



XLIX CONGRESSO REGIONALE S.O.Si.

PRESIDENTE: PROF. PASQUALE ARAGONA

10-12 APRILE 2025

UNAHOTELS - NAXOS BEACH SICILIA (ME)



University of Messina

Dep. of Biomedical Sciences

EYE CLINIC

SCHOOL OF OPHTHALMOLOGY

EXCELLENCE REGIONAL CENTER FOR OCULAR SURFACE DISORDERS

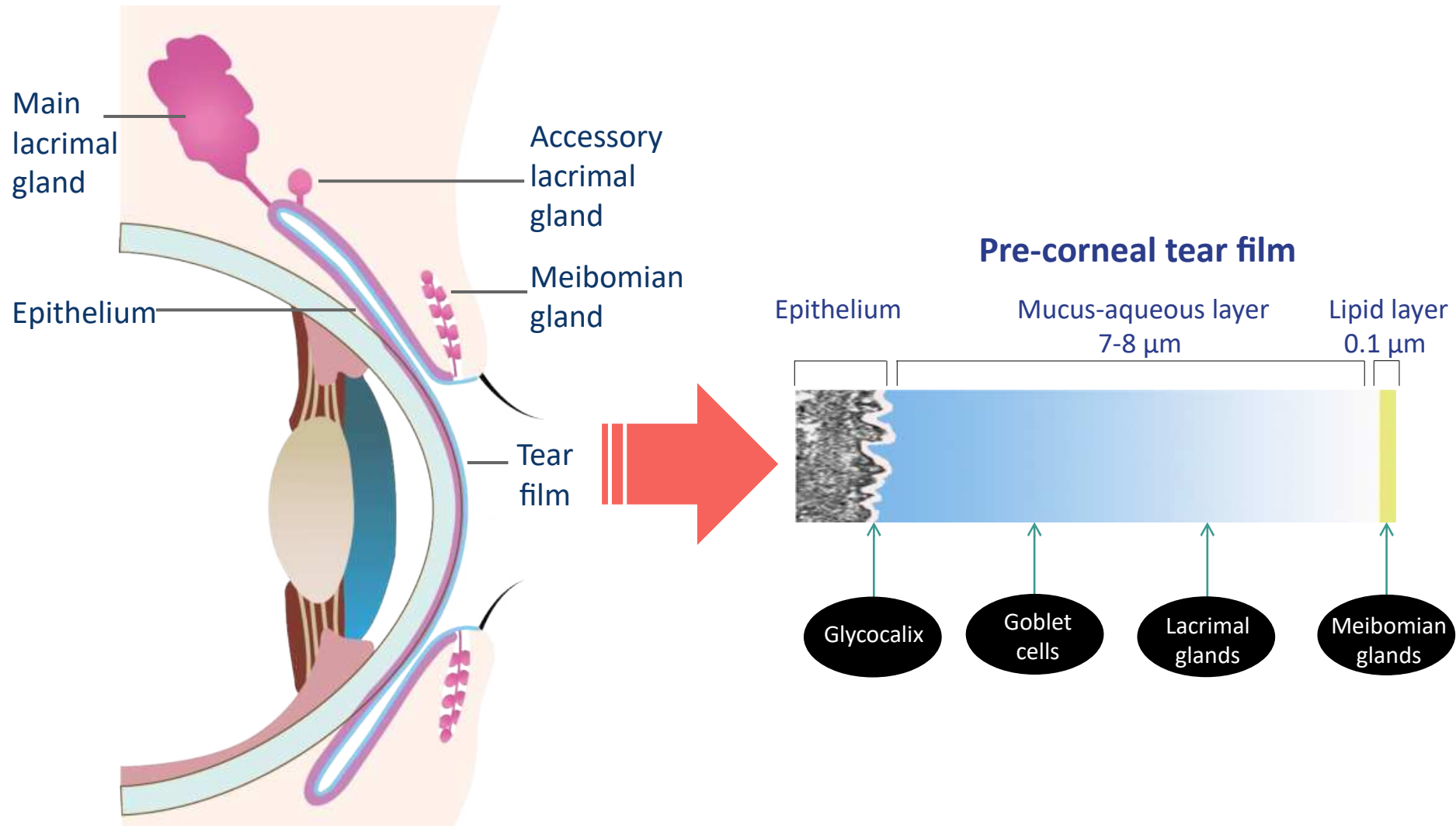
EXCELLENCE REGIONAL CENTER FOR RARE DISEASES IN OPHTHALMOLOGY

Head: Prof. Pasquale Aragona

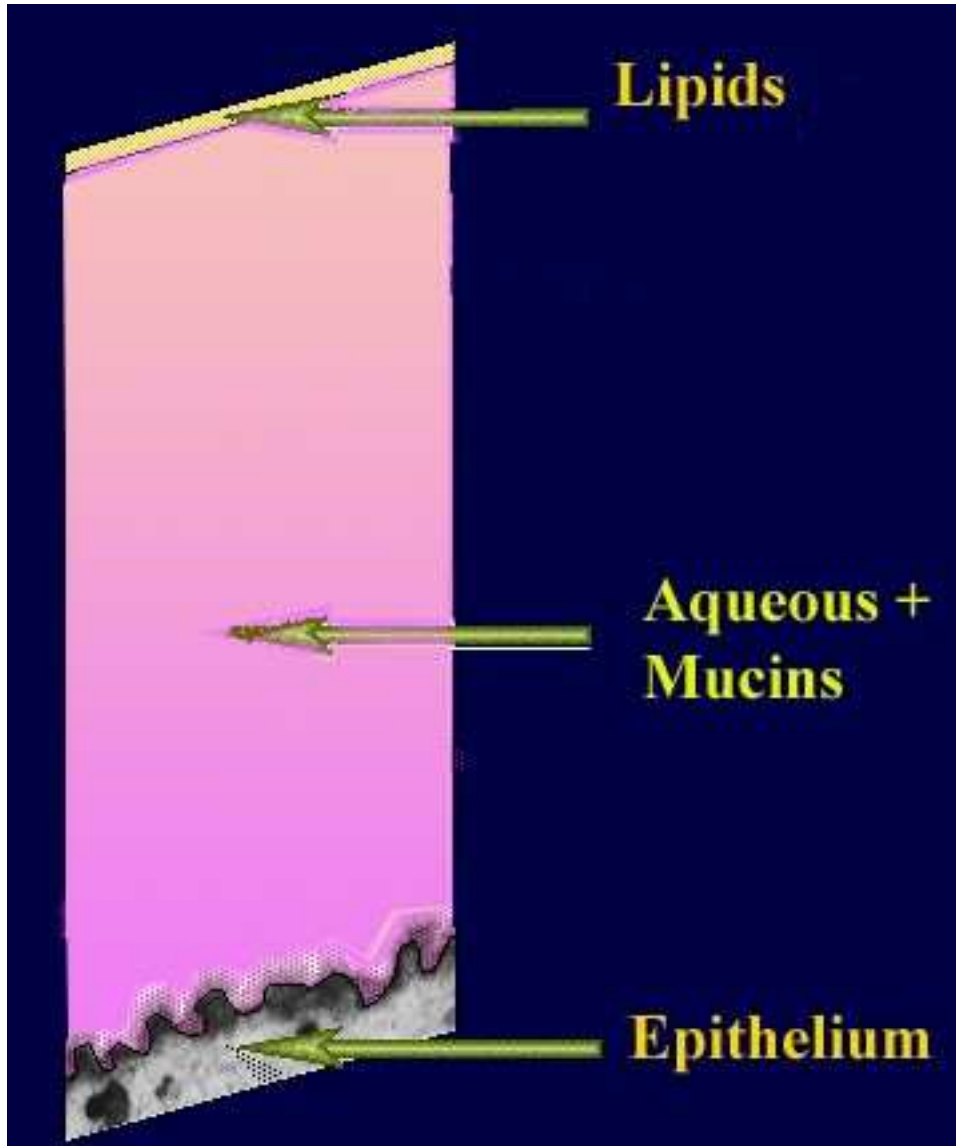
IL RUOLO DELLA PARAINFIAMMAZIONE NELLE MALATTIE DELLA SUPERFICIE OCULARE

Elisa Imelde Postorino

The ocular surface system



THE LIPID LAYER OF THE TEAR FILM



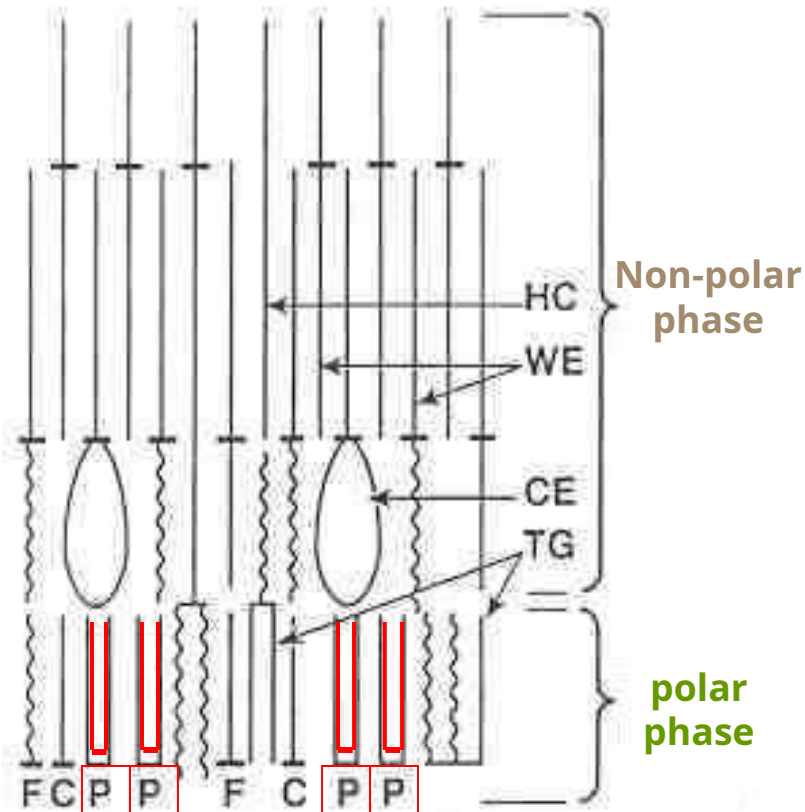
Lipid film thickness varies (40-100 nm) according to lipids produced by MG and to the amount of lipids present on lid margins.

In the tear film are present about 9 mcg of lipids.

On the lid margin the lipid bulk is of about 300 mcg.

The Lipid Layer of the Tear Film

Air-lipid interface



Aqueous-mucin interface

The chief lipids in the meibomian secretions are apolar lipids (ca. 60%).

The remainder includes an important contribution of polar lipids small amounts of free fatty acids, sterol esters, and free sterols.

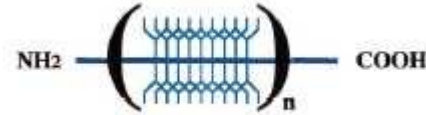
Polar phospholipids form the interface between the aqueous phase of the tear film and the

