Dry Eye: Etiology & Diagnosis

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A prudent question is one-half of wisdom

—Francis Bacon 1561-1626

English philosopher, statesman, scientist, lawyer, jurist and author

Proverb (Addendum)

- A specialist is a doctor who trains his patients to become ill only during office hours—*Anonymous*

Lecture Outline

"WHAT IS DRY EYE?"

ETIOLOGIC CLASSIFICATION

- Aqueous deficient
- Evaporative

CONTRIBUTIONS

- Intrinsic/systemic
- Extrinsic/ environmental

DELICATE BALANCE OF HEALTHY TEARS

- Mucus, aqueous & lipid

Lecture Outline (cont)

- DIAGNOSTIC TOOLS
  - Questionnaires
  - Old & New Testing Modalities
- 4 LEVELS OF DRY EYE SEVERITY (DEWS)
- OVERVIEW OF TREATMENT STRATEGIES

Approach to the Dry Eye Patient

Classic Eye Care Practitioners' Approach to Dry Eye Patient

Classic Approach to the Dry Eye Patient

Is Dry Eye Important?

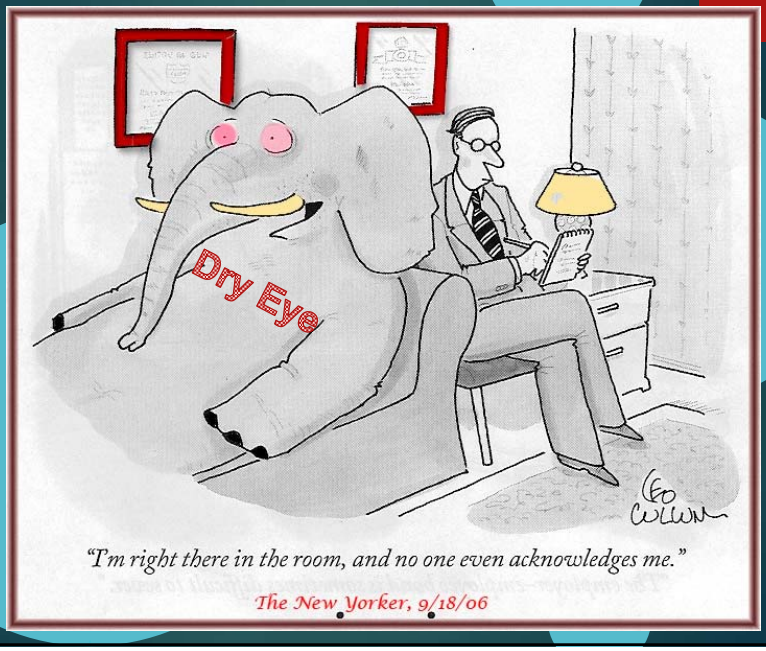
- Dry eye hasn't gotten any respect
- The dry eye corner was a ***very lonely place*** for a long time
- The "crabgrass" of eye care

UNTIL

- Studies began to show effect of dry eye on corneal ***topography*** and ***post cataract surgery visual acuity***:
  - treating dry eye actually causes significant VA improvement
- Dry Eye is now the "hot dot" of eye care

  Source: Darrell White, MD

- Still skeptics PROOF study Peter McDonnell MD med dir



New starlet of Eye Care: Dry Eye

Golden globe award

What is Dry Eye?

