



Azienda Ospedaliero – Universitaria  
“Policlinico – Vittorio Emanuele”  
Catania



Unità Operativa di Oftalmologia  
*Direttore: Prof. Teresio Avitabile*



# Ormoni e disfunzione lacrimale: ruolo dei fitoestrogeni

***C. Gagliano, D. Scollo, R. Amato, G. Scollo, D. Rocca, T. Avitabile***

XXXV Congresso SOSI  
Terrasini 15/17 Aprile 2010



**NEST**  
NEUROVISUAL SCIENCE TECHNOLOGY



**PROGETTO  
DONNAe  
OCCHIO**

**PREVENZIONE DEI DISTURBI  
NEUROVISIVI NELLA DONNA**

in stato di:

**GRAVIDANZA • MENOPAUSA  
CONTRACCEZIONE • TERAPIA ORMONALE**



**Gender Difference**

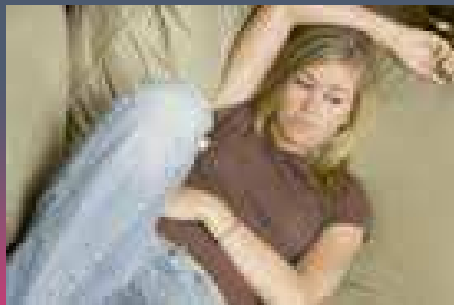
**MIUR: PRIN**

**Ott. 2007 - Ott. 2010**

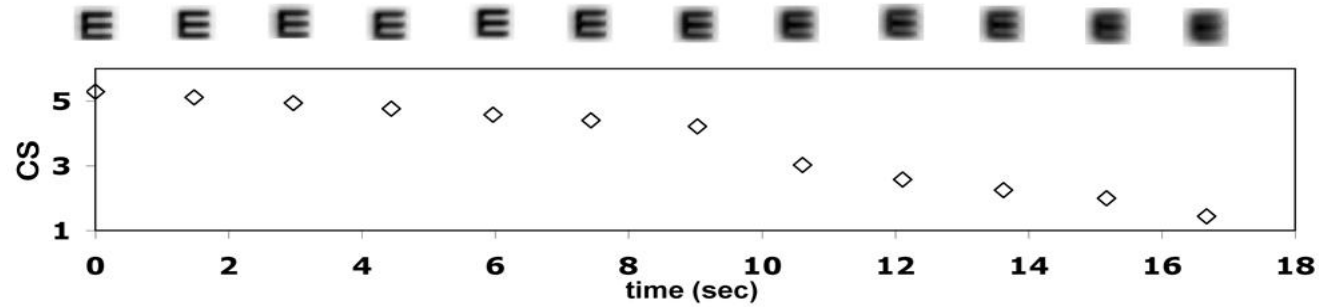
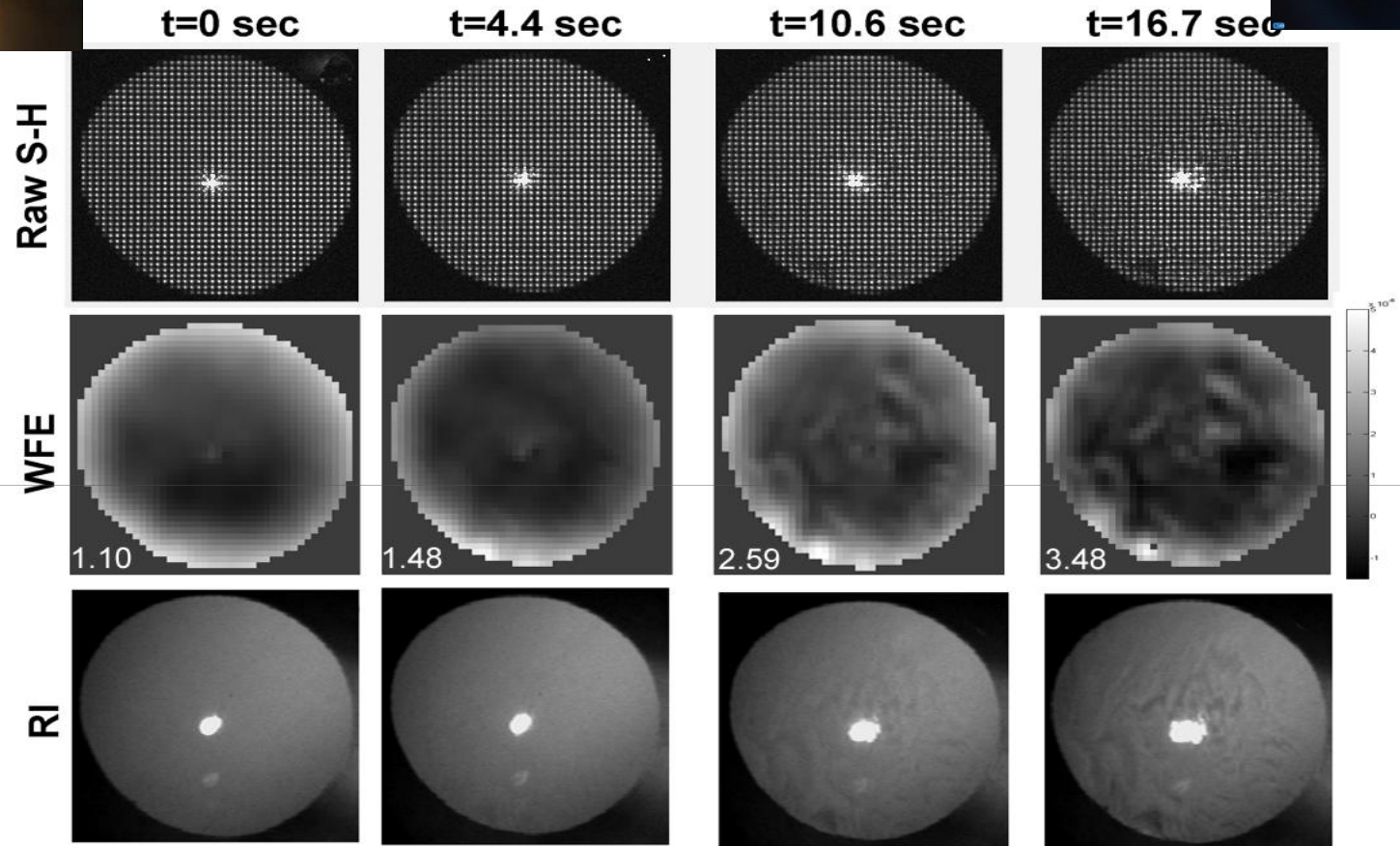
## Variazione degli ormoni in base al sesso, età e stato ormonale