Illustration from
McAlley & Shine 1998

TEAR FILM MUCINS

SOLUBLE

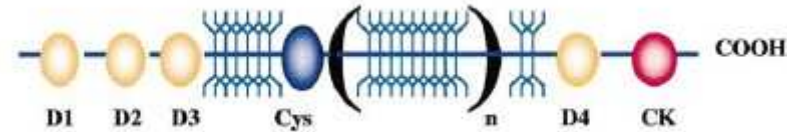
MUC7, MUC9



SECRETORY

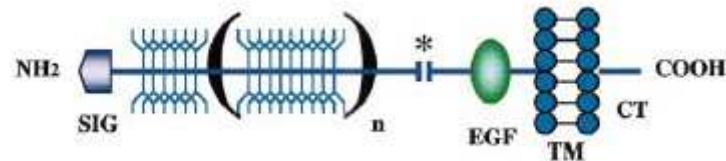
GEL
FORMING

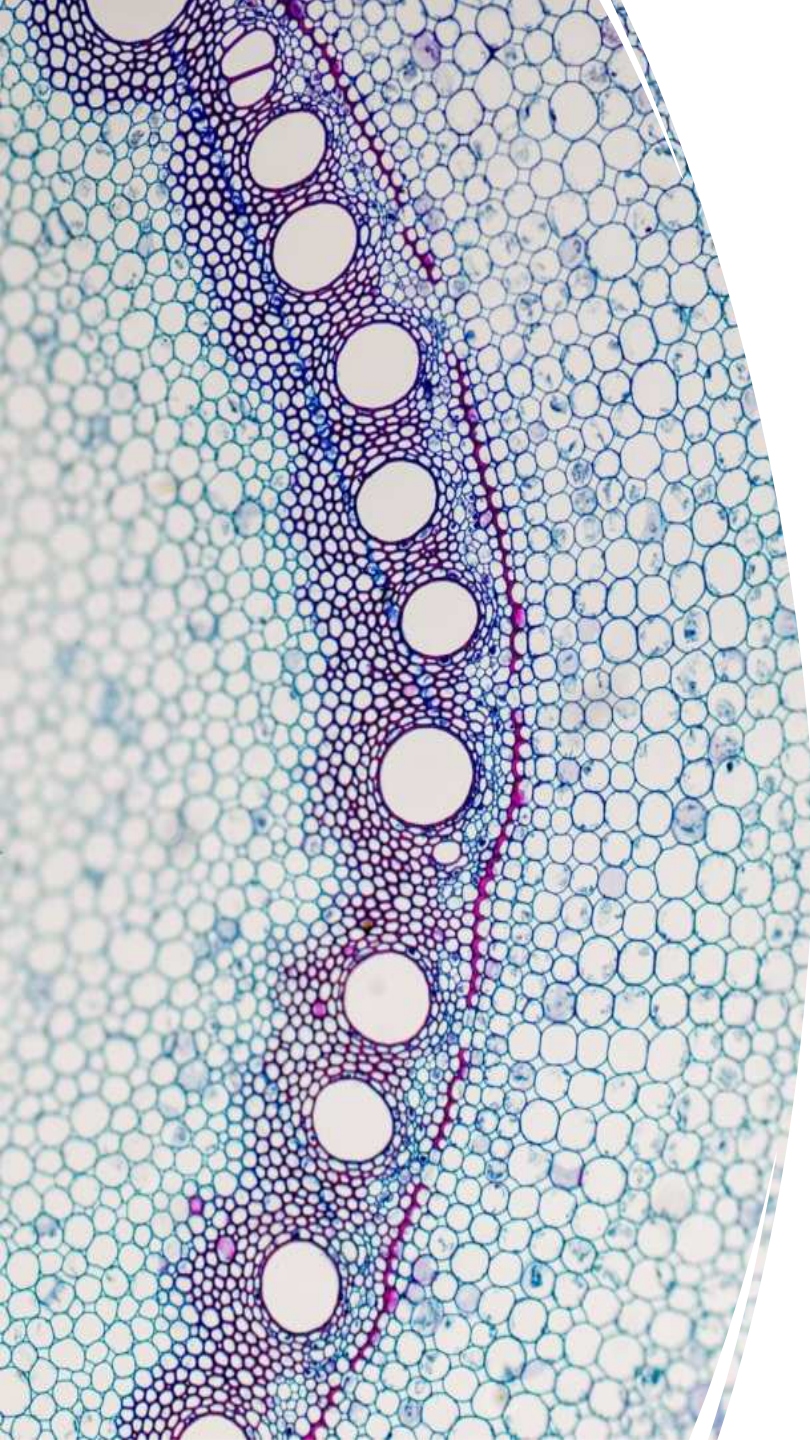
MUC2,
MUC5AC,
MUC5B, MUC6



TRANS-MEMBRANE

MUC1, MUC3A, MUC3B, MUC4,
MUC12, MUC13, MUC16





Functions of Tear Film Mucins

- Hydration of the ocular surface
- Lubrication and anti-adhesive properties between the cells of the ocular surface and conjunctiva during the blink
- Contribute to the epithelial barrier against infections
- Gel-forming mucins clear foreign bodies and pathogens from the ocular surface by trapping them in the mucus layer and, with the help of blinking, move them towards the nasolacrimal duct

Tear Film Proteins (Physiological Constituents)