Definition of Dry Eye Syndrome/ Keratoconjunctivitis sicca

- Dysfunction of the integrated lacrimal unit
  - Unstable tear film
  - Altered tear composition
  - Ocular surface and glandular inflammation
  - Ocular surface epithelial disease
  - Discomfort and reduced visual function

– Pflugfelder, Stephen : "Dry Eye: The Problem" in Pflugfelder, Beuerman and Stern: Dry Eye and Ocular Surface Disorders 2004

The Dry Eye Workshop (DEWS) 2007 Report

Dry Eye:

- multifactorial disease of the tears and ocular surface
  - tear film instability
  - potential damage to the ocular surface
  - increased osmolarity of the tear film
    - inflammation of the ocular surface
  - symptoms of discomfort, visual disturbance

Dry Eye Workshop (2007). Ocul Surf 2007 Apr;5(2):75-92

DED is an immune mediated disorder

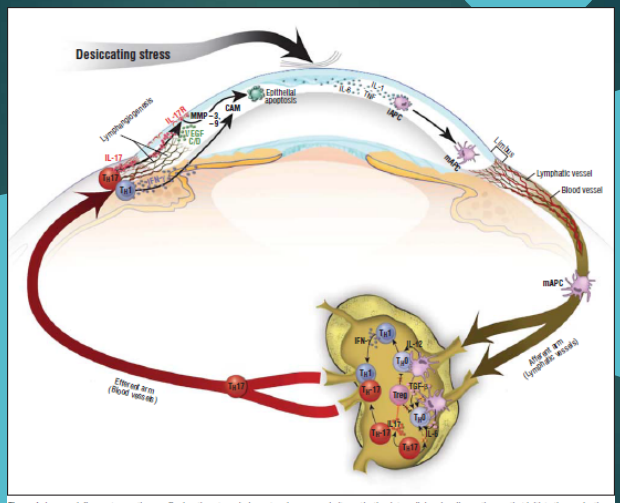


Figure 1. Immunoinflammatory pathways. Desiccating stress induces tear hyperosmolarity, activating intracellular signaling pathways that initiate the production of proinflammatory cytokines (eg, interleukin [IL] 1, tumor necrosis factor [TNF], and IL-6). This proinflammatory milieu facilitates the activation and maturation of immature antigen-presenting cells (iAPC). Mature APCs (mAPC) migrate through the afferent lymphatics to draining lymph nodes, where they induce effector helper T cell 1 (T_H1) and T_H17 cells that subsequently migrate through efferent blood vessels to the ocular surface. The T_H17 cells antagonize regulatory T cell (Treg) functions and lead to further expansion of T effectors in the draining lymph nodes. Effector T_H1-secreted interferon (IFN) γ and T_H17-secreted IL-17 exert their pathogenic effects by promoting the production of proinflammatory cytokines, chemokines, matrix metalloproteinases (eg, MMP-3 and MMP-9), cell adhesion molecules (CAM), and prolymphangiogenic molecules (vascular endothelial growth factor [VEGF] D and VEGF-C) that facilitate the infiltration of pathogenic immune cells, leading to further damage of the ocular surface. IL-17R indicates IL-17 receptor; TGF, transforming growth factor.

Stevenson, Chauhan, Dana. Arch Ophthalmol 2012; 130(1):90-100

- Healthy Tears:

  The tear film and ocular surface:

