



**NEST**  
NEUROVISUAL SCIENCE TECHNOLOGY



# Le lacrime

***Caterina Gagliano***

XXXVI Congresso Società Oftalmologica Siciliana  
Tavola rotonda "L'occhio che invecchia: cornea e congiuntiva"  
Acireale 14-16 Aprile 2011

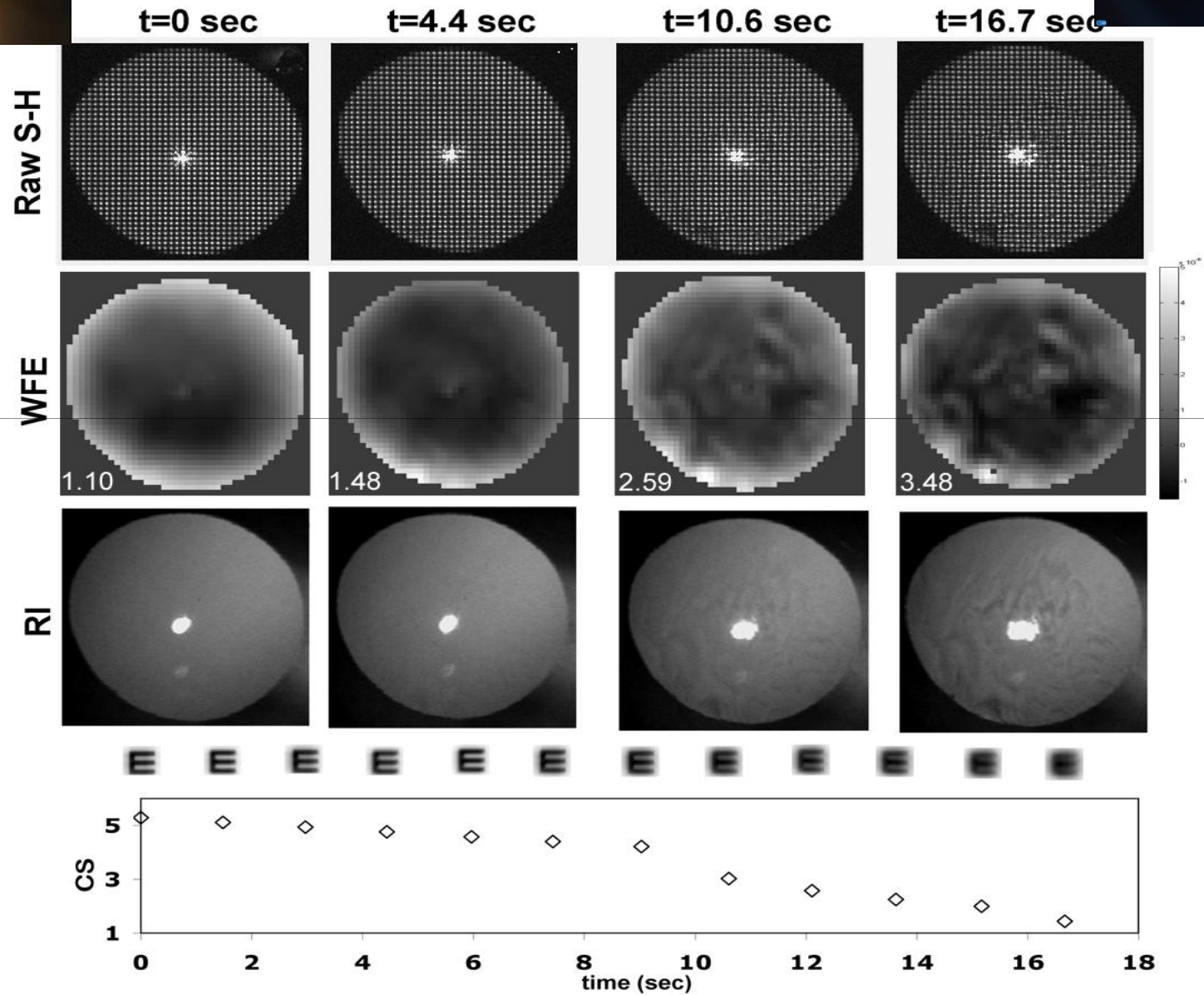


# Dry Eye WorkShop (DEWS 2007)

- International Conference on the Tear Film & Ocular Surface. Basic Science and Clinical Relevance (TFOS 2010)

- International Meibomian Gland Dysfunction Workshop: Report (March 2011)

# Effetti ottici e visivi dell'instabilità del film lacrimale



# Meccanismi coinvolti nel produrre una “blurry vision”

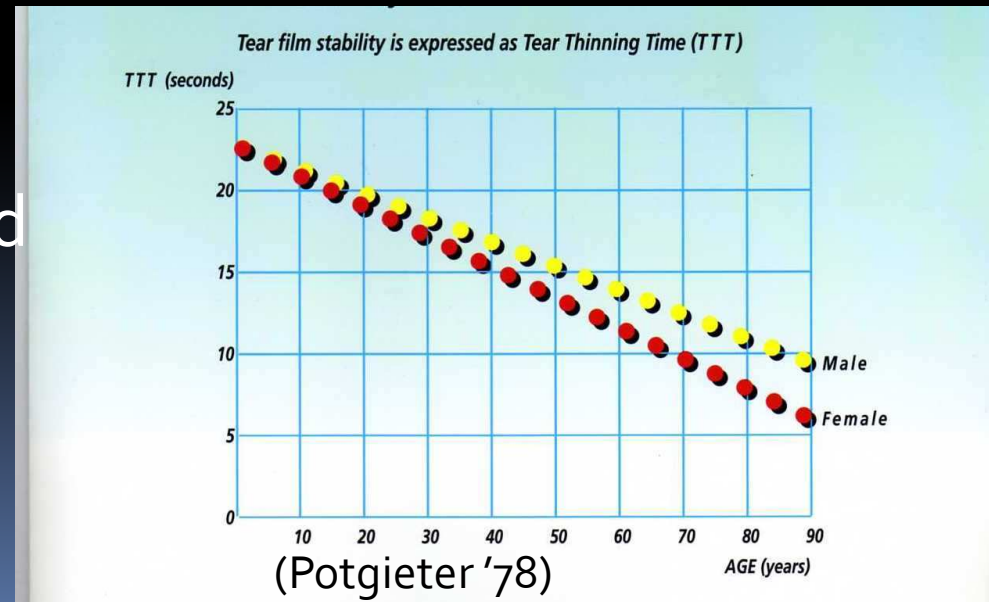
- Elevata differenza nell'indice refrattivo tra aria e film lacrimale.

