-mucin layer; the four most important present in tear concentration are: lysozyme, lactoferrin, lipocalin, and secretory IgA. Lysozyme, lactoferrin, and lipocalin are secreted through acinar tissue in the lacrimal gland, while IgA is through interstitial plasma cells embedded in the lacrimal gland, but outside the acinars[25].

Lysozyme represent up to 20-30% of total proteins, in basal as well as in reflex tears. They are secreted through the main and accessory lacrimal glands and degrade the cell envelope through hydrolysis of cell wall skeleton peptidoglycans, causing lysis and bacterial death. Additionally, it attaches to the negatively charged pores of the cell envelope through its high cationic activity, altering cell permeability[26].

Gram-negative bacteria like, among others, *Pseudomona aeruginosa* and *Escherichia coli*, are intrinsically resistant to lysozyme; other gram-negative bacteria, as well as gram-positive bacteria, have developed mechanisms to avoid lysozyme actions, modifying cell envelope peptidoglycans to make them resistant to hydrolysis, expressing lysozyme inhibitors to avoid being destroyed by them and changing a cell envelope's negative charge for a more neutral one, lowering its binding to lysozymes[26-27].

Lactoferrin represents between 20 to 30% of total proteins in basal and reflex tears. It is secreted by acinar cells in the lacrimal gland[28-29], can bind to free iron —which is needed for bacterial growth and the production of some toxins— and also has cationic activity that disrupts the cell membrane of bacteria, fungi, and virus. It has anti-inflammatory properties due to its ability to reduce complement activation and eliminate oxygen free radicals[30].

Lipocalin represents 15% to 33% of tear proteins. It is produced by acinar cells in the lacrimal gland and possibly the meibomian glands[28]. Its functions are: sweeping lipids off the corneal and conjunctival surface in order to maintain a viscosity that will not cause surface abrasion during blinking[28]; removing lipids that are usually insoluble in water and potentially damaging for the ocular surface and conducting them to the lacrimal drainage system; serve as an endonuclease by blocking viral DNA; it also plays an antibacterial and antifungal function by interfering with pathogens' ability to absorb iron[29].

Secretory IgA is composed of two IgA molecules (dimeric IgA), binded by a joining protein (J chain). It is the most abundant antibody in tear

film; its role is to provide immunity protection to the ocular surface. It is produced by plasma cells in conjunctival-associated lymphoid tissue (CALT), as well as plasma cells in the lacrimal gland and accessory lacrimal glands. It assists pathogen elimination, neutralizing it and keeping it from binding to host cells[25].

Proteins with defensive functions

Other proteins that also have defensive functions are:

- **β-defensins (hBD-2 and hBD-3):** defensins are a small group of peptides with a broad antimicrobial spectrum; it is assured that they have epithelial-healing properties and can positively self-regulate following corneal surgery, as well as during chronic diseases[31].
- **S100 proteins**: they impede bacterial adherence to mucin epithelial cells, are present in tears, and also increment during chronic swelling[32].
- **Phospholipase A2 enzymes** are active against gram-positive bacteria; they are produced by the lacrimal gland and corneal and conjunctival epithelial cells[33].
- **Secretory leukocyte protease inhibitor**: although it has antiprotease activity, it is known to also have anti-inflammatory and antimicrobial properties; it is active against gram-positive and gram-negative bacteria, fungi, and HIV. It is produced by the lacrimal gland and ocular surface epithelial cells[4].
- **Surfactant protein (SP)**: A and D bind to pathogens and regulate host defense, produced by lacrimal gland cells and also corneal and conjunctival epithelial cells[34].
- **SP-A/D in tears**: facilitates pathogen elimination in the presence of neutrophils[35].
- **SP-D**: helps protect corneal epithelial cells from *P. aeruginosa*[36] invasion.
- **C-type lectins**: they bind to carbohydrates on microbial surfaces s and phagocytic receptors, promoting microbial elimination[37].

Proteins with epitheliotropic and support functions

Other mucin layer proteins have epitheliotropic and support functions:

- The mucin layer contains multiple proteins, including factors involved in growth and cell support. They are present for homeostasis purposes (for instance, suppressing inflammation, maintaining innervation or the barrier), while others mainly take part in epithelial and/or stromal wound repair[38].
- Growth factors, such as epidermal growth factor, which is responsible for assisting corneal epithelium cell division and transforming growth factor beta (TGF-β), which it regulates by inhibiting or stimulating cell growth. Growth factors regulate the immune system by promoting extracellular matrix synthesization and deposit during wound repair[20]. Certain factors, like epidermal growth factor, are secreted through the lacrimal gland and promote corneal epithelial cell proliferation and migration and hasten wound repair[39]. Others, like TGF-β, are produced by stratified epithelial on the ocular surface (TGF-β1 and β2) and goblet cells (TGF-β2)[40-41]. It has been noted that TGF-β1 and TGF-β2 inhibit corneal epithelial proliferation in a dose-dependant fashion[42].
- Matrix metalloproteinase (MMP): endoproteinase that degrades the extracellular matrix and basement membrane, and is involved in wound healing. Present in tear film are MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10 y MMP-13. MMP-9 is potentially destructive, given that it attacks collagen. MMP-8 and MMP-14 are found in high levels in healthy tears and are involved in wound healing[4].
- Cytokines —mainly IL-1β, IL-6, IL-8, IL-10, e IL-12— are a very broad category of very small proteins; they're found in very low concentrations in regular tears and can be either inflammatory or not[43].

Tear film lipid layer

The tear film lipid layer is a dynamic structure on the ocular surface that contracts and expands every time a person blinks[44]. In the late 20th century it was described as a bilayer made up of inner polar lipids, and outer non-polar lipids[45]. Since then, the definition has moved on to a description made by King-Smith and collaborators[46],

who characterize it as a multilayer found in a liquid-crystal state with mixed proteins that likely come from cytokines[47].

Just like in the aqueous-mucin layer, there is a variability of lipid components depending on what technique is used[48-50]. Two sampling procedures are generally used: absorbent material or capillarity. Regardless of the employed procedure, ocular-surface-related research demands that tears be initially gathered to avoid reflex tears at least two hours after a person wakes up in order to avoid collecting closed-eye tears. Attention must be also be paid to the use of contact lenses and ongoing treatments, whether they are topical or systemic[51].

As we have previously mentioned, the main purpose of the tear film lipid layer is to delay tear evaporation from the aqueous-mucin layer by reducing superficial tension, while also forming a barrier between the aqueous-mucin layer and the palpebral conjunctival.

In order to fulfill its purpose, the lipid layer —its normal growth is between 50 to 100 nm— contains cholesterol, wax esters, fatty acids, and phospholipids that interact with the aqueous-mucin layer. These are mostly secreted by the meibomian glands located on the palpebral margin[53] and tasked with producing inner polar lipids and outer non-polar lipids[54].

Diagnostic improvements of recent years have greatly advanced tear film component knowledge, specifically of the lipid layer. The study of these components —known as "lipidomics"— has allowed us to discover over 600 fatty molecules in 17 different lipids that make up the layer[54].

There are several lipid classifications: the simplest one separates them as simple and complex. Most studies at the ocular level have shown that the lipids found in meibum and tear film belong to the complex group[55]. Another possible lipid listing is based on its water solubility, grouping them as polar (capable of ionizing and/or creating hydrogen bonds with water molecules), non-polar (highly insoluble in water), and amphiphile (can behave as polar and non-polar)[55].

According to a study by Lam *et al.*, human tear film contains 17 different lipids (table 1)[54].

Polar lipids

Polar lipids are made up of phospholipids (mainly phosphatidylcholine and phosphatidylethanolamine) and omega hydroxy acids ($HOCH_2$-$(CH_2)n$-COOH)[56]. Its main function is tied to its amphiphilic properties (molecules with polar and non-polar characteristics), which allow an interface between the lipid non-polar layer and the aqueous-mucin layer, aside from the fact that they are indispensable for lipid layer expansion[57]. This intermediate layer offers structural stability by reducing superficial tension in the aqueous component, raising viscoelasticity, and promoting adequate tear film molecule segregation, enabling normal tear distribution and preventing ocular surface dehydration[58].

Meibum phospholipid concentration values have been reported to be up to 16%, although with great variability, and up to 12% in tear film[59]. Phospholipid is more prevalent in tears then in meibum, while omega hydroxy acid has been reported at 3.5% in meibum and up to 4.4% in tear film[59-60]. However, as previously mentioned, lipid concentration amongst different types of tears varies. Rohit *et al.* compared the lipid profile of basal and reflex tears and found differences within polar lipids ($p<0.05$) as well as non-polar ($p<0.5$). Concentration of all types of polar lipids (phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, and OAHFA) was higher on basal tears, while phosphatidylethanolamine was the least abundant lipid type[61].

It is still unknown what is the minimum amount of polar lipids required to carry out its function. Bustovich posits that tear film must have at least 5% of polar lipids[55].

Although all types of known lacrimal polar lipids have been involved in ocular diseases, results so far have only been able to prove correlation but not causation[60].

Non-polar lipids

They are made up of wax and cholesterol esters, diesters, triglycerides, diglycerides, mono-

Table 1. Description of lipids present in human tear film.

Neutral lipids	Phospholipid
Cholesteryl ester	Phosphatidylcholine
Wax ester	Phosphatidylethanolamine
Triglycerides	Phosphatidylserine
Diglyceride	Phosphatidic acids
Free cholesterol	Phosphatidylinositol
Sphingolipid	Phosphatidylglycerol
Sphingomyelin	Lysobisphosphatidic acids
C8 glucosyl(β) ceramide	Other lipids
Ceramides	O-Acyl-ω-hydroxy Fatty Acids
NeuAcα2-3Galβ1-	Cholesterol sulfate
4Glcβ -Cer C17-sphingosine-phosphate	-------

Adapted from Lam *et al.*[54]

glycerides, free sterols, and free fatty acids[56, 62], with a predominance of wax esters, cholesterol esters, and triglycerides. The classic approach posits that these lipids avoid tear evaporation, provide a clear optical surface, and present a barrier against foreign objects and organisms[63], although recent results suggest that their role in evaporation has not been well established[64]. Meibum is its main source, and more than 140 wax ester molecular species have been described[65]. Rohit *et al*. found a greater concentration of all non-polar lipids (cholesterol esters, free cholesterol, wax esters, and triglycerides) in basal tears, with cholesterol being the most abundant[61].

As with polar lipids, concentration and component alteration of non-polar lipids have been reported in several clinical conditions, such as dry eye[66-67] and clouding in scleral lens' users[68]. Contact lens use, however, does not appear to modify these parameters[69].

Other components

Aside from the lipids already listed, multiple recent investigations have tried to find new biomarkers for different conditions, like evaporative dry eye disease, where it was discovered that wax esters of low molecular weight and esters containing saturated fatty acid remains dropped specifically due to the disease and heavily correlated with several dry eye clinical parameters[70]. In other diseases, like Meibomian gland dysfunction, participants had six lipid mediators significantly higher in 20% of cases, and three times as much in participants with reduced expressivity[71]. Even when comparing tears from healthy controls with those from patients with pterygium, pro-inflammatory and angiogenic eicosanoids were found, such as prostaglandin derived from COX (PGE2 and TxB2), leukotrienes derived from lipoxygenase (LOX), and 12-hydroxyoctadecanoic acid (12-

HETrE) derived from CYP, which were found to be undetectable in healthy tears[72].

Lipid peroxidation products in tears are being amply investigated due to their role as disease biomarkers. These include malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), and hexanoyl-lysine (HEL)[73]. The oxidation of unsaturated omega-6 fatty acids produces HEL, which is a new biomarker of lipid peroxidation[74].

Proteomic and metabolomic

The rise of proteomic and metabolomic research opens a new path into tear film investigation introducing new biomarkers, defined as indicators of whether a biological process is normal or pathologic, or what is the response to a certain treatment[75], which allow us to make earlier diagnosis and also explain the mechanisms of certain ocular and systemic pathologies and thus improve treatment focus[76-77].

Biomarker use has already been studied: Liyan Chen *et al.* revised the latest developments in metabolomic application to try and identify biomarkers in ocular pathologies like diabetic retinopathy, age-related macular degeneration, dry eye, and keratoconus, among others[78]. They are yet to be used in concrete clinical settings, but studies like the one conducted by Lopez-Lopez *et al.*, which discovered that the most altered proteins in keratoconus patients were those involved with the main physiopathological processes of the disease, like swelling, oxidative stress, matrix proteolysis, and iron homeostasis. These findings bring us closer to a more practical and clinically-applicable knowledge[79].

Advances in mass spectrometry and chromatography techniques over the past two decades have allowed us to identify hundreds of tear peptides and proteins. In 2006, De Souza reported the identification of 491 new proteins[80], a list that grew following studies conducted by Zhou *et al.* that identified 1543 proteins in healthy tear film[81]. Garrett Jones' group identified over 3,000 unique proteins, not all of which were found in study subjects[82]. The 50 most important proteins discovered by Jones G *et al.*, which were identified in samples using in-strip protein digestion and HCD fragmentation[77], are shown in table 2.

Nakatusaka *et al.* were the first to do a tear metabolomic analysis to identify and characterize amino acids in tears from normal eyes, as well as in eyes with different corneal, scleral, and ocular surface pathologies[83].

In 2011, Liyan Chen *et al.* published the first global metabolomic description of the tear. The study was a challenge due to the very small sample sizes and the available technology, which is currently more developed.

Chen *et al.* identified close to 60 tear metabolites, many of which had not been previously described. A brief list of the metabolites that were found: amino acids, alkanolamine, amino ketones, aromatic acids, carbohydrates, carnitines, cyclic anions, dicarboxylic acids, nucleosides, nucleotides, peptides, phospholipids, purines and derivatives, pyridoxine and derivatives, quaternary ammonium cations, and tricarboxylic acids[84].

Final concepts

Tears are extremely complex substances with components set in a dynamic equilibrium that react to the different needs of the ocular surface. New components are constantly found and new functions discovered, which in turn help bring clarity to physiopathological aspects of dry eye. Due to the characteristics previously mentioned, no artificial product can currently replace tears.

Final reviews

Present information

- Lacrimal fluid is a complex substance.
- Components with ocular and general functions are constantly discovered.
- Component presence and concentration is dynamic.

Future needs

- Develop accessible methods to determine lacrimal components in daily practice.

Table 2. List of the 50 proteins most frequently found in human tears.

Tear proteins				
Lactotransferrin	Zinc alpha 2-glycoprotein	Annexin A1	Keratin, type II cytoskeletal 5	Protein Glutamine Gamma Glutamyltransferase 2
Lipocalin 1	Ig heavy chain, constant kappa	Deleted in malignant brain tumors 1 protein	Glutathione S-transferase P	Ig heavy chain, constant mu
Albumin	Cystatin S	Complement C3	Actin alpha cardiac muscle 1	Leukocyte elastase inhibitor
Prolactin inducible protein	Mammaglobin-B	Serotransferrin	Cystatin –SA	Mucin-5AC
Ig heavy chain, constant alpha-1	Proline-rich protein 4	Ig lambda like polypeptide 5	Ig heavy chain, constant gamma-3	Keratin, type II cytoskeletal 6A
Lysozyme C	Cystatin SN	Subunit 3 of activating signal cointegrator 1	Pyruvate kinase PKM	Ceruloplasmin
Polymeric Ig receptor	Keratin, type II cytoskeletal 4	Ig heavy chain, constant gamma-1	Ig J chain	Aldehyde dehydrogenase 1A1
Extracellular glycoprotein lacritin	Prepropeptide opiorphin	Ig light chain, constant lambda 2	Heparan sulfate proteoglycan nucleus protein	Ig heavy chain, constant gamma-4
Ig light chain, kappa constant	Actin, cytoplasmic 1	Keratin, type I cytoskeletal 13	Annexin A2	Ig heavy chain, constant gamma-2
Ig heavy chain, constant alpha-2	Alpha-enolase	Keratin, type I cytoskeletal 19	Ig heavy chain, constant Mu	Keratin, type I cytoskeletal 7

Adaptation from Jones *et al.*[77]

- Investigate lacrimal components involved in general health (aside from ocular health).

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2

WHAT IS DRY EYE AND WHAT IS THE STATE OF TEAR FILM IN IT?

We will begin this chapter by addressing the first part of the question with an original definition this work group created after reviewing different explanations of what dry eye is. We will then answer the second part of the question regarding the state of tear film in this condition, given that the evolution of both concepts over time has been to try and understand the disease and the ensuing therapeutic management of it.

LUBOS definition of dry eye

After reviewing all current scientific evidence, analyzing new physiopathological concepts, and discussing clinical issues, the expert group assembled for the current consensus formulated the LUBOS definition based the following four statements:

- *Dry eye is a multifactorial disease affecting the ocular surface that can be defined as an alteration in tear film homeostasis.*
- *It can be classified as evaporative, aqueous-deficient, or mixed.*
- *It is a condition accompanied by different degrees of ocular and visual symptoms or signs in which tear film instability and hyperosmolarity, inflammation, tissular damage, and sensorineural abnormalities play an important role in its etiology.*
- *Lifestyle and environmental factors can bring on or worsen the disease.*

All four LUBOS statements of this new definition of dry eye have been scientifically validated and are backed by the contents of this work.

Evolution of dry eye definition over time

The first proposed definition of dry eye is relatively recent and was made by a group of experts and documented by Lemp *et al*. in 1995[1]. Multiple definitions have appeared since then and we will review the most important ones.

In 2007, the Tear Film and Ocular Surface Society published a definition of dry eye known as TFOS DEWS I[2]. Ten years later, and following a seminar that gathered dry eye disease specialists, academic researchers, optometrists and ophthalmologists, the same society proposed a new definition based on clinical effects and associated signs[3]. The Asian Dry Eye Society (ADES) also published its definition of dry eye in 2017[4]. In 2018, the American Academy of Ophthalmology (AAO) proposed the new Preferred Practice Patterns (PPP) for dry eye syndrome[5].

In 2020, Tsubota and colleagues proposed another definition based on a consensus agreed upon by dry eye disease experts from different parts of the world based on prior definitions (TFOS DEWS II, ADES, and AAO PPP)[6]. In 2022, a Mexican consensus revised the definition of dry eye and its complications and proposed classifying the disease based on its severity as mild, moderate, and severe, by using a methodology capable of diagnosing and classifying dry eye in a way that is objective, practical, and accessible to any specialist, as well as setting treatment guidelines based on disease severity[7].

The definitions proposed by the different groups can be seen in tables 1 and 2.

Despite the different proposed definitions of dry eye, there is no worldwide consensus and,

Table 1. Main authors and/or groups involved in consensus and/or reviews to establish a definition of dry eye.

GROUPS	YEAR
NEI/Industry Workshop on Clinical Trials in Dry Eye[1]	1995
Pflugfelder[9]	2003
Japanese Dry Eye Research Group[10]	2006
TFOS DEWS I[2]	2007
Korean Corneal Disease Study Group[11-12]	2014
Chinese Medical Association Ophthalmic Branch Corneal Group[13]	2013
Japanese Dry Eye Research Group[14]	2016
Asian Dry Eye Society[4]	2017
TFOS DEWS II[3]	2017
Dry Eye Syndrome PPP[5]	2018
Tsubota *et al.*[6]	2020
Mexican Dry Eye Disease Expert Panel	2022
Lubos	2023

NEI: National Eye Institute. TFOS: Tear Film & Ocular Surface Society. DEWS: International Dry Eye Workshop. PPP: Preferred Practice Patterns.

over the years, it has changed depending on group, region, and focus. The first definition from 1995 used the term "disorder" and not "disease"; the original TFOS DEWS work group was the first to acknowledge that dry eye is indeed a disease with a multifactorial etiology[2-3].

The TFOS I definition of dry eye recognized the symptoms (discomfort and transient vision alteration) as primordial. Dry eye consequences were described in terms of symptoms and tear film instability. Patients also suffered an increase in osmolarity and tear film inflammation. This definition did not include dry eye disease mechanisms or etiology. Basically, the increase in osmolarity and inflammation were described as casual instead of causal markers of the disease[2].

The TFOS DEWS II definition posited that the unifying element of dry eye was a loss in tear film homeostasis. Ocular symptoms (discomfort and vision alteration) remained one of the main disease characteristics. The key etiological factors like tear film instability, hyperosmolarity, inflammation, and ocular surface damage were considered valuable in recognizing the cyclical process of the disease[3].

The ADES definition emphasized tear film instability and the importance of visual impairment, highlighting tear film break-up time as a key test of disease evolution[4]. The AAO-PPP definition of dry eye disease describes it as a group of tear film disorders caused by reduced tear production or tear film instability[5]. Tsubota *et al*. highlighted the importance of an unstable tear film, inflammation, discomfort, and visual impairment, while also including epitheliopathy and sensorineural abnormalities[6].

The final TFOS workshop, titled "A lifestyle epidemic: ocular surface disease", emphasized how lifestyle and environment can cause ocular surface alterations[8]. This workshop described key factors like air pollution, nutrients, cosmetics, and other factors that affect dry eye disease. It is because of this that any modern definition of dry eye must take into account these factors, which are part of

Table 2. Definition of dry eye according to the groups cited in table 1.

GROUP	DEFINITION OF DRY EYE
The NEI/Industry workshop (1995)[1]	Dry eye is a tear film disorder due to tear deficiency or excessive tear evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.
TFOS (2007)[2]	Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.
ADES (2017)[4]	Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage.
TFOS-DEWS II (2017)[3]	Dry eye is a multifactorial disease of the ocular surface characterized by a loss in tear film homeostasis and the appearance of ocular symptoms, in which tear film instability, hyperosmolarity, inflammation, ocular surface damage, and neurosensory abnormalities play etiological roles.
AAO-PP (2018)[5]	Dry eye disease (also known as dry eye syndrome) refers to a group of disorders of the tear film that are due to reduced tear production or tear film instability, associated with ocular discomfort and/or visual symptoms and inflammatory disease of the ocular surface.
Tsubota *et al.* (2020)[6]	Dry eye is a multifactorial disease characterized by a persistently unstable and/or deficient tear film causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation, and sensorineural abnormalities.
LUBOS (2023)	Dry eye is a multifactorial disease of the ocular surface characterized by a loss in tear film homeostasis. Its origin can be classified as evaporative, aqueous-deficient, or mixed. It is accompanied by ocular and/or visual symptoms and/or signs, in which tear film instability, hyperosmolarity, inflammation, tissular damage, and sensorineural abnormalities play important etiological roles. Environmental and lifestyle factors are capable of triggering and/or worsening the disease.

NEI: National Eye Institute. TFOS: Tear Film & Ocular Surface Society. DEWS: International Dry Eye Workshop. PPP: Preferred Practice Patterns. ADES: Asia Dry Eye Society.

patients' daily lives. It is important to remember the definition and scheme proposed by DEWS I in which the associated factors were a key part of how we define and consider dry eye disease.

After analyzing all prior and current definitions, our study group highlighted the following aspects which were then taken into account to posit the LUBOS definition:

1. Dry eye is an ocular surface "multifactorial disease".
2. Because tear film affectation is key, we opted to use the term "loss in homeostasis" when referencing it in order to group all possible alterations together.
3. Disease origin can be evaporative, aqueous-deficient, or mixed.
4. Hyperosmolarity and/or inflammation and/or tissular damage and/or sensorineural abnormalities play an important role in its etiology.
5. Patients may display different degrees of ocular and/or visual symptoms and/or signs. Some patients may not have any ocular or visual symptoms, but show ocular signs.

Faced with this situation, first we must rule out reduced corneal sensitivity.

6. Environmental and lifestyle factors should be included as elements capable of triggering and/or worsening the disease.