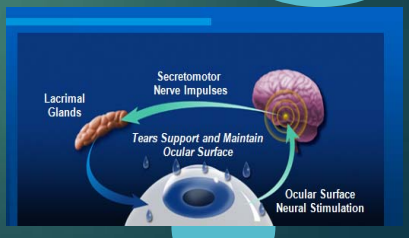
  --form an integrated physiologic unit

  --surface epithelia and secretory glands ***linked via neural network.***

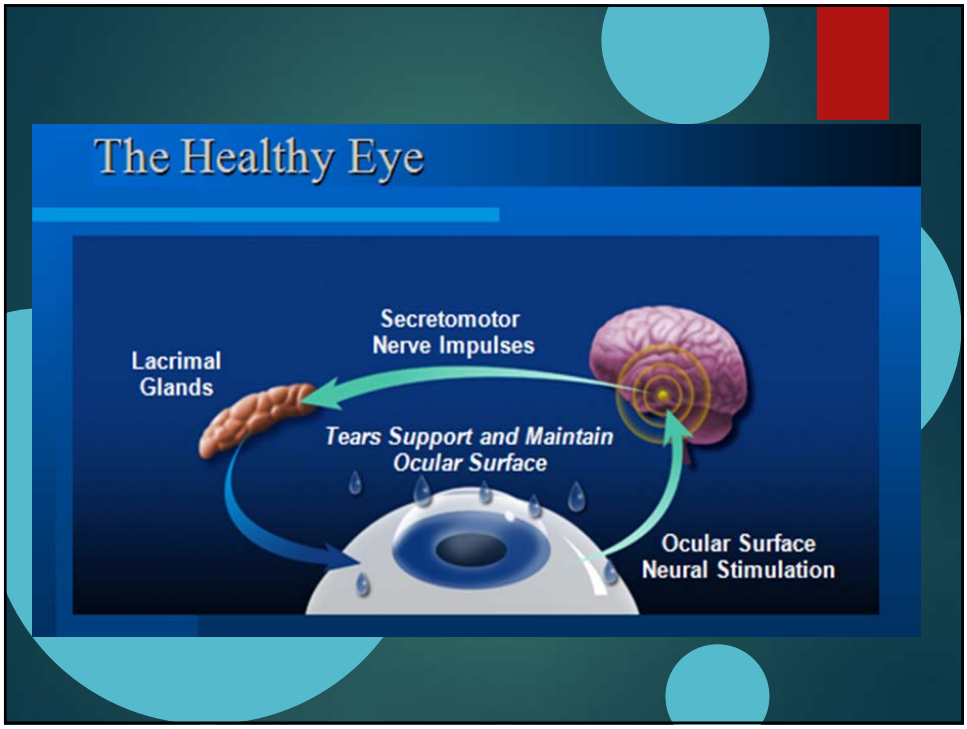
  Sensory-driven network

  --regulates secretory activity in <u>quantity</u> and <u>composition</u>

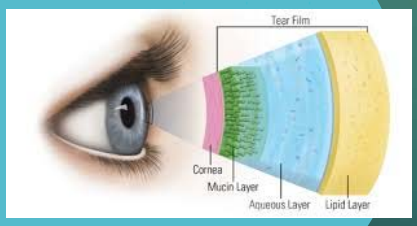
  --supports homeostasis of the system.



Lemp MA; AJO **2008** Sept;146(3):350-6



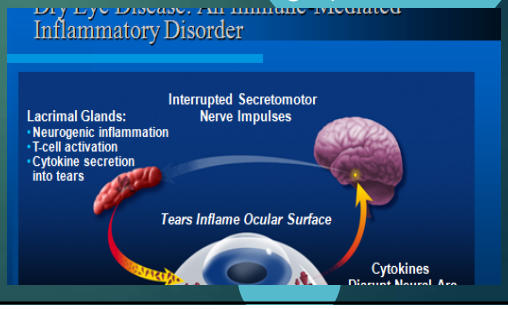
The tear film
- forms a metastable covering between blinks,
- subserving clear vision,
- maintains health and turnover of the ocular surface cells



Lemp MA; AJO 2008 Sept;146(3):350-6

Disturbance of *Intrinsic & Extrinsic Factors* result in final common pathway at the tear film & ocular surface resulting in Dry Eye Disease

- ***Intrinsic***, e.g.
  - --increasing age
  - --hormone balance
  - --local & systemic autoimmune disease
  - --systemic drugs
- ***Extrinsic***, e.g.
  - --topical meds
  - --environmental stress
  - --contact lens wear
  - --refractive surgery



Lemp MA; AJO **2008** Sept;146(3):350-6

Consequences of K. Sicca

- mucus excess
- decreased luster
- punctate keratopathy
- filaments
- keratinization
- band keratopathy

Consequences of K. Sicca

- corneal ulceration
- perforation

And if there is any doubt dry eye prevention & treatment is important…

Cyclosporine study 0.05% (Restasis)