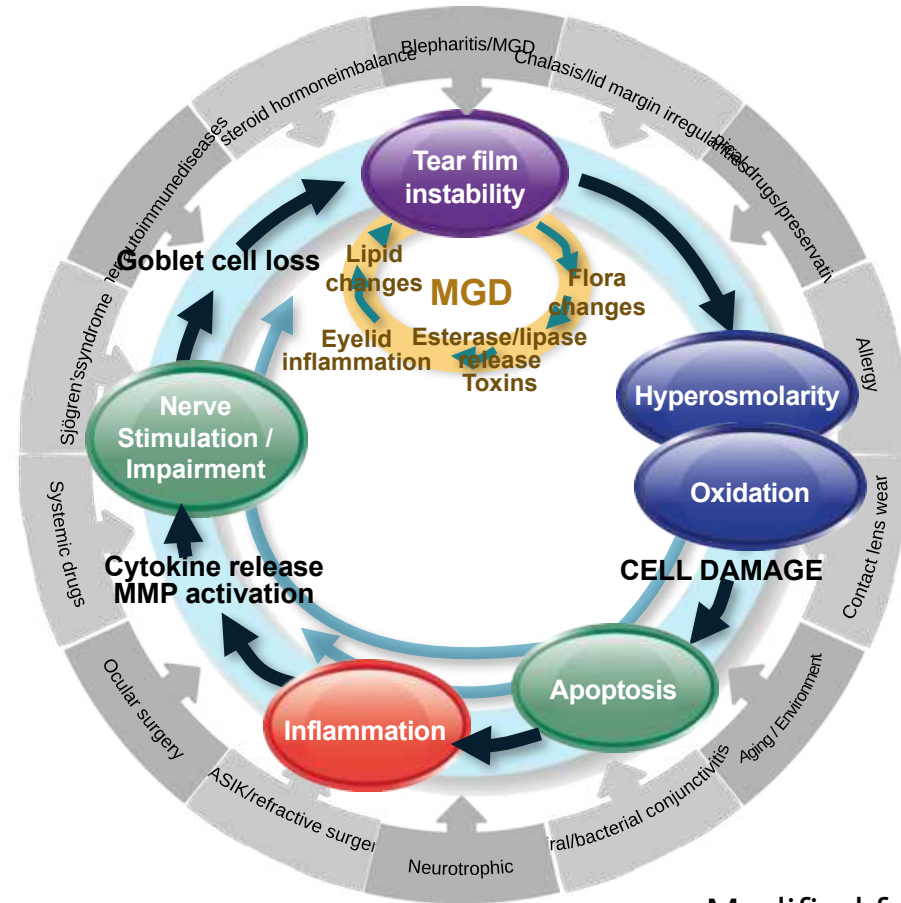
DEFENSIVE ACTIVITY

- Lysozyme
- Lactoferrin
- S-IgA
- Igs

STRUCTURAL ACTIVITY

- Lipocalins
(lipid/aqueous
interaction)
- Glycoproteins

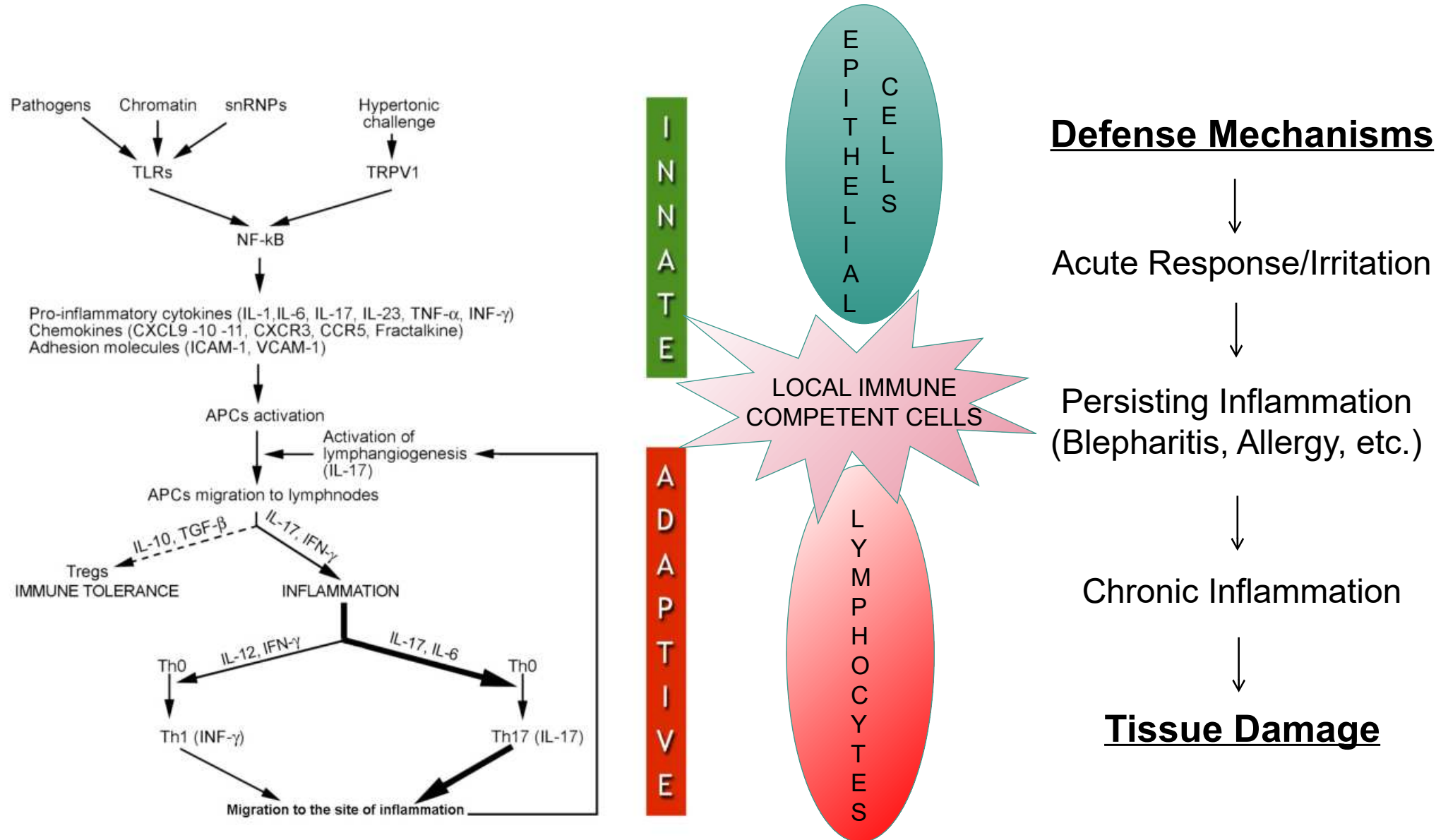
Key Mechanisms of Ocular Surface Damage



Modified from: Baudouin C, Aragona P et al. *Ocul Surf* 2013

INFLAMMATION

FROM DEFENSE TO TISSUE DAMAGE



Ocular Surface Inflammation Pathogenesis

- Allergic
- Neurotrophic
- Autoimmune
- Dysfunctional
- Iatrogenic



**DRY EYE
DISEASE**

Allergic tears biomarkers

- IL-4, IL-5 and IL-13 (mast cells, basophils, activated T cells, eosinophils/tears)
- Eotaxin-2 Protein (Eosinophils)
- Eosinophil Cationic Protein (Eosinophils)
- IgE (B-lymphocytes)
- Histamine (Mast-cells)
- Triptase and Chimase (Mast-cells)
- Acidic Mammalian Chitinase (Epithelial cells)

Suarez-Cortez T, et al. *Exp Eye Res* 2022
Musumeci M, et al. *Cornea* 2008

Dre eye diseases

Tears biomarkers

- MMP9 (Produced Epithelial cells)
- TG2 (Produced Epithelial cells)
- IL-1 β (macrophages, monocytes, fibroblasts, and dendritic cells/tears)
- MUC5AC (Goblet cells)
- Prolactin Inducible Protein (PIP) (lacrimal gland)
- Prolin-rich Lacrimal Proteins 1 and 4 (PRL-1 and 4) (Goblet and lacrimal gland)