Tear film: dry eye disease alterations

Following our review of dry eye definitions, we will outline the tear film's condition and what are the alterations caused by dry eye disease.

The tear film in dry eye is unstable. It experiences a loss in homeostasis that lead to inflammation and tissular damage, resulting in a loss of its normal functions of lubrication, defense, repair, healing ocular surface wounds, as well as its key role as part of the visual optic system[3].

Homeostasis can be physiologically described as the state of balance of body, system, organs, or tissue regarding physiological functions as well as tissue and fluid composition[3, 15]. Altered homeostasis can mean multiple changes taking place in the tear film and ocular surface in response to one or several underlying causes[3, 15]. Physical and chemical changes taking place in a tear film suffering dry eye are closely related to the loss of homeostasis its components are undergoing[16].

Many advances have been made ever since dry eye disease began to be considered a relevant and prevalent pathology, with evidence of its growing incidence within the general population. However, despite the appearance of new diagnostic procedures, testing equipment, and a better understanding of its histopathology and pathophysiology, the complex nature of its different components, and its different paths of interaction and regulation still present a diagnostic and therapeutic challenge for ophthalmology and a vast investigative field to develop.

It has been proven that the tear film is made up of numerous and varied substances including, among others, the following: water, lipids, proteins, mucins and electrolytes, which undergo alterations in their composition, proportion, structure, and regulation when affected by dry eye disease. Dry eye specifically causes abnormalities in the tear film's proteome, metabolome, and lipidome[16-17].

Proteome-related abnormalities

Tear film proteins (proteome) show alterations due to dry eye disease[3]. More than 1,800 proteins have been identified in proteome and multiple studies related to the topic have been published. The ones most affected by the disease are: epidermal growth factor[18-20], interleukin 1 (IL-1α)[21], interleukin 6 (IL-6)[22-23], lactoferrin (LTF)[24], lipocalin 1 (LCN1)[25-26], matrix metalloproteinase-9 (MMP-9)[21], MUC5AC[27-28], plasmin activity through plasminogen (PLG)[29], phospholipase A2 group IIA (PLA2G2A)[30-31].

Metabolome-related abnormalities

The aqueous-mucin layer of the tear film has electrolytes (like sodium, potassium, calcium, magnesium, chlorine, phosphate, and bicarbonate) and protein fragments like peptides and metabolites (like amino acids, urea, glucose, and lactic acid). More than 85 metabolites have been identified in tears[17, 32-34]. Alterations of many of them are present in dry eye disease: carnitine, taurine, methionine and arginine, diadenosine polyphosphates, glucose, lactic acid, formic acid, N-acetylglucosamine, and serotonin[33].

Osmolarity tends to be augmented, causing structural and functional changes that lead to progressive corneal and conjunctival epithelial damage.

Osmolarity variations in the tear film within a ± 10 mOsm/L range are currently accepted as normal[35]. This variability is tied to evaporative phenomenons, since a reduction in tear solvent (aqueous component) naturally tends to raise the amount of solute, thus increasing its concentration.

The tear film aqueous component is affected by two main tracts that juxtapose and/or synergize with each other: reduction of aqueous-component production and evaporation increase. A decrease in production is generally associated with a disorder or lesion affecting the tear gland, frequently due to an autoimmune condition like Sjögren syndrome, while a rise in evaporation is intimately related to lipid component alteration[36].

Lipidome

The lipid component alteration most frequently associated is Meibomian gland dysfunction[37]. Glandular conduct alteration favors bacterial proliferation, which in turn secrete lipases and esterases, raising viscosity and temperature to the level required to liquify the meibum and complete the vicious cycle of glandular conduct obstruction and inflammation.[38] Association to skin conditions like rosacea and hormonal cycles play an important role in the alteration of lipid components[39-40].

Final concepts

As we have previously stated, defining a pathology with a simple-sounding name (dry eye) entails great complexity given that it is a disease that, even though it manifests locally, causes our whole organism to change and react. Although several very suitable definitions already exist, the LUBOS definition of dry eye was crafted by using top current knowledge, but also taking into account practical issues of general ophthalmology. Dry eye complexity is partly expressed in the unresolved mysteries regarding changes in the tear film, given that, although practical relevant aspects and characteristics have been identified —for instance, the fact that tear pH rises in dry eye[41] —there are many topics that still remain unknown.

Synopsis

Present information

- LUBOS developed a definition of dry eye by unifying different ideas and bringing them up to date.
- It is a multifactorial disease that can be classified as evaporative, aqueous-deficient, or mixed.
- It has different severity levels and can be triggered or worsened by environmental and lifestyle factors.

Future needs

- Unify terminology and dry eye concepts within the Latin American medical community.
- Disseminate and teach these concepts to medical doctors at different formation levels.

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3

WHAT IS THE COST AND BURDEN OF DRY EYE DISEASE?

According to the DEWS II (Dry Eye Workshop II) report, dry eye prevalence varies depending on population and diagnosis employed. It is generally estimated that it affects between 5% and 50% of the adult population worldwide. Despite the estimate variance, due to the differences in definition and diagnostic criteria used by different studies, the disease is expected to entail a high cost[1].

Disease and healthcare costs carry considerable socio economic implications as they are the sum of direct, indirect, and intangible costs. Direct costs include conventional hospital care, alternative care, and transportation; indirect costs are related to low productivity, while intangible costs mainly refer to pain-related disability. Three parties are involved in this situation: the healthcare system, society, and the patient[2]. We will proceed to develop these aspects.

Direct costs of dry eye disease

These are costs extrapolated from dry eye, as Pflugfelder *et al*. say, referencing costs like medical consultations, prescriptions, specialized glasses, medical procedures, reduced effective work time, low productivity, changes in type of work, lower quality of life, lost leisure time, as well as social, economical, and physical decline[3].

Between 1997 and 1998, costs in the United States were reported at US$228 per patient for six months; 70% of that was due to doctor visits. Surveys have also shown that direct costs for dry eye patients were around US$25 a month.

In 2011, the direct annual cost for a dry eye patient was US$783 dollars. According to disease prevalence, total cost is estimated at approximately US$3.4 billion. Total annual costs to treat a patient vary depending on dry eve severity, whether it is low, moderate, or severe, with values at US$678; 771, and 1,267, respectively[4].

Information pertaining to the situation in Asian countries was obtained for 2008 and 2009 from the pharmacy and clinic inventory database of the Singapore National Eye Center. Results show that total annual expenses for dry eye treatment was US$1,509,372.20 in 2008 and US$ 1,520,797.80 in 2009, respectively. Pharmacological treatment made up 99.2% of total costs, with lubricants representing 79.3% of that amount. Cost per patient was US$55.86 in 2008 and US$56.16 in 2009[5].

In three health centers in that area, particularly in China, the annual cost of dry eye treatment per patient was determined to be US$4,422.60, 391.30 and 265.40 respectively. Compared to per capita income that year (2018), those figures represented 3.16%, 2.31%, and 2.44%, respectively for each center. The cost of dry eye is influenced by economic status and the treatment centers where the evaluation is made[6].

Surveys in Europe found that the total annual cost of medical attention of 1,000 patients with dry eye syndrome treated by ophthalmologists varies between 270,000 U.S. dollars in France to 1,1 million in the United Kingdom.

Compared to previous studies, annual cost per patient in 2003 and 2004 seems to be higher in the UK (US$110 per patient), followed by Spain (US$800), Italy (US$600), Germany (US$500), Sweden (US$400), and France (US$300). These costs include all expenses related to medical attention, like consultations and pharmacological as well as non-pharmacological treatments. Visits to specialists was the lion's share of the cost in France, Germany, and Spain, at 40% of total

expenses; diagnostic tests were the predominant factor in Italy and Sweden, while prescription medication was the top expense in the UK[7].

The cost of using cyclosporine and punctal plugs in dry eye treatment grows depending on case severity: US$2,964 (mild), US$2,959 (moderate), and US$2,698 (severe), with an average cost of 783 U.S. dollars per patient[4].

Cyclosporine has been proposed as a strategy to reduce the cost of dry eye disease by lowering the amount of doctor visits and the need for punctal plugs. Topic cyclosporine affects the underlying inflammatory process in dry eye and can potentially reduce the economic burden of the disease by decreasing trips to the doctor and the use of other medications, like artificial tears. A phase 3 study discovered that cyclosporine reduced the need for artificial tears, which impacted not only the cost of tears but also patient quality of life[8-9].

Quality of life, intangible cost, and indirect cost of dry eye disease

When studying the economic impact of dry eye disease, we must take into account not only the efficiency of lubricants and/or devices, but also variables regarding productivity and patient quality of life. What do we mean when we talk about quality of life? The World Health Organization defines quality of life as a multifaceted concept que intertwines physical health, physiological state, level of independence, social ties, and relationship with the environment[10]. Dry eye disease has a negative impact on patient quality of life as it not only affects their physical health and physicological well-being, but also their level of independence and environmental impact. Pain and ocular discomfort, blurry vision due to inadequate production and/or bad quality of tears, and poor sleep quality associated to dry eye are the main factors impacting physical health. At the physicological level, the disease's frequent association with chronic ocular hyperemia, especially ocular rosacea, have a negative influence on emotional health and can lead to social anxiety and general anxiety disorders[11].

There are also difficulties related to thinking, learning, memorizing, and concentrating, mostly due to the negative effect that ocular pain and the interruption of tasks that require visual concentration have on cognitive processes[12]. Because it is a chronic incurable condition, treatment duration creates additional secondary burdens in its integration into daily life, reducing a patient's sense of independence as people with low manual dexterity due to neurodegenerative and/or autoimmune pathologies. We must also mention the patient's sense of dependency on medication and the reduction in work capacity.

Finally, there is environmental impact, caused by a decrease in economic resources and leisure activities due to potentially coming in to contact with factors that may worsen the disease[10].

Measuring the impact of dry eye disease on patient productivity takes us directly to the heart of the indirect cost and two related concepts: absenteeism and presenteeism. Absenteeism is understood as employees being away from their workplace while they are ill, while presenteeism is when employees are at their jobs but not are not completing their tasks and are less productive. The latter generates higher economic costs and is harder to evaluate.

In order to measure the impact of absenteeism and presenteeism, Japan decided to use a scale from 0 to 100 rating the difficulty of several work-related issues from non-existent to absolute. They calculated economic impact based on sale and salary loss[13] and found that patients with a definitive diagnosis of dry eye lose approximately 3.1 work days a year, which entails a loss in productivity of US$6,160 per person for those with dry eye, and US$2,444, for those with probable dry eye. This led to 1.38 million U.S. dollars in losses per year for the group under study[13].

Canada measured presenteeism and absenteeism for seven days using the Work Productivity and Activity questionnaire (WPAI), where presenteeism turned out to be the greater contributor to the disease[14]. Reported annual costs per patient in Canadian dollars in 2018 was CAD$2,324 for direct costs and CAD$24,331 for indirect ones. Of those amounts, 79.34% were attributed to

presenteeism, while 11.11% to absenteeism. This shows the higher impact of indirect cost in dry eye disease and the importance of keeping these factors in mind when calculating disease costs. It is also important to take into account the rise in cost due to dry eye severity and the presence or not of Sjögren syndrome.

The Eye Dryness Score Visual Analog Scale (EDS VAS) was used to classify dry eye severity. The scale goes from 0 to 100, from no discomfort to full discomfort. Scores below 40 were considered mild, between 40 and 60 moderate, and over 60 severe. For mild, moderate, and severe cases, direct cost was CAD$957, 1,302, and 2,766, respectively. Indirect cost was CAD$5,960, 16,525, and 25,485 respectively.

Direct cost for cases with Sjögren syndrome was CAD$2,689 and 2,203 for patients with no Sjögren. Indirect costs were CAD$41,093 for cases with and 17,694 for those without.

In 2021, an examination was conducted on patients in the UK to determine the gravity of ocular disease and its impact on their quality of life[15]. The National Eye Institute Visual Function Questionnaire of 25 items (NEI VFQ-25), which included six additional items (A3-A8), was among the questionnaires used. Other questionnaires used were the 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L), Impact of Dry Eye in Everyday Life (IDEEL), 5-Item Dry Eye Questionnaire (DEQ-5), and Standardized Patient Evaluation of Eye Dryness Questionnaire (SPEED). The Ocular Comfort Index (OCI), the Work Productivity and Activity Impairment Index (WPAI), and the eye dryness score using the visual analog scale (EDS VAS), were also taken into account.

Over 80% of patients said they use digital screens or engage in daily tasks like reading. Twenty five percent of dry eye patients reported that they were exposed to air conditioning or recirculating air, compared to 15.4% of patients without this condition; 32.3% were exposed to wind or air drafts compared to 12.3%; and 17.6% faced forced ventilation or heating compared to 8.4%. Regarding exposure to environmental facts, 13.5% of patients were exposed to pollution compared to 7.6%; and 15% faced low humidity compared to 5.8%[16].

According to the VFQ-28R, it is evident that dry eye patients face greater limitations and difficulties for socio-economical functioning than people not affected by the disease. The ED-5D-5L shows that dry eye patients are more prone to greater difficulties regarding mobility as well as self care and its related tasks, while also suffering more pain or discomfort, and more anxiety or depression[15].

Screen exposure has been associated with dry eye symptoms due to a reduction in blinking frequency, incomplete blinking, and an increase in tear evaporation[16]. The physiopathological mechanism has been amply described and technological revolutions related to the general rise in screen usage as a work tool have earned this aspect a special mention. Dry eye prevalence among screen users varies between 26% and 70%, with the caveat that disease prevalence grows in line with patient age. It is important to point out that one of the possible causes of high prevalence found in this report could be associated with the use of contact lens, air conditioning, inadequate control of office temperature, or low humidity[16].

The combined population of Latin American countries was estimated at 616 million people in 2022[17]. These countries have different socio economic and geo-environmental factors compared to nations from other continents studied previously, which can affect the magnitude and impact of the economic burden of dry eye. There currently is no reliable data on the economic cost of dry eye in Latin American countries. Studies on dry eye prevalence and incidence within the region would allow us to better understand the burden of this condition. There is a pressing need to conduct socio economic population studies, in particular investigations done by public and private health institutions that can reflect the direct and indirect cost to improve how governments and health institutions use available resources in the future[18].

Indirect costs make up the lion's share of the economic impact of dry eye. From a public health standpoint, reducing direct costs of dry eye treat-

ments should not be the sole focus, but rather an approach that seeks treatment efficacy to reduce total cost by affecting indirect costs.

It should also be highlighted that the direct and indirect cost of dry eye is variable and dynamic, depending on dry eye status and taking into account the chronicity of each state. Early and efficient detection and intervention are also important steps to avoid atrophic presentations that generate more costs for the healthcare system.

Final concepts

Large swaths of the population suffer some degree of dry eye. Risk factors related to lifestyle and the environment are on the rise. This means that dry eye disease has a sizable economical impact which is also rising, not only because of the costs of direct medical attention, but also due to indirect costs related to its effects on lifestyle, visual performance at work, and the possibility of suffering transitory or permanent visual impairment. Reviewing this topic and placing it within the context of our region allowed us to detect that there is a need to include the economic impact of dry eye in Latin American studies on the topic. This type of studies will allow us to collect information and evidence that will be of great use in taking healthcare-related decisions.

Synopsis

Present information

- Due to its characteristics, dry eye disease has a sizable economical impact worldwide.
- There is a direct cost due to medical issues, and also an indirect cost (potentially important due to alterations in visual performance and quality of life).

Future needs

- Conduct research that includes Latin American economic variables to measure direct and indirect impact of dry eye disease.
- Communicate this information to health-related organisms that are perhaps unfamiliar with the real economic impact of dry eye in the general community.

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4

WHAT IS THE INCIDENCE/PREVALENCE OF DRY EYE AND ITS EFFECTS ON QUALITY OF LIFE?

Dry eye prevalence

Determining the prevalence/incidence of dry eye is complex since there is no homogenous, constant, and consistent definition in the different population studies we have examined. The number of variables (signs, symptoms or signs, or combined symptoms) analyzed in prevalence and incidence studies in different parts of the world vary. For the present work, we revised a number of studies and meta-studies to determine dry eye prevalence around the world, including Latin America. These studies determine prevalence and look to identify variables like age, gender, computer use, and geographic distribution.

Dry eye prevalence according to gender, age, and geography

A meta-analysis conducted in China in 2010 to measure dry eye prevalence according to age, gender, and geography revealed prevalence was 13.55% when taking into account patients showing signs and symptoms, and 31.4% when considering only dry eye symptoms[1]. Given the enormity of China's population, this amounts to 170 and 394 million people, respectively. The risk factors for a higher prevalence of ocular dryness that were taken into consideration include female gender, advanced age, and higher geographical latitudes[2].

Electronic questionnaires were sent to 124,469 people in Canada searching for dry eye symptoms in all age groups[3]. Out of the 5,163 responses obtained, 1,135 reported suffering ocular dryness. Researchers found that prevalence grew with age. Prevalence among people between 25 and 34 was 18.4%, and 24.7% among 55 to 64-year-olds, a difference that is clinically significant ($p < 0.05$). Prevalence in women was also higher, 24.7%, which is also clinically significant ($p<0.001$).

A dry eye prevalence study conducted electronically in 2013 in the United States among 75,000 people over 18 found that 5,051 people suffered dry eye[4]. These results showed that dry eye prevalence among the U.S. population is 6.8%, approximately 16,4 million people. Prevalence in people age 50 or over was 72%, a higher figure that coincided with findings in China and Canada. Prevalence in women was 62%, also higher than the general figure. Differences based on gender and age were clinically significant ($p<0.01$).

Regarding age, the Ural Eye Study was conducted among 1,493 people 85 or older and found that 34.3% of patients had a Schirmer test result of less than 5 mm, while 31.4% suffered meibomian gland dysfunction (MGD). Cases with a 2.36 odds ratio were predominant among women[1].

A meta-analysis published in 2021 offered dry eye disease prevalence estimates worldwide and in subgroups based on: diagnostic critera, gender, geographic location, and age using a Bayesian approach[5]. Global dry eye disease prevalence was estimated to be 11.59% (DE = 0.04). Symptomatic dry eye estimates were 9.12% (DE = 0.04), with 9.5% for woman (DE = 0.05) and 6.8% for men (DE = 0.06). Prevalence was lower in North America, 4.6% (DE = 0.03), and higher in Africa, 47.9% (DE = 1.8). Prevalence in patients with dry eye signs was 35.2% (DE = 0,3), with 34.7% for woman (DE = 0,7), and 37.6% for men (DE = 0.7). North America again had the lowest regional prevalence with 3.5% (DE = 0.4), and East Asia had the highest, 42.8% (DE = 0.4). Based on the TFOS DEWS II diagnostical criteria, global prevalence was 29.5% (DE = 0.8), with 28,1% for woman (DE = 1.2), and 24.9% for men (DE = 1.4).

A systematic review and meta-analysis recently published (2024) including 14 Latin American studies on dry eye (11,594 participants), showed prevalence to be 41% (IC-95 39-44%) in Mexico and 13% (IC-95 12-14%) in Brazil[6]. Dry eye prevalence was 70% (IC-95 56-80%) among interior workers, 71% (IC-95 65-77%) among students, and 83% (IC-95 77-88%) in general ophthalmology clinics.

Two studies showed that MDG prevalence was 68% among patients of tertiary ophthalmological clinics and 23% among surgical residents. Both studies showed that dry eye prevalence measured with OSDI was higher than MDG prevalence.

Dry eye prevalence and digital screen use

The association between dry eye and prolonged screen use has become more important in recent years. There is growing interest in trying to determine whether it is a risk or an associated factor. One meta-analysis addressing this issue was found. It is worth noting that out of 9,049 studies, only 16 —surveying 11,365 computer users— were included for evaluation[7]. Using two criteria points, dry eye prevalence was determined to be 54%. When three criteria points were used, however, prevalence dropped to 11.6%. It was also discovered that prevalence was higher in women and grew with age. The authors concluded that, given the diversity of dry eye definitions, some studies are not reliable.

Based on this, dry eye prevalence (i.e., the number of cases in a given population) varies between 6.8% and 54% according to a review of different studies and meta-analysis. However, some important considerations must be made: prevalence tends to be higher if studies focus only on symptoms, but lower if signs are also included. All studies consistently show that dry prevalence is higher in women and increases with age.

Final concepts

Designing epidemiological population studies with homogenous questionnaires and precise definitions in order to determine a reality-based prevalence of the disease is of great importance, considering the relevance of the topic and the fact that there is still plenty to investigate, especially in Latin America.

Global data continues to show that it is more frequent in women and that it correlates with aging. However, other aspects related to lifestyle, such as screen usage, are increasing its prevalence among young people. These are relevant aspects to consider given their potential implication in altering quality of life and raising health costs.

Synopsis

Current information

- Dry eye disease is more frequent among women and it increases with age.
- There is a rise among young people, partly due to the use of digital devices (screens).

Future needs

- Conduct epidemiology reports in every Latin American region in order to compare data and improve disease understanding.
- Unify registration and follow-up tasks among countries, as well as education and prevention among the general population.

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5

WHAT IS THE ETIOLOGY OF DRY EYE?

General physiopathological concepts

The general mechanisms of dry eye physiopathology are instability and tear film hyperosmolarity[1]. From an etiological standpoint, there are two predominant types of dry eye: *aqueous-deficient dry eye* and *evaporative dry eye*[2]. A drop in tear production is the main mechanism of the first case, while the second is due to a lacrimal lipid deficiency that increases tear evaporation and is usually associated with Meibomian gland dysfunction[3].

Hyperosmolarity is a key factor in both types of dry eye[4]. This can be the product of a drop in tear secretion or secondary to a rise in evaporation, which facilitates an inflammatory cascade that contributes to conjunctival and corneal epithelial cell apoptosis, as well as goblet cells[5]. Tear production regulates to keep osmolarity constant[6]. The trigeminal innervation of the ocular surface (corneal and conjunctival epithelium, and palpebral margins) is the afferent nervous branch. It is made up of receptors that react to a broad range of stimuli, including pain, temperature, and chemical and mechanical changes[7]. On the other hand, the parasympathetic innervation of the main tear gland and its accessories, goblet cells, and Meibomian glands is the system axis efferent[7-8]. Evidence suggests that cold thermoreceptors are capable of reacting to hyperosmolarity and corneal cooling produced by a rise in evaporation, which stimulates secretion, blinking frequency, and ocular perception that, for some individuals, can even cause physical discomfort[1, 9]. Tear secretion is also influenced by environmental stimuli and circadian rhythm[10]. In fact, its lowest output is registered after prolonged periods of ocular closure which take place, for instance, during sleep[11].

It has been hypothesized that dry eye is a local inflammatory disease caused by an unbalance in the immunoregulatory mechanisms of the ocular surface. It therefore produces a vicious cycle where mitogens (MAPK) and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) trigger an early activation of protein kinase, unleashing a cascade of inflammatory events that favor gene transcription that codify matrix metalloproteinases (MMP), especially MMP-9 and other pro-apoptotic factors[12-14]. Figure 1 shows the physiopathological development of dry eye proposed by LUBOS.

Ocular surface inflammation can cause dry eye through various mechanisms. It is hypothesized that it occurs due to an alteration in tear film composition through direct harm to the corneal conjunctival surface and accessory surfaces like the Meibomian glands and goblet cells. This way, the inflammatory phenomenon interrupts production and normal secretion of lipids and essential mucins to maintain tear film stability[14-16]. This leads to a rise in evaporation and the subsequent perpetuation of the vicious negative cycle of hyperosmolarity and inflammation.