- Over course of 1 year
  - 32% of AT patients progressed DE severity;
  - 6% on cyclosporine therapy

PROOF study

- Prospective 5 year: results in 2018
- Study of DES natural history
- >250 patients enrolled

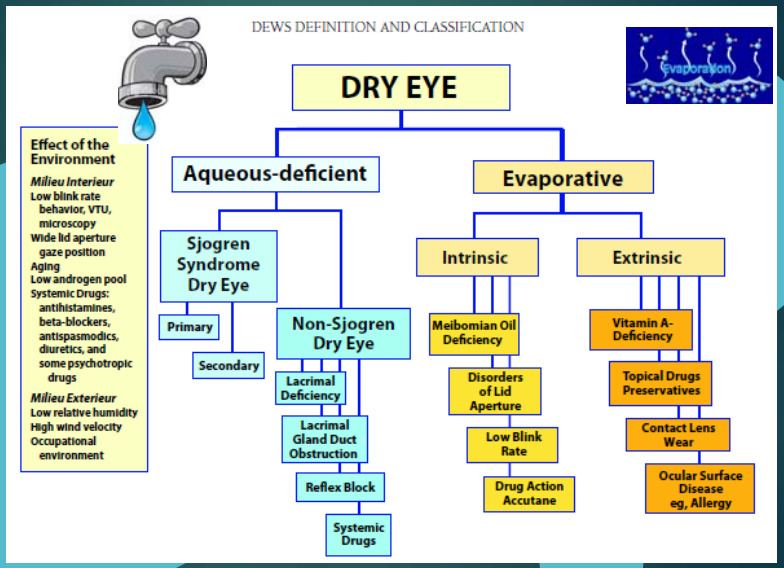
McDonnell, Pflugfelder, Schiffman, et al. IOVS 2013;54 E-Abstract 4338

Critical for good cataract and LASIK surgery outcomes

Etiologic Classification of Dry Eye

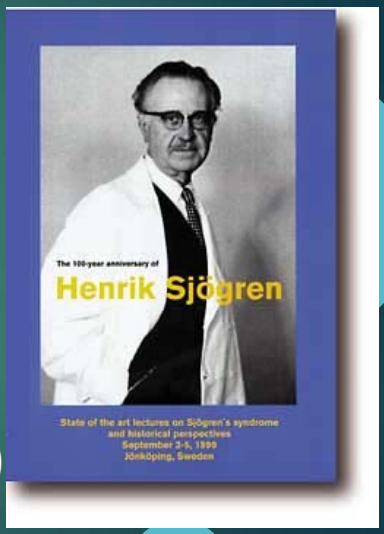
- Aqueous Deficient
- Evaporative

DEWS Workshop Classification



Dry eye workshop 2007

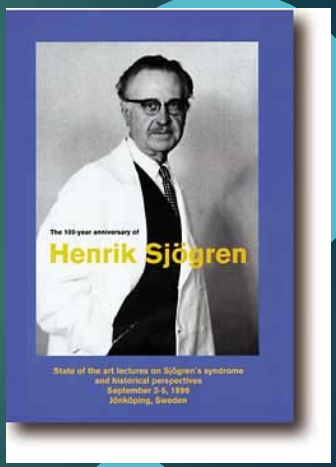
Etiologic Classification of Dry Eye



Aqueous Deficient

- Sjogren's Syndrome
  - Primary
  - Secondary
- Non-Sjogren's
  - Lacrimal gland deficit
  - Reflex block (e.g. surgery)
  - Systemic drugs