- S100A8 and A9 (S100 calcium-binding protein family) (granulocytes, monocytes and tears)
- Acidic Mammalian Chitinase (Epithelial cells)

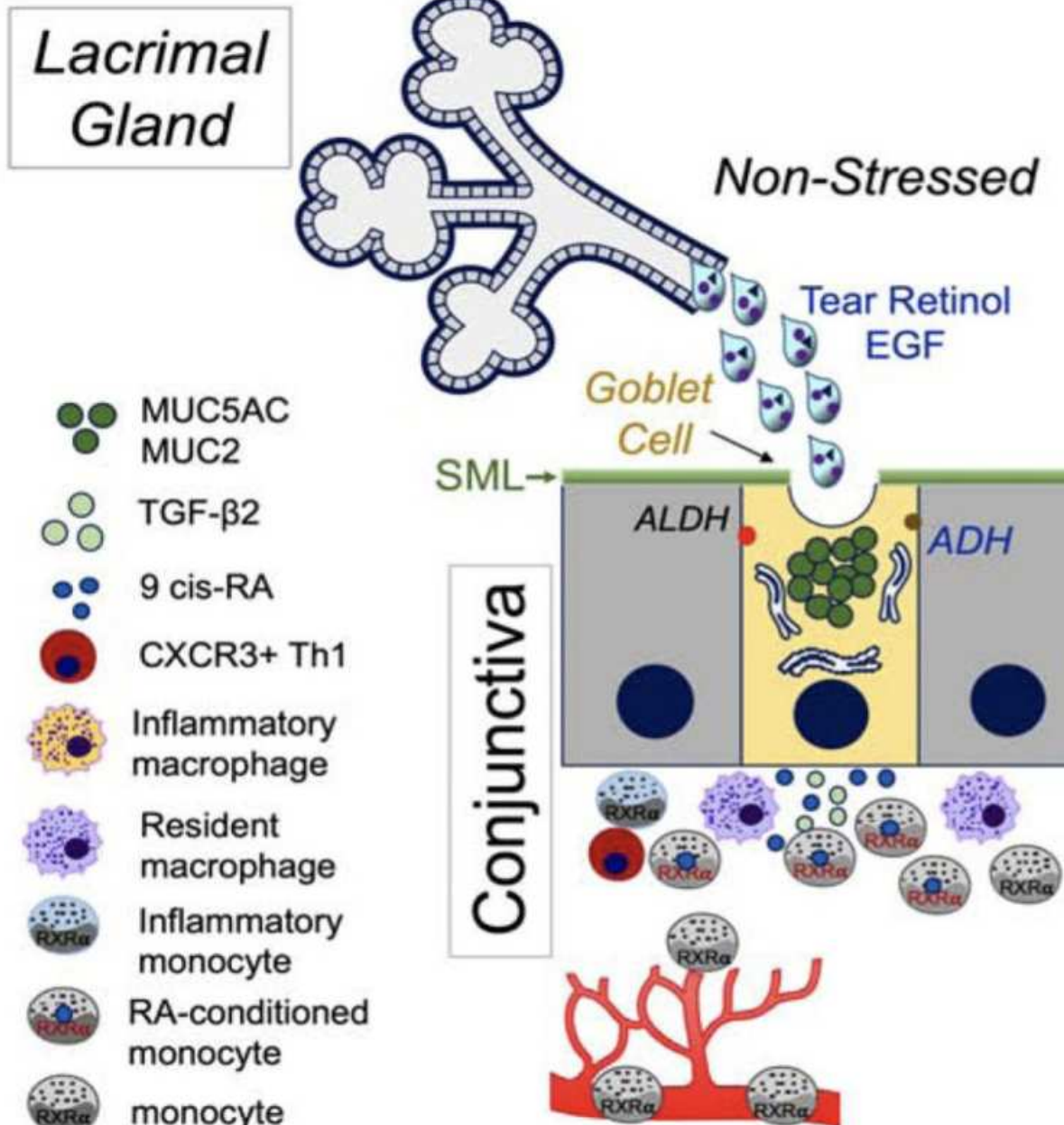
Aragona P, et al. *Ophthalmology* 2013; Suarez-Cortez T, et al. *Exp Eye Res* 2022; Musumeci M, et al. *Cornea* 2008

EPITHELIUM

Altered by a not adequate lubrication

Presence of Squamous Metaplasia with **goblet cells loss** and **epithelial flattening**

Goblet cells significantly participate in inflammation control, through the mechanism of tolerance of the microbial flora



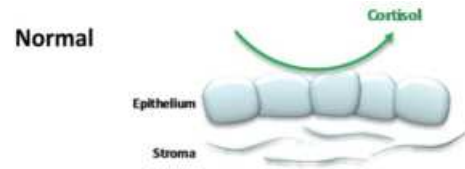
Alam J, et al. *Ocul Surf* 2020
 Rescigno M, et al. *Curr Opin Immunol* 2008

PARA-INFLAMMATION IN OS HEALTH AND DISEASE

- Between basal homeostasis and inflammation there is a condition called PARA-INFLAMMATION
- This is an adaptive response of the immune system to low levels of tissue stress (i.e. a low-degree of “dangerous” stimuli), such as environmental changes like mild pollution of the air, where oxidative stress accumulates bit by bit for months or years.
- Para-inflammation aims to maintain (or re-set) the homeostasis of the tissue and restore its functionality
- A well-controlled para-inflammation may, therefore, be beneficial while a dysregulated para-inflammation, detrimental.