	<i>Donna Giovane</i>	<i>Donna EP</i>	<i>Donna Peri Menopausa</i>	<i>Donna Menopausa</i>	<i>Gravidanza</i>	<i>Uomo giovane</i>	<i>Uomo anziano</i>
Estrogeni	N	N	N o ↑	↓ ↓	↑	N	N
Progestinici	N	N	↓	↓ ↓	↑	N	N
Androgeni	N	N	N o ↓	↓	↑	N	↓

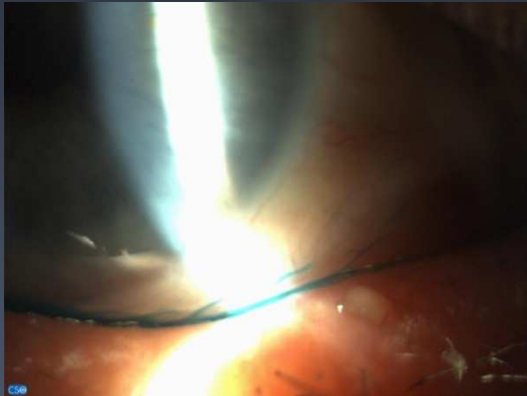
N = tasso di base ; ↑ o ↓ rispetto al tasso di base ; EP : estro-progestinico.



# Disfunctional Tear Syndrome



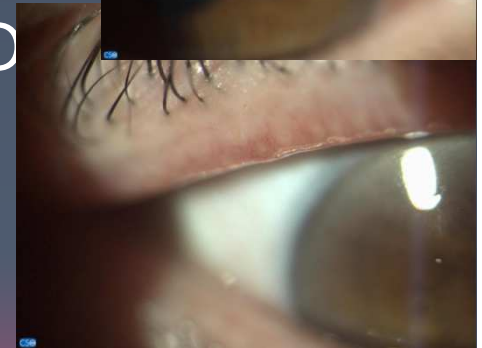
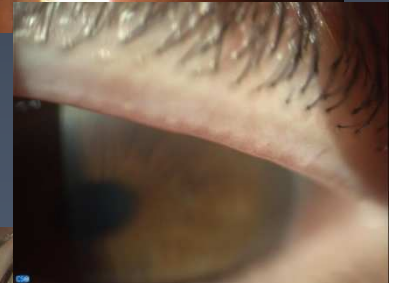
# Meibomian gland dysfunction (MGD)



1) FREQUENZA (80%)