- Superficie corneale irregolare che causa diffrazione della luce



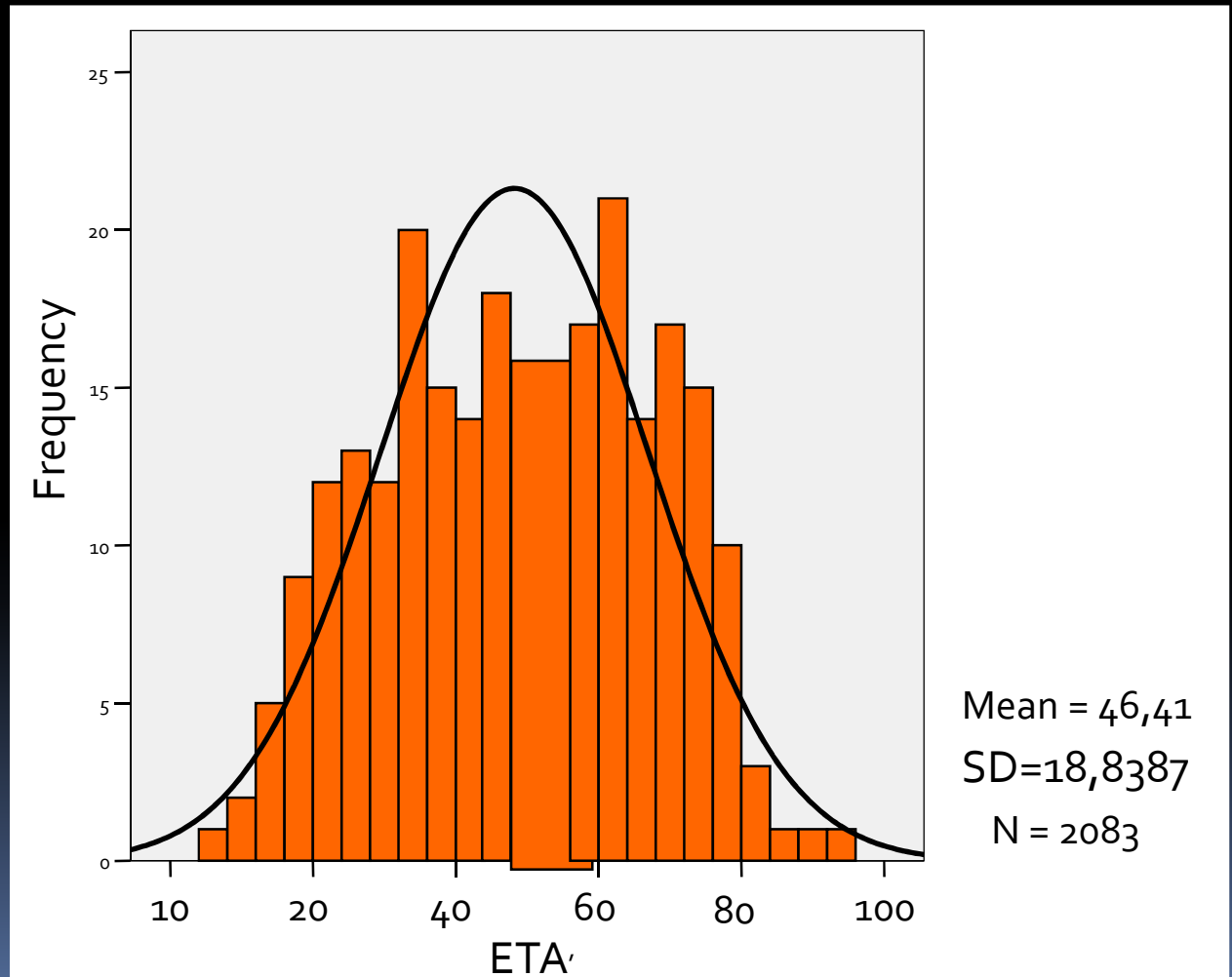
Il processo di invecchiamento è associato ad una più alta incidenza di disturbi "tear related": la riduzione della produzione di lacrime raggiunge il 90% negli "over 70" (Lemp '03)

La secrezione lacrimale, nel paziente anziano, è legata ad atrofia age-related della ghiandola lacrimale( Norn e coll. '92).





POPOLAZIONE CAMPIONE = 2083 DONNE  
PERIODO = GENNAIO 2006 – GENNAIO 2011

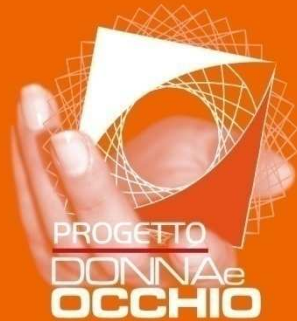






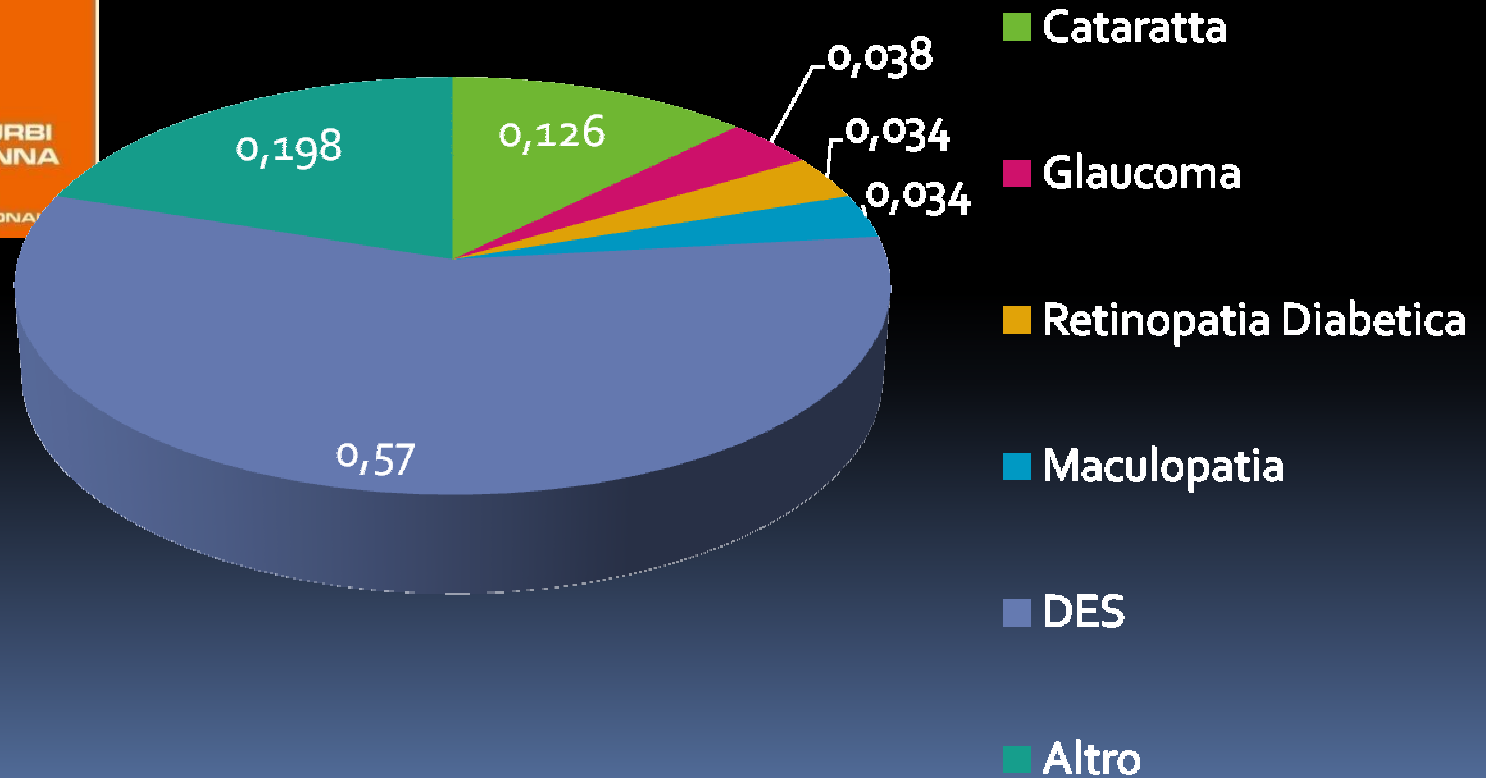
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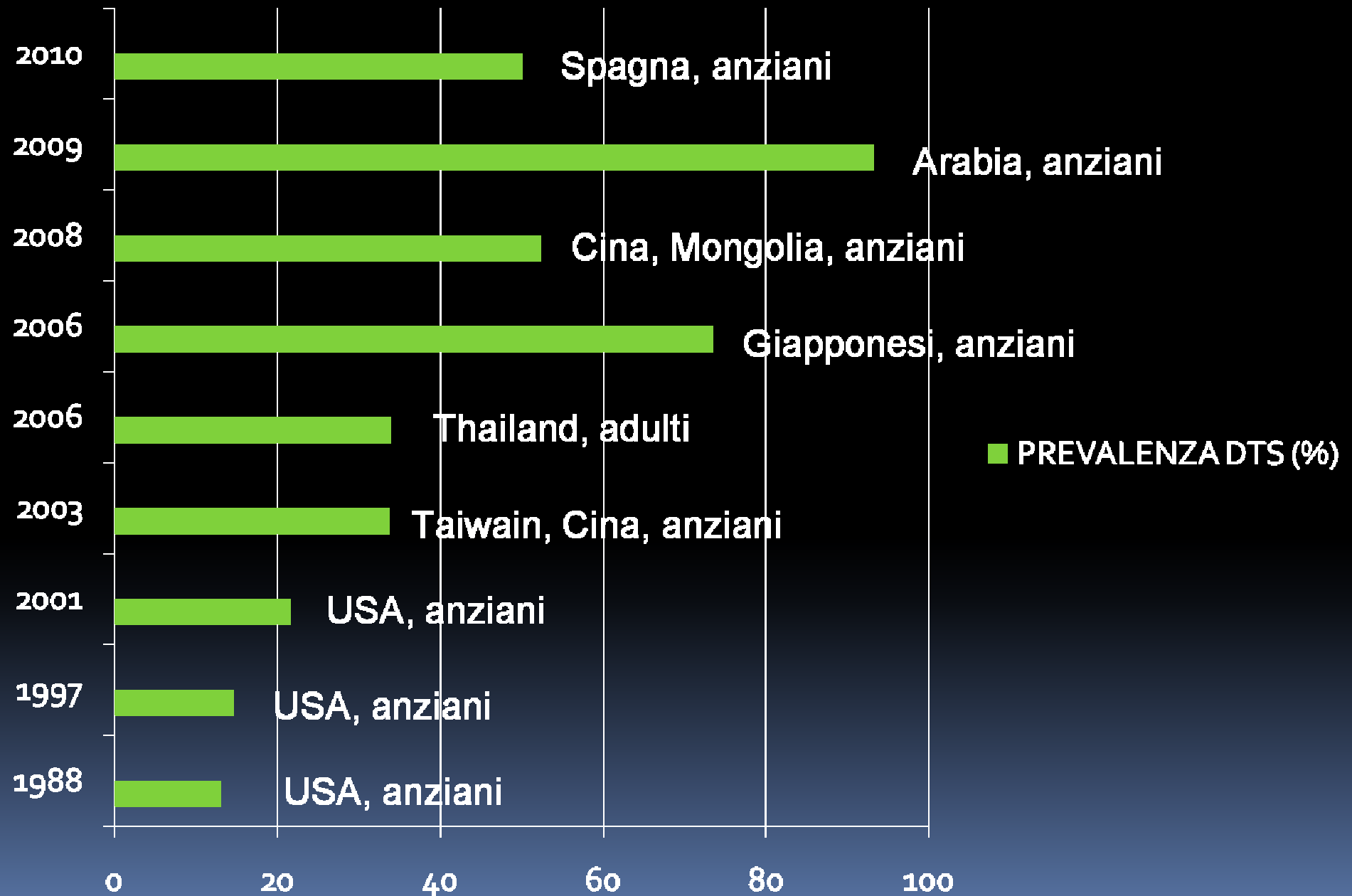
PREVENZIONE DEI DISTURBI  
NEUROVISIVI NELLA DONNA  
in stato di:  
GRAVIDANZA · MENOPAUSA  
CONTRACCEZIONE · TERAPIA ORMONALE