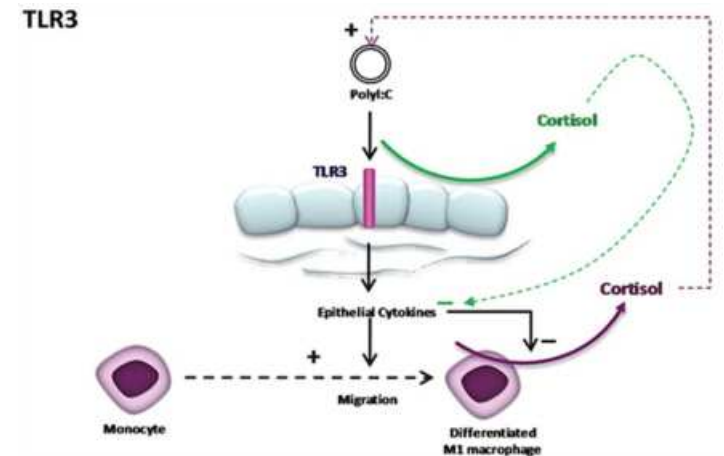
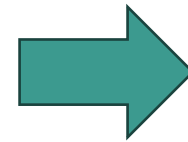
What happens on the ocular surface?

Insults or stress of minimal entity (e.g. dust, wind) generate a functional parainflammation that is normally controlled by the release of cortisol by the epithelia.

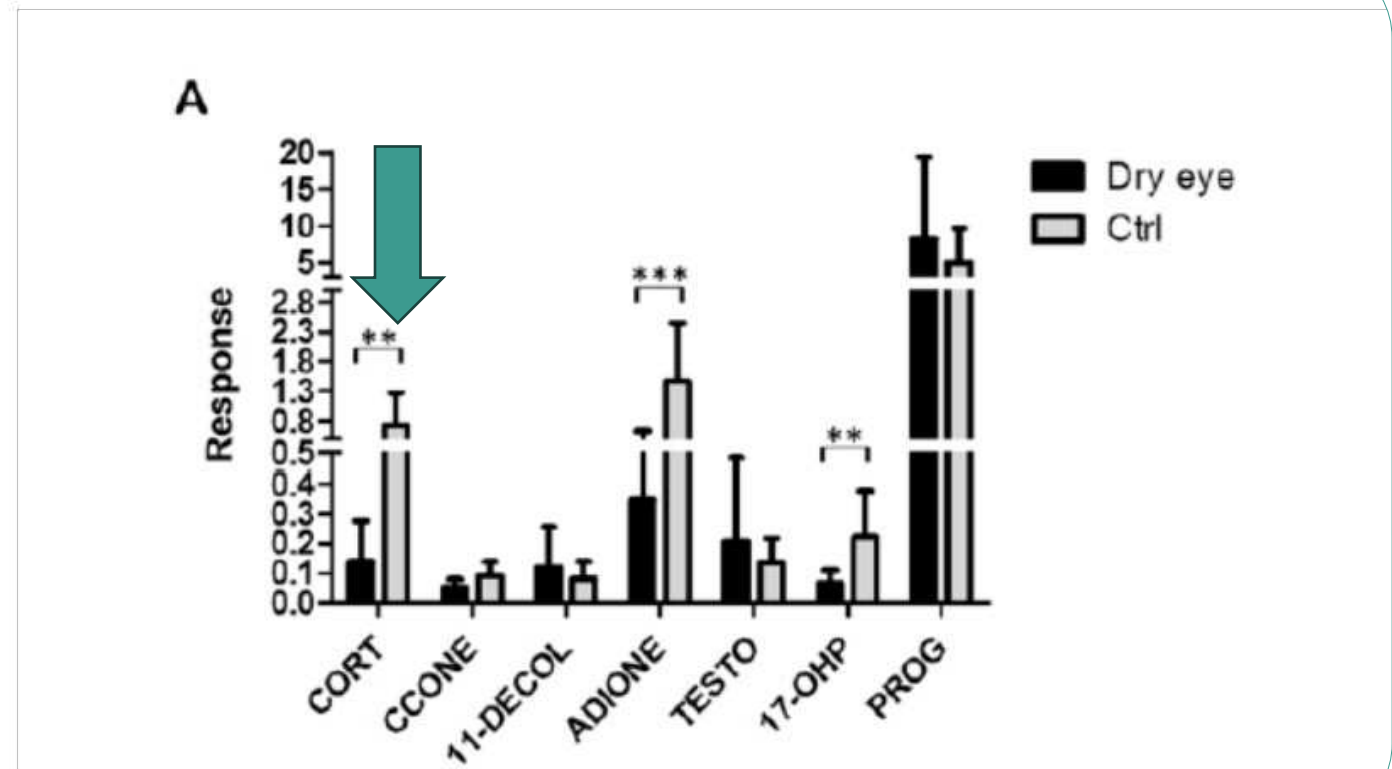


The release of cortisol with anti-inflammatory action restores homeostasis

With age or following significant stimuli, this innate ability to restore homeostasis is lost because cortisol synthesis is blocked and (dysfunctional) parainflammation with the release of inflammatory markers takes over



In dry eye, in fact, endogenous tear cortisol is significantly reduced



Thus the proinflammatory markers of parainflammation are no longer neutralized

1 out of 3 cataract surgery patients with no ocular surface problems before surgery develops tear dysfunction after surgery

Saudi Journal of Ophthalmology (2019) 33, 34–40

Original Article

Incidence and pattern of dry eye after cataract surgery

Saba Ishrat^{a,1}; Nitin Nema^{a,*}; S.C.L. Chandravanshi^b

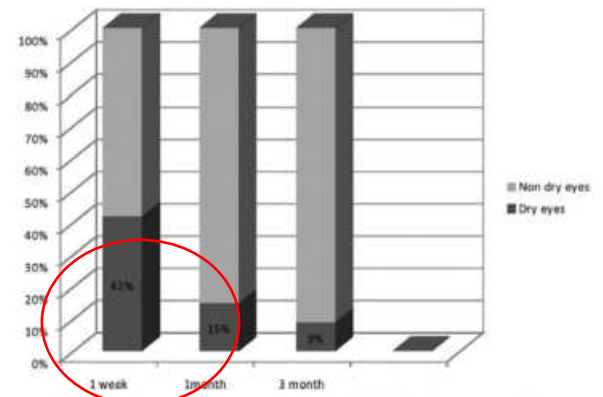


Fig. 1. Development of dry eyes at 1 week, 1 month and 3 months postoperatively.