2) DEFICIENZA DELLO STRATO LIPIDICO

3) INFLUENZA DELLO STATO ORMONALE  
> FREQ. NELLA DONNA



## EVAPORATIVE DRY EYE SYNDROME

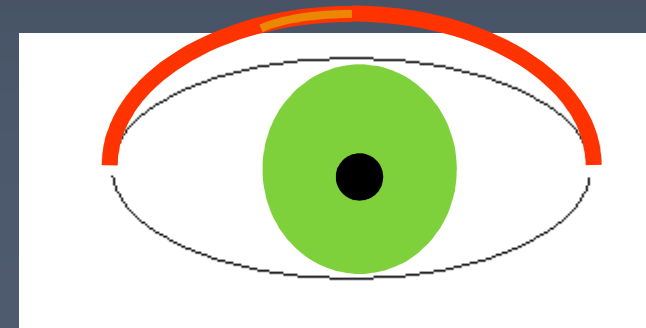
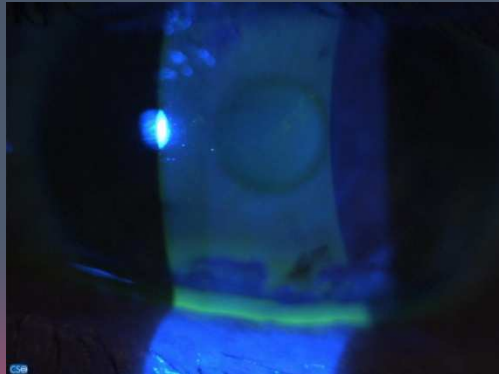
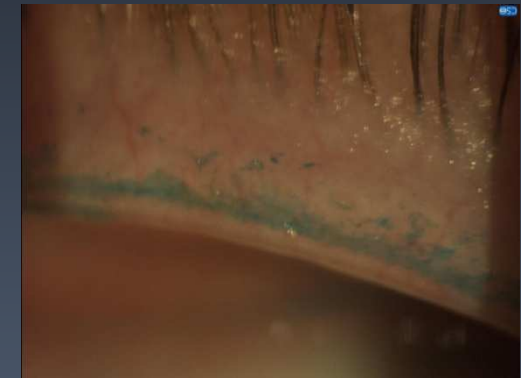


# Meibomian gland dysfunction (MGD)

## Lid Margin Disease

### IMPORTANTE!

- 1) Ispezione orifizi meibomio
- 2) Diagnosi dopo lieve compressione del margine palpebrale
- 3) Coloranti



**Linea di Marx**

Meibomian glands : part III. Dysfunction - argument for a discrete disease entity and as an important cause of dry eye. [Knop E](#), [Knop N](#), [Brewitt H](#), [Pleyer U](#), [Rieck P](#), [Seitz B](#), [Schirra F](#) *Ophthalmologe*. 2009 Nov;106(11):966-79

# 2007 REPORT OF THE INTERNATIONAL DRY EYE WORKSHOP (DEWS)

Test Bibliografia	Valore di cut-off	Sensibilità (%)	Specificità (%)
Questionari	any	98	97
Rosa Bengala	any	25	90
Schirmer test I	< 3 mm	10	90
BUT	< 5 sec	98	63
Altezza del menisco	$\leq 0,35$ mm	93	67
Raggio del menisco	$\leq 0,25$ mm	89	78
Osmolarità	> 312 mOsm/L	95	94



Terapia sostitutiva in menopausa?  
Influenza degli androgeni?  
Influenza degli estrogeni?  
Influenza dei progestinici?  
Di tutti?





# self-stimulated loop

Età – Disturbi ormonali  
– Influenze ambientali

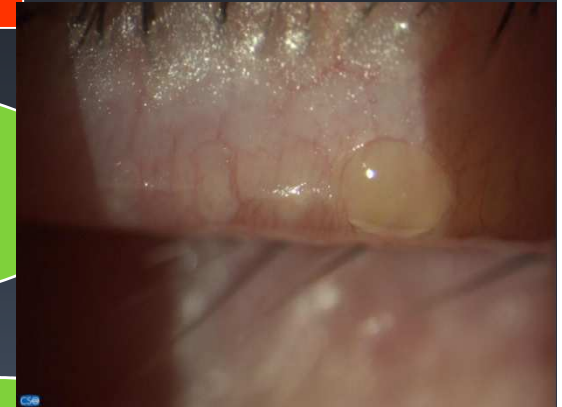
Alterazioni qualitative meibum  
Ipercheratinizzazione  
Ostruzione dotti e orifizi

Ostruzione cronica delle  
GHIANDOLE  
di  
MEIBOMIO

Stasi  
> Pressione  
Dilatazione dotti  
Atrofia acini  
Degen. tessuto ghiandolare secretorio

EVAPORATIVE  
DRY EYE  
SYNDROME

Therapeutic strategies to leave the loop



# Androgen Influence on the Meibomian Gland

David A. Sullivan Invest  
*Ophthalmol Vis Sci. 2000;41:3732-3742*

Schepens Eye Research Institute and Department of Ophthalmology, Harvard Medical School, Boston, MA, USA.

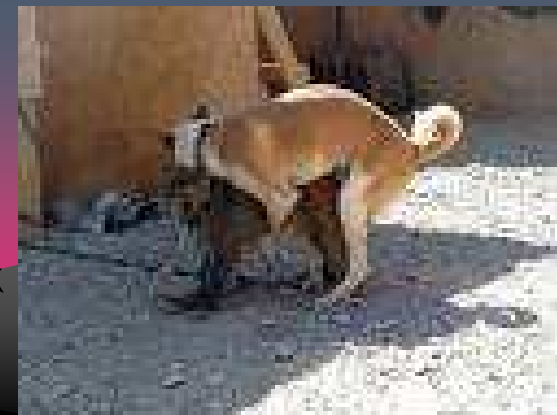
- Meibomian gland is an androgen target organ
- Androgens influence the lipid profile
- 19-nortestosterone treatment modulated the fatty acid profile in the total and neutral lipid fractions of the rabbit meibomian gland