On the other hand, inflammatory mediators can directly affect the function of the lacrimal gland and neural pathways that control tear secretion, which can result in a reduction of basal as well as reflex tears[8, 19].

Aqueous-deficient dry eye

The central mechanism of aqueous-deficient dry eye is a reduction in tear production. This type of dry eye can be caused by diseases that affect the afferent and efferent pathways, as well as the lacrimal gland[20]. One way the afferent

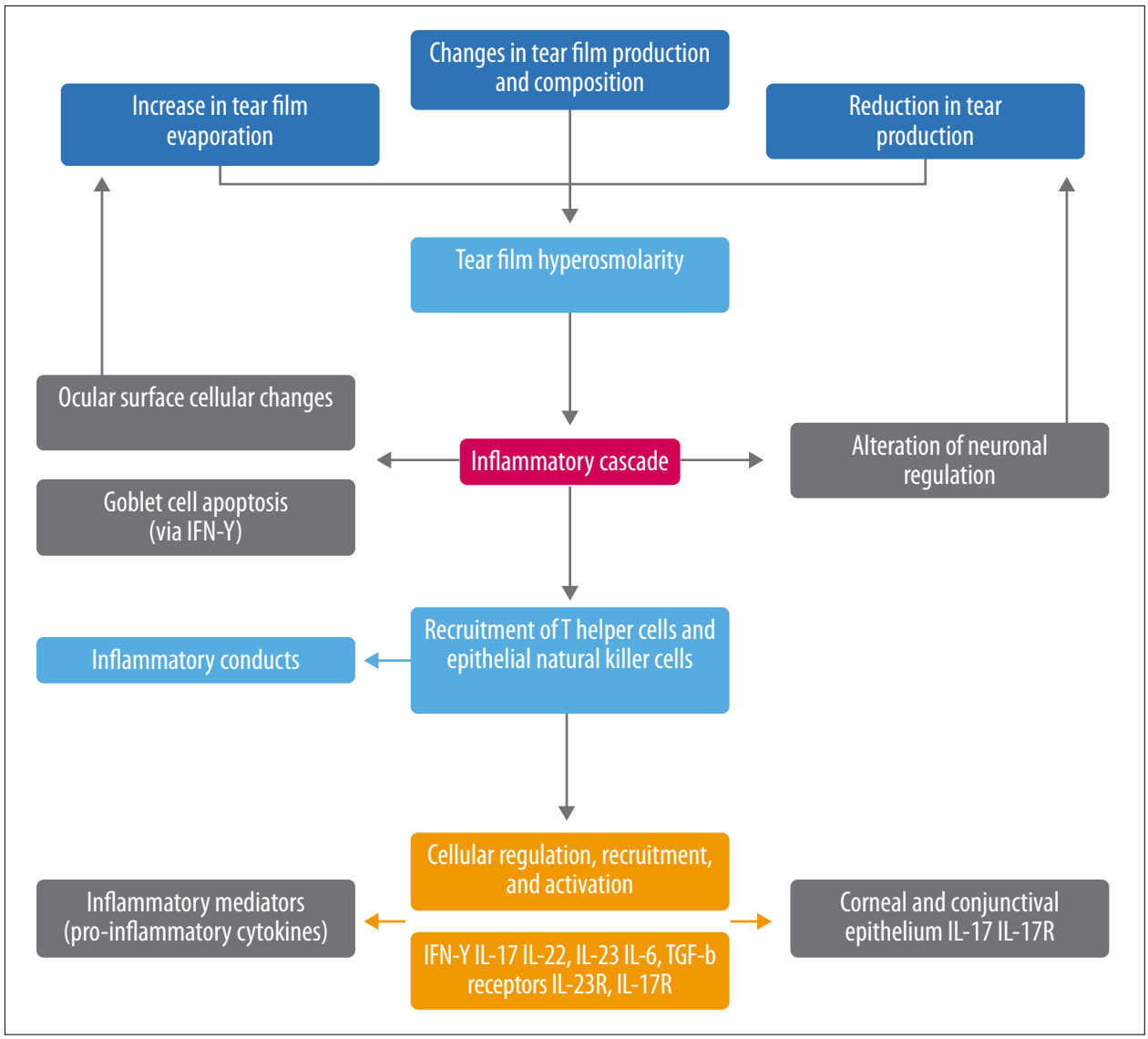

Figure 1. LUBOS diagram of dry eye physiopathology.

pathway can be compromised is through chronic abuse of local anesthetics, direct harm to the trigeminal nerve, or keratorefractive surgery. On the other hand, lacrimal gland pathology appearing itself as a secondary alteration of the drainage system, which can appear in ocular cicatricial diseases like pemphigoid and trachoma, can cause lacrimal hyposecretion and alter tear film dynamic. Other relevant factors that may reduce tear secretion are systemic medication (antihistamines, beta blockers, diuretics, and certain psychotropic medications, among others), as well as age.

One frequent cause of aqueous-deficient dry eye is lacrimal gland inflammatory infiltration due to autoimmune diseases like Sjögren syndrome. Based on this, relevant consensus like TFOS DEWS II have classified aqueous-deficient dry eye causes as being either Sjögren syndrome-associated, or non-associated entities.[1] Sjögren syndrome is primary in the first group, as well as other associated autoimmune rheu-

matologic diseases. In the second group, we find congenital diseases like alacrima, age-related hyposecretion, intrinsic lacrimal gland deficiency, inflammatory/infiltrative pathology (sarcoidosis, lymphoma, and infectious diseases), cicatricial conjunctivitis, states of hyposecretion, graft-versus-host disease, and systemic diseases like diabetes mellitus.

Evaporative dry eye

Meibomian gland dysfunction has been described as the main physiopathological factor in evaporative dry eye. It is characterized by hyposecretory or obstructive conditions (the latter being the most common) due to inflammation and structural changes to the distal part of the glandular excretory ducts, and a hypersecretory condition that is either primary or associated to meibum production disorders like seborrheic blepharitis. This leads to an inadequate lipid layer and, because of this, greater tear evaporation. Evaporative dry eye causes can be classified according to palpebral affectation as primary (meibomian seborrhea) and obstructive (cicatricial and non-cicatricial dysfunction), or secondary to meibomian glands[21]. Secondary affectations are caused by local palpebral conditions (anterior blepharitis, ocular surface inflammation, and contact lenses), skin diseases (rosacea, seborrheic dermatitis, psoriasis), chemical exposure (retinoids, antiandrogenics), and genetic syndromes (meibomian gland agenesis and Turner syndrome)[22-26]. They can also be secondary to an alteration in blinking frequency, modulation, and dynamic, like Parkinson's disease or ocular surface alterations secondary to allergic conjunctivitis, a deficit in vitamin A, and post surgical dry eye. Anatomic or functional diseases of the palpebral border like lagophthalmos, entropion, ectropion or lax eyelid, can cause evaporative dry eye. In these type of diseases, primary alteration is not initially the meibomian gland but palpebral motility and failures in excretory duct compression to expel meibum, which leads to a rise in tear evaporation[1].

Aqueous-deficient and evaporative dry eye (mixed-etiology) in clinical practice

Drawing a line between evaporative and aqueous-deficient dry eye makes sense from a physiopathological standpoint. However, it is more likely that both types coexist in one patient, considering that multiple factors —like aging, for instance— are related to both subtypes[27-28]. It is also common for aqueous-deficient dry eyes to present chronic persistent inflammation leading to an obstruction of excretory gland ducts and, over time, higher tear evaporation[29]. Dividing dry eye into two subtypes can be useful at the onset of the disease but as it progresses, however, all cases will generally present an evaporative component[20].

Dry eye is a complex pathology in which a person's individual traits and genetic makeup, as well as their medical and ocular history, play a key role in disease physiopathology. There are, however, other highly relevant aspects that need to be taken into account in order to understand dry eye. Among them are lifestyle and social factors, work and living conditions, social-cultural and environmental conditions, as well as digital use. Several lifestyle factors have been linked to dry eye[30]. For instance, there is correlation between psychiatric pathologies like depression and post traumatic stress disorder and dry eye[31-33]. On the other hand, it is crucial to understand that, given the characteristics of tear composition and its micro volume, internal and external environmental conditions, as well as a person's activity, are relevant to dry eye physiopathology. Therefore, environmental conditions including temperature, humidity, and wind speed, together with a person's behavior and habits (blinking frequency, ocular opening, position of gaze, and medication use) have a key role in dry eye pathogeny[34].

Iatrogenic dry eye

Dry eye disease can be caused by a number of iatrogenic interventions, including medication use, contact lenses, and surgical procedures[35]. Several local and systemic drugs can be tied to

Table 1. Topic active agents considered to cause or worsen dry eye.

Hypotensors	**(examples)**
Beta blockers	timolol, betaxolol
Prostaglandin analogues	bimatoprost, latanoprost, travoprost
Adrenergic agonists	apraclonidine, brimonidina
Carbonic anhydrase inhibitors	brinzolamide, dorzolamida
Cholinergic agents	pilocarpine
Antihistamine	olopatadine
Antivirals	aciclovir, trifluridine
Decongestants	naphazoline, tetrahydrozoline, oxymetazoline
Mydriatics	cyclopentolate, tropicamide
Miosis	dapiprazole
Anesthetics	proxymetacaine, tetracaine, proparacaine
Non-steroidal anti-inflammatories	nepafenac, ketorolac, diclofenac, bromfenac

Adapted from Gomes *et al*.[35]

dry eye (tables 1 and 2). Preservative substances like benzalkonium chloride (BAK) have been identified as causal agents of dry eye disease due to their pro-inflammatory and toxic effect[36-37]. The use of contact lenses has been tied to lipid layer slimness and irregularity, tear film instability, lower basal tear renewal, and tear meniscus reduction[38-39].

Corneal photorefractive surgeries are traditionally described as a frequent cause of iatrogenic dry eye. It is hypothesized that dry eye appears in these cases due to a corneal nerve lesion[40]. Corneal hyposensitivity following laser refractive surgery can be secondary to direct harm to corneal nerves or abnormal neuronal remodeling, which causes an alteration in afference with secondary loss of corneal sensitivity and lacrimal hyposecretion[41]. There is also a rise in partial blinking, as well as an alteration in tear film distribution and Meibomian gland expression, with a subsequent increment in tear evaporation[42].

Other ophthalmological procedures have also been linked to iatrogenic dry eye: keratoplasty, cataract, glaucoma, retinal, and strabismus surgeries; as well as oculoplastic and reconstructive surgeries[43]. Surgeries can cause tear film dysfunction due to a reduction in corneal sensitivity, goblet cell loss, a rise in inflammatory mediators, and the effects of collyrium used in pre- and postoperative care which contain preservative and anesthetic substances[44]. Reconstructive procedures can cause morphological changes in eyelids and Meibomian glands and alter blinking dynamic.

Final concepts

Understanding what causes dry eye disease will allow us to improve prevention and therapeutic care. Conditions that determine whether a dry eye is evaporative, aqueous-deficient, or mixed, can be very different and either a condition related to local

Tabela 2. Agentes ativos sistêmicos considerados causadores ou agravantes do olho seco.

Analgesics	
Antirheumatics	aspirine, ibuprofen
Cannabinoid	dronabinol, tetrahydrocannabinol
Opioids	fentanyl, methadone, morphine
Anesthetics	ether, nitrous oxide
Anticholinergics	
Antihistamines	cetirizine, chlorphenamine, desloratadine, ketotifen
Antiarrhythmics	atropine
Antidepressants	amitriptyline, bupropion, duloxetine, fluoxetine, paroxetine, sertraline
Anti-Parkinsons	levodopa
Antipsychotic	clozapine, haloperidol, lithium carbonate, olanzapine, quetiapine, risperidone
Antispasmodic	homatropine, oxybutynin
Decongestants	oxymetazoline, phenylephrine
Antihypertensives	
Adrenoblockers	atenolol, carvedilol, clonidine, propranolol
Diuretics	hydrochlorothiazide, polythiazide
Antimalarials	hydroxychloroquine
Antineoplastics	cyclophosphamide, interferon, methotrexate, mitomycin C
Anxiolytic	alprazolam, lorazepam, zopiclone
Calcium chelate	alendronic acid, pamidronic acid
Vitamines	isotretinoin, niacin
Hormone therapy	finasteride, tamsulosin, estrogen, progesterone
Neurotoxin	botulinum toxin a and b, phenobarbital

Adapted from Gomes *et al.*[35].

ocular problems, or an ophthalmological manifestation of a general disease. In clinical practice there are cases of dry eye secondary to medication, surgical procedures, and environmental conditions.

Discovering dry eye disease etiology in a patient can be simple and quick when the cause is apparent. It can, however, also become an arduous task of constant evaluation, like in the case of diagnosing uveitis, requiring consultations with doctors from other fields, who, in turn, may also assist with specific treatments, either main or complimentary.

Synopsis

Current information

- LUBOS developed a simple and practical up-to-date diagram of dry eye physiopathology.

- Clinical practices should address ocular as well as general causes that affect tear film quality and quantity.
- It is important to bear in mind the potential impact some commonly used medications have on tear secretion.

Future needs

- Investigate dry eye physiopathology and new associations with general health disorders.
- Emphasize the importance of medical history and evaluation methods of patients with dry eye and educate the medical community.

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6

HOW MANY DRY EYE SEVERITY LEVELS ARE THERE BASED ON ETHIOLOGY?

General considerations on dry eye severity and etiology

As previously mentioned, dry eye severity is a pathology with high global prevalence. Despite collaborative efforts to unify classification and diagnostic criteria, however, there are still worldwide shortcomings evidenced in the various diagnostic criteria used by different studies[1]. When putting together a classification, it is important that etiology be related directly to therapeutic approach. The TFOS DEWS II classification previously mentioned —the most used and well known— is based on an etiology that divides dry eye into evaporative, aqueous-deficient, and mixed. This is very clear in theory, but in practice, general ophthalmologists find it difficult to conduct staging and take adequate decisions regarding approach.

Other groups at the international level have tried to standardize a classification of dry eye disease severity, among them the Mexican panel on dry eye[2], the Italian group[3], and the Asian Dry Eye Society[4]. All of them have sought to rigorously define categorization modality. Evidence shows that they tend to grade dry eye on a scale of between 2 and 4 severity levels. These classifications are broadly in line with clinical findings observed in dry eye patients, and take into account frequency of presentation and impact on quality of life and visual function, all aspects intrinsically linked to this pathology.

Murube *et al*. have been presenting a classification since 2005 that takes into account causes, affected glands or tissue, and severity level[5]. The application of such a broad classification, however, can present certain difficulties, as well as being impractical for ophthalmologists in everyday practice.

The approach proposed by Barabino *et al*. suggests incorporating inflammatory elements together with signs and symptoms into dry eye classification[3]. Although these elements are important, examinations like interleukin and osmolarity measurement should be reserved for research projects, given that they require technologies that are not universally available, as well as being expensive and impractical in routine dry eye clinical settings. We highlight the importance of carrying out an independent classification of the causal agent and thus guiding matters towards optimal clinical options.

The group led by Tsubota of the Asian Dry Eye Society presented a classification based on tear film stability independently of underlying mechanisms that may disturb ocular homeostasis[4]. This approach looks to simplify treatment decision making through a more automatized categorization. Aside from tear breakup, it assesses clinical signs including a patient's altered vision as well as related pathologies and possible clinical correlations.

Rodríguez-García and the panel of Mexican experts propose an approach based on qualitative, quantitative, and non-invasive criteria for patient assesstment[2]. Nine different criteria points are taken into account: symptom frequency and duration, dry eye-related questionnaires, tear film break-up time, ocular surface staining, Schirmer's test, conjunctival hyperemia, palpebral state, and ocular surface restoration. These criteria points converge in a classification proposal covering three severity levels: mild, moderate, and severe. The group also recommends a management strategy based on these categories and aligned with a tiered treatment approach adapted to affection severity[2].

Criteria	Severity scale*			
	LUBOS - I Mild	LUBOS-II Moderate	LUBOS-III Severe	LUBOS-IV Plus
OSDI questionnaire	13-22 points	23-32 points	33-100 points	LUBOS-III plus any of the following criteria: • Irreversible damage to the ocular surface. • Schirmer's test: I = 0 mm/5 minutes in at least one eye. • Lagophthalmos with epithelial erosion or defect. con erosión • Symblepharon formation affecting more than half of the corneal surface. • Corneal anestesia. • Corneal surface keratinization >50%.
Tear break-up time †	8-10 seconds	5-7 seconds	< 5 seconds	
Ocular surface staining (SICCA OSS)‡	3-4	5-8	9-12	
Meibomian glands functionality §	++	+++	++++	

* Severity assessment: ≥ 2 criteria from the highest severity level in the worst eye.
OSDI: Ocular Surface Disease Index. SICCA: Sjögren's International Collaborative Clinical Alliance.6
+ Low fluorescein staining, the patient is asked not to blink while the tear film is observed by a slit lamp with a cobalt blue filter. Tear breakup time (TBUT) is registered as the number of seconds that pass between the last blink and the appearance of the first dry stain on the tear film.
+ 1 to 4 minutes after fluorescein administration to lower staining dissemination using cobalt blue filter (excitation filters = 465-495 nm).
§ Altered expression and secretion quality (Nichols KK et al.7).
• Consider aggravating circumstances and lifestyle factors: environmental factors, digital environmental, nutrition, social, and cosmetic challenges.

Figure 1. LUBOS dry eye disease severity levels.

LUBOS group classification: four severity levels

The LUBOS group proposes its own classification of disease severity and divides it into four levels: mild, moderate, severe, and plus. The "plus" category complements the "severe" level, dealing with more complex cases that demand a more aggressive therapeutic approach from the moment of initial assessment (Fig. 1).

The criteria employed to elaborate the LUBOS classification has been carefully selected based on the need to provide all specialists with practical and effective tools that will help them stratify patients under their daily care. In line with this goal, patient symptoms were assigned relevance through the OSDI questionnaire, tear break-up time (ideally done in a non-invasive manner through some objective device; it can also be calculated manually and subjectively), ocular stain score (OSS), also known as SICCA for the group that created it, the Sjögren's International Collaborative Clinical Alliance[6]. This is presented schematically in figure 2, which is complemented by figure 3 (where the LUBOS assessment is also introduced). Therefore, it is important to follow recommendations for stain application as explained here:

Corneal fluorescein staining

- Use paper strips stained with fluorescein sodium moistened with a sterile saline solu-

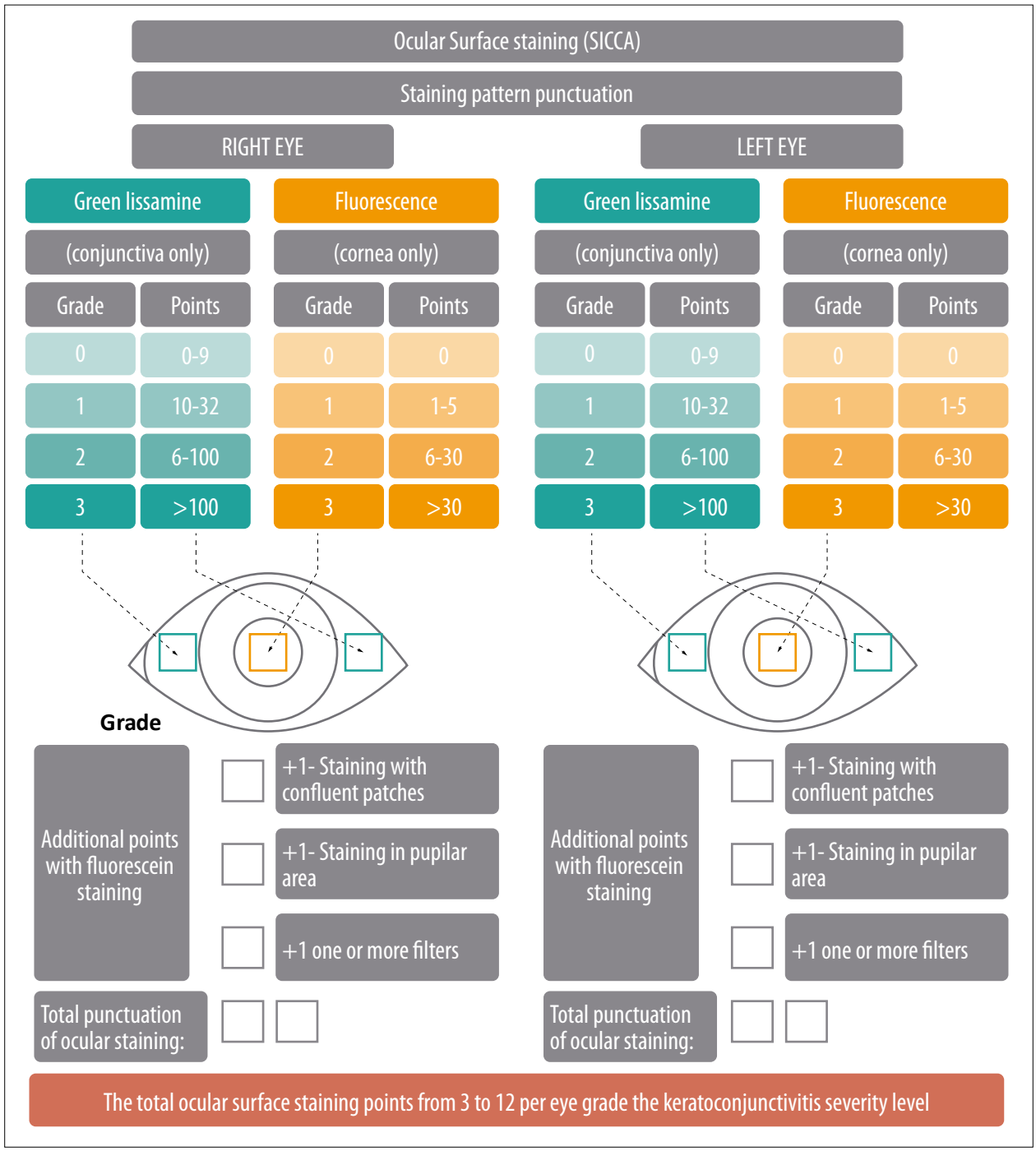

Figure 2. SICCA scheme to evaluate ocular surface staining level (this scheme maintains guidelines proposed by its author, Whitcher JP *et al.*[6])

tion. Eliminate excess moisture through a slight tap to reduce fluorescein stain dissemination.