Ophthalmol Ther (2022) 11:1309–1332
<https://doi.org/10.1007/s40123-022-00513-y>

REVIEW

Prevalence and Characteristics of Dry Eye Disease After Cataract Surgery: A Systematic Review and Meta-Analysis

Maria Miura · Takenori Inomata · Masahiro Nakamura · Jaemyoung Sung · Ken Nagino · Akie Midorikawa-Inomata · Jun Zhu · Keiichi Fujimoto · Yuichi Okumura · Kenta Fujio · Kunihiko Hirokawa · Yasutsugu Akasaki · Mizu Kuwahara · Atsuko Eguchi · Hurramhon Shokirova · Akira Murakami

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ABSTRACT

Dry eye disease (DED) after cataract surgery is associated with various risk factors, while causing a wide range of heterogeneous symptoms including decreased quality of vision. This systematic review and meta-analysis aimed to determine the prevalence and characteristics of DED after cataract surgery. We searched PubMed and EMBASE and included studies on patients with

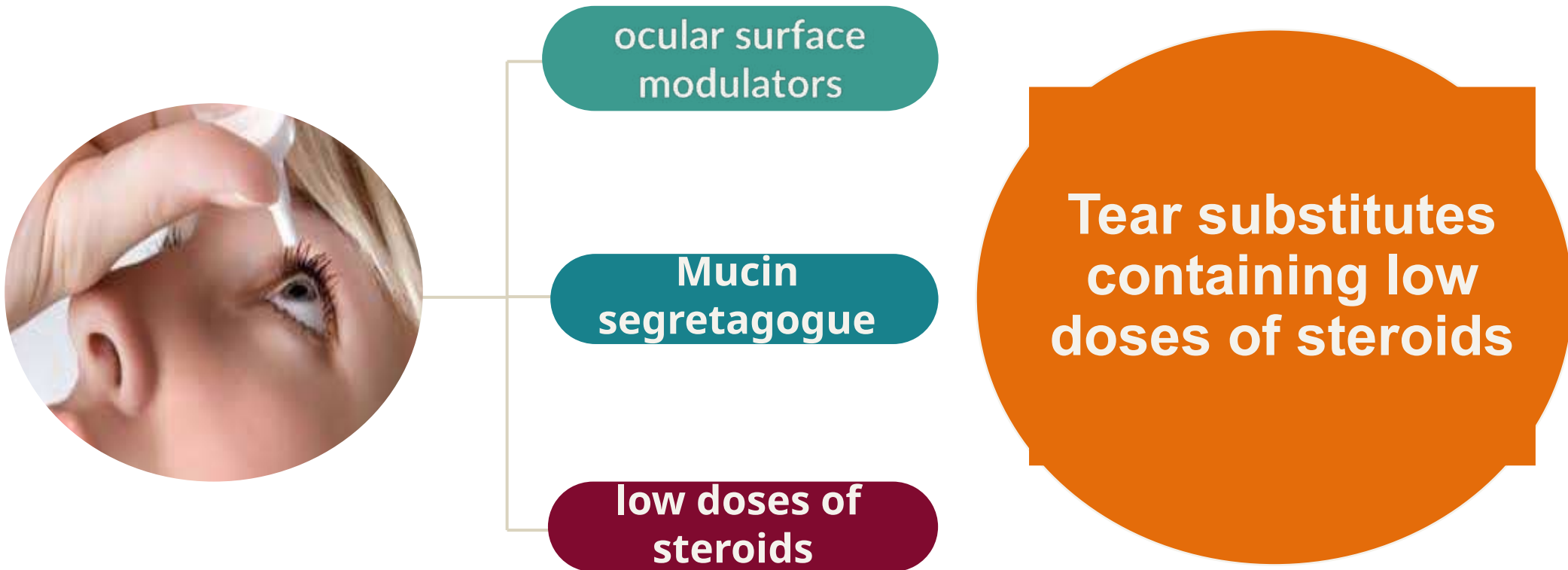
DED after cataract surgery, between January 2011 and June 2020. Study-specific estimates (DED prevalence rates after cataract surgery in patients without preexisting DED) were combined using one-group meta-analysis in a random-effects model. We included 36 studies published between 2013 and 2020. We included nine of these in the meta-analysis of DED prevalence after cataract surgery. Overall 37.4% (95% CI 22.6–52.3; 206/775) of patients without preexisting DED developed DED after cataract surgery. The risk

DISCUSSION

This is the systematic review and meta-analysis to comprehensively present DED prevalence after cataract surgery that included 775 individuals from nine articles [6, 18, 20, 23, 30, 32, 37, 50, 51]. We observed that 37.4% (95% CI 22.6–52.3; 206/775) of patients without preexisting DED developed DED postoperatively, highlighting the importance of perioperative DED management in addressing postoperative patient dissatisfaction and decreased QOV. The global DED prevalence is 5–50% [75]; inclusion of cataract surgery

Postoperative tear dysfunction that occurs after the use of antibiotic + corticosteroid combinations may be supported by dysfunctional parainflammation

Therapeutic options



Rationale for a **hyaluronic acid** and ancillary dose **hydrocortisone** based tear substitute

Hyaluronic acid 0,2%

To hydrate, integrate the tear film, promote the repair processes of the SO and provide relief from discomfort



Hydrocortisone 0,001%

To physiologically and safely integrate tear cortisol (of which it is a chemical analogue) and neutralize parainflammation

When an active ingredient (e.g. hydrocortisone) has an ancillary role, its concentration is much lower than the pharmacological one and its function is supportive of that of the main component

Hydrocortisone is the chemical analogue of tear cortisol so it is absolutely biocompatible

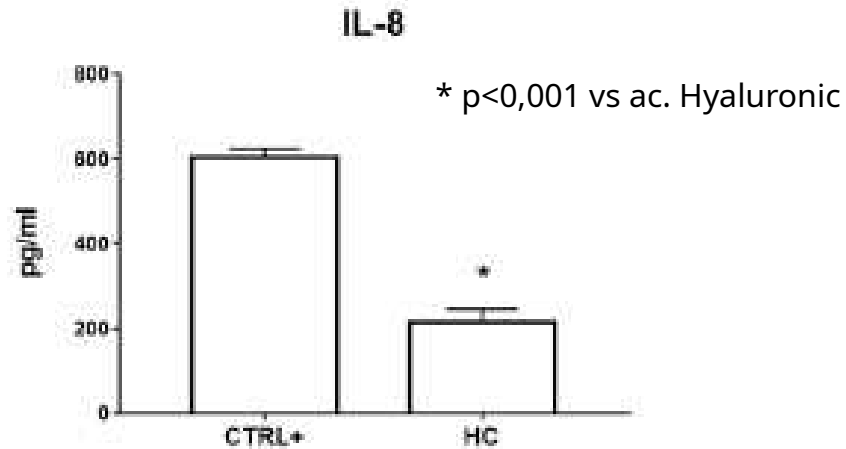
- Mild anti-inflammatory activity
- Established use in Ophthalmology
- Poor propensity to cross the corneal barrier and determine an increase in IOP
- At very low doses, it neutralizes markers of dysfunctional parainflammation



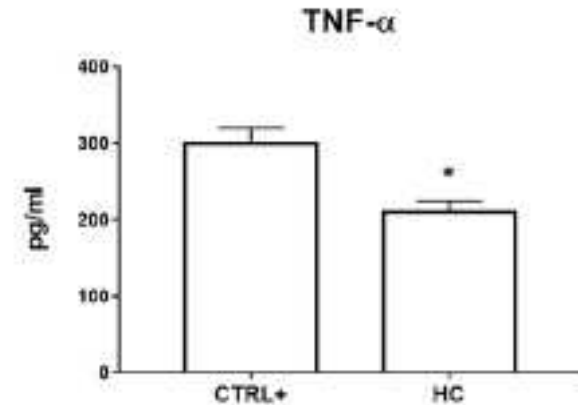
Rolando M et al. J of Ocular Pharmacology and therapeutics 33 (2017):

The tear substitute based on hyaluronic acid and low-dose hydrocortisone significantly reduces the markers of parainflammation compared to traditional tears

Effect of a hyaluronic acid-based eye drop and a standard tear, after 3 days of treatment, on inflammatory cytokines induced by an experimental in vivo model of dry eye.