Etiologic Classification of Dry Eye



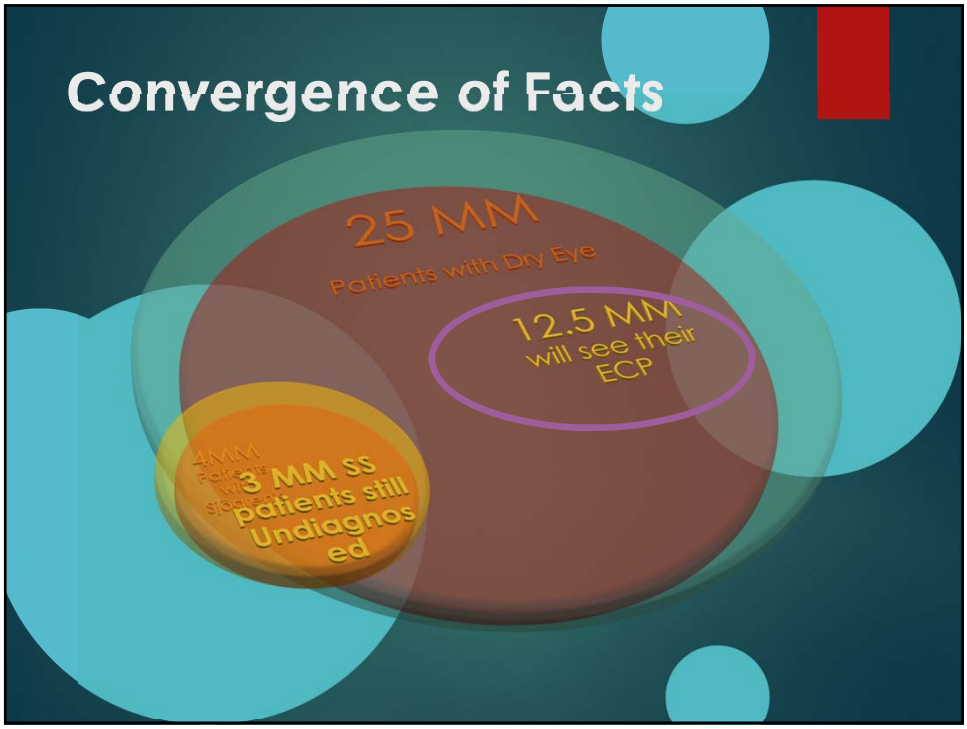
Aqueous Deficient

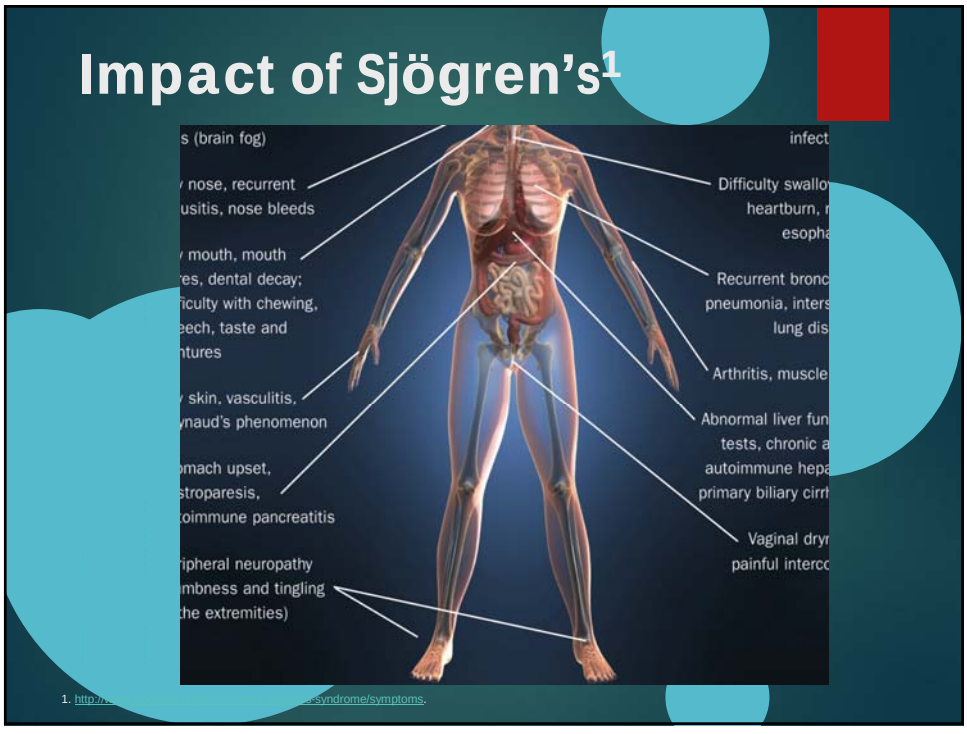
- Sjogren's Syndrome
  - Primary
  - Secondary
- SJO testing
  - Finds up to 30% of DED patients may have systemic disease