- Evaluation is done between 1 and 4 minutes after fluorescein administration —in order to allow spreading— with a cobalt blue filter

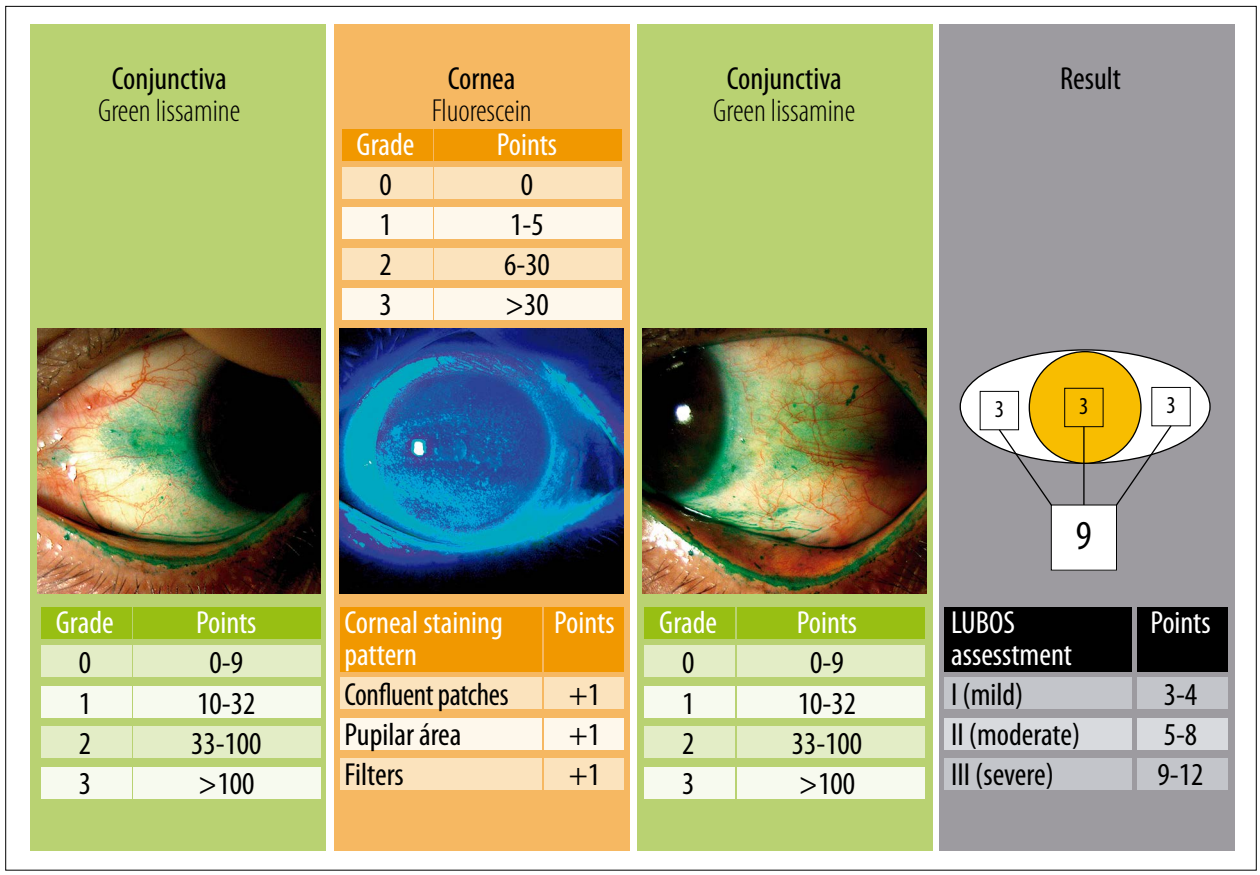

Figure 3. Representation complementing the ocular surface staining punctuation system in line with the OSS system (SICCA), adding the LUBOS punctuation system (bottom right).

(excitation filter = 465 -495 nm) available on most slit lamps.

Conjunctival staining with lisamine green

- Use paper strips stained with lisamine green moistened with a sterile saline solution. Eliminate excess moisture through a slight tap to reduce overcoloring. For application, it is recommended the inferior eyelid be lowered with the patient looking upwards, monitoring possible spillage with a paper tissue on the inferior fornix and asking the patient to close their eyes and move them around.
- Evaluation is conducted between 2 and 4 minutes after lisamine green administration —to avoid discoloration— with white light under a diffuser (filter).

Double staining (fluorescein + lisamine green)

- The 2% fluorescein-1% green lisamine mix offers optimal staining without adverse sensations. In order to see the change, alternate between white light for green lisamine, and raising magnification and using cobalt blue filter for fluorescein.
- Double staining with a mixture has the potential to show ocular surface staining quicker and more efficiently. Staining is visible with both dyes, so no there is no cancellation effect.

And finally, as a guide to classify the number of matching possibilities, we added a scheme adopt-

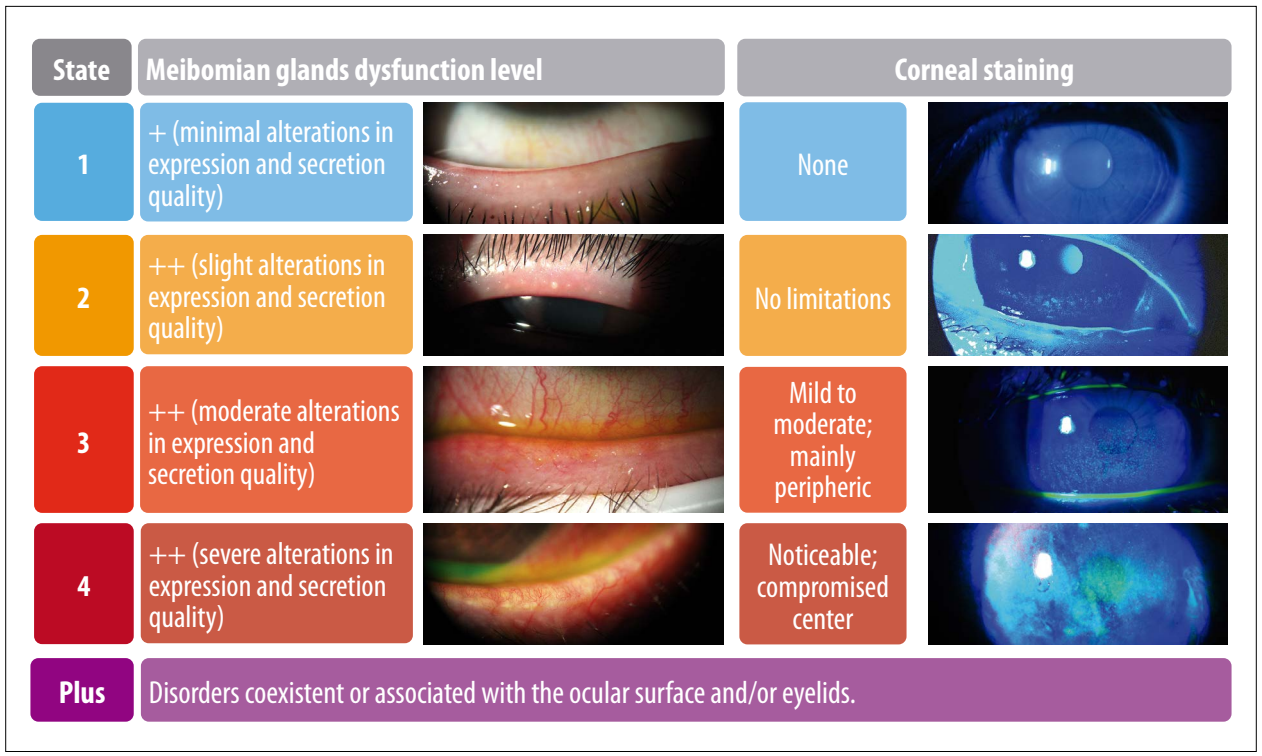

Figure 4. Meibomian glands dysfunction levels (meibum expression and quality) (chart adapted based on Nichols KK *et al.* [7])

ing the classification used by Nicholas *et al.*[7] representing affectation levels of Meibomian gland functionality (Fig. 4).

Final concepts

As a conclusion, the LUBOS classification criteria has been established through consensus with the intention of providing ophthalmology professionals with a precise and pragmatic tool to stratify and adequately approach the complexity of dry eye disease in daily clinical practice with up-to-date knowledge based on scientific evidence.

Synopsis

Current information

- Establishing dry eye severity levels helps make therapeutic decisions.
- LUBOS established four levels: mild, moderate, severe, and plus.
- The OSDI test, the OSS scheme (SICCCA), and the degree of meibomian gland dysfunction are taken into account.

Future needs

- Spread and use the LUBOS severity graduation scale in Latin America and verify its usefulness over time.
- Conduct clinical studies that incorporate the LUBOS dry eye severity levels.

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7

WHAT IS THE ROLE OF ARTIFICIAL TEAR COMPONENTS?

Introduction to artificial tears

Ocular lubricants —also known as artificial tears— are the first treatment option for dry eyes. In order to do this, its many components must be able to carry out a number of general functions:

- Provide ocular surface lubrication and hydration.
- Infer corneal-conjunctival epithelium with osmoprotection.
- Keep the aqueous-mucin layer from evaporating.
- Remain on the surface (retention or residence time) resisting the rheological forces of excessive blinking.
- Indirectly reducing ocular surface inflammation.
- Reduce dry eye disease symptomatology.
- Restore tear film homeostasis.

There currently is a diverse and growing number of pharmacological products grouped under the term artificial tears. The sheer quantity of products can sometimes be confusing instead of helpful for a physician when trying to improve a therapeutic path and establish a personalized treatment. Ophthalmologists must understand the basic differences between available ocular lubricants in order to use them adequately, justifying their use based on objective evidence. Considering that they are generally products with high security margin, artificial tears are usually prescribed indiscriminately for various reasons, which minimizes their usefulness and even leads to them being employed as "pseud-placebo" (doctors who prescribe tears so that patients can perceive that they are being treated). In this chapter, we will comment on general formulations of ocular lubricants and describe artificial tear components and their proposed function.

General aspects of ocular lubricant formulations

Diseases affecting the ocular surface are generally treated in a topical fashion, given that ophthalmological solutions applied where the problem is located offer greater concentration and efficacy. Once the jar of any topical formulation is opened and its contents exposed to the environment, they must be discarded after a certain period; depending on the formulation and whether or not it has preservatives, that window is about a month. The package must also be kept clean and in a fresh location, away from direct light and high temperatures to avoid decomposition or contamination. Ophthalmological products must be manufactured in a sterile environment free of pyrogens and correctly packaged in order to guarantee proper preservation[1].

The goal of topical dosage is to administer enough pharmaceutical active principles for the ocular surface to absorb, but not too much to cause excessive spillage. Because of this, optimal volume eye drop varies between 5 and 20 microliters. Typical volumes administered by commercial eye droppers, however, vary between 25 and 56 microliters[2].

Multidose eye droppers must be flexible to allow squeezing but also rigid enough to avoid flooding the ocular surface and wasting product. Bottle walls must be thick enough to impede water loss during long storage periods. Bottle manipulation is also important and eye droppers that are very small and rigid can be difficult for people who are older or have rheumatic diseases[3]. Pressing the bottle walls generally releases a vol-

ume between 30 and 40 microliters, depending on tip angle and formulation surface tension. Preservatives like benzalkonium chloride (BAK) alter drop size and viscous solutions take longer to form a drop on the tip. Plastic multidose eye droppers have some problems: absorption of antimicrobial agents, the erosive effect of BAK on the polyethylene jar wall, and the leaching of ink through labels and jar wall plasticizer to its contents. Since polyethylene does not resist self-seal sterilization, other options like ethylene oxide or radiation must be used[4-5].

Contamination of the eye dropper tip is a serious problem. Patients must release the dose near the eye, which increases the chances of contamination by the eyelashes. As thumb-applied pressure to the jar relaxes, suction reintroduces the drops' contaminated remains back in to the solution (negative pressure)[5-6].

Following application instructions can reduce contact between the tip and eyelashes and eyelids. The required pressure to administer a single drop varies significantly between different bottle types, oscillating between 0.5 and 5.34 kg/f across 17 different single single dose bottles placed in a vertical position. Therefore, complete omission of the eye is a common occurrence and self-administering eye droppers usually carry difficulties. At least 50% of patients admit having difficulties administering collyrium to themselves and coordinating aim and pressure. Even studies conducted on glaucoma patients show that only 5 out of 165 managed to fully instillate the eye, while 49 out of 165 touched the eyelid while administering the drop. In another study, 12% of patients failed at placing the drop in the eye, and 42% touched either the ocular surface, eyelids, or eyelashes[6].

The physical difficulty of putting in eye drops can be exacerbated by patient fear related to a natural protective response expressed by the instinctive reflex of turning away their face and blinking when an object approaches the eye. It is important to be careful and not hurt the eye with the tip of the bottle. Bad vision, scarce grip, and the inability of maintaining muscular tension can worsen the problem. There currently are multiple systems to apply drops. The Xal-Ease (SHL Medical) is placed on the bottle and helps withdraw the top and place the medication in the eye. The Autosqueeze™ Eye Drop Dispenser (Owen Mumford) is a device with pliers to help squeeze the bottle. There are platforms based on glass vials that allow the precise administration of 10 to 50 microliters of powder or liquid in the eye, practically with any hand-head orientation. Bottles with flexible areas or pumping mechanisms to facilitate a more precise administration have also been used[7-8].

Topical ophthalmological formulations: concepts and classification

To put it simply, we can say that an artificial tear is a pharmacological product made to be applied in a topical fashion at the ocular level. It is made up of an *active principal and a number of substances* destined to favor the active principal effect, maintaining sterility. Several topical formulations, which must be sterile in order to avoid potential infections, are used to treat ocular surface diseases.

Ophthalmological formulations of artificial tears can be classified according to their pharmaceutical presentation as: *solutions, suspensions, gels, and ointments*. Topical administration of an ocular lubricant can produce blurry vision, cold sensations, irritation, and burning. The appearance of these unwanted effects depends on the formulation type, active component, molecular weight and formulation saturation, pH, as well as any preservative or buffering agents they may have. Drops can also be felt in the nose and mouth due to the nasolacrimal duct[1].

Ophthalmological solutions are the most commonly used formulations. The active element is dissolved in liquid. In ***suspensions***, on the other hand, the active element is finely divided and suspended (undissolved) in liquid. Suspensions are useful when an active element is either unstable within a diluted solution, is non-soluble, or when its sustained effect is required[1].

Considerations regarding tonicity and solubility tend to limit active principal concentration to around 2% w/v, which is equivalent to a 500-600 microliter dose in a single drop. Solutions

between 0.5 and 1% are more frequently used[1]. This tonicity aspect will be treated at greater length later in this chapter.

Saturation concept

All appropriate components must be included in the drop in order to produce a solid dose formulation. The components are: buffer solution, solubility enhancer, pH regulator, active ingredient, EDTA, preservant, and polymer. The inclusion of each of them varies on whether it is a single-dose or multi-dose presentation[1].

Physical state of the active ingredient

It can create additional variables, like presentations in the form of solutions, gels, suspensions, and ointments. In order to guarantee good solubility, we must choose an adequate salt or use a solubilizer excipient. There are also other chemical strategies, like the use of prodrugs[1].

Agents that improve viscosity (lubrication/ hydration)

These agents, called demuscents, are the most used ingredients and make up the lion's share of ocular lubricant formulations. There are at least six categories of these agents that can be used in formulations[9]:

1. Cellulose derivatives
2. Dextran
3. Gelatin
4. Liquid polyol
5. Polyvinyl alcohol
6. Polyvidone

Demuscents increase tear film thickness (mucoviscosity) and ocular lubricant retention (mucoadhesive) on the ocular surface. They act as water retaining agents (hygroscopic properties) that allow them to moisten the ocular surface and prevent water loss[10-11]. These agents are mucoadherent and mucomimetic due to their branched structure similar to mucin-1, an amine made up of goblet cells that protects the ocular surface[12-13]. Viscosity-enhancing agents can be used to replenish and help maintain the tear film's mucin layer caused by pathologies that inflict mucin deficiencies. The source and properties of these agents (their molecular weight, for instance) vary and can influence their interaction with the ocular surface.

Hydroxypropyl methylcellulose (HPMC) is a cellulose-based polysaccharide. Due to its molecular weight, it is less viscous than carboxymethyl cellulose, which is why it is combined with dextran. Upon instillation, it forms a reticle due to its differences in pH with the ocular surface, which in turn allows lubrication[9-12].

Carboxymethyl cellulose (CMC) is a cellulose derivative of high molecular weight. It has a high anionic charge with mucoadhesive and mucoviscous properties, offering excellent humidification and lubrication[9-12].

Dextran is a complex branched polysaccharide made up of numerous glucose molecules forming units of varied chain length. It functions as a moisturizer of high molecular weight with a minimal effect in viscosity rise, which is why it is only used in combination with other demuscents[9-12].

Polyols are mostly used in lubricants. They currently are: propylene glycol (PG), polyethylene glycol (PEG), glycerin and HP-guar. These components help reduce ocular surface inflammation and irritation by forming protective gels. Some of these viscosity-enhancing agents can experience a solution-to-gel (sol-gel) process by coming into contact with the ocular surface and a change in pH, such as carbomer or HP-guar. Administered as eye liquid, these "in situ gellable systems" form a gel (the higher pH alkalinity, the higher gelification) when they mix with tears[14-15].

Viscosity-enhancing agents can help ocular surface lubricants raise retention time and at least partially compensate the mucin layer in cases of deficiency[16].

Polyvidone is a water-soluble polymer of varied molecular weight and viscosity. It is used to raise the contact time of ophthalmological products by enhancing the viscosity (thickness) of pharmacological solutions, and also acting as an effective lubricant. The use of 2% polyvidone-based lubricants with no preservatives has been associated with an improvement of the following symptoms: eye strain, dryness, and inadequate focusing associated with computer vision

syndrome. It also kept the corneal surface unaltered and improved dynamic visual acuity[18].

Tonifying agents and the concept of tonicity

Tears are a glandular isotonic fluid secreted with blood and formed through ultrafiltration. They contain a mixture of electrolytes and weak organic acids and proteins, and are capable of neutralizing non-fluid solutions through a combination of protein contributions and the body system of bicarbonate and carbon dioxide[19]. Products with tonicities equivalent to the 0.7 to 1.5% interval in sodium chloride weight can be created with the addition of tonifying agents. Most solutions, however, are quickly eliminated from the eye; a simple aqueous solution has an average span of 20 seconds, measured through a lacrimal scintigraphy[20].

Posterior retention phases —measured in the central corneal region— reflect the way in which polymers like hyaluronic acid can help stabilize the tear film. The conjunctival membrane acts like a secondary reservoir of the drug and keeps it for a few minutes. When several individual drops are administered, it is important to wait 5 minutes between drops. This also justifies combining dosis to reduce time between applications, allowing for greater patient compliance while also offering them more comfort[20].

The role of electrolytes in artificial tears

Naturally secreted electrolytes are an important part of the tear film, insofar they maintain osmotic balance on the ocular surface. Because of this, electrolytes (sodium, potassium, chlorine, magnesium, and calcium) are used in ocular lubricants to reproduce the electrolyte panel of a healthy tear film[21-22]. Electrolytes play a key role in maintaining healthy osmolarity of the tear film by providing ions that are essential for homeostasis of corneal epithelial cells, countering tear film hyperosmolarity induced by dry eye disease. Several hypoosmolar substances have been used to formulate tear substitutes in order to counter hyperosmolarity produced by dry eye[23].

Some electrolytes, like borate, can act either like buffers to stabilize formulation pH, or as preservative agents when combined with sorbitol, zinc, and propylene glycol[24-25].

PH buffers

Most ophthalmological formulations are either weak base or weak acid because a ionizble and lipophilic mixture must be spread across the epithelium in order to get through the epithelium and the corneal stroma[26].

In theory, tear film has good pH buffering, although it is important to point out that dry eye tear pH rises. Artificial tear formulations can be non-buffered solutions, or buffering agents can be added to raise stability and spread the product across tissues[26-27].

The recovery of tear film pH following drop instillation is mostly due to tear renewal and the buffering effect, which directly impacts a patient's ocular comfort. Weak buffering agents are the preferable option in ophthalmological formulations because of this. Among the most common anions are sodium maleate, acetate, borate, and phosphate[26, 28].

Boric acid is a Lewis acid with a pKa of 8.92-9.24 that reacts reversibly with alcohols like polyvinyl alcohol and is used in ophthalmological formulations to raise anti-microbial efficacy (preservative), like contact lens solution[27]. High phosphate concentration can cause problems, because calcium phosphate has a low solubility limit and can produce corneal calcification[19]. Trisodium citrate and phosphate are among the buffering agents within ophthalmological formulations with the highest toxicity, which affects the viability of corneal and conjunctival epithelium[19].

Osmoprotection

Osmoprotectors have been used in some ocular lubricant formulations to avoid inflammation and cellular apoptosis caused by dry eye hyper-

osmolarity. Osmoprotectors are compatible solutes with the osmotic capacity of attracting water that penetrates the cell and allows the reestablishment of epithelial functions. They are small, hydrophilic, and osmotically active compounds capable of modifying cellular water captation and protecting the ocular surface from hyperosmolarity-induced inflammation. Its function is to safeguard ocular surface epithelial cells from hyperosmolar stress, protein denaturation, cellular damage, and apoptosis. Osmoprotectors also reduce matrix metalloproteinases (MMP) synthesis and oxidative stress, and can regulate the autophagy process[29-31].

Osmoprotectors include polyols (erythritol, glycerine, sorbitol), methylamine (trimethylglycine, glycine), certain amino acids (L-carnitine, taurine), and trehalose. More recently, a combination of trimethylglycine, L-carnitine, and taurine proved in vitro to be capable of protecting epithelial cells exposed to hyperosmotic stress[30-31].

Trehalose is a disaccharide that carries out its water-regulating properties by forming a gel protective shield around the organelles during cellular dehydration (anhydrobiosis function). It protects cells from various threats like inflammation and autophagy process deregulation. Therefore, it plays a cytoprotective role to corneal and conjunctival epithelial with the goal of avoiding apoptosis[32-33].

Erythritol is a polyol formed by four carbons. It is a biological sweetener with pharmaceutical applications. It is small enough to penetrate the corneal epithelium through water canals present in the cellular membrane known as aquaporins. Erythritol stabilizes proteins and reduces mitogen-activated proteins, leading to a positive effect especially on corneal epithelial cells subject to hyperosmotic stress[28, 30].

L-carnitine (gamma-trimethyl-beta-hydroxybutyrobetaine) is an aminoacid found in several foods that is synthesized by the liver. It is a small molecule with a broad presence in all cells. Its cell penetration depends on transporters located on the cellular membrane. Hyperosmolarity interrupts the antioxidant defense system by reducing the production of antioxidant enzymes like superoxide dismutase and glutathione peroxidase, among others. L-carnitine, however, can restore the levels of these antioxidant enzymes[28, 30].

Glycerol, a polyalcohol containing three hydroxyl groups, is an important intermediary in the prokaryote and eucaryota cell metabolism. It has an osmoprotective effect on corneal epithelium cells[28, 30].

The combination of hyaluronic acid and carboxymethyl cellulose has a significant and proven osmoprotective effect, reducing symptomology in dry eye disease patients[28].

Agents that improve ocular lubricant retention or residence time

Retention time (residence) plays a crucial role in the efficacy of ocular lubricant drops. This becomes especially relevant when choosing the right treatment strategy for each patient, taking into account dry eye disease severity and the environmental changes eyes are subject to day and night.

Hydroxypropyl-guar (HP-guar, or HPG) gum is a polysaccharide with a very high molecular weight and non-Newtonian behavior, meaning that its viscosity changes depending on blinking intensity (rheological forces of blinking). This trait plays a key part in the rise of retention time of the tear film's aqueous-mucin layer in dry eye patients[34]. HP-guar is a semisynthetic compound containing numerous hydroxyl groups that promotes the retention of other demulcents (PG and PEG) by forming a net (a protective mesh) over microvilli of corneal epithelial apical cells, emulating glycocalyx and thus stabilizing tears[35]. In a dry eye with alkaline pH, HPG interacts with borate once it separates from sorbitol (buffer agent) to form a polymeric net of variable viscosity in line with tear pH and blinking friction, thus raising its bioadhesive properties and promoting demulcent retention. This complex polymer offers elastic, electrostatic, and osmotic resistance, forming an interphase that can be easily cut, which ensures its retention on the ocular surface[35].