- Alterations in its lipid content during androgen deficiency.
- Androgens are known to regulate the development, differentiation, and lipid production of sebaceous glands throughout the body
- Androgen receptor protein is present in the **rat** meibomian gland
- Topical or systemic 19-nortestosterone administration increase total lipid fraction of meibomian glands (**rabbit**)

Esmaeli B, Harvey JT, Hewlett B.  
Immunohistochemical evidence for estrogen  
receptors in meibomian glands. *Ophthalmology*.  
2000;107:180–184

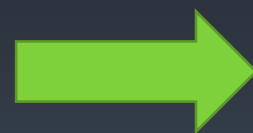
- Our findings demonstrate that sex steroid receptor mRNAs exist in a variety of ocular tissues (humans) and suggest that these sites may represent target organs for androgens, estrogens and/or progestins.
- Rabbit meibomian gland contributes very little to the tear film lipid layer: The vast majority of lipids on the rabbit's ocular surface originate from other adnexal tissues. This situation contrasts sharply with that in humans, in which the meibomian gland is the primary source of tear film lipids.

**The rabbit does not appear to be an ideal model for determining whether androgen–meibomian gland interactions promote the formation of the tear film lipid layer.**





- Dosi elevate di estrogeni
- Dosi elevate di androgeni



Peggiorano la  
funzione lacrimale



- Associazioni estroprogestiniche
- Terapie con antiandrogeni
- Gravidanza



Migliorano la  
funzione lacrimale

Presidente Prof. Salvo Caruso  
Segretario Prof. Vieri Boncinelli

FISS

Vice Presidente Dr. Franco Avenia  
Vice Presidente Prof.ssa Roberta Rossi

Federazione Italiana di Sessuologia Scientifica

La sindrome dell'ovaio policistico  
(iperandrogenismo) migliora o riduce l'incidenza  
di disfunzione lacrimale ?

**Assolutamente NO!**

Al contrario nelle  
adolescenti  
iperandrogeniche la  
disfunzione lacrimale è una  
costante.

-[Yavas GF](#), [Ozturk F](#), [Kusbeci T](#), [Ermis SS](#), [Yilmazer M](#), [Cevrioglu S](#), [Aktepe F](#), [Kose S](#). .  
**Meibomian gland alterations in polycystic ovary syndrome.** Curr Eye Res. 2008  
Feb;33(2):133-8. Meibomian gland function and tear film lipid layer affected in cases  
with PCOS.

-[Bonini S](#), [Mantelli F](#), [Moretti C](#), [Lambiase A](#), [Bonini S](#), [Micera A](#). **Itchy-dry eye  
associated with polycystic ovary syndrome.** Am J Ophthalmol. 2007  
May;143(5):763-771. Epub 2007 Mar 23. Women with PCOS were more likely to have  
itchy-dry eyes, decreased tear film BUT, and increased goblet cell density.

Testosterone,  $17\beta$ -estradiol and progesterone exert multiple effects on the lacrimal and meibomian glands. These sex steroid actions are sex-specific and/or opposite.

Our analyses did not identify any gene that was uniquely and significantly expressed in female, as compared to male, glands.

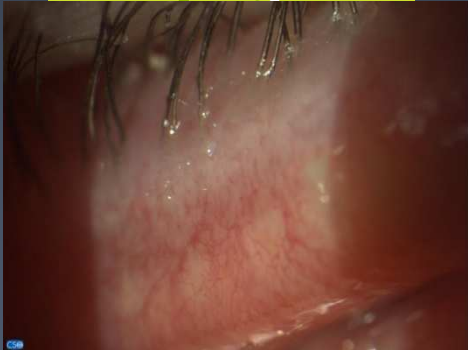
These opposing sex steroid effects may play a role in the pathogenesis of dry eye syndrome.



D.A. Sullivan, R.V. Jensen, T.Suzuki, S.M. Richards Do sex steroids exert sex-specific and/or opposite effects on gene expression in lacrimal and meibomian glands?  
*Molecular Vision* 2009; 15:1553-1572



# FITOESTROGENI



**BAGNO  
ORMONALE**



**Modulazione recettoriale**



# -Phytoestrogens

- Because of its differential binding affinity to estrogen receptor (ER) isoforms, genistein is described as a **selective estrogen receptor modulator** (SERM).
- The phytoestrogen induced aromatase activity in the cells; it regulates **aromatase-B** expression in the brain in an ER-dependent manner

- 

Ye L, Chan MY, Leung LK : Mol Cell Endocrinol. 2009 Apr 10;302(1):73-80



# -Phytoestrogens

- Phytoestrogens have been shown to exert **anti-estrogenic** and estrogenic effects in some tissues

Bandera EV, Williams MG, Sima C, Bayuga S, Pulick K,  
Wilcox H, Soslow R, Zauber AG, Olson SH Cancer Causes