## TASSO DI PREVALENZA

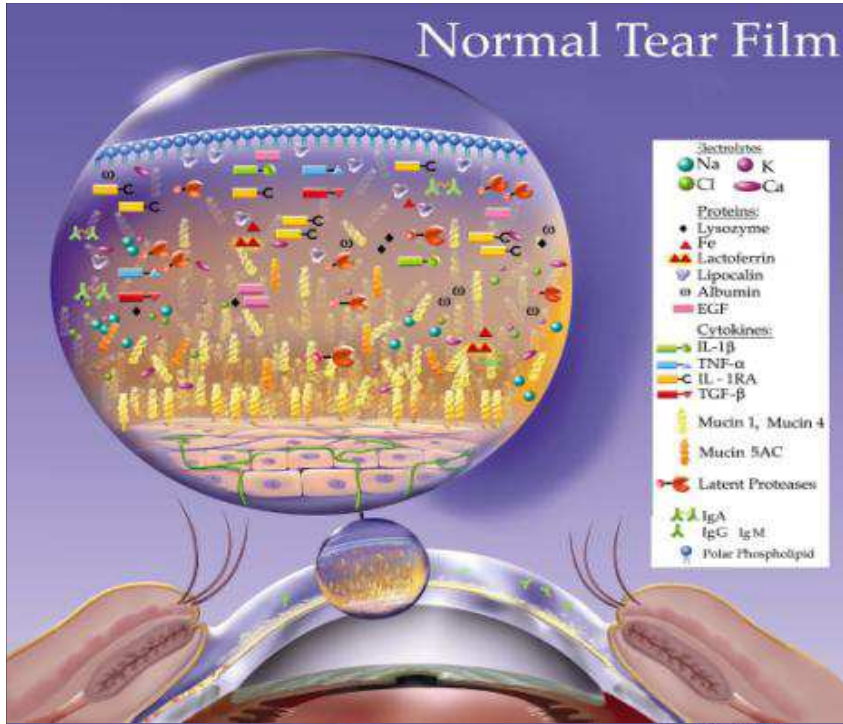




# Studi demografici DTS



## Normal Tear Film



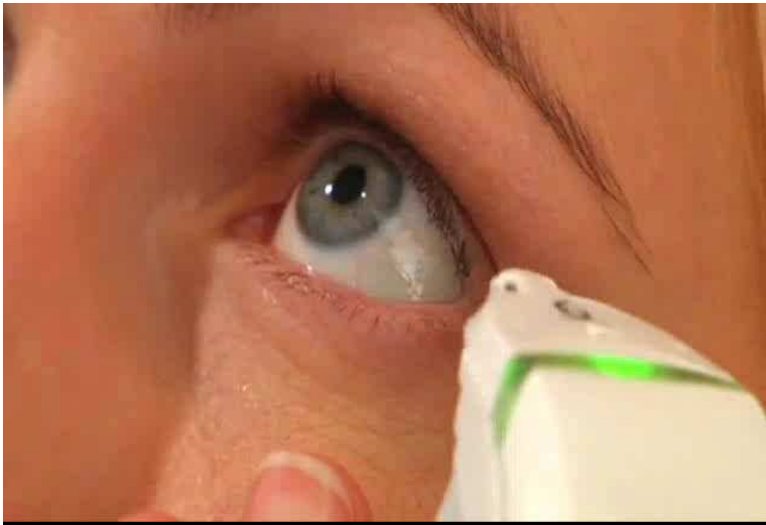
- Electrolytes**
- Na ● K
- Cl ● Ca
- Proteins:**
- Lysozyme
- ▲ Fe
- ▲ Lactoferrin
- ▽ Lipocalin
- Albumin
- EGF
- Cytokines:**
- IL-1 $\beta$
- TNF- $\alpha$
- IL-1RA
- TGF- $\beta$
- Mucin 1, Mucin 4
- Mucin 5AC
- Latent Proteases
- ▲ IgA
- ▲ IgG
- ▲ IgM
- Polar Phospholipid



- Electrolytes**
- Na ↑ ● K ↑
- Cl ↑ ● Ca
- Proteins:**
- Lysozyme ↓
- ▲ Fe
- ▲ Lactoferrin ↓
- ▽ Lipocalin ↓
- Albumin ↓
- EGF ↓
- Cytokines:**
- IL-1 $\beta$  ↑
- TNF- $\alpha$  ↑
- IL-1RA ↓
- TGF- $\beta$  ↑
- Mucin 1, Mucin 4
- Mucin 5AC ↓
- Active Proteases ↑
- ▲ IgA ↓
- ▲ IgG ↑
- ▲ IgM ↑
- Polar Phospholipid
- Desquamating, Inflamed, Pre-Apoptotic Cell