Lipophilic or oil-based agents

Oil-based agents are found mainly in the form of liposomes and oil-based nanodrops. Their function is to either emulate or replace the lipid layer of the tear film[31, 36]. Liposomes are made up of phospholipids forming a spherical vesicle of one or more concentric lipophilic bilayers with the same number of aqueous compartments and applied on the ocular surface as a spray[37]. Another type of tear-replacement formulation containing oil-based agents are oil-in-water emulsions. They are made up of oily drops stabilized in water through surfactants or emulgents. Several types of oils and surfactants have been used to create ophthalmological emulsions[38-39]. Emulsions can be ionic, anionic, or cationic depending on the formulation's components. One interesting characteristic of cationic emulsions is that the oily drops with a positive charge can interact with the mucin layer of the tear film, which has a negative charge, which helps stabilize the tear film[40-42].

Several formulations have included polar surfactants similar to lipids, such as cetalkonium chloride (CKC) and dimyristoyl phosphatidylglycerol. Oil-based agents and surfactants represent a group of beneficial ingredients that are important in complementing lipid layer thickness altered by evaporative dry eye, the most common dry eye category induced by meibomian gland dysfunction. Oil-based agents can also assist in providing the cornea with a smooth optic surface, which helps to keep good vision acuity[43-47].

Antioxidants

Tear-replacement formulations also use antioxidants or oxygen free radical eliminators like vitamin A, vitamin E, coenzyme-Q10, and lipoic acid[48].

Erythritol and trehalose, which are already used as osmoprotectors in tear-replacements, can also protect cells from oxidative stress[49].

A recent study also revealed that taurine can protect corneal epithelial cells from oxidative stress[50].

The use of lipoic acid as an antioxidant has also been tested in dry eye patients, improving tear film stability[51].

Preservatives

Multidose units usually require preservatives to avoid microbial growth inside the bottle and to raise its stability and life span[28]. Patients with chronic and severe ocular diseases like Sjögren syndrome, graft-versus-host disease, Stevens-Johnson syndrome, and ocular mucous membrane pemphigoid can instill drops very frequently (up to every 20 minutes), which is why understanding and differentiating preservatives is relevant, since they can cause harm and toxic alterations to the ocular surface[22].

The most used modern preservatives are perborate, polyquad, and oxychloride. Borate has a mild antimicrobial activity and 1.2% w/v borate-pH7 ratio. It also has inhibitory activity against the growth of Staphylococcus and Pseudomonas aeruginosa[53].

Benzalkonium chloride (BAK) is the most commonly used preservative, an efficient bactericide and fungicide. It is a mixture of alkylbenzyldimethylammonium chlorides of various alkyl chain lengths, from C8 to C18, but mostly from C12 to C14. Because it is a mixture of cationic surfactants, the preservative smoothens the external membrane of the pathogen but also affects host cells, which causes corneal cell loss as well as a rise in drug permeability.[1] With a 0.01% w/v, BAK is useful in the full pH scale of ophthalmological formulations, and is stable in autoclave. Continuous exposure to BAK due to daily use causes a cumulative effect and poses the risk of worsening ocular symptoms including superficial punctate keratopathy in dry eye disease. It can also generate allergy symptoms, dermatitis, and blepharitis[54].

Polyquaternium induces significantly less in vitro cytotoxicity compared to BAK and hydrogen peroxide. However, it reduces the number of goblet cells, which affects the tear film's mucins.[54] It has been proven that the absence of preservatives

improves the healing of ex vivo corneal wounds, something that was not observed even with the use of light preservatives like hypochlorite[55-57].

Sodium perborate is an oxidative preservative which, after becoming hydrogen peroxide in a solution, has a bactericide effect through oxidative stress and denatures bacterial proteins[58].

Among the older preservatives that are hardly used we find chlorhexidine, sorbic acid or potassium sorbate, chlorobutanol, and mercurial preservatives like thiomersal. Parabens are still present in some preparations, but their use is diminishing. The similarities between nasal and ophthalmological mucins indicates that similar formulations can be used for both[59].

More recently, preservative-free formulations have proven to be effective in reducing adverse symptoms[60]. Other possible devices include adding a 0.2 μm filter to avoid organism reflux from the contaminated tip to the solution (ABAK system) and a sealed system with a pump with no air and check valve[61].

Ethylenediaminetetraacetic acid (EDTA) raises preservative efficacy given that it is a calcium and magnesium chelating agent, which are needed for bacterial and fungal metabolism. It has been proven in several combinations that it has low toxicity for cultivated corneal cells, causes similar (albeit milder) effects to the ones caused by BAK, including plasma membrane disruption, and generally raising cellular permeability. Combined with hyaluronic acid of high molecular weight, these damaging effects can be reduced[62].

Agents that favor healing and reduce inflammation

It has been proven in vivo that hyaluronic acid, especially if it has high molecular weight, hastens epithelial healing following corneal debridement and abrasion, and alkali burns[63-64]. It also improves tear film break-up time and allows the reduction of ocular surface cell apoptosis compared to hyaluronic acid of low molecular weight. Haliuronic acid has also been combined with other agents to improve recapitalization[65]. T-LysYal, a supramolecular system made up of lysine hyaluronic acid, thymine, and sodium chloride was studied in vitro and its potential to restore corneal cells damaged by dry eye disease was proven, showing anti-inflammatory activity as well[66-67].

Excipients (polymers)

Excipients are usually inactive substances added to formulations in order to give them form and consistency. Salts, sugars, fillers, agglutinants, and lubricants are included in that category. In ophthalmological compositions, cellulosic polymer, polyvinyl alcohol, and gum derivatives are usually employed as viscosity-increasing excipients (Fig. 1).

Hydrophilic compounds, like cellulosics, retain water through weak hydrogen links and humidify surfaces, resisting superficial drying. Excipients interpenetrate lacrimal and superficial mucins: chain length, polymer flexibility, and chain segment mobility are key properties of non-ionic polymers[1]. They offer a broad viscosity range (400-15,000 cps) and are compatible with many topical pharmaceuticals. Polyvinyl alcohol is also a highly used drug delivery system and a component of ocular lubricant preparations. This polymer can reduce superficial tension in the oil/water interface, improving surface remoisturizing. Polymeric solutions are, therefore, functional ingredients in the supplementation of mucin-deficient tears in postmenopausal dry eye[1].

Although the effect of viscosity on ocular retention is evident, another advantage is that exposure to unabsorbed drugs slows down. There is a point of maximum advantage: for instance, for hydroxyethyl cellulose (HEC) with a concentration higher than 0.3%, there is significant rise in contact time that reaches a usable maximum at 0.5% w/v[68].

Polyvinyl alcohol is a polymer usually employed in ophthalmological solutions with concentrations ranging from 0.25% to 3% w/w depending on molecular weight. Available pharmaceutical quality levels are low (20,000 g mol), medium

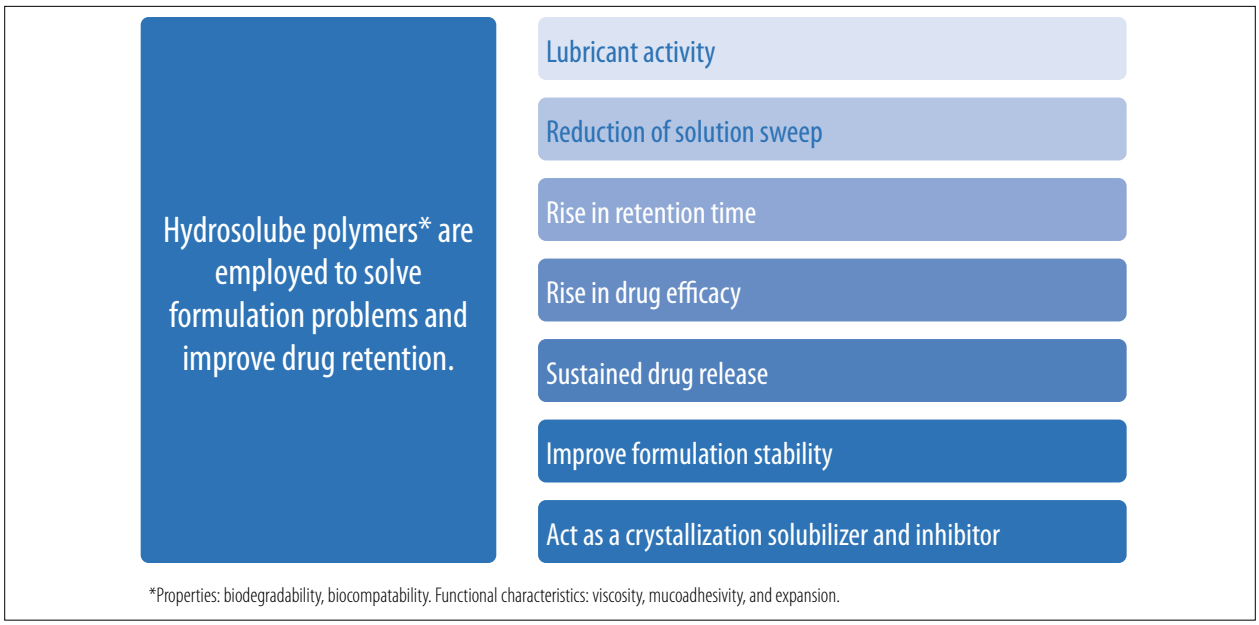

Figure 1. Essential functions of synthetic and natural hydrosolube polymers employed in ophthalmological lubricant formulations.

(130,000 g mol), and high viscosity (200,000 g mol)[1]. When there is an extended hydrogen bond between a polymer and a surface or a solute macromolecule, the polymer is classified as bioadhesive. Bioadhesion is a phenomenon where a synthetic or natural polymer adheres to a biological substrate through interfacial forces; however, if viscosity is too high, the formulation will lose blinking resistance and turn uncomfortable[1].

In ophthalmological formulations it is common to look for polymers that adhere to mucin or a mucous membrane like the conjunctiva or the cornea, staying in contact with pre-corneal tissue until surface mucin is replaced. Polymeric chains must have enough length and mobility in order to facilitate molecular interlacing. The threshold in flexible chain polymers has been defined as being around 100.000 Da. When anionic polymers are used, maximum interaction is produced at an acid pH, which suggests that polymers must be in their protonated form in order for a viscoelastic synergy with superficial mucins to take place[1]. Thixotropic solutions show a shear thinning, which supposes an advantage in ocular formulation. Essentially, this characteristic imitates mucin properties[1].

Sodium hyaluronate is a polymer with high molecular weight —of 1-3 Mda— extracted through a patented process. It consists of a non-ramified non-sulfated lineal polyanionic glycosaminoglycan, made up of a repeated disaccharide unit of sodium D-gluconate and N-acetylglucosamine. It forms an open-spiral flexible configuration with random molecule orientation, providing high thinning resistance at low friction speeds. Polymers are mucin adhesive: the carboxyl groups from the hyaluronate form hydrogen bonds with the sugar hydroxyl group from the mucins, which produces intimate corneal contact. Pseudoplastic behavior (where viscosity in the resting stage is higher) provides a thicker tear film, slowing down drainage and guaranteeing better corneal distribution during blinking[69].

Sodium hyaluronate and hyaluronic acid are the most common moisturizers acting as hygroscopic agents to improve water retention on the ocular surface.

Hyaluronic acid is a polysaccharide (natural glucose-aminoglycan) of high molecular weight present in aqueous humor, synovial fluid, and connective tissue. As a moisturizer, hyaluronic

acid increases its molecular weight in water 100 times (water retainer), suffering changes in viscosity due to its nature as a fluid with non-Newtonian properties regarding thinning[69-70].

Sodium hyaluronate, a semisynthetic sodium salt derived from hyaluronic acid with low molecular weight, has mucous-adhesive properties that are responsible for raising its residency time on the ocular surface, in addition to its humidifying characteristics. Structurally made up of carboxyl and hydroxyl groups, sodium hyaluronate is a more stable version of hyaluronic acid that absorbs great quantities of water in order to stabilize the aqueous-mucin layer of the tear film. Sodium hyaluronate also plays an important role in maintaining a protective barrier for corneal epithelial cells given that it has a similar molecular structure to mucin[69-70].

Mixing sodium hyaluronate with Xantham gum or HP-guar produces a formulation that is more similar to natural tears, with the objective of producing a lacrimal mucin mymethic with similar viscoelastic and remoisturizing properties. These formulations provide permanence times that are up to 8 times longer in humans when compared to saline solution[69, 71].

In situ gelation systems allow a prolonged eye presence thanks to sol-gel transition. This can be triggered by a change in pH (HP-guar, for instance), temperature (poloxamer F127), or ionic force[71-72].

Gellan gum is an anionic polysaccharide formed in an aqueous solution that becomes a transparent gel under the influence of growing ionic force. Gelation rises in proportion to the number of univalent or divalent cations. Sodium concentration in human tears (~2,6 μg/μL) is particularly adequate in inducing gellan gum gelation following topical instillation in the conjunctival sac. Reflex lacrimation raises gellan gum viscosity even more by increasing volume and, therefore, cation concentration. Scintigraphy studies prove that Gelrite (0.6% w/v) can significantly extend ocular retention in humans by forming a gelled deposit on the scleral margin[73].

Carbomers are polymers (polyacrylic acid) with a structure that changes depending on temperature and pH. They are low-viscosity aqueous dispersions that turn into rigids gels once instilled in the conjunctival sac. When anionic polymers interact with mucin (which is also anionic), maximum adhesive interactive force is produced at an acid pH, suggesting that protonated mucous-adherents are responsible for mucin adhesion. The precorneal residence observed in the carbomer formulation during a scintigraphy study was attributed to this type of interaction[73]. Carbomers offer several advantages for ophthalmological administration: high viscosity at low concentrations, strong adhesion to mucin, thickening properties, compatibility with many active principles and low-toxicity profiles. Polymers are more fluid at a pH of 5.0, and therefore easier to dispense at this mark[74].

There are commercial products that contain a synthetic polymer of reticulated polyacrylic acid that stabilize drug molecules in an aqueous matrix, keeping therapeutic doses on the ocular surface for up to 6 hours. This technology is used in azithromycin solutions administered once a day for treating bacterial conjunctivitis, which was also modified with an additional chitosan fraction to reduce clarification[75].

Lipid emulsions

Lipid emulsions come in three types[76]:

- An oil-in-water emulsion (the most common)
- a water-in-ion emulsion
- a bicontinuous lipid emulsion

Emulsions stabilize with an adequate surfactant, like an anionic lipid emulsion containing 0.05% of cyclosporine A, which is used for treating chronic dry eye[77].

Many of the more recent oil-based systems are classified as lipid nanotransporters, and include nanoemulsions and liposomes[34]. The positive charge of a liposomal formulation greatly reduces whitening in rabbits, compared to liposomes with negative or neutral charges[76].

Ointments

Ocular ointments are useful for nocturnal application before the patient goes to sleep, considering that the white vaseline/liquid vaseline base causes persistent blurry vision. Due to their long retention, they're ideal for treating dry eye as a lubricant in cases of severe ocular dryness. The market has adopted non-oily alternatives like polymer-based gels. One advantage that ointments have is that they can be used anhydrous, which is useful for hydro labile drugs[1].

Non-aqueous and non-lipid delivery systems

There is interest in new non-aqueous and non-lipophilic delivery systems based on fluorocarbons that were used for the first time as blood substitutes, given that liquid dissolves oxygen.

Perfluorodecalin can be used externally as a novel way of administering a suspension of small drops that show instant eye dispersal. Since the drop is small, superficial tension is extremely low and suspended particles are dry, the system disperses instantly to the edge of the eye and dosages the Meibomian gland margin. This suggests that it could be used to treat mucus-secreting cells on the edges of the eyelash. The delivery system is being investigated in various new ways to administer cyclosporine[78-79].

Suspensions

Although solutions are the preferred delivery system, the stability of diluted solutions can limit the lifespan of the active element. Also, important anti-inflammatories like dexamethasone and prednisone have greater distribution on the corneal epithelial and achieve more fluidity through suspensions compared to soluble salts[80].

Particle size is important because particles ≥ 15 μm are irritant. Therefore, typical specifications dictate that the average size of 95% of them be under 10 μm. In theory, larger particles extend the duration of the effect due to greater deposit size; however, there is risk of irritation and that suspended particles be dragged into the dissolution, reducing bioavailability. In the case of radioactively marked dexamethasone administered in 5, 7.5, 11.5, and 22 μm suspensions, it has been proven that the dissolution of the largest particles was so slow that they ended up out of the eye before process completion[80].

Agglomeration is another complicating factor. Tear film mucins coat particles with glycoprotein and produce the concretion of mass that is later expelled. This can be reduced through the addition of polymers like polyvinyl alcohol or polyvinylpyrrolidone as crystallization inhibitors and viscosifiers that also maintain dispersion. As a system, suspensions are kinetically stable but thermally unstable, and problems appear when they are cyclically exposed to heat and cold, which can favor crystal growth and sedimentation in the bottom of eye droppers. It is therefore important that particles remain in a deflocculated state[81].

Nanotechnology applied to ophthalmologic formulations

Nanotechnology-assisted administration employs amphiphilic molecules that include the administration of nanomicelles, liposomes, dendrimers, nanospheres, and nanocapsules. These systems are located on the border between the mechanisms of intracellular entry and membrane fusion. Endocytosis mechanisms have been proposed to explain the rise in permeability. Externally placed nanoparticles are eliminated by lymphatic drainage[82].

Liposomal formulations, which are capable of supplying phospholipids and tear stabilizing factors, have been thoroughly investigated as carriers given that they can encapsulate hydrophobic and hydrophilic drugs. The cornea has a 3.2 isoelectric point, which means that it has a negative charge related to most carriers. This is something to be leveraged by this technology, since corneas attract more liposomes with a positive charge than ones with a neutral or negative charge[83].

LUBOS consensus statement on artificial tears

Based on the content presented here, we prepared a series of final concepts to be taken into consideration when choosing ocular lubricants.

1. Viscosity-enhancing agents are effective in replenishing and stabilizing the aqueous layer of the tear film. Adding electrolytes also allows better reproduction of the natural aqueous layer. Tear replacements that contain these two types of ingredients can be included in the "moisturizing agents" category.
2. The use of oily and surfactant agents is beneficial in complementing and stabilizing the tear film's lipid layer, which is deficient in most patients with evaporative dry eye.
3. Osmoprotectants are beneficial in countering tear film hyperosmolarity, and hypotonic alternative tears represent another strategy to correct osmolarity. Tear replacements containing lipids or osmoprotectants can be considered "multiaction tear replacements", because they offer more effects than just simply lipid layer replenishment.
4. Antioxidants can be used to prevent cellular apoptosis caused by oxidative stress, although more clinical studies are needed to show their efficacy with dry eye disease signs.
5. Cationic emulsions and hyaluronic acid reduce expression and secretion from pro-inflammatory factors. Because of this, they seem adequate in reducing dry eye-induced ocular inflammation and promoting healing. Tear replacements made of these ingredients can be considered "ocular surface modulators", although some live studies should be conducted in order to validate this conclusion. Consequently, these ingredients can be especially beneficial for patients with dry eye signs after a surgical intervention. Ingredients of these tear replacements can act upon the main causes of dry eye disease.
6. Each ingredient and their concentration must be carefully selected in order to provide the patient with a safe and effective product. Electrolytes may be beneficial for patients with aqueous-deficient dry eye to reproduce the natural aqueous layer. On the contrary, electrolytes raise lubricant osmolarity, which can exacerbate (or, in a best-case scenario, not reduce) tear film hyperosmolarity.
7. Oily agents have proven to be effective in patients with evaporative dry eye. However, high concentrations in certain surfactants —which are needed to solubilize the oily agent— have displayed potential complications, including ocular toxicity. Surfactant type and concentration should be carefully considered in order to stabilize the lipid layer and avoid toxic effects.
8. Considering potential instillation frequency and occasional chronic use of ocular lubricant, and taking into account the absence of preservative-free products, it is preferable to use those that contain small amounts of preservatives, or have "light preservatives".

Synopsis

Current information

- There are different ocular lubricants featuring different characteristics and functions.
- There currently is no product capable of replacing natural human tears.
- It is preferable to use lubricants with no preservatives, or light preservatives.

Future needs

- Develop a lubricant with a more prolonged effect and capable of carrying out more functions.
- Carry out an international multi-centered investigation on lubricant use and efficacy in different situations.

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8

WHAT IS THE IDEAL TEAR FOR EVERY TYPE OF DRY EYE ACCORDING TO ETIOLOGY AND SEVERITY?

Introduction

In the previous chapters we revised components and functions of ophthalmological formulations for dry eye treatment. From there we highlighted that replacing tears through ocular lubricants commonly known as "artificial tears" is a fundamental part of treating dry eye patients. It is the first therapeutic line of the treatment process, together with patient education regarding their condition, changing environmental factors, lifestyle considerations, nutrition supplements, and the evaluation of aggravating risk factors like concomitant pathologies and the use of topical or systemic medication[1].

The main objectives of artificial tear prescription are to relieve symptoms, stabilize the tear film, and replenish the ocular surface[2]. However, there is no ideal tear type for all patients: the choice must be based on a careful examination of an individual's medical history while also taking into consideration the aspects laid out in the previous chapter. This evaluation will identify the predominant dry eye type the patient is suffering, together with its severity, leading to the selection of the most adequate artificial tear available[3].

We must remember that most patients suffer evaporative dry eye, followed by aqueous-deficient dry eye. Although it is estimated that 35% of cases are mixed dry eye, this percentage could be much higher in chronic conditions, up to 70% due to overlap of both conditions[1, 4-5].

Symptom severity and which external factors aggravate them is also something that should be evaluated through interviews (OSDI questionnaire or similar), as we emphasized in the LUBOS proposal of severity classification. The result of this evaluation greatly conditions the type of formulation that should be used (collyrium composition, frequency, and viscosity level)[6-7].

Ninety percent of ophthalmological formulations are topical drops, but their bioavailability is reduced by the protective mechanisms of the eye, making their frequent use over long periods of time a necessity which, in turn, lowers treatment adherence and success. It is also important to remember that a treatment must be used under strict conditions for at least a month in order to judge its effectiveness, which means evaluating a product's real tolerance and frequency use[8].

Aspects to take into account when selecting an artificial tear

From a formulation standpoint, we can point to the general aspects of an artificial tear:[9]

- Have neutral pH.
- Be iso or hypotonic regarding tear film osmolarity.
- Contain osmoprotectors.
- Contain polymers that favor retention, as well as formulation and epithelial regeneration bioavailability.
- Be preservative-free, or at least have preservatives with the least toxicity.
- Should not affect patient visibility following instillation.
- Should be ideally capable of combining components that have different therapeutic goals in order to improve effectivity, bioavailability, and treatment objectives, while reducing side effects.

Depending on case severity, formulations must be conceived with prolonged compound retention on the tear film (collyriums of high viscosity)

for day-time use, and for night-time use (gels) in severe cases. Some authors suggest achieving this goal through cationic modifications that facilitate solubility, or with non-aqueous delivery systems[9].

Lubricant selection according to dry eye type

Aqueous-deficient eye dry

Lubricants intended for aqueous-deficient dry eye must be mucomimetic and have the ability to reestablish mucosecreting cellular health. The composition must include demulcents capable of hydrating and protecting corneal and conjunctival epithelial; osmoprotectors to neutralize hyperosmolarity and either be preservative-free, or have preservatives with low or no toxicity. It is important that the lubricant has a pH, osmolarity, and electrolyte composition similar to physiological values.

Evaporative dry eye

In the case of patients with evaporative dry eye, lubricants must protect corneal and conjunctival epithelial and, above all, contain lipid components. It is recommended that this component come in the form of an emulsion that allows it to stay in the tear film without causing vision alterations while also avoiding aqueous component evaporation. The most common form is in nano or microemulsions. This helps maintain visual acuity, since the size of lipids drops are lower than the wavelength of visible light. Even though one could posit that collyriums with lipid component could create some sort of problem regarding instillation during contact lens use, studies like Bayhan *et al*. and Guthrie *et al*. prove otherwise[10-11].