CTRL= ac. Hyaluronic 0,2%



* p< 0,05 vs ac. Hyaluronic

HC= ac. Hyaluronic 0,2% e hydrocortisone 0,001%

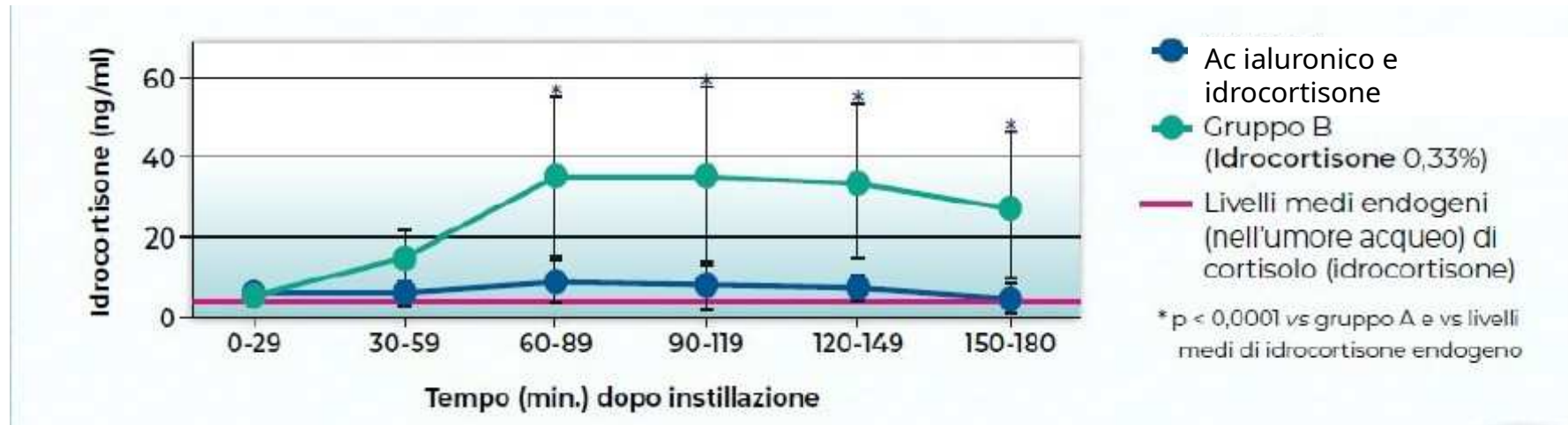
The association of hyaluronic acid and hydrocortisone controls dysfunctional parainflammation thanks to the low-dose steroid

Bucolo C, et al. Frontiers in Pharmacology 2019

The tear substitute based on hyaluronic acid and hydrocortisone is safe for IOP even after long-term treatment because it is not absorbed intraocularly

In humans, after instillation of artificial tears, **hydrocortisone levels in the aqueous humor** are physiological

Aqueous humor concentration of endogenous cortisol and hydrocortisone after random instillation of an artificial tear with hyaluronic acid and 0.001% hydrocortisone or a drug containing 0.33% hydrocortisone



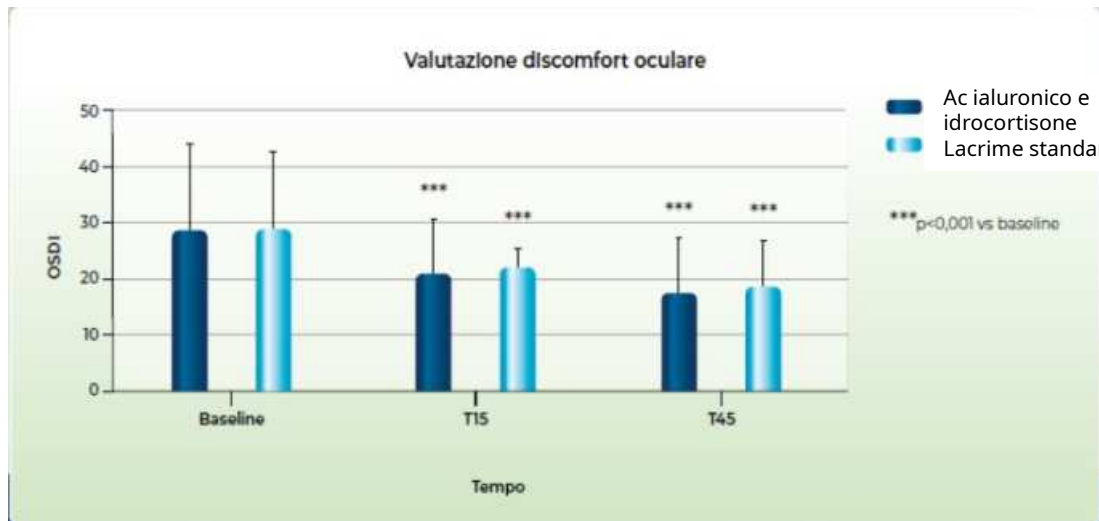
In clinical trials conducted on patients with tear dysfunction, the normal IOP value detected at baseline remains unchanged even after 6 months of treatment with the study tear at full dose

Cagini C. et al Int. J. Clin Pract. 2021; 75: e14987; Rolando M et al. Curr Eye Res 2023

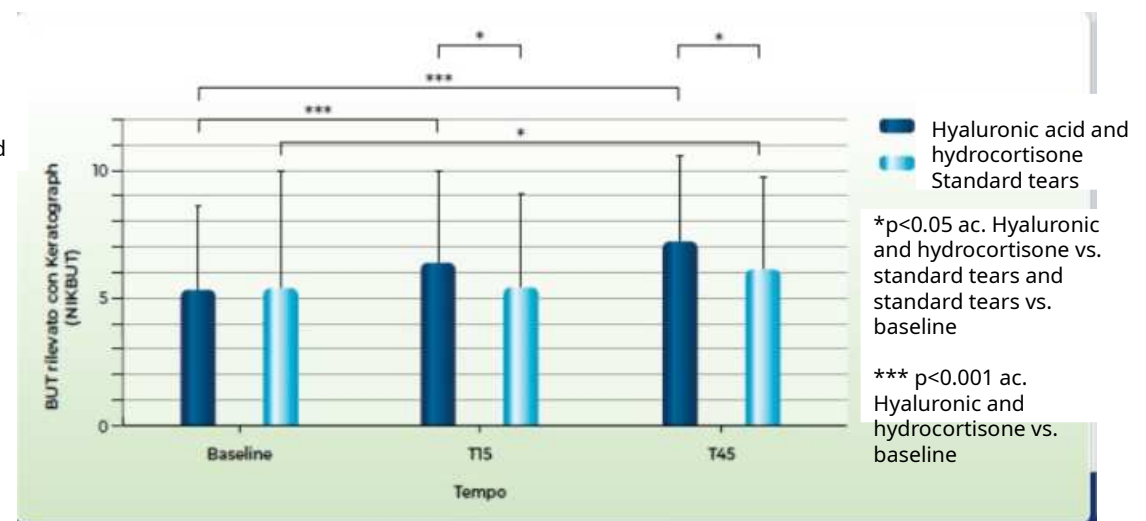
Tear dysfunctions of various nature: hyaluronic acid and hydrocortisone vs standard tears