- • **Aqueous-deficient dry eye**
- – Autoimmune disease (e.g. Sjögren's Syndrome)
- • **Lipid-deficient dry eye**
- – Meibomian gland dysfunction
- – Hormonal changes
- • **Mucin-deficient dry eye**
- – Goblet cell loss
- • **Neural loop-associated dry eye**
- – Blink disorders
- – Corneal hypoesthesia (e.g. Riley-Day syndrome)
- • **Environmentally-caused dry eye**
- – Arid, windy, polluted conditions

International Meibomian Gland Dysfunction Workshop: Report (March 2011)



Flogosi  
Gh. di  
Meibomio

Aumentata  
evaporazione

Lacrima  
iperosmolare

Ridotta  
produzione  
lipidica

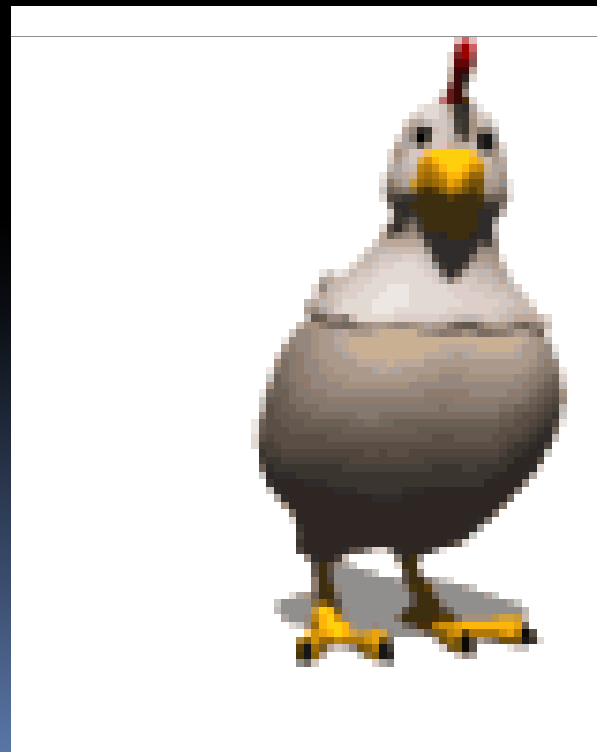
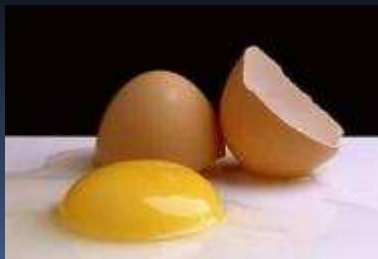
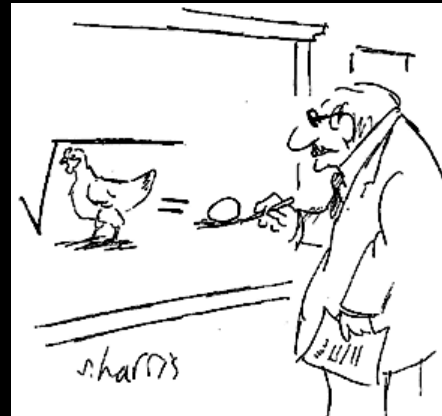
Lacrima  
infiammatoria

Ridotta  
sensibilità

Ridotta  
produzione di  
lacrime



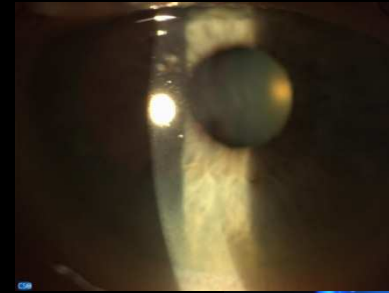
# I cambiamenti nella composizione delle lacrime sono la causa o l'effetto ?



# TEAR FILM and BLINKING DYSFUNCTIONS



REDUCED QUALITY OF OPTICAL IMAGE

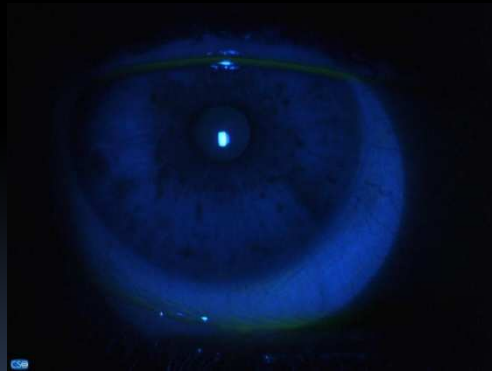


INTACT LIPID TEAR FILM:

- < evaporation 90÷95%
- stabilize tear film
- smooth ocular surface



IMPROVE OCULAR SURFACE HEALTH

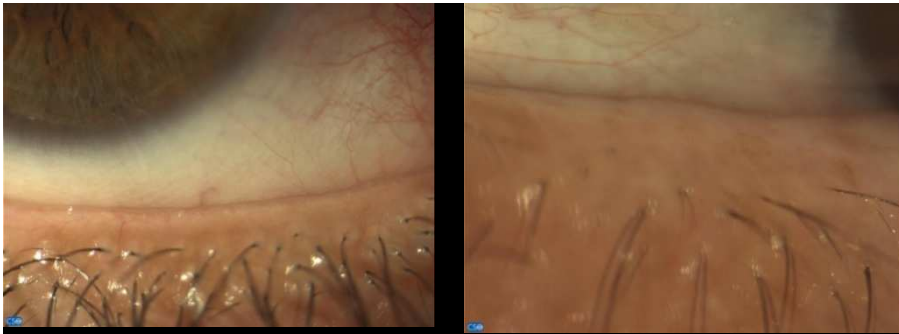


80% DTS



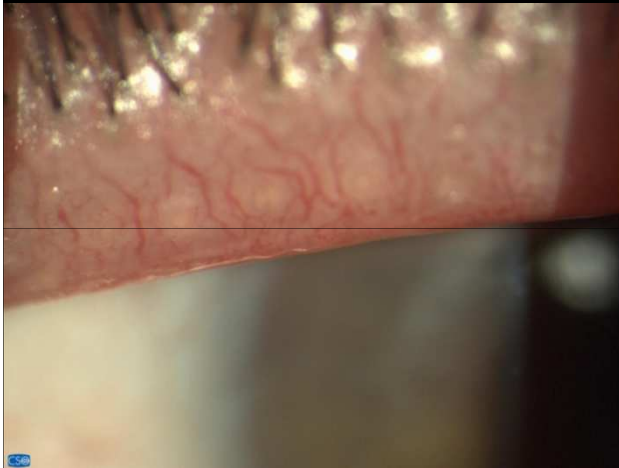
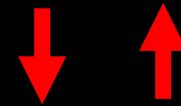
Lipo-deficient

(Heilingenhaus A.- Ophthalmologe '06, Lozato - J Fr Ophthalmol '01)