Mixed dry eye

This is the most frequent situation (patients with a mixed dry eye pathology) and all components previously mentioned must be taken into account, because even though some artificial tear formulations contain all the listed requirements, their therapeutic efficacy must be evaluated on a case-by-case basis, considering patient tolerance to the prescribed product[12-15]. It is frequent to combine and alternate different formulations in these cases, with a focus on fixing aquodeficiency (iso or hypoosmolar agents with hygroscopic properties) through formulations that contain lipids. It is extremely complex, if not impossible, to create a formulation containing all required ingredients for both dry eye subtypes —aqueous-deficient and evaporative— without saturating the formulation, causing it to become unstable and intolerable for application.

Final therapeutic goal of artificial tear use

Based on what this expert group has studied, the final goal of a treatment with artificial tears for all patients must:

- Reduce dry eye symptoms and signs.
- Raise tear film break-up time by producing stability.
- Reduce staining levels on the ocular surface.
- Raise lacrimal meniscus level.
- Not affect patient vision upon instillation and this avoids compromising quality of life.

Relevance of conducting preservative-use analysis or not

As we have stated in the previous chapter, the issue of preservatives is relevant. It is important to remember that preservative-free collyrium-based lubricants are ideal, although there is some evidence that some preservatives —excluding benzalkonium chloride (BAK)— show low toxicity for the ocular surface[16].

The disadvantage of treatments with preservative-free lubricants is the discomfort regarding monodose discards, difficulty in handling multidose eye droppers with a filtering system, and cost. If preservatives are used, it is necessary to use those that cause minimum surface toxicity. These concepts are especially relevant when frequency use is over 4 times a day over an extended period of time, when dealing with surfaces altered

by chronic dry eye disease, and when other topical medications are used (anti-glaucoma drugs).

Future tendencies

The use of glycoproteins similar to mucin (lacritin and lubricin) applied as ophthalmologic drops reduces ocular surface inflammation and dry eye signs and symptoms, according to results of preliminary studies[2].

A recently proposed strategy of handling dry eye disease is inducing the production of tears and its different components through secretagogues rather than replacing them, which seems like a logical conclusion but is not that easy to achieve. There are currently musin-secretor drugs on the market like rebamipide and diquafosol; other pre-clinical and clinical products aimed at neurostimulation of the lacrimal gland in order to induce aqueous secretion are currently being investigated[2].

Topically used biological derivatives like human serum albumin, hormone steroids, mesenchymal cells, amniotic membrane extract, hemoderivatives, autologous serum and platelet-rich plasma and growth factors, are other topical alternatives for effective therapeutic dry eye treatment, given that they act on physiopathological factors of dry eye disease[2].

Nanomedicine has been introduced as a treatment option for this pathology through numerous nanocarriers, some of which are commercially available while others remain in a research stage[2].

When artificial tears, together with environmental measures as well as the detection and correction of aggravating factors, are not enough for our patient, measures of higher efficacy should be implemented for more complex cases[17]. New and improved topical anti-inflammatories, non-topical medical treatment, and even surgical procedures will be proposed depending on case severity.

Final concept

As a final conclusion we must emphasize that establishing a general treatment protocol for every patient is impossible. On the contrary, the vast availability of different lubricants allows us to conduct individualized treatments by selecting the most adequate, not only for each patient but also for the different moments and stages of severity and evolution in dry eye patients.

Synopsis

Current information

- A lubricant must diminish symptoms and dry eye signs without affecting vision.
- Lubricant selection must be personalized depending on case type and severity.
- Indicate lubricants dynamically, modifying and controlling their use according to evolution and need.

Future needs

- Investigate AI-based algorithms to indicate lubricants based on symptoms and signs.
- Objective tools that determine when to raise and lower their use (perhaps through lubricant-associated biosensors).

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9

WHAT IS THE FUNCTION OF NON-PHARMACEUTICAL DRY EYE TREATMENTS?

Although this consensus has centered on the role of artificial tears and their function in the therapeutic management of dry eyes, it also has revised the main non-pharmaceutical therapeutic strategies. These range from massages and palpebral hygiene, treatments mediated by medical devices, up to considerations relating to lifestyle and nutrition. No brand names or specific commercial products will be mentioned in this chapter, but we will specify the foundations and/or principles that sustain their use. We will leave related data in the reference list for readers interested in more details. We also would like to point out that each country has different regulations, meaning that some devices may be approved in some places but not in others. This is not necessarily tied to their efficacy or security but rather to the interest of manufacturers and/or importers/distributors to conduct the necessary administrative steps each country requires. Before using a therapeutic procedure, it is recommended a patient verify its status with the local regulatory agency and scientific-academic institutions, which might be able to endorse the off-label use of some device and/or treatment.

A. Eyelids, lacrimal ducts, and treatments mediated by medical devices

Introduction

As we will now see, several of these therapeutic strategies are aimed at eyelid care, considering that Meibomian gland dysfunction (MGD) is one of the most frequent causes of dry eyes. We will first revise some concepts to understand the therapeutic foundations of dry eye relating to said glandular dysfunction. In 2011, the Tear Film and Ocular Surface Society organized the International Workshop on Meibomian Gland Dysfunction, which proposed the following definition: "It is a chronic, diffuse abnormality of the Meibomian gland, commonly characterized by terminal duct obstruction and/or qualitative or quantitative changes in the glandular secretion. These changes lead to alterations in the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface diseases"[1]. Several devices to diagnose and treat MGD have been developed since, leading to a new variety of therapeutic resources that can be chosen and/or combined depending on each patient and the severity of the condition.

Meibum fluidity is key for effective glandular structure drainage and distribution on the ocular surface[2]. While meibum in healthy people has a transition phase temperature of about 28 degrees Celsius, it has been observed that patients with Meibomian gland dysfunction require 32°C to obtain the same meibum fluidity[3-4]. This difference in transition temperature results in substantially different meibum consistency at physiological temperatures in which the eyelids usually maintain a temperature around 33°C[4-5]. The difference in meibum properties is also seen at higher temperatures. In subjects with MGD, meibum at 38.5°C showed a viscosity level similar to meibum heated to 36.0°C in healthy patients[4, 6]. Therefore, many MGD treatments are based on rising eyelid temperature, which in turn reduces viscosity and facilitates meibum secretion from the glandular structure[4, 7-8]. Applying heat on the eyelids favors the fusion of altered meibum in MGD patients and the expansion of glandular orifices, helping oily secretion flow without restrictions just as

it does in healthy individuals. It was recently discovered that the minimum temperature for this therapy is 41.5°C[6].

Several methods can be employed to administer heat and humidity to the eyelids and dilute Meibomian gland secretion: from homemade solutions, like applying towels or hot compresses over closed eyelids, up to medical devices capable of maintaining adequate temperature in a way that can be standardized and reproduced[9]. We will now go over some of these methods in more detail.

Hot compresses

One study observed that applying a 45°C hot towel for at least four minutes, replacing the towel for a new one at the same temperature every two minutes, heated the eyelids enough to melt meibum in patients with MGD[10]. However, it is unlikely that this type of procedure can be reproduced in a reliable fashion by all patients who want to conduct a hot compress treatment in their home. Therefore, and although the application of a hot towel is the simplest form of a hot compress treatment, this method has not been standardized for MGD treatment and patients apply the towel for different durations and temperatures, with varying degrees of compliance[9-13]. Despite the efficacy shown by hot compresses in many clinical studies, compliance tends to be low due to the required time and the difficulty in maintaining compress temperature for a prolonged period[7].

Thermal masks and chambered hot moist air devices based on steam and radiating heat

Some devices can be manipulated by patients in their homes by using a microwave or an oven to heat the masks. Other models are meant to be used during a visit to the doctor. Several masks were studied, showing their efficacy and superiority over compresses and hot towels. There are also reports on the benefits regarding the possible reduction in the amount of *Demodex folliculorum*[14-15]. Some masks produce heat via a sustained thermal reaction that provides a 35 to 50°C heat for 10 to 30 minutes starting 30 to 60 seconds after activation; these masks can be reused[16-19]. The same applies for electrical thermal facemasks, controlling temperature (ideally 45°C) and application time (10 to 15 minutes) through a digital controller. Some electrical facemask models also provide the option of dry or humid heat, and massages[20-21]. The large supply available online has made these products more economically accessible.

Chambered hot moist air devices based on steam and radiating heat

Other thermal devices based on the same concept of using heat have been developed, like thermal ocular coverings, which are usually considered the first line of treatment against Meibomian gland dysfunction, a procedure the TFOS DEWS II classified as phase I of management strategy for mild dysfunction[22]. It requires daily use and compliance in order to maintain efficacy. TFOS DEWS II classified moisture chamber spectacles as a phase 2 strategy for dry eye treatment[23]. There are different types of spectacles on the market, with active heating and latent heating to warm the palpebral margin with the goal of facilitating drainage and unblocking Meibomian gland orifices. Some devices use pre-heated thermal elements to template the moistened annular inserts, in order for the interior part of the spectacles reach 100% moisture and a desired temperature of 42°C. Spectacles should be plugged into an electrical outlet for 15 minutes prior to its use for thermal elements to reach 50°C[24].

Spectacles allow patients to blink freely, favoring the natural secretion of meibum. Chambered hot moist air devices appear to be a safe and efficient way to elevate eyelid temperature to therapeutic levels in a controlled fashion and improve dry eye signs and symptoms according to short and long-term studies. In treatment studies, symptoms improved systematically with 2 to 3 months of treatment, while the improvement in signs varied depending on the study; it is still not clear if they offer a greater benefit than other eyelid-heating therapies[4].

Heat and pressure devices

Similar to what we stated previously, some devices used to treat moderate and severe MGD cases can simultaneously provide a combination of heat and also exert pressure for a varied period of time, leading to an improvement in symptoms and tear film stability[25-26]. Because of the capacity these devices have to maintain improvements in dry eye signs and symptoms for a long period of time, they might be adequate for patients who do adhere to a daily treatment with hot compresses. Most of these devices use disposable components that are discarded at the end of each session, which increases treatment costs. Therefore, case severity, associated pathological traits, patient compliance, costs, and possible side effects must be taken into account when making a decision regarding what method to use[22-27].

Meibomian gland manual expression

Meibomian gland expression with therapeutic goals is a procedure that has been taking place during consultation for at least a century. This is done by pressing the eyelid strongly either against each other, or between a rigid object (like a cotton rod or a metallic palette) on the inner surface of the eyelid and a thumb or another rigid object on the outside[9]. Squeezing blocked glands can require considerable force; it varies depending on the case and is limited by the pain it causes[28]. Despite the pain, however, several studies have shown the efficacy of meibomian gland manual expression for MGD treatment. It is recommended the procedure be done daily, preferably at night and immediately after applying heat on the eyelids for more efficacy until gland dysfunction is fixed[9].

Eyelid hygiene

MGD patients are often recommended they practice eyelid hygiene combined with heat and massages in domestic environments[25, 29]. After applying a hot compress, patients must wash their eyelids, especially around the cilia, with lateral movements using a finger and warm water, or special sanitary wipes for eyelids. It has been proven that washing and massaging eyelids raises tear film stability in patients suffering MGD[29]. Eyelid cleaning products like eyelid cleanser and shampoo for eyelid hygiene improve ocular symptoms and reduce ocular surface inflammation in patients with blepharitis or MGD. Shampoo for eyelid hygiene and ophthalmological ointment also improved tear film stability. It has also been observed that washing with ophthalmological wipes improves the state of the eyelid margin regarding eyelid staining and meibomian gland expression[29]. Eyelid hygiene is also considered important due to the links between Demodex mites and MGD[30]. Individuals with Demodex infestation must practice long-term eyelid hygiene, given that it is a chronic affection requiring chronic treatment; in the next chapter we will see that pharmacological topical products can also be used to improve therapeutic efficacy[14-15].

Intraductal probing

Intraductal probing is done with a microcannula during a medical consultation with the goal of opening gland orifices and relieving symptoms in MGD patients. This procedure, which is done with the assistance of a slit lamp, consists of introducing a 2 mm. probe directly into the orifice of each gland to unblock meibum flow[31]. It is a painful and invasive procedure; it can cause alterations like eyelid hemorrhaging, and some patient might also need more than one treatment session[32-33]. Most studies on this method have only been done over short periods of time and have not been compared to other treatments like eyelid heating and hygiene, or Meibomian gland expression. Because of this, more studies are needed to confirm its medium and long-term efficacy and safety[31-33].

Punctal and canalicular plugs

The goal of this treatment is to block the lacrimal duct in order to retain tears on the ocular surface. The blockage, which used to be done surgically through stitches and punctal cauterization, is now mostly done with silicone plugs,

and its efficacy in treating dry eye signs and symbols was quickly proven[34]. The main indicator to use punctal plugs is moderate or severe ocular dryness caused by aqueous-deficiency. They improve clinical signs and the state of the ocular surface while also reducing the use of tear replacements, which is used as a complementary measure in patients that are not well controlled[34]. The development of new biocompatible materials followed by absorbable materials has considerably improved the tolerance as well as the placing of these devices. These improvements have widened the scope of its application to different ocular surface disorders[35]. However, a meta-analysis criticized the heterogeneity of the methodologies used in the existent clinical studies because it prevented the obtainment of reliable scientific evidence[36].

The use of punctal plugs for MGD is controversial and the number of publications on the topic is very limited[37]. With or without a dysfunction, plugs allowed a more homogenous extension of the tear film and an increase in lipid layer thickness, which suggests the potential usefulness of punctal plugs in dysfunction without major inflammation, especially when it is linked to an aqueous-deficiency[37]. Punctal blockage is also a useful contributing therapy for immune diseases that affect the ocular surface, and its efficacy has been proven in Sjögren syndrome associated dry eye[38-39], in superior limbic keratoconjunctivitis, and in ocular affectation of graft-versus-host disease[38, 40-42]. Blockage is also a part of cicatricial conjunctivitis associated to epidermolysis bullosa diseases (Stevens–Johnson syndrome, toxic epidermal necrolysis, and ocular mucous membrane pemphigoid)[43]. The severity of these diseases, however, requires a combination of therapeutical approaches and it is recommended that the plugs not be inserted until the ocular surface inflammation has been controlled[44]. Punctal plugs are contraindicated in patients who are allergic to the materials, in cases with blocked lacrimal ducts, ectropion or active ocular infection (conjunctivitis, keratitis); its complications include plug loss and partial extrusion, toxic tear syndrome, pyogenic granuloma, epiphora, punctal stenosis, local irritation, distal migration, and canaliculitis[7, 13, 45].

Intense pulsed light

Intense pulsed light (IPL) was initially used by dermatologists and plastic surgeons for rejuvenation, hyperpigmentation, and vascular problems, among other pathologies, but it was used on patients with rosacea over two decades ago, showing an improvement in dry eye symptoms. Numerous studies since then have confirmed that intense pulsed light combined with Meibomian gland expression can improve symptoms, tear film features, and MGD clinical signs[46-49].

IPL systems contain high-intensity light sources that emit polychromatic and non-coherent light, ranging from the visible spectrum (515 nm) to the infrared (1200 nm). Light is directed at tissue and the target structure absorbs it selectively, producing heat. Adequate wavelengths can be selected depending on light absorption and penetration deepness; specific filters can be chosen to produce a selective heat administration. The wave length produced can interact with several chromophores, like melanin (400-750 nm) and hemoglobin (578 nm)[47]. Intense pulsed light reduces inflammation in patients with dry eye disease secondary to MGD by targeting this pathway through selective photothermolysis, coagulating eyelid margin telangiectasias by interrupting the release of inflammatory markers. Its underlying mechanisms can include a thermal effect, allowing the liquefaction of meibum and its ensuing secretion. Reduction of IL-17 and IL-6 levels can have a significant correlation with the improvement of signs and symptoms[48].

The patient's phototype (Fitzpatrick) must be evaluated to adjust parameters[47, 49-50]. Patients with lighter skin (lower Fitzpatrick score) require more energy than those with darker skin. Parameters like filter, wave length, pulse duration, and fluency are selected based on the desired goal. Due to safety reasons, most devices do not recommend intense pulsed light treatment for patients with darker skin (above IV). However, new devices for use in V phototypes with reduced energy have been approved.[49] Likewise, the patient's entire face should be examined before beginning the session and their pigmented lesions covered[46, 50]. The region meant for treatment is cleaned (the infraorbital and temporal regions) and ocular

protectors are placed. Ultrasound gel is later placed on the infraorbital and temporal regions to protect the skin and direct the light, although gel use is not always necessary. Doctors and patients must wear protective goggles during the flashes. The number of pulses (normally between 4 and 6) varies depending on each manufacturer. The number of treatments is also a key factor. Current evidence suggests that intense pulsed light efficacy is related to the number of sessions. Every treatment cycle contains between 3 and 4 sessions (usually one every three weeks), which can be followed by a maintenance session 4 to 12 after. A follow-up consultation six months after the final treatments is recommended. A meibomian gland manual expression performed under a slit lamp is required at the end of every session[49].

A prospective multicenter study compared the efficacy of intense pulsed light combined with Meibomian gland expression with intense local heat combined with Meibomian gland expression to treat MGD. The results showed that the former was significantly more efficient that simultaneous hot compresses followed by expression, suggesting that pulsed light truly contributes in improving signs and symptoms of evaporative tear dysfunction[50]. A meta-analysis of randomized clinical studies aiming to evaluate safety and efficacy of intense pulsed light combined with Meibomian gland expression concluded that this combination was better than just expression alone in treating patients with MGD-related dry eye[51]. According to the literature, intense pulsed light must be done in dry eye cases that are refractory to conventional treatment strategies, such as eyelid hygiene as well as lubricant and massage use, having been proven as a safe option for I-IV skin types when security protocols are correctly followed, with no relevant side effects[49-50]. Most studies show improvement in symptoms and objective indicators like non-invasive tear break-up time (TBUT) and lipid layer thickness[52].

Low-level light therapy (LLLT) has also been studied. It is a type of photobiomodulation in which low-power red monochromatic light is applied for a longer period of time, favoring tissue repair and reducing inflammation[53]. An observational study comparing the sole use of intense pulsed light therapy (IPL) with IPL plus LLLT was conducted in order to evaluate safety and efficacy. Results showed the objective and subjective efficacy of the former in treating patients with MGD, which could be related to lower eyelid inflammation and greater tear film quality following treatment. The conclusion was that IPL was efficient and safe in treating the dysfunction and its use combined with LLLT could improve lacrimal gland function and tear production even more, but more studies are required to confirm this finding[53].

Other non-pharmacological treatments

Other options to treat dry eye through devices and/or non-pharmaceutical procedures are being studied, even those considered to be alternative therapies like those described by Mittal[54]. That work included transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, stem cell or royal jelly therapy, cutaneous nerve blockage, botulinum toxin and even acupuncture and antibacterial agents like manuka honey, nervous growth factor, plasma-rich products, corneal neurotization, and polysaturated fatty acids. There are also surgical options, the most traditional being tarsorrhaphy, particularly in the case of lagophthalmos with exposure keratopathy[55]. Even therapeutic contact lenses can function as a complement in some severe stages of persistent epithelial affectation, as well as the new applications currently being studied, mainly scleral contact lenses[56]. These options must be undoubtedly updated in the near future.

This consensus is only giving the information that this therapeutic branch exists and is in clear expansion, a development generally rooted in the great technological advancements of the last decades and the impulse this field within the science of vision is having.

B. Considerations regarding lifestyle and local environment

The Tear Film Ocular Surface Society (TFOS) published a full report in 2023 with a detailed

review on what is the relevance and impact of a person's lifestyle and local environment on ocular surface disorders. Lifestyles define the way we live[57]. Our way of living can influence our environment. The environment can also influence our lifestyle, and both can affect our health. The global environment is changing due to multiple factors, but the main changes are connected to the global agri-food industry, the use of energy resources, new construction technologies and architectural developments, together with new technologies that tend to digitalize our surroundings. Several of these have been tied to dry eye syndrome, such as drying conditions of the environment, air pollution, nutrition, the use of digital devices, cosmetics, contact lenses, as well as the adverse effects and interactions systemic and topical medications can have[7, 58]. Each one of these aspects is very interesting and extensive, which is why we will only mention basic concepts that any doctor must keep in mind when evaluating a dry eye patient given that, regardless of the recommended pharmaceutical therapy, an unfavorable environment can totally or partially counter any medical effort. The need to learn and think about these issues shows that they should be included within the initial questionnaires while putting together a patient's medical history. Just as an example, it is important to know a dry eye patient's labor environment, number of hours using digital devices, and aspects related to sleep quality and quantity.

Technology and digital content are changing how we relate, learn, work, and entertain ourselves. The prolonged use of digital devices and computer screens lowers blinking rate significantly and induces ocular tension[58]. Humidification, as well as active and deliberate blinking, are essential. Certain professional activities are dangerous, which is why workers should take precautionary measures when faced with a reduction in tears or a rise in evaporation. Some medications reduce tear production, mainly drugs prescribed for hypertension and depression, as well as isotretinoin and antihistamines[59-60].

A study conducted by Morthen *et al.* concluded that dry eye disease has a significant impact on labor performance, absenteeism, and concern over job loss. The impact of very symptomatic dry eye can also have an impact on labor performance that is comparable to depression. Particularly noteworthy is the fact that undiagnosed dry eye causes lower job performance than diagnosed dry eye with a similar symptomatic burden[61].

These comments are merely meant to express the importance of these issues in the care of ocular health and their impact on the ocular surface and dry eye. Educating the population is a preventive as well as a therapeutic action, given that changing any lifestyle aspect considered to be a potential risk factor can be of great use to complement care for a person with established dry eye and/or prevent a temporary ocular surface alteration in a healthy person from becoming a chronic pathology that can affect their quality of life.

C. Diet and nutritional supplements

We recently reviewed how lifestyle issues and a person's environment can be related to ocular surface disorders and trigger a pathology; what we didn't mention was diet, a highly relevant aspect Markoulli *et al.* analyzed in a separate chapter within the TFOS 2023 report on the impact of lifestyle on the ocular surface[62]. Diet —as a voluntary act— and nutrition —as the involuntary and physiological capacity to harness nutrients acquired through eating— are highly important when studying and understanding ocular surface problems. There is also a varied and extensive group of commercial products called nutraceuticals that are neither foods nor drugs and can complement a person's diet and nutrition. We will now mention some of the known concepts that are backed by scientific evidence, together with the more relevant diet and nutritional principals tied to dry eye. But in reality, medical studies and biochemical analysis should be done on each person in order to determine which nutrients must be stabilized or complemented. The issue is not always the deficit of one particular nutrient, but rather a multicausal micronutrient unbalance, even due to digestive disorders by malabsorption; if this is not studied and handled in an interdis-

ciplinary way, the underlying digestive disorder will not be fixed and the implementation of a good diet and multivitamin supplements will be wasted, a situation that occurs with the diagnosis and therapeutic management of celiac diseases[63]. Dosages, proportions, and brand names of commercial products will not be mentioned as they surpass the scope of this work, with the aim of highlighting that a nutritional supplement is not a placebo but a complement to the therapeutic dry eye treatment that must be prescribed in appropriate cases. For many patients, an interconsultation with a nutritionist can be advisable and required.