OSDI score and tear stability (NIK BUT) detected with KERATOGRAPH. General population 155 pts
Hyaluronic Acid and Hydrocortisone vs. Standard Tears



All tears in the study significantly reduce ocular discomfort

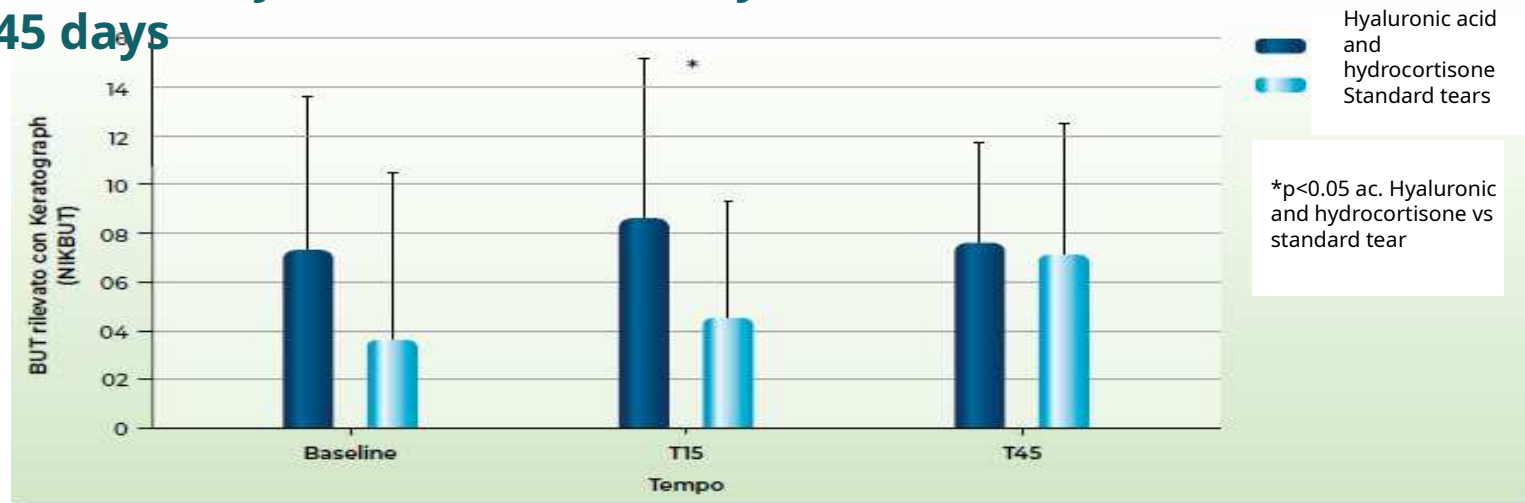


Hyaluronic acid eye drops with hydrocortisone improve tear stability more consistently and rapidly

Blepharitis Tear Dysfunction: Hyaluronic Acid and Hydrocortisone vs. Standard Tears

Ac. Ialuronico e idrocortisone vs lacrime standard

Tear stability detected with Keratograph in **the subgroup of 29 patients affected by tear dysfunction due to blepharitis**, treated with a tear based on hyaluronic acid and hydrocortisone or with standard tears for **45 days**



In patients with tear dysfunction due to blepharitis, hyaluronic acid and hydrocortisone eye drops rapidly increase BUT. Traditional tears do not provide significant benefit

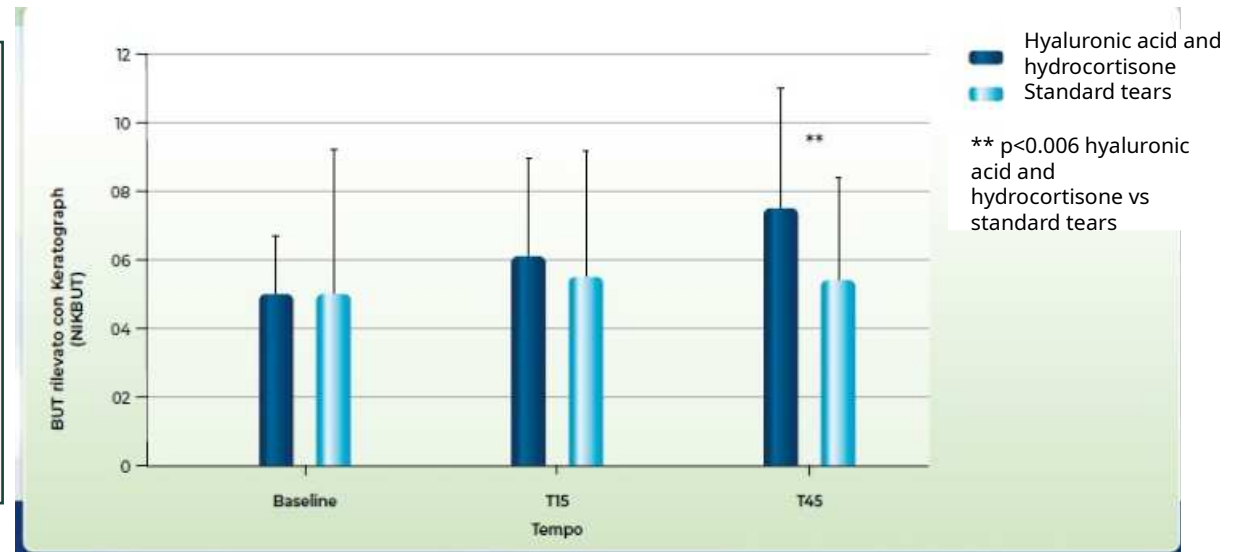
P. Fogagnolo et al. Ophthalm. & Therapy 2023

In postoperative tear dysfunction: hyaluronic acid and hydrocortisone vs. standard tears

OSDI Score and Tear Stability (NIK BUT) Detected with Keratograph in Patients with Post-Cataract Surgery Tear Dysfunction N =74 Patients

Supplementary Table 4. OSDI score in patients with post-cataract lacrimal dysfunction; comparison between groups

	Acial e idrocortisone (n=37), mean±SD	Standar group (n=37), mean±SD	p-value
Baseline	19.7±7.5	21.4±8.2	0.509
15 days	17.6±6.4	20.2±6.0	0.071
45 days	15.7±6.6	18.1±6.4	0.048



P. Fogagnolo et al. Ophthalm. & Therapy 2023

The comparison shows that the ancillary action of hydrocortisone makes the difference (after 45 days) on the discomfort and stability of the tear film

CONCLUSIONS

DED IS A COMPLEX,
MULTIFACTORIAL
DISORDER OF THE OCULAR
SURFACE

INFLAMMATION PLAYS A
RELEVANT ROLE IN ITS
PATHOGENESIS AND MAY
DERIVE FROM A
CONDITION OF
UNCONTROLLED PARA-
INFLAMMATION

IT IS OF THE UTMOST
IMPORTANCE TO BLOCK
ITS DEVELOPMENT IN
ORDER TO AVOID A STABLE
DAMAGE TO THE OCULAR
SURFACE STRUCTURES

CONCLUSIONS

To treat ocular surface pathologies supported by dysfunctional parainflammation, one must intervene in a "targeted" way

The association of the best viscous polymer (hyaluronic acid) with hydrocortisone, a chemical analogue of tear cortisol, is rational, targeted and effective

The presence of the steroid, even at low doses, expresses an added value for its direct action on the inflammatory mediators of dysfunctional parainflammation

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Grazie per l'attenzione