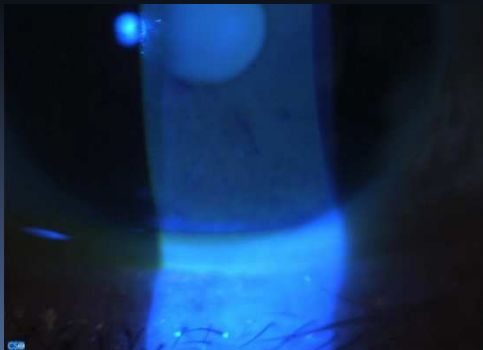


Tear film instability/  
imbalance

External disorders



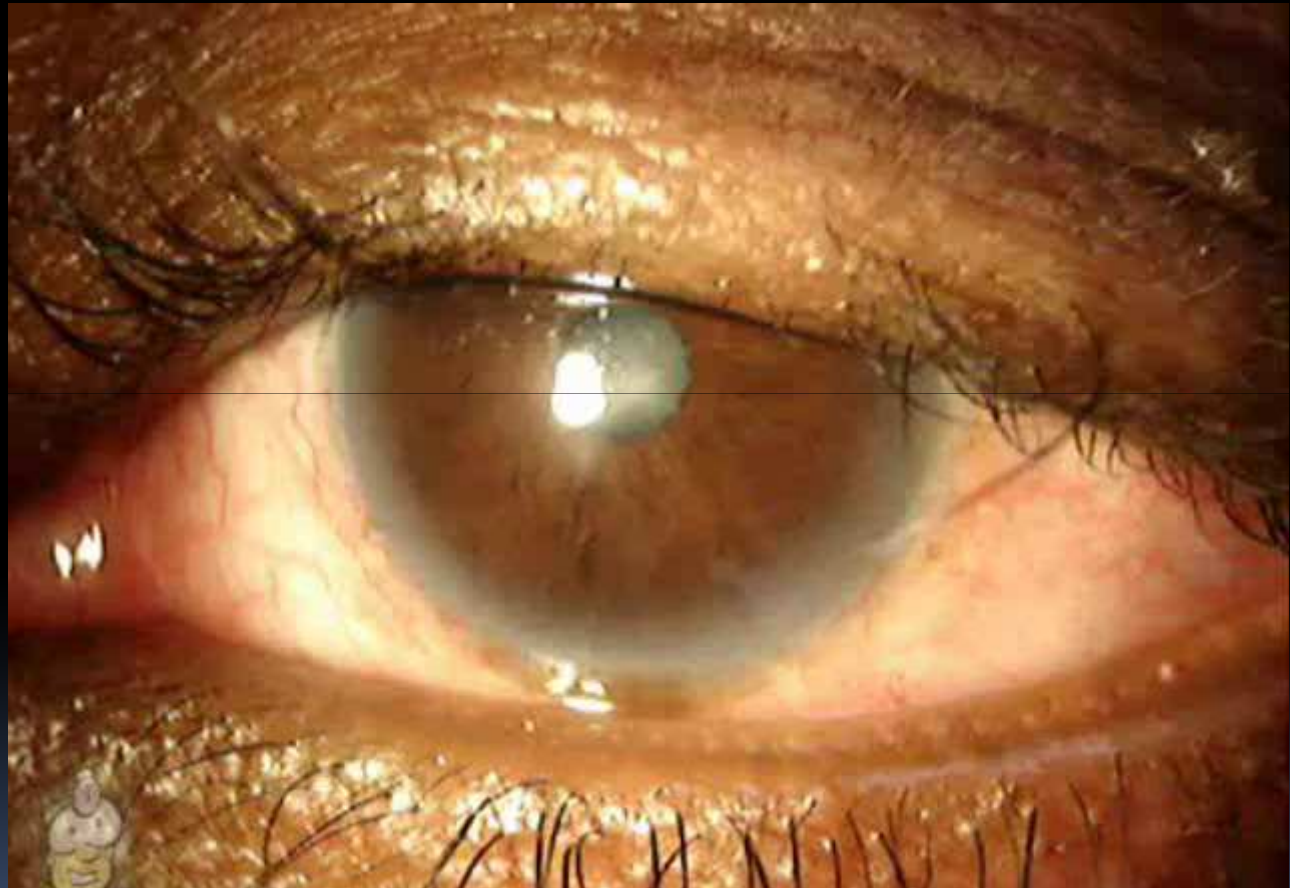
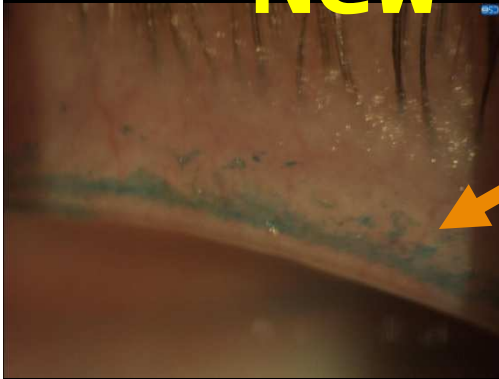
Ocular surface epitheliopathy





# New diagnostic approach

Marx's line



The mechanistic view of dry eye disease



# Therapeutic strategies to leave the loop

To reconstitute lipid layer of the  
lacrimonal tear film



What is it need

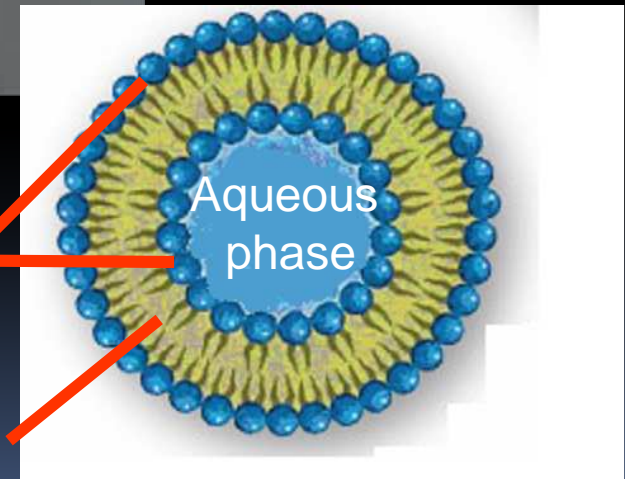
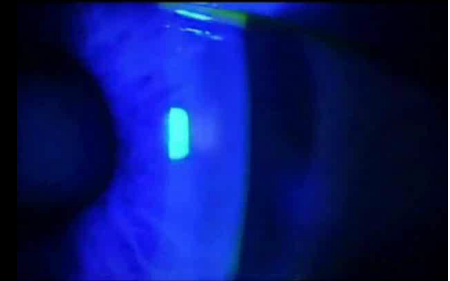
# Therapeutic strategies to leave the loop



New way of administration (nebulization)

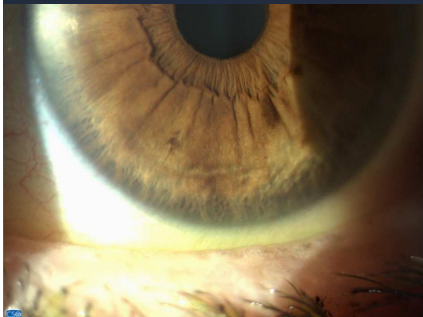


Double lamellar Structure

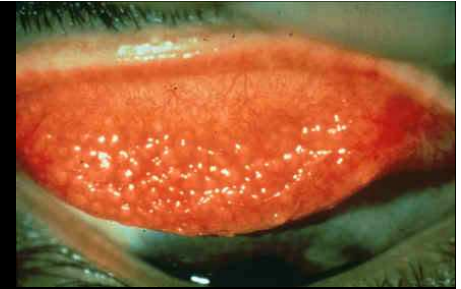
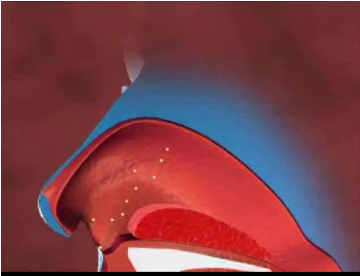


Phosphatidylcholine (94%)

New formulation (liposomes)

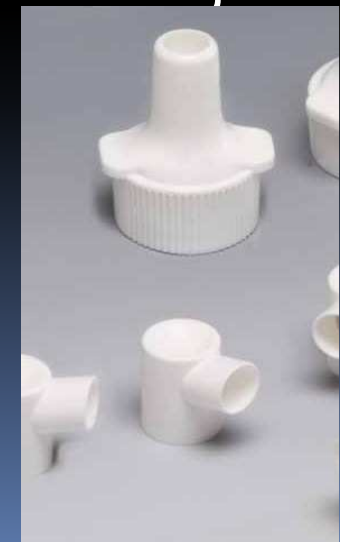


# Osservazioni sull'apparato ORL

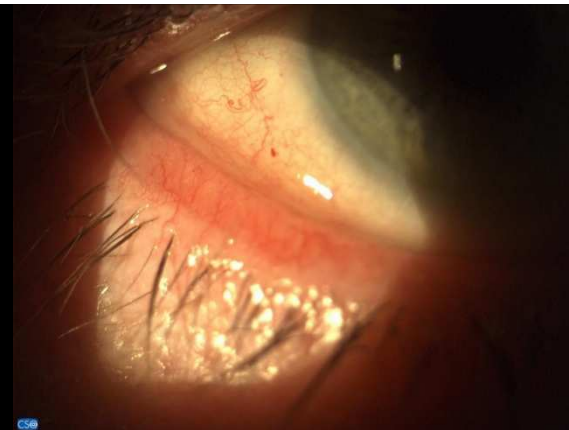


- Presenza di liposomi fluoresceinati nella mucosa e nelle secrezioni nasali dopo applicazione sulle palpebre in corrispondenza del canto interno \*
- Maggiore protezione della mucosa nasale
- Diluizione degli allergeni e delle citochine proinfiammatorie
- Riduzione tempo di contatto della mucosa con gli allergeni ambientali
- Miglioramento della rinorrea e della sintomatologia ORL

Spray liposomiale con doppio erogatore per la superficie oculare e per la cavità nasale.