Control. 2009 Apr 8



## LACRISEK® cps

**-Phytoestrogens (fenugreek 200 mg)**

**-Lipoic Acid (100 mg)**

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

Diosgenin

Steroidal saponins  
alkaloids

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

# -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 polynsaturated fatty acid supplementation on older people: the older people and n-3 long-chain polynsaturated fatty acids (OPAL) study protocol”

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

## LACRISEK® cps

-Phytoestrogens (200 mg)

-Lipoic Acid (100 mg)

-EPA (eicosapentanoic acid) (240 mg)



LACRISEK® Capsule  
30 capsule

Treatment of Dysfunctional Tear Syndrome:  
role of Phytoestrogens

1st EuCornea Congress  
Venice 2010



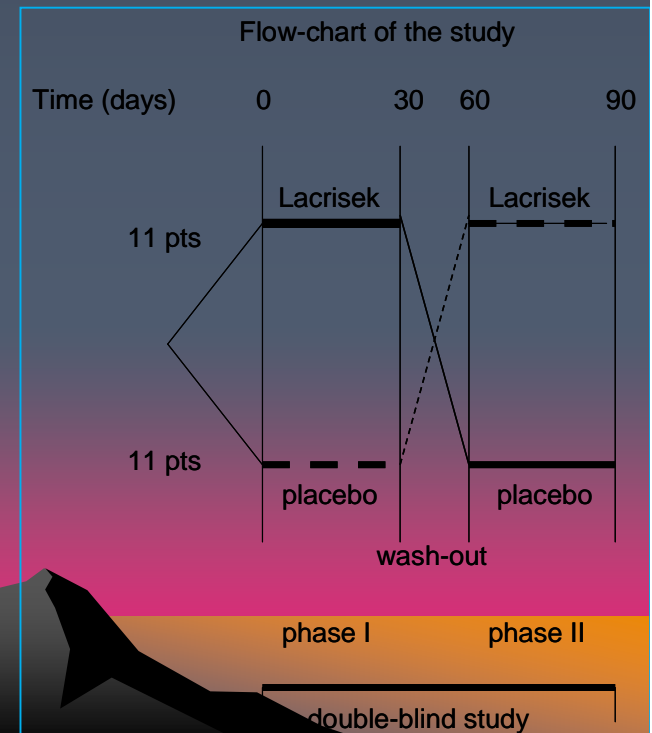


## Subjects

Twenty-two postmenopausal women aged between 52 and 63 (mean 57) with severe DTS and below-normal levels of sex steroid hormones were included in this study. The DTS (stage 3 or 4) conditions were considered according to the recently published Dry Eye Workshop criteria.

## Study design

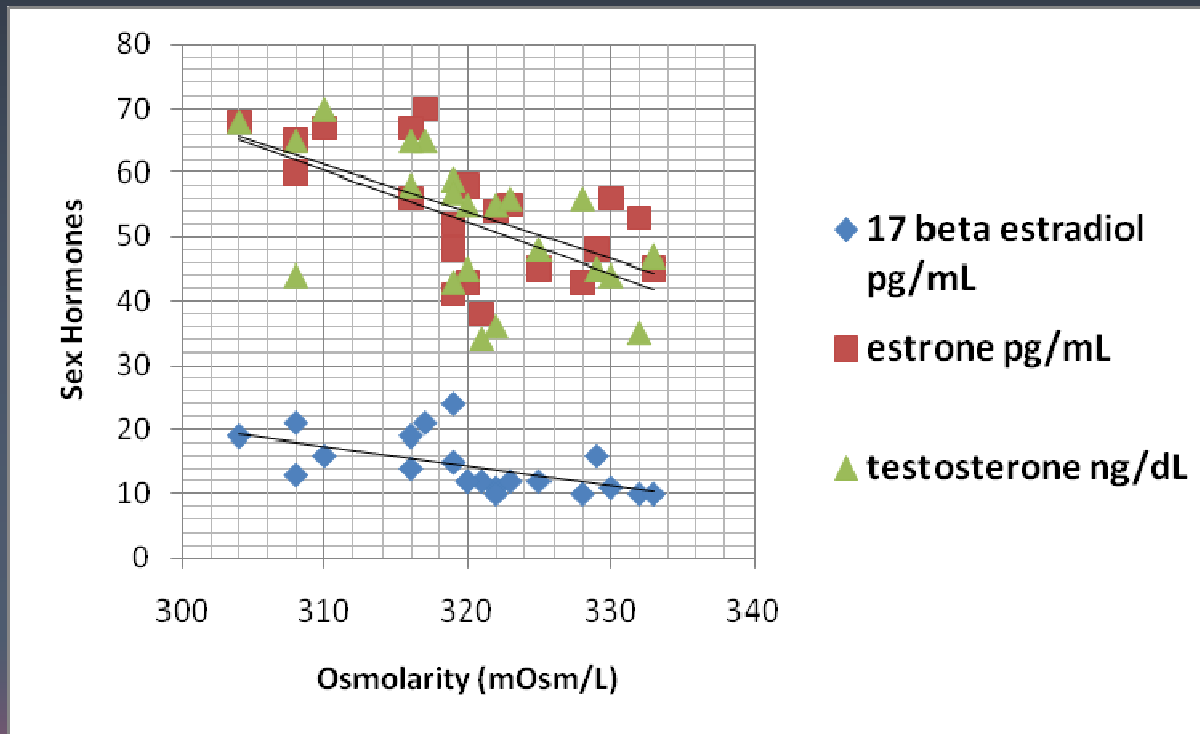
Randomized placebo-controlled two-period cross-over trial of a fenugreek seed extract (Lacrisek® cps), according to a Latin square design. The two 30-day treatment periods were separated by 30-day washouts.