Water

Given that water makes up the largest portion of our bodies, it is simple to understand how a hydric unbalance could eventually affect our tear production, but it is not clear that drinking water in abundance can be a protective factor against dry eye. In fact, it could actually be detrimental, as Nguyen *et al*. concluded in a study with over 50,000 participants in which they proved that normal water consumption did not lead to a lower risk for dry eye, but found that people with higher water consumption had more ocular dryness-related symptoms[64]. This is a very interesting study mainly for its ability to incentive researching this topic, but it also is a very complex issue to approach given the dynamic nature of our metabolism and the large number of factors among the population being studied that are difficult to standardize, such as each person's metabolic state, something that is particular and variable. Although drinking abundant water is sound medical advice, it is necessary to keep in mind that, in certain people, its excess may not be beneficial for dry eye, contrary to what common sense might indicate.

Fatty acids

Omega-3 and omega-6 are essential polysaturated fatty acids that are absorbed from food and present in all body cellular membrane; however, omega-3 competes with omega-6 for inclusion based on dietary intake[65]. Arachidonic acid —one of the components of omega-6 fatty acid— is turned into pro-inflammatory mediators once cells are activated by external stimuli. This mediator diminishes when omega-3 displaces omega-6 due to a rise in omega-3 ingestion. This is the main anti-inflammatory mechanism of omega-3. A tie between tear film stability and omega-6/omega-3 ratio has been clinically proven, where a rise in this ratio exacerbates dry eye disease symptoms; on the other hand, a higher intake of omega-3 dietary supplement led to an improvement in signs and symptoms. A daily oral 500 milligram dose of omega-3 fatty acid (eicosapentaenoic acid, docosahexaenoic acid, and alpha-linolenic acid) is recommended for patients with dry eye associated with systemic autoimmune inflammatory disorders. There is also data proving that a rise in omega-3 intake can increase the risk of prostate cancer. In fact, this is still a controversial aspect, as seen in the systemic review of the Cochrane series published in 2019 that researched the effects of polysaturated fatty acids omega-3 and omega-6 and concluded that, after evaluating all available evidence, omega-3 was potentially useful, but that data was inconsistent and insufficient[65]. This happens many times in science, especially in studies that are complicated in nature because they require large people samples participating over long tracking periods. In fact, a new systemic review in 2022 analyzing new studies that included only randomized controlled clinical trials of over 1,100 cases concluded that there was enough evidence —using GRADE methodology— that omega-3 supplementation improved dry eye symptoms[66]. Briefly, the reason omega-3 has as role in dry eye treatment is due to its antioxidant effect[67].

Vitamin D supplements

The importance vitamin D has to our health is mainly related to bone metabolism. However, it also plays a role in the ocular surface, since there is enough evidence showing that its deficit is linked to a rise in dry eye symptoms as well as a drop in tear break-up time[68]. Its use via nutraceuticals has also been tied to improvements,

although it is harder to completely understand its detailed action mechanism; it has been posited that its beneficial effects is due to the improvement of ocular surface immunity, which inhibits pro-inflammatory cytokine secretion in tears, favoring the antioxidant environment.

It is interesting to point out that vitamin D deficiency and its impact on dry eye are also connected to a lack in sun exposure during labor activities, or in living environments that limit outdoor activities, something that is more severe in women who are postmenopausal[69-70].

Vitamin A

The work published by Faustino *et al*. conducted a very interesting revision on the function of vitamin A in the eye, highlighting that its deficit causes a severe ocular surface alteration called xerophthalmia[71]. In this condition, we see extreme ocular dryness that, even to this day, can also lead to blindness in some parts of the world, mainly due to child malnutrition and alteration in the development of the visual system[72]. Therefore, when considering the use of this supplement in cases that are warranted, there are therapeutic benefits that exceed the problem of dry eye, highlighting its relevance even more.

Zinc

The function of this micronutrient at the ocular level has been highly researched and is tied to its effects as an antioxidant and as the main defense against retinal degenerative processes[67, 73]. Its specific function regarding general ocular surface disorders and dry eye disease is currently a bit confusing, although nutraceutical formulations where it is combined with other nutrients are being studied[74]. There is currently not enough evidence to completely understand the role of zinc in dry eye, although it possibly plays a relevant role in ocular surface immunobiology.

Lutein and zeaxanthin

As we mentioned with zinc, lutein and zeaxanthin are two micronutrients that have been studied and associated with age-related macular degeneration[75]. They are substances with an antioxidant effect, which is why they are usually considered favorable as a complement to nutraceutical formulations developed specifically for dry eye, although more recent studies are aimed at investigating its direct topical application on the ocular surface[76-78].

Intestinal microbiome

The relevance of the intestinal microbiome in general health is a current, vast, and growing topic that also encompasses the ocular surface and dry eye[79-83]. Its alteration could affect nutrition absorption but also psychoneuroendoimmunology homeostasis, which is why understanding and handling it is relevant in autoimmune diseases that produce dry eye, like Sjögren syndrome and mucous membrane pemphigoid. This topic was integrally covered in Muravchik's review, considering microbiome relevance in the context of systemic ophthalmology, something that is specially justified in the approach of ocular surface problems due to its relationship with other systemic alterations and the environment, as we have previously seen in this document[83].

Final concepts

There are several non-pharmaceutical options available that an ophthalmologist must know, given that they may be key for dry eye treatment. Most device-mediated dry eye therapies are generally complementary to pharmacological treatments, recommendations regarding lifestyle, and adequate nutrition. Before using devices or prescribing nutraceutical products, their status must be checked with the regulatory agencies of every country in order to avoid inadequate instructions or unauthorized use. In the case of devices approved in your region, it is important to adhere to the instructions for use established by the manufacturer. In order to adequately use nutritional supplements, an interconsultation with a nutritionist is advised in order to select the right nutrition proportion, which is not always

available on multivitamin formulations. Finally, all these interesting therapeutic aspects are sustained by a great rise in investigations and developments that are generating dynamic changes in concepts and knowledge; because of this, it is relevant to stay up-to-date and conduct a critical and cautious review in order to identify scientific evidence that back future decision-making processes.

Synopsis

Current information

- There are non-pharmaceutical dry eye treatments of great complementary utility.
- Point out that eyelid and lacrimal duct care can be done through several medical devices.
- Environment, lifestyle, diet, and the possibility of using nutritional components must always be taken into consideration.

Future needs

- Conduct more studies of high-quality evidence on medical devices, and also control their functioning over time.
- Unify regulatory aspects in Latin America on medical devices for dry eye treatment.
- Conduct and/or monitor the evidence-level of dry eye studies and nutritional products, diet, lifestyle, and the environment.

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10

WHAT PHARMACOLOGICAL ACTION MECHANISM COMPLEMENTS DRY EYE TREATMENT WITH LUBRICANTS?

Dry eye disease management is multifaceted and involves several pharmacological therapeutic options. These treatments were developed not only for eye lubrication but to also take into account the underlying pathology, including the inflammatory process, hyperosmolarity, and Meibomian gland dysfunction. We will now review some available pharmacological therapeutic options beyond lubricants.

Anti-inflammatory agents

Inflammation plays a crucial role in dry eye, and the use of anti-inflammatory agents can help relieve symptoms and improve tear film stability. Focusing on the pathogenesis of the ocular surface inflammation process and the role of elements secreted by the lacrimal system play is considered relevant. Inflammation greatly affects tear composition, and these inflamed tears give way to a cyclical process which in turn leads to quantity deficit; as this process raises its chronicity, its severity will rise.

Corticoids

It is one of the main anti-inflammatory therapeutic resources available for all dry eye severity levels. Several formulations exist, as Liu *et al.* evaluated in a systemic review published in 2022[1]. We briefly point out that for moderate and severe dry eye cases, surface corticoids in drops, preferably preservative-free, should be used from 2 to 4 weeks —for instance, fluorometholone phosphate, loteprednol etabonate, dexamethasone phosphate, or hydrocortisone— have shown notable improvements in dry eye symptoms and clinical signs. For long treatments, however, corticoids can produce side effects like cataracts and a rise in intraocular pressure (IOP), which is why it is only indicated for short periods[2]. Hydrocortisone is recommended for severe dry eye cases like Sjögren syndrome, although we should be watchful of potential side effects[3-4]. Loteprednol can also be used, given that it potentially has lesser impact on the rise in IOP and cataract development[5].

In the case of general or autoimmune inflammatory diseases, like Sjögren syndrome for instance, systemic corticoids are recommended in short spurts, but always under supervision and clinical control. In general, topical and/or systemic corticoids improve dry eye symptoms and signs.

Cyclosporine

Cyclosporine is a calcineurin inhibitor with anti-inflammatory and immunosuppressant properties that prevents T cell activation, inhibiting the production of IL-2 and inflammatory cytokines[6]. As a way of summarizing what was presented in the review published by Tong *et al.*, topical cyclosporine (0.05%) improves Schirmer test scores and corneal fluorescein staining, while also raising goblet cell density[6]. It relieves dry eye sickness symptoms and signs in almost 50% of patients, although the application of this drug is usually associated with irritation[6]. A comparative study of topical cyclosporine treatment in moderate-severe dry eye administered in two different

concentrations (0.05 and 0.1%) produced significant improvements compared to the vehicle in corneal fluorescein staining and Schirmer test scores. Cyclosporine 0.05% also produced significant improvements in blurry vision, necessity of concomitant artificial tears, and doctor evaluation of global treatment response[7].

A systemic review of Cochrane on the efficacy and safety of topical cyclosporine 0.05% found that, despite the generalized use of topical cyclosporine to treat dry eye, evidence regarding its effects on ocular discomfort, as well as on ocular surface and tear film parameters like corneal fluorescein staining, the Schirmer test, and break up time (BUT) are inconsistent and on occasion show no difference against the vehicle or artificial tears in the studies mentioned. Topical cyclosporine can raise the number of goblet cells. However, current tests do not support that a betterment in conjunctival mucin production translates to an improvement of ocular surface and tear film symptoms and parameters[8].

Tacrolimus

Tacrolimus is another immunomodulator one hundred times more potent than cyclosporine that can also be used topically to treat different ocular surface diseases, including severe dry eye disease, given that it is associated to inflammation[9]. Tacrolimus 0.03% acts primarily upon T cells. Tacrolimus binds to an intramuscular protein called FK-binding protein 12 (FKBP12), and this drug-protein compound binds to and inhibits an enzyme called calcineurin, which is critical to T cell activation[10]. Active calcineurin normally de-phosphorizes the nuclear factor of activated T cells (NFAT) preventing interleukin-2 (IL-2) production, a cytokine that promotes T cell proliferation. This relieves inflammation caused by severe dry eye disease, leading to symptom reduction[9].

A randomized controlled study of patients with Sjögren syndrome found that tacrolimus 0.03% offered significant improvements in Schirmer's test, BUT, corneal fluorescein staining, and rose bengal corneal staining against the delivery[11].

In another comparative study on cyclosporine 0.05% and tacrolimus 0.03% administered to patients with severe dry eye, no significant differences were found in OSDI questionnaire results, ocular surface staining (OSS-SICCA), and Schirmer tests[12]. Due to its high molecular weight and hydrophobicity, tacrolimus 0.03% has been coupled with anionic Gellan gum in a nano-formulation and also with cationic liposomes to improve its residency and bioavailability time[13-14].

Lymphocyte function-associated antigen-1 (LFA-1) antagonists

Lifitegrast ophthalmic solution 5% is the first of a new kind of drugs called integrin antagonists, specifically LFA-1, meant to treat dry eye symptoms and signs[15]. By blocking this integrin, the main ligandin of intercellular adhesion molecule 1 (ICAM-1), it halts the migration and chemotaxis of adaptive immune system effector cells —mainly T cells and bloodstream monocytes— towards the interstitium, thus inhibiting their inflammatory action on the ocular surface of dry eye patients, especially associated to autoimmune conditions like Sjögren syndrome and graft-versus-host disease[16].

Lifitegrast efficacy and safety for treating dry eye disease has been studied in different randomized controlled multi-centered trials, including a great number of cases (n=2464) involving placebo, among them the original phase 2 lifitegrast study, three phase 3 trials (OPUS-1, OPUS-2, and OPUS-3), and one year-long study (SONATA).

All these studies —analyzed jointly— revealed a significant improvement in symptoms and signs of dry eye patients treated with lifitegrast compared to placebo. However, the phase 2 study and OPUS-1, 2, and 3 clinical trials did not provide data on the long-term therapeutic efficacy of lifitegrast, given that they lasted only 12 weeks[17].

Furthermore, a recently published meta-analysis of 10 studies analyzing the therapeutic efficacy and safety of lifitegrast in treating dry eye

patients —5 randomized controlled trials, one study of cases and control, and 4 longitudinal or retrospective studies (n=3197 participants) which included the SONATA and the three OPUS studies— proved that lifitegrast was superior to placebo, improving corneal fluorescein staining, nasal staining with lissamine green, tear break-up time, ocular discomfort and dryness scores, as well as OSDI scores. However, lifitegrast also showed a greater risk for ocular and non-ocular side effects during treatment in general, although at mild and moderate levels[18].

Finally, the combined analysis of these studies on lifitegrast tolerance and safety published by Nichols *et al*. proved that ocular side effects to treatment was >5% in all groups, all related to the instillation zone: irritation (lifitegrast 15.2%, placebo 2.8%), reaction (lifitegrast 12.3%, placebo 2.3%), and pain (lifitegrast 9.8%, placebo 2.1%). The most common non-ocular side effect was dysgeusia (lifitegrast 14.5%, placebo 0.3%). However, just as in the findings of the meta-analysis previously mentioned, most side effects were mild and moderate[17].

Mucin secretagogues

Mucin secretagogues are pharmacological agents that facilitate mucin synthesis and liberation, a key element that determines tear film stability and lubricant capability[19]. The appearance of topical secretagogue formulations, which are applied directly on the ocular surface, represent a new therapeutical approach to stimulate aqueous and/or mucin secretion. These agents work as purinergic receptor agonists P2Y2, interacting with ocular surface receptors, stimulating conjunctival epithelial cells to secrete water (as evidenced by the application of 3% diquafosol tetrasodium ophthalmic solution) and also acting upon conjunctival goblet cells to make them produce mucin (as evidenced by 3% diquafosol tetrasodium ophthalmic solution and rebamipide 2% ophthalmic solution)[19]. They have a beneficial impact on tear film stabilization and assist in repairing damaged corneal epithelial. The rise in tear secretion through secretagogue agents can be achieved through local as well as topical administration.

Certain agents like cevimeline and pilocarpine stimulate saliva and tear secretion and are particularly beneficial in cases of Sjögren syndrome[20]. Oral pilocarpine is typically administered three to four times a day with an initial dose usually set at 5 milligrams. It is generally well tolerated but its effectiveness is insufficient, and a gradual rise can be considered, in some cases going as high as 7.5 to 10 mg, three or four times a day[20]. We should point out that the efficacy of oral secretagogues seems higher in treating oral symptoms rather than ocular manifestations.

Antibiotics

Macrolides

Antibiotics generally play an important role in handling tear film dysfunction, especially when blepharitis and MGD are the main cause of dry eye. Azithromycin is a macrolide with anti-inflammatory and anti-bacterial effects, and several studies have reported that azithromycin 1% ophthalmic for blepharitis treatment improves lipid layer secretion and tear film stability[21].

Tetracyclines and derivatives

Tetracycline and its derivatives like doxycycline, minocycline, and lymecycline have anti-inflammatory and bacteriostatic effects[21]. They diminish interleukin-1 alpha (IL-1α) and tumor necrosis factor (TNF-α), and reduce the activity of several matrix metalloproteinases, collagenases, and phospholipase A2. They have been successfully used for treating MGD, particularly associated to ocular rosacea, and corneal ulceration in low oral dosages (40-400 mg/day for doxycycline, 50-100 mg/day for minocycline, and 150-300 mg/day for lymecycline); high doses, however, can cause side effects in the gastrointestinal tract and the skin. It has been proven that using medications in low doses for 6 to 12 weeks reduces inflammation and improves corneal surface regularity, tear production, and tear film stability[21-22].

Hemoderivatives

Hemoderivatives are products obtained from peripheral blood or the umbilical cord of a patient (autologous) or a donor (allogenic), which are employed in the restoration, proliferation, vitality, and migration of corneal and conjunctival epithelial in ocular surface diseases, including dry eye[23-24].

The different hemoderivative products currently employed in the clinical and surgical treatment of the ocular surface are: autologous and allogeneic serum, rich plasma serum, plasma rich in growth factor serum, platelet lysate, and umbilical cord serum[25].

The products most employed to complement dry eye treatment are autologous serum and plasma rich in growth factors. The scientific foundation on how hemoderivatives treat or relieve dry eye symptoms is based on the multiple factors that make up its biochemical composition, which resembles that of tears and contributes to wound-healing and ocular surface protection.

The therapeutic benefits of autologous serum drops are multifactor and can be explained by its composition which, just like tears, contain carbohydrates, lipids, and several electrolytes, but 10 times more proteins, like albumin, fibronectin, and transferrin[23, 25]. The serum also has more natural antimicrobial components, such as IgG complement, but less lysozyme than tears. Tears and serum provide vitamins and both share a similar osmolarity (close to 300 mosm/l), given that they contain similar levels of sodium and anions, as well as a similar pH (close to 7.4)[23]. Tears have five times the ion potassium that serum has, but lower levels of calcium ions and phosphates.

Treating dry eye with autologous serum drops was first described in patients with Sjögren syndrome[26].

Autologous serum has the advantage that many of its biochemical characteristics —including pH, nutrient content, vitamins, fibronectin, and growth factors like epithelial growth factor and nerve growth factor— are similar to those of human tears[27]. Several in vitro and in vivo studies have proven that serum and other blood derivatives improve corneal epithelial wound-healing, probably due to these factors. It was also discovered that serum inhibits the release of inflammatory cytokines and raises goblet cells and conjunctival mucin expression in a series of clinical cases, mechanisms that are clinically reflected in its efficacy and safety profile[27-28].

There are at least 6 randomized controlled studies that have investigated the efficacy of autologous serum in treating severe dry eye. These studies report a significant improvement in symptoms and signs (tear break-up time, corneal fluorescein staining, and conjunctival impression cytology) after treatment with autologous serum with or without artificial tear support. A crossover randomized study of patients with severe dry eye comparing autologous serum treatment for 3 months with conventional treatment, found a significant improvement in symptoms and impression cytology following serum treatment[29].

Two other recent dry eye crossover trials showed greater symptom score reduction in the autologous serum group compared to the control group treated with tear substitutes; nevertheless, only one study informed of significant BUT improvement in the serum group[30-31].

Essential fatty acids

In the previous chapter we saw the ties of polysaturated fatty acids omega-3 and omega-6 to nutrition and dry eye via orally administered products called nutraceuticals. We will now see that there are pharmacological developments of topical ocular formulations like omega-3 eye drops, that could have the potential benefit of improving ocular inflammation in dry eye disease, but are still being researched[32].

Varenicline

The pharmacological neuro activation of the nasolacrimal reflex of the tear film presents an innovative therapeutic strategy for handling dry eye disease. Varenicline intranasal formulation, a water-soluble small-molecule nicotinic acetylcholine receptor (nAChR) agonist, was approved in the United States for dry eye disease treatment[33].

The specific mechanism underlying the effectiveness of intranasal varenicline in treating dry eye has not yet been determined; however, it is posited that this therapeutic benefit springs from the binding of varenicline and nAChR, which results in agonist activity of the sensory trigeminal nerve endings located in the anterior nasal cavity[33]. It is believed that the subsequent activation of the nasolacrimal/trigeminal parasympathetic pathway (NLR/TPP) stimulates endogenous tear film secretion.

Three randomized controlled studies totaling 1,063 dry eye patients have so far analyzed the efficacy and safety of varenicline nasal spray: ONSET-1 and 2, and MYSTIC[34-36].

A meta-analysis on varenicline nasal spray efficacy and safety in treating dry eye that included the three trials previously mentioned concluded that the 3 studies had low bias risk and that varenicline treatment versus controls (vehicle) showed a statistically significant improvement in the average Schirmer score, comparing the initial visit with the final one (day 28). The joint analysis did not find significant differences in ocular and nasal side effects caused by the treatment between experimental and control group; however, varenicline did have a significant effect on the development of nasal cavity side effects (cough and sore throat)[37].

Mucolytics

Mucins are large and strongly glycosylated proteins responsible for the gelatinous properties of mucous. When these proteins get tangled, they form a thick sticky substance that can become hard to remove. Mucolytics thin or loosen mucous by decomposing its chemical molecular structure, thus reducing its viscosity. Acetylcysteine (NAC), known for its mucolytic properties, has proven to be effective in specific dry eye syndrome cases, although its use in this context is not widespread[38]. Application for severe dry eye, particularly cases accompanied by copious mucous secretion or the formation of corneal filaments, generally requires NAC prepared as a topical solution given that it is not commercially available as collyrium. Common concentrations vary between 5 and 10%[38].

In certain dry eye cases, especially in Sjögren syndrome, tear film can exhibit abnormal thickness and stickiness due to an overproduction of certain components. NAC helps break this abnormal tear film, promoting the production and distribution of a healthier tear. The antioxidant properties of NAC also allow it to neutralize detrimental oxygen free radicals, which can temper inflammation and improve tear film health. Preliminary investigations suggest that NAC can help stimulate tear production, although additional validation is required.

Despite these promising benefits, acetylcysteine is not generally considered a first-line treatment option for dry eye syndrome, mainly due to its lack of a commercially convenient form and its possible side effects, including ocular irritation. It is most frequently used in the palliative treatment of filamentary keratitis, a possible complication of dry eye disease[38], although there are developments tying it to chitosan with promising experimental results[38-39].

Another problem with NAC is its instability and lability at room temperature, which is why it should be kept refrigerated, not lasting too long (approximately 7 to 10 days) before denaturalizing and losing its anti-mucolytic properties.

Hormones

Insulin

Human insulin, mainly known for its role in regulating glucose metabolism, has additional biological activities that can be beneficial for ocular health. The ocular surface, including the cornea, conjunctiva, and lacrimal gland, have insulin receptors, indicating the possible participation of insulin in maintaining ocular homeostasis; several studies have evaluated this and highlighted the anti-inflammatory, antioxidant, and wound-healing properties of insulin, turning it into a promising candidate for dry eye therapy[40].

The high concentration of insulin-like growth factor 1 (IGF-1), which is one of the more potent neurotrophins that stimulates epithelial regenera-

tion, is highly useful in dry eye patients, especially in cases associated with neurotrophic keratitis and persistent epithelial defects.

A retrospective series in which topical insulin was used off-label on people with dry eye also showed promising results in patients with treatment-resistant corneal epithelial damage[40-41].

Insulin-based ophthalmologic administration systems

Several ophthalmologic administration systems are being researched to try and harness the therapeutic potential of insulin for treating dry eye syndrome[42-43]. These systems aim to improve the bioavailability, stability, and action duration of insulin on the ocular surface. Some noted approaches include nanoparticles, liposomes, gel systems, and contact lenses[43]. But more research is needed to establish the safety, efficacy, and long-term effects of insulin-based treatments for dry eye syndrome. Clinical trials are required to evaluate optimal doses, as well as treatment frequency and duration. Possible interactions and synergies between insulin and other existing dry eye treatments should also be explored in order to determine the best therapeutic combinations[44].

Sexual hormones

Systemic sexual hormones, especially estrogen and androgen, play a role in ocular surface tissue health and tear production, which may implications in treating dry eye diseases[45-46]. Current dry eye treatments center mainly on tear supplementation and inflammation control, although the role of sexual hormones in maintaining ocular surface homeostasis suggests it has a possible role in treating this anomaly[45].