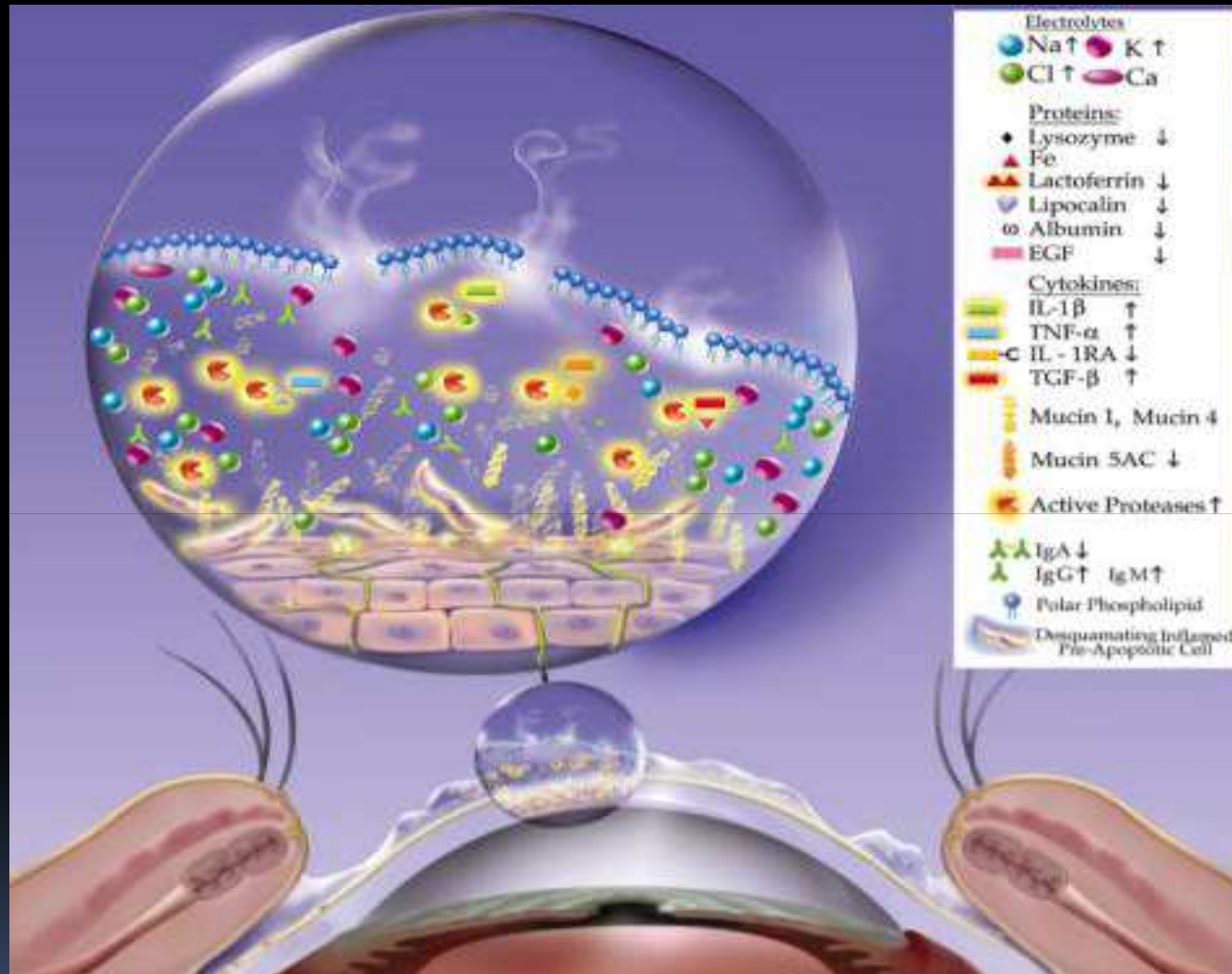
# Disfunzione Ghiandola di Meibomio



# Ofloxacina monodose nelle sindromi da disfunzioni lacrimali gravi con MGD

- Studio randomizzato caso-controllo con un numero di campioni statisticamente significativo
- Valutazione dell'effetto antinfiammatorio del farmaco mediante dosaggio (metodo ELISA) di IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, TNF- $\alpha$ , MMP(9) in campione di film lacrimale prelevato nei pazienti prima e dopo il trattamento.
- Valutazione dell'attività lipasica ed esterasica

# E' sufficiente la terapia topica?



Può essere utile una terapia sistemica?



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IOVS  
Investigative Ophthalmology  
& Visual Science

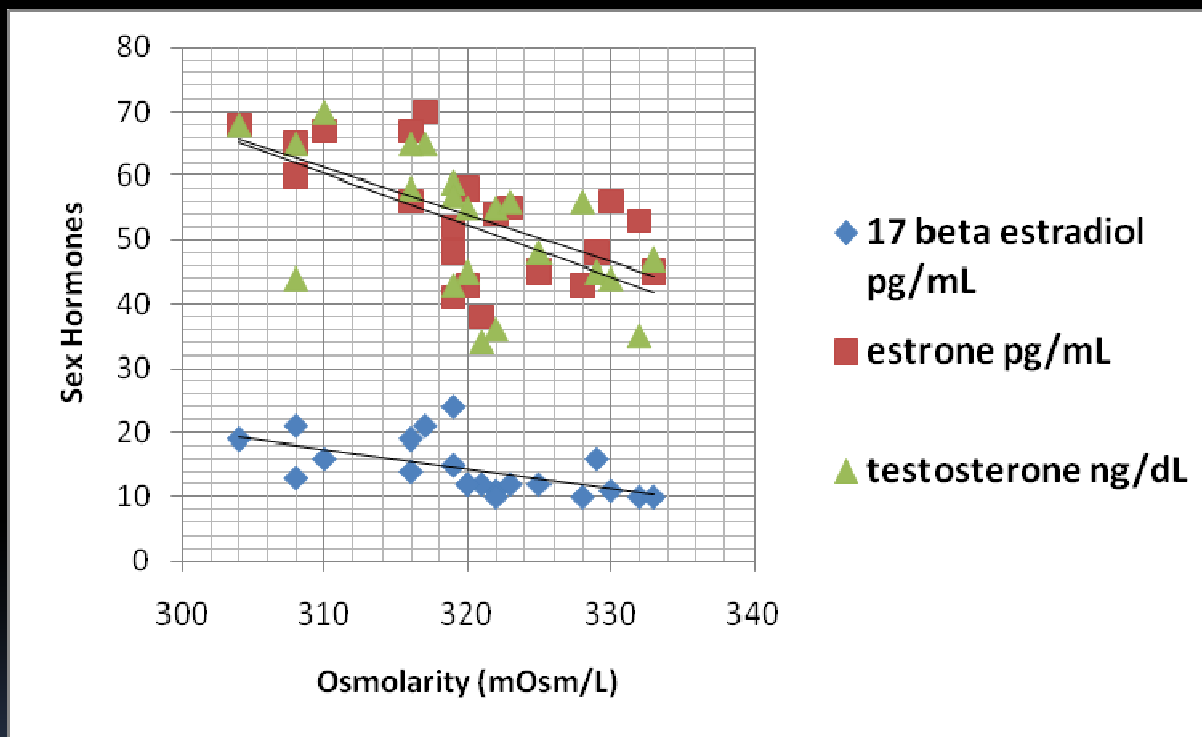
# Dysfunctional Tear Syndrome: Role of Phytoestrogens