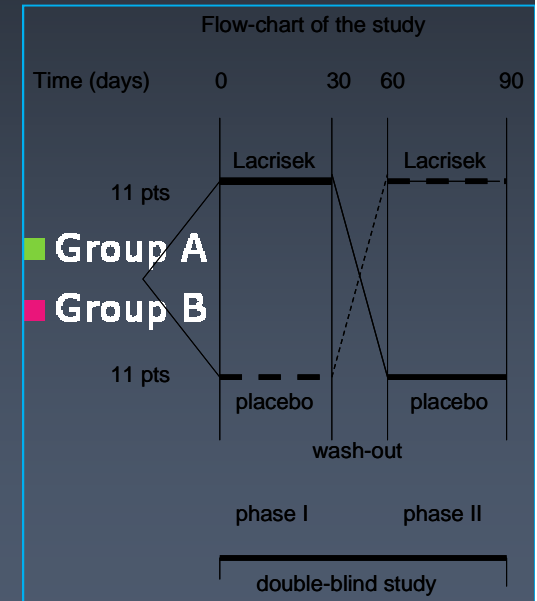
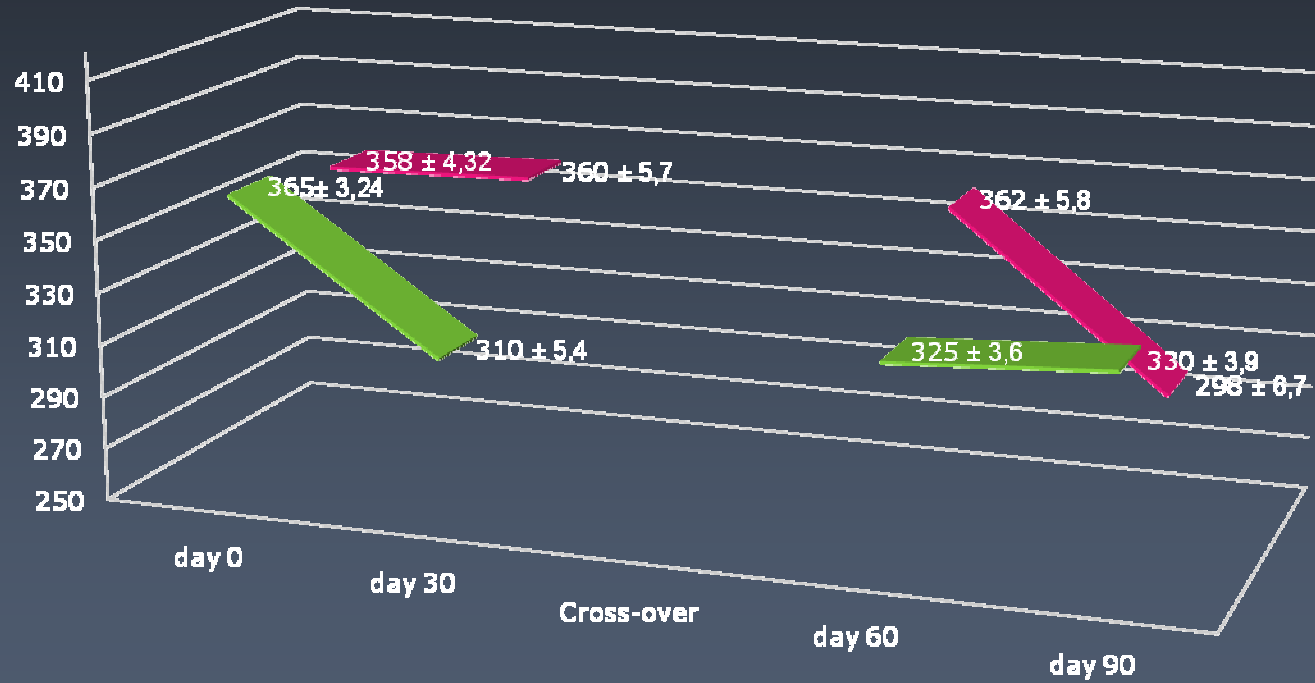
# TABLE 1

<i>Parameters</i>	<i>Placebo</i>		<i>Lacrisek® (Fenugreek seed extract: 400mg/day)</i>		
	Baseline (n=11)	Post-treatment (n=11)	Baseline (n=12)	Post-treatment (n=12)	
Weight (kg)	72.5±2.0	72.4±2.0	72.2±1.9	72.1±2.0	
Triglycerides (mmol/L)	1.0±0.1	0.8±0.1	0.9±0.1	0.8±0.1	
Total cholesterol (mmol/L)	4.9±0.2	4.5±0.2	4.7±0.2	4.4±0.2	
High-density lipoprotein-cholesterol (mmol/L)	1.2±0.1	1.1±0.1	1.2±0.1	1.1±0.1	
Fasting plasma	5.0±0.1	4.8±0.1	4.8±0.1	4.8±0.1	