Androgen drops

Androgenic hormones, specifically testosterone, have a known tie to Meibomian gland health. These glands are responsible for secreting the lipid layer of the tear film, which are key in avoiding tear evaporation[45]. Gland dysfunction, often related to androgen deficiency, is a prominent cause of evaporative dry eye[46]. Given this connection, the application of topical androgens as a potential treatment for dry eye has been explored. Topical androgens tested in initial studies showed promise in mitigating dry eye disease symptoms by restoring the lipid layer of the tear film[47]. Topical androgens can improve tear film stability and reduce tear evaporation by raising lipid production, thus providing relief for dry eye symptoms. A Cochrane review of clinical studies on the efficacy and safety of using androgen for dry eye treatment included 7 trials in which androgen was applied, either topically through collyrium, or systemically via oral or transdermal administration. Most studies showed that androgen notably improved dry eye-related symptoms and raised tear secretion. Elderly men and perimenopausal women with lower androgen circulation responded better to the therapy. However, a study on patients with Sjögren syndrome showed no improvement in the therapeutic group compared to the control group (placebo) or basal level. Side effects were also frequent but limited to mild skin problems. This meta-analysis concluded that androgenic therapy is a potential alternative for dry eye disease, especially for people with primary androgenic deficiency, and its short-term application is relatively safe[48].

According to reviews made for this work, however, we can say that the issue needs further research given that, for instance, the specific mechanisms of how topical androgens could help treat dry eye disease are not yet fully understood. More extensive and exhaustive clinical trials are also required to confirm the safety and efficacy of this approach, including the understanding of possible side effects and establishing better doses and application procedures[49-51].

Estrogen drops

The connection between estrogen and dry eye disease is more complex and still not yet fully understood, although it has been linked to systemic levels of estrogen, especially when they are high like in postmenopausal hormonal replacement therapy, with a higher risk for dry eye[46]. Estrogen seems to affect tear-producing lacrimal glands and lipid-producing meibomian glands, both of them essential components of a healthy tear film.

Given the complexity of this connection, using topical estrogen to treat dry eye disease requires cautious exploration. The impact of directly applying estrogen on the ocular surface is not fully understood and research has so far delivered mixed results.

Only one retrospective series —non-comparative and interventional— on the systemic combination of esterified estrogens and methyltestosterone as hormonal replacement therapy for postmenopausal women showed certain efficacy in several dry eye etiologies[52].

Another comparative series on women in menopause (n=88) who were treated with a combination of estrogen and oral medroxyprogesterone acetate versus a control group without therapy showed improvements on the Schirmer test only in women under 50, with no BUT changes between the hormonal replacement group and the control groups without treatment[53].

Finally, a systemic review and a meta-analysis on hormonal estrogenic replacement for treating dry eye in menopause failed to find enough evidence of tear production and BUT improvement of said therapy[54].

Therefore, and although theoretically topical estrogen could help modulate ocular surface and tear film health, its use to treat dry eye diseases is still not established. More research is needed to fully understand the possible therapeutic role of topical estrogen and judge its safety.

Progesterone drops

The possible use of progesterone in treating dry eye disease is based on its known anti-inflammatory properties[45, 55]. Inflammation is a key factor in this disease: it damages the ocular surface and disturbs tear film stability. Progesterone eye drops could therefore suppress inflammation and offer dry eye symptom relief[55]. However, as with the other hormones mentioned, the use of topical progesterone for dry eye treatments is still mostly a hypothetical option. There is limited research regarding its possible benefits, efficacy, or security.

In a randomized controlled double-blind trial of parallel groups of 42 postmenopausal women with dry eye syndrome that did not receive any medication, one group was administered progesterone. The 21 patients of the experimental group received 17 beta-estradiol transdermal (50 milligrams per day) and medroxyprogesterone acetate (2.5 milligrams per day) continuously for three months, while the 21 patients of the control group were given transdermic oral placebo. Although the hormonal treatment group reported improvement in dry eye symptoms, this difference was not statistically significant compared to the control group, leading to the conclusion that there is no evidence to support that the combination of topical medroxyprogesterone and estradiol transdermal is efficient in treating dry eye[56].

Additional robust clinical trials are required to explore these aspects and determine if progesterone drops can provide safe and effective dry eye disease treatment.

Antiparasitic agents: ivermectin

Oral ivermectin is an oral antiparasitic agent traditionally used to treat parasitic infections, including onchocerciasis (river blindness), strongyloidiasis, and scabies[57]. The medication acts by selectively and strongly binding to glutamate-activated ionic chloride chambers, which are present in the nerve and muscle cells of invertebrate. This causes a rise in cell wall permeability to chloride ions, resulting in the hyperpolarization of the nerve or muscle cell, leading in turn to parasite paralysis and death[58]. Oral ivermectin has been proven to be an effective treatment in cases of ocular demodicosis. Holzschuh *et al*. carried out a study in which patients with ocular demodicosis were treated with a single dose of oral ivermectin (200 μg/kg)[59]. The authors reported a significant reduction in mite count and an improvement in ocular discomfort symptoms after two weeks of treatment. Despite these promising results, it is important to keep in mind that oral ivermectin is not recommended as a first-line therapy due to its possible systemic side effects, which can include dizziness, itchiness, nausea, or diarrhea, even though these effects are usually mild and temporary[59].

Because of its systemic nature, oral ivermectin also has the advantage of being able to target mite

in areas of difficult access for topical treatments, like the deeper parts of hair follicle[60]. Although it is typically used for cases in which topical treatments have failed or when infestation is severe, an extensive number of cases treated with topical ivermectin as ointment was recently reported, which proved its efficacy and safety in over 4,300 eyes and cases with a five-year following[61]. But this promising data comes from a single study done with a compounding; despite the benefits, more investigation is needed to understand the optimal dosage regimen for oral ivermectin in treating ocular demodicosis and exploring possible resistance mechanisms in *Demodex folliculorum*.

Final concepts

Integral treatment of dry eye disease goes beyond simple ocular surface lubrication and entails a multifaceted physiological approach to the condition. Therapeutic strategies include anti-inflammatory agents like corticosteroids, cyclosporine, tacrolimus, and LFA-1 antagonists that relieve ocular inflammation and improve tear film stability. Antibiotics like macrolides and tetracyclines are beneficial in cases of chronic blepharitis and bacterial infections, while autologous tears, which contain nutrients and growth factors, are helpful supporting corneal health in severe cases. Supplements with fatty acids like omega-3 also contribute to reducing inflammation and improve dry eye disease symptoms. Neural activators like varenicline also offer an innovative strategy by improving tear film endogenous production.

In second place, mucin secretagogues have appeared as new therapeutic agents, stimulating mucin secretion that strengthens tear film stability and helps repair corneal harm. Mucolytics like N-acetylcysteine also play a role in handling dry eye disease by reducing the viscosity of abnormal tear film —usually associated with Sjögren syndrome— and thus promoting more healthy tear production. Although its lack of availability in a convenient form and potential side effects limit its generalized use, its antioxidative attributes offer significant benefits. In short, dry eye management is an intricate process that requires a variety of pharmacological interventions aimed at many aspects of disease physiopathology, and these treatment strategies complement dry eye treatment beyond lubrication.

Synopsis

Current information

- Different drugs with multiple action mechanisms are relevant in treating dry eye disease.
- It is important to know which ones are the most suited for each case and decide their use while also taking into account their side effects.
- Judge the use of new products (topical and systemic) or new uses of existing products; be cautious when faced with a lack of scientific evidence.

Future needs

- Develop greater clinical experience with new immunomodulators, secretagogues, and topical growth factors.
- Include economic impact and patient opinion-satisfaction surveys in studies evaluating new pharmacological products.

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11

LUBOS DIAGNOSTIC-THERAPEUTIC ALGORITHM

Following a review of the scientific evidence presented in questions one through ten, and after discussing the different topics, the LUBOS panel members reached a consensus in order to elaborate and offer their peers concepts aimed at practical issues that are part of the daily clinical practice of ophthalmologists in Latin America, hoping that the present material can be evaluated for possible inclusion and adapted to other parts of the world.

Finally, we will now give an overview of the LUBOS products that were elaborated following the development of the present consensus:

1. LUBOS definition of dry eye.
2. LUBOS diagnostic algorithm.
3. LUBOS severity levels.
4. LUBOS dry eye therapeutic algorithm.

1. LUBOS definition of dry eye

We will highlight the LUBOS definitions that allow us to understand and think about dry eye disease in the current context as a complex multi factor pathology connected to and influenced by our body, as well as the environment and our lifestyle.

LUBOS DEFINITION

- • Dry eye is a multi-factor disease affecting the ocular surface and characterized by an alteration in tear film homeostasis.
- • It can be classified as evaporative, aqueous-deficient, or mixed.
- • It is accompanied by different degrees of ocular and visual symptoms and/or signs in which tear film instability and factors like hyperosmolarity, inflammation, tissular damage, and sensorineural abnormalities play an important role in its etiology.
- • Lifestyle and environmental conditions are elements that can trigger or aggravate the disease.

2. LUBOS diagnostic algorithm

The LUBOS group developed a diagnostic algorithm with the goal of offering its peers a practical tool to identify people with dry eye. There are four methods we need to apply (Fig. 1).

a. Medical history

It is the first stage to acquire and register relevant information, using anamnesis to inquire about dry eye risk factors, remembering, for instance, the importance of asking questions regarding medical background and medication use, as well as patient lifestyle and diet.

b. Questionnaire

This point is related to using a psychometric tool to obtain relevant information on patient perception. As previously mentioned, the questionnaires set to be employed must be internationally validated, like the OSDI questionnaire, for instance.

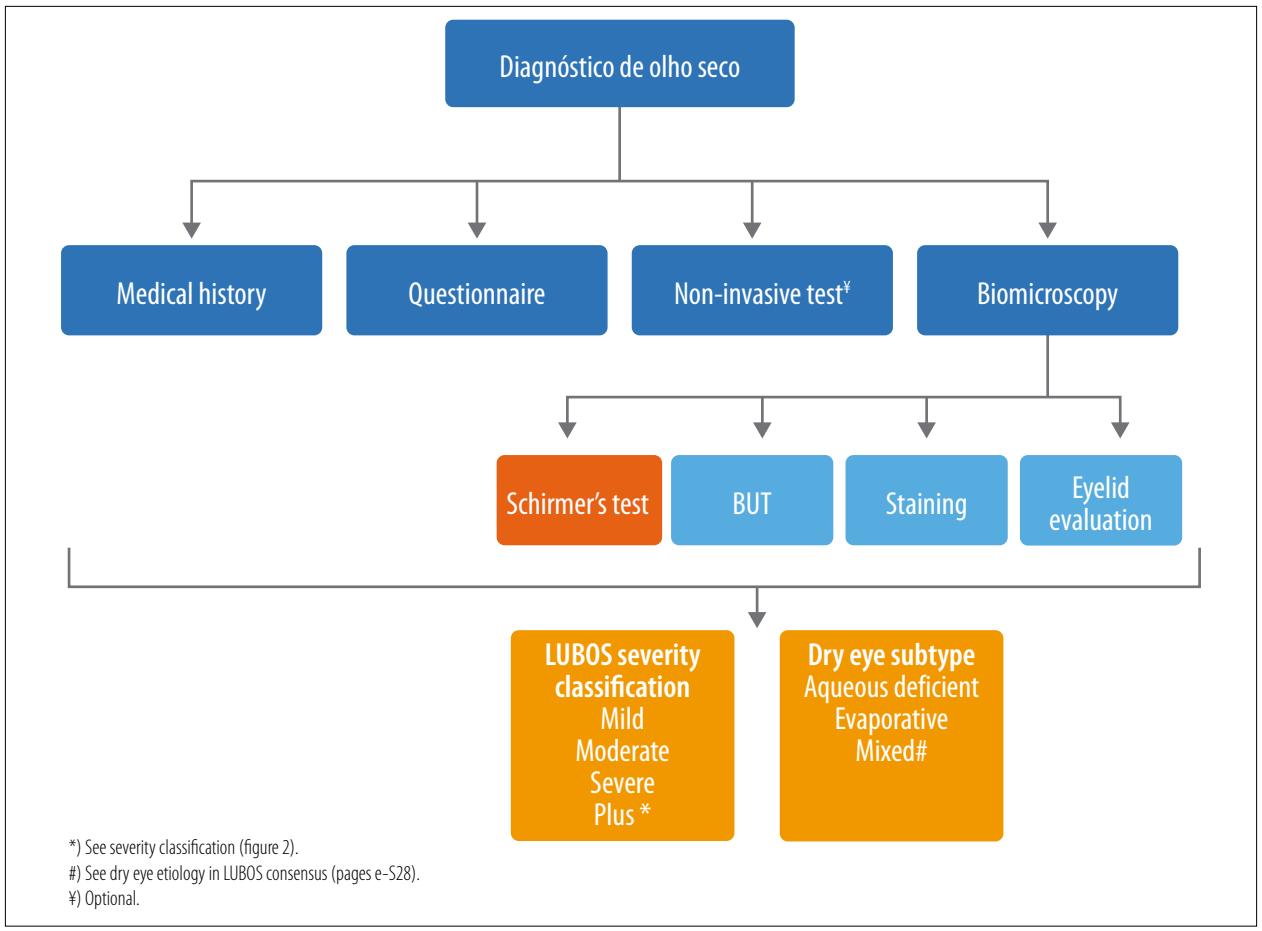

Figura 1. Algoritmo diagnóstico LUBOS de olho seco (adaptado de Rodríguez-García *et al.*[1]).

c. Non-invasive tests

They are considered optional and complimentary, although it is true that they can be good support tools for adding objective reproducible information through images and video. Considering the great advances in medical technology and the surge of artificial intelligence, this point of the LUBOS algorithm could be modified over time and become more relevant.

d. Biomicroscopy

Biomicroscopical exploration of the ocular surface remains a fundamental tool to obtain information that allows dry eye diagnosing and staging, done specifically through four tests: Schirmer's test, tear break-up time (BUT), staining, and eyelid evaluation.

When conducting eyelid evaluation, the following must be observed: thickness increase, superior quadrant rounding, irregularities, presence of telangiectasias, madarosis, bad eyelash position, lack of blinking apposition, anterior inflammation and secretion (scabs, flakes, collarettes), changes in mucocutaneous binding (antero or retro displacement, striation, keratinization, and mucous absorption), Marx line posterior migration.

After applying the four tools previously mentioned, the LUBOS severity classification can be used and the dry eye subtypes can be determined, as we can see in figure 2.

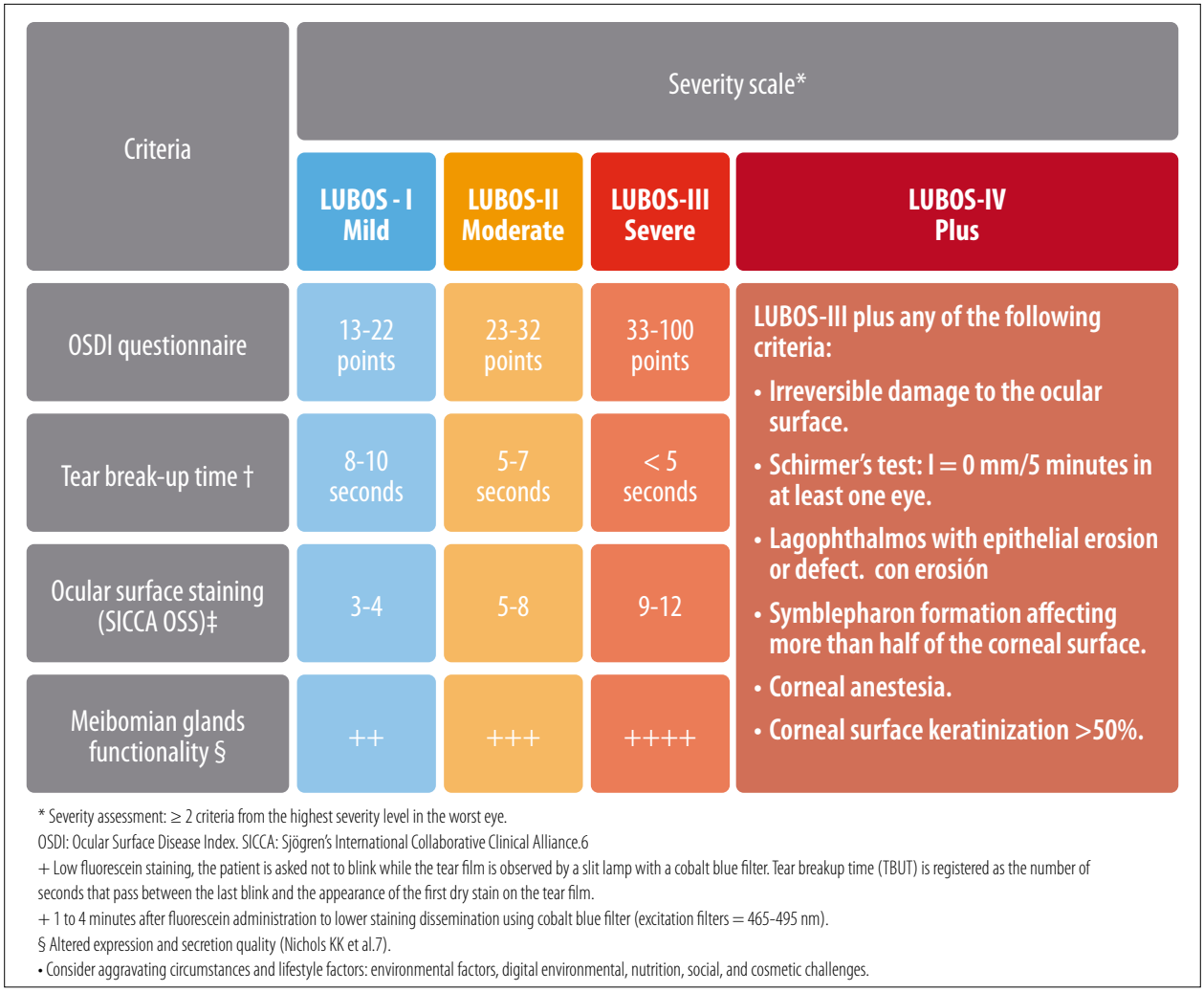

Figura 2. Níveis de gravidade LUBOS da doença do olho seco (adaptado de Rodríguez García *et al.*[1]).

3. LUBOS severity levels

Here we will show the figure presented in the chapter corresponding to figure 6 in order for this information to be visibly accessible to the rest of the products developed by the LUBOS consensus.

4. LUBOS dry eye therapeutic algorithm

Once the patient has been diagnosed, a therapeutic algorithm is presented, which takes into account current available treatment options (Fig. 3). Recommended treatments, as well as the complimentary connections connected to the different stages, are identified, as we see in the top part of the algorithm, which in turn is associated with the LUBOS severity level, presented in the lower part of the scheme. The importance of patient education, lubricant use, and palpebral care —in their different stages and phases— is something that should be pointed out for all cases.

Final conclusion

The present work evaluated the issue of dry eye and ocular lubricants, as well as revising topics connected to tear film composition, epidemiological data, economic aspects related to dry eye,

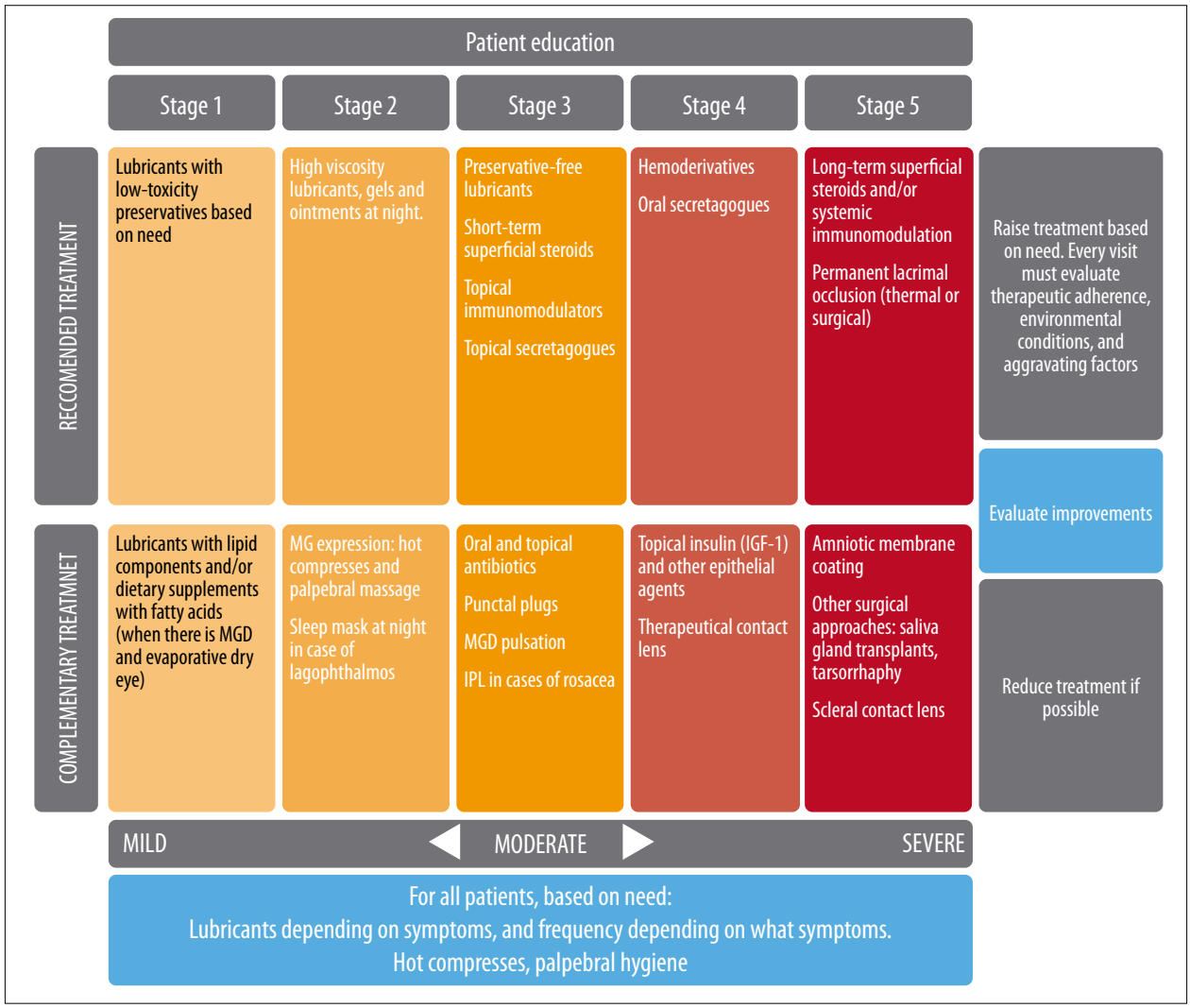

Figure 3. Management according to LUBOS dry eye severity classification (adapted from: Rodríguez-García A *et al.*[1]).

and therapeutic options beyond ocular lubricants. After revising available scientific evidence, a diagnostic-therapeutic algorithm considering dry eye severity levels and different principles and characteristics of artificial tear ocular formulations was developed by consensus.

Considering that all issues treated in this work are developing in a dynamic fashion, we used a methodology that is reproducible over time which we hope will allow us to reevaluate concepts of the current consensus, as well as compare and replicate it.

Reference

1. Rodríguez-García A, Babayán-Sosa A, Ramírez-Miranda A *et al.* A Practical approach to severity classification and treatment of dry eye disease: a proposal from the Mexican dry eye disease expert panel. *Clin Ophthalmol* 2022; 16: 1331-1355.

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