Gagliano. C. MD, Avitabile T. MD, Scuderi G. MD, Caruso S. MD, Amato R. MD, Ortisi E., MD

Manuscript ID: IOVS-10-6663.R1



## CORRELAZIONE INVERSA TRA LIVELLI EMATICI DEGLI ORMONI SESSUALI ED OSMOLARITA' LACRIMALE



**A controlled Double Masked Clinical Assessment  
Study of Phytoestrogens, Lipoic Acid and  
Essential Fatty Acid (EPA) Supplement and Its  
Effect on Dysfunctional Tear Syndrome**

**-Phytoestrogens (fenugreek 200 mg)**

Diosgenin  
Steroidal saponins  
alkaloids

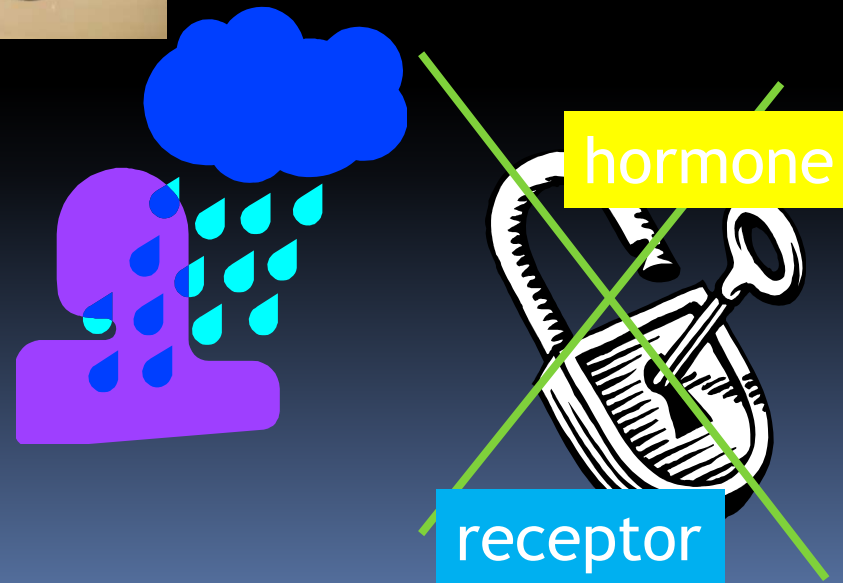
**-Lipoic Acid (100 mg)**

**-EPA (eicosapentanoic acid) (240 mg)**

# PHYTOESTROGENS



HORMONAL BATH



Receptor modulation

# -Phytoestrogens

- Because of its differential binding affinity to estrogen receptor (ER) isoforms, genistein is described as a **selective estrogen receptor modulator (SERM)**.

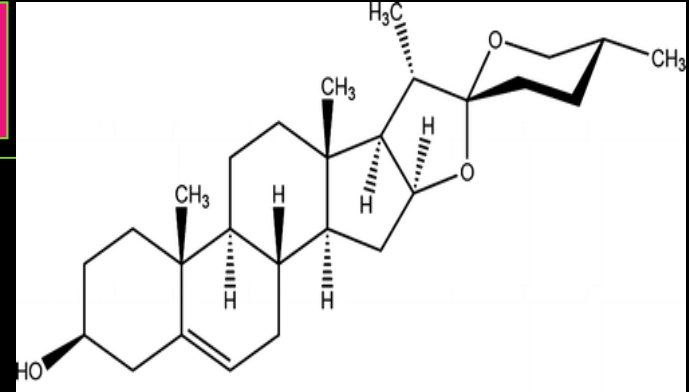
[Ye L, Chan MY, Leung LK :](#)

Mol Cell Endocrinol. 2009 Apr 10;302(1):73-80

# Other effects of phytoestrogens

## Diosgenin

- Antiandrogenic activity
- Improvement the lipid profile
- Modulating oxidative stress
- Anti-inflammatory properties.
- Improvement of aged skin
- Anxiolytic effects .



# -Lipoic Acid

- L'acido alfa-lipoico ha un potente effetto antiossidante, riduce l'accumulo di radicali liberi sulla superficie oculare conducendo ad una maggiore stabilità del film lacrimale ed una riduzione della sintomatologia ad esso associata.

(Pinhiero '07, Stern '04, James '01)

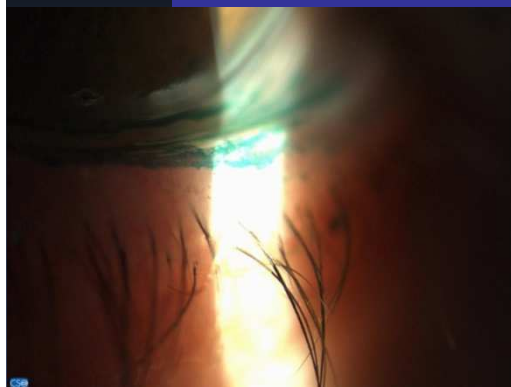
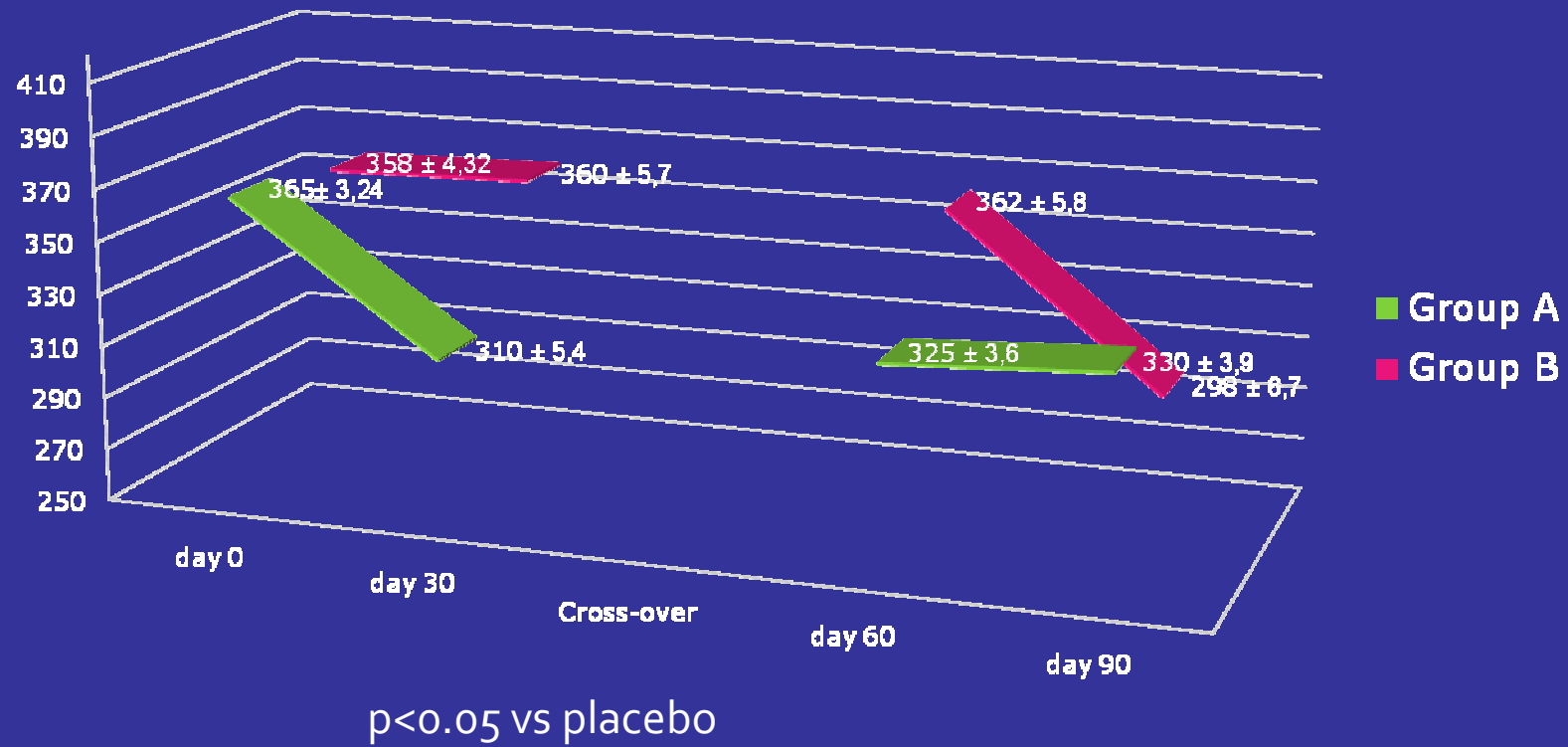
## - EPA