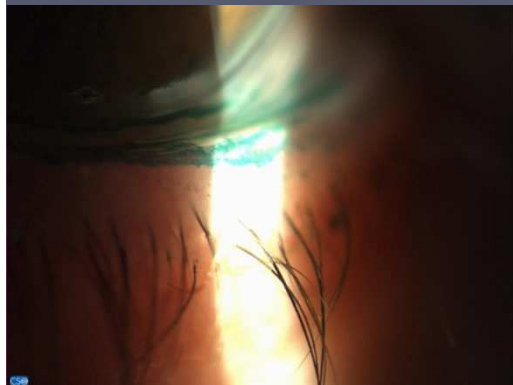
# CORRELAZIONE INVERSA TRA LIVELLI EMATICI DEGLI ORMONI SESSUALI ED OSMOLARITA' LACRIMALE



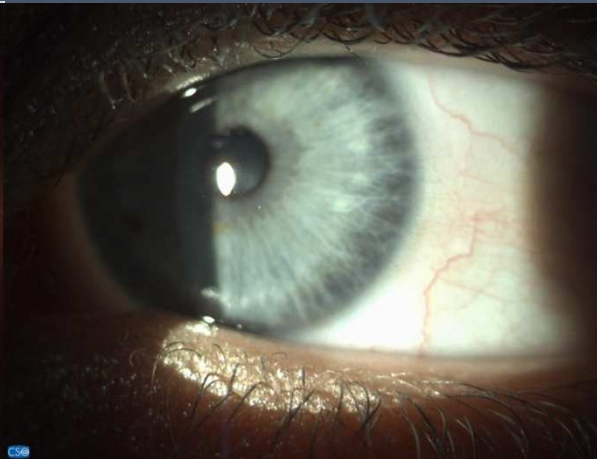
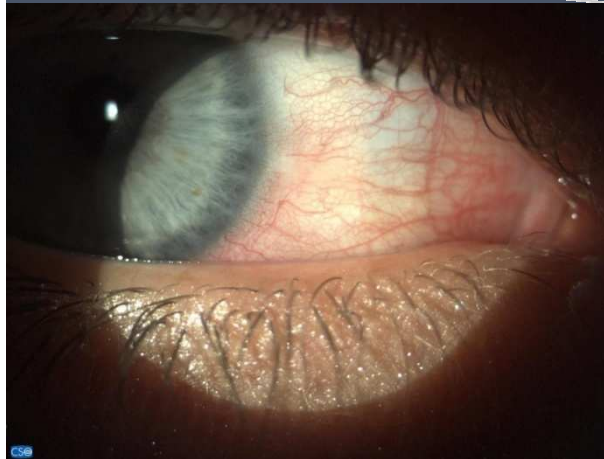
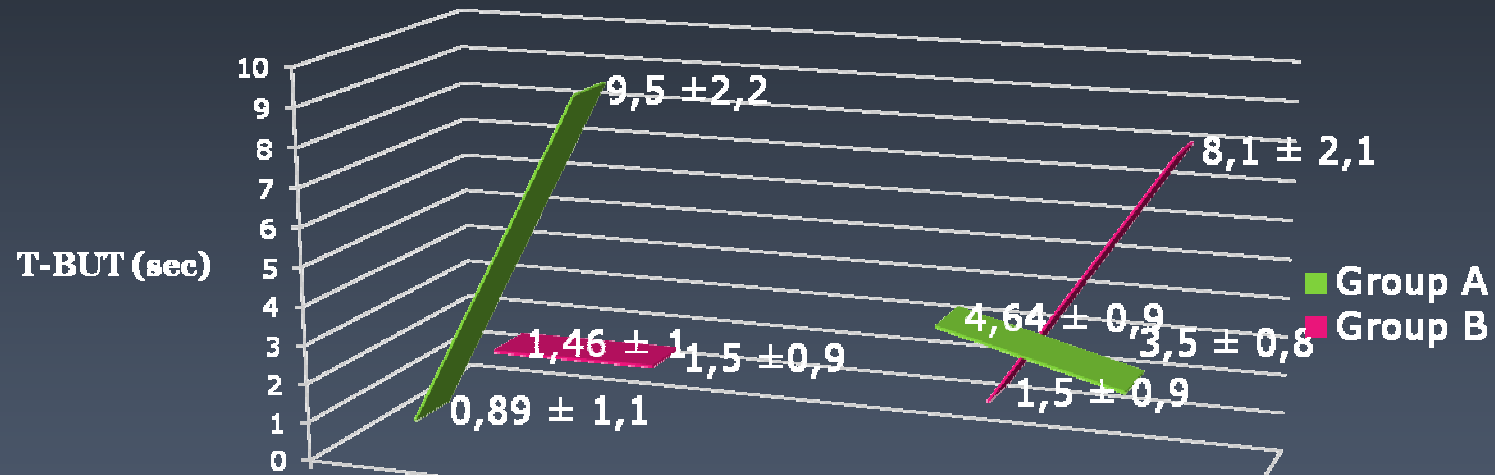
# Osmolarity after Lacrisek® or Placebo



p < 0.05 vs placebo

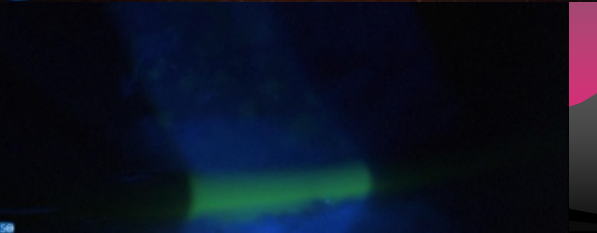


## T-BUT after Lacrisek® or placebo



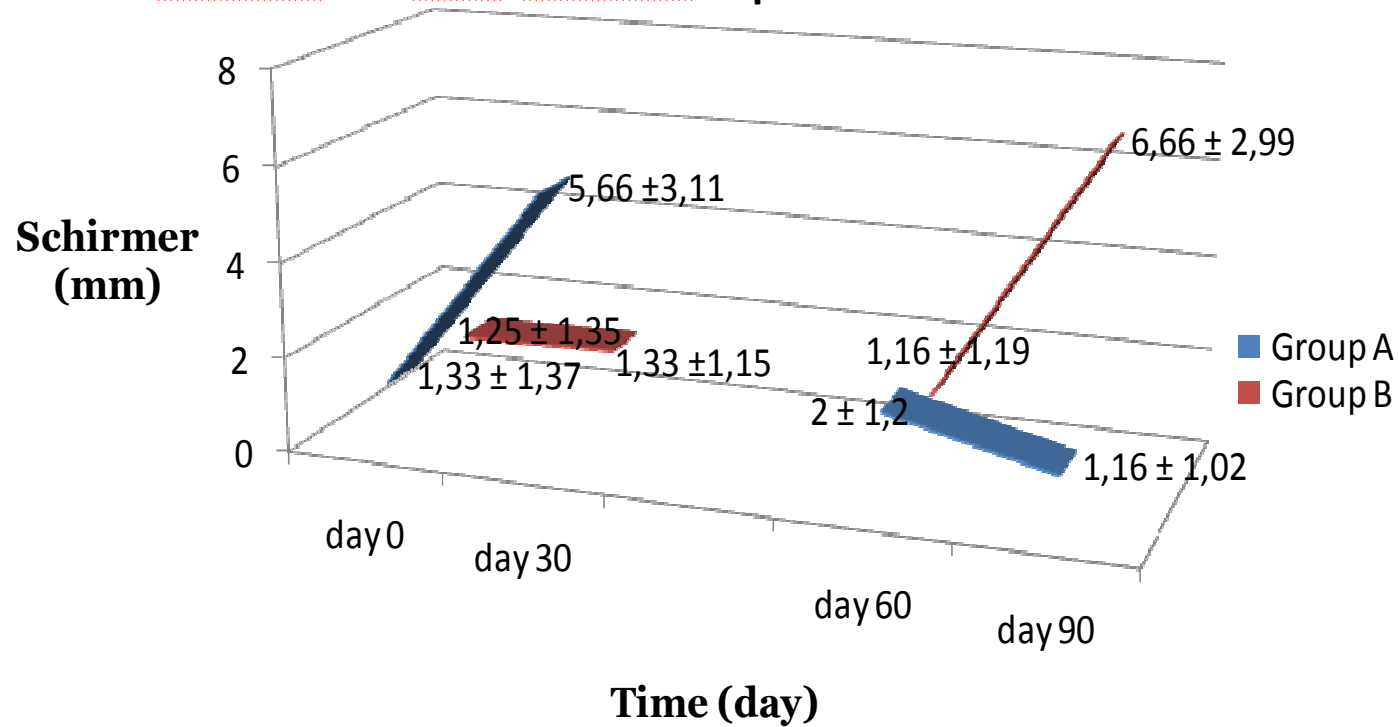
Day 90

< 0.001 vs placebo





### Schirmer test after Lacrisek® or placebo



$p < 0.001$  vs placebo

# Conclusions

- 1) Osmolarity correlated negatively with sex hormones levels (estradiol, estrone and testosterone).
- 2) Further results reveal for the first time that a 30 day treatment with phytoestrogens (Lacrisek ®) significantly **decreased tear osmolarity** while increasing Schirmer values and T-BUT in menopause women, without any significant side effect.
- 3) From this study, it can be concluded that a daily supplement of phytoestrogens may be used as a **valid support** in the treatment of the severe Dysfunctional Tear Syndrome.

# FUTURO: FITOESTROGENI VEICOLATI DA LIPOSOMI?



*MIUR: PRIN*  
*Ott. 2007 - Ott. 2010*