“A randomized controlled trial investigating the effect of n-3 long chain polyunsaturated fatty acid supplementation on older people: the older people and n-3 long-chain polyunsaturated fatty acids (OPAL) study protocol”

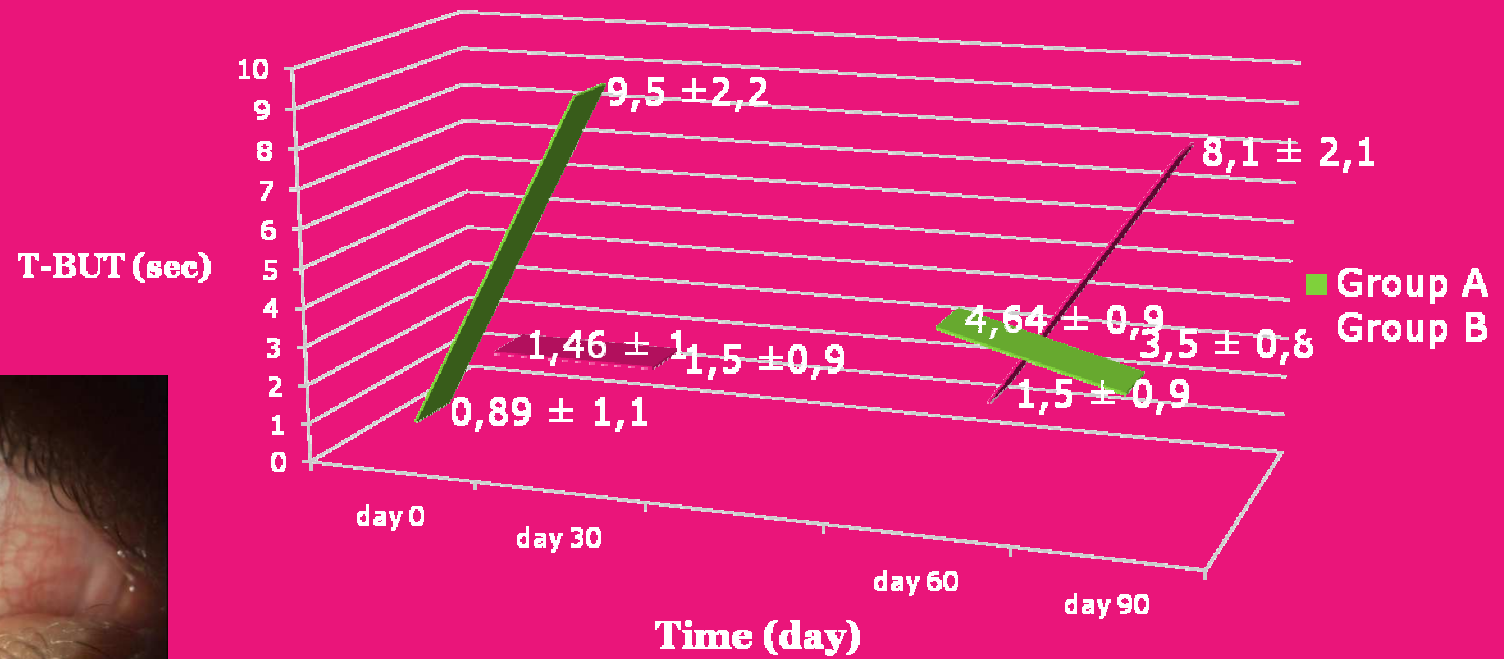
Dangour A.D.: Nutrition Journal 6 Mar. 2007.



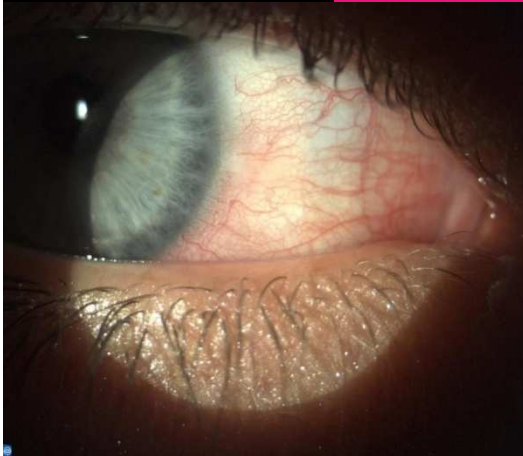
# Osmolarity after Lacrisek® or Placebo



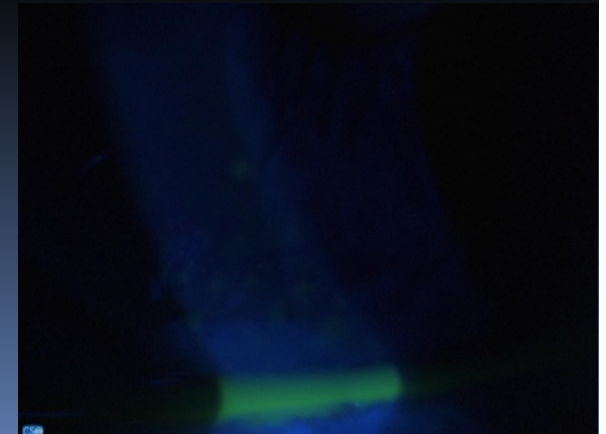
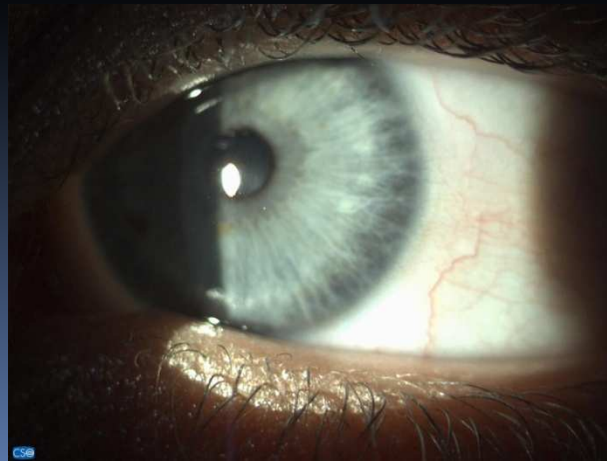
# T-BUT after Lacrisek® or placebo



p < 0.001 vs placebo



pre



# Conclusions

Phytoestrogens significantly:

- 1) Decreased tear osmolarity
- 2) Increased Schirmer values
- 3) Increased Tear-BUT

Valid support in the severe  
Dysfunctional Tear Syndrome.

FUTURE: PHYTOESTROGENS CARRIED BY  
LIPOSOMES?