SJO TESTING —New Diagnostic!

Myths of Sjögren's

- *"All Sjögren's patients are identified and diagnosed"*
- *"There are only a few patients in my practice"*
- *"Nothing can be done for the patients if they are diagnosed"*
- *"Sjögren's Syndrome does not have serious long-term consequences, it is just a nuisance"*


Convergence of Facts
25 MM
Patients with Dry Eye
12.5 MM
will see their ECP
4 MM
Patients with
Sjögren's
3 MM ss
patients still
Undiagnos
ed

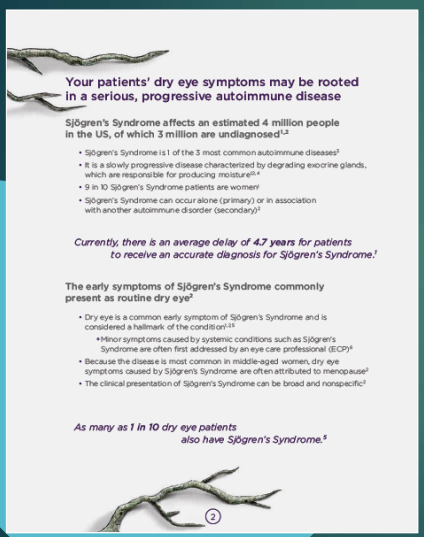

Impact of Sjögren's[1]
s (brain fog)
nose, recurrent
usitis, nose bleeds
mouth, mouth
es, dental decay;
iculty with chewing,
ech, taste and
ntures
skin, vasculitis,
ynaud's phenomenon
mach upset,
troparesis,
oimmune pancreatitis
ripheral neuropathy
mbness and tingling
the extremities)
infect
Difficulty swallo
heartburn,
esopha
Recurrent bronc
pneumonia, inters
lung dis
Arthritis, muscle
Abnormal liver fun
tests, chronic a
autoimmune hepa
primary biliary cirr
Vaginal dry
painful interc
1. http://a
syndrome/symptoms.

Don't forget Sjogren's in Men

- Primary Sjogren's in men represent about 10% of all primary SS patients
- Men usually diagnosed decade later than women—61 vs 50 years (p<0.01)
- 92% report dry eye on presentation
- Men more likely to present with more serious ocular complications than women
- SS extraglandular manifestions more likely e.g. interstitial nephritis, vasculitis p=0.07
- Men more likely negative for SS-A, SS-B, & ANA than women (36% vs 11% p=0.01)

AJO 2015 June 17 Mathews et al

Sjö Diagnostic Testing



Your patients' dry eye symptoms may be rooted in a serious, progressive autoimmune disease

Sjögren's Syndrome affects an estimated 4 million people in the US, of which 3 million are undiagnosed[1,2]

- Sjögren's Syndrome is 1 of the 3 most common autoimmune diseases[3]
- It is a slowly progressive disease characterized by degrading exocrine glands, which are responsible for producing moisture[3,4]
- 9 in 10 Sjögren's Syndrome patients are women[1]
- Sjögren's Syndrome can occur alone (primary) or in association with another autoimmune disorder (secondary)[3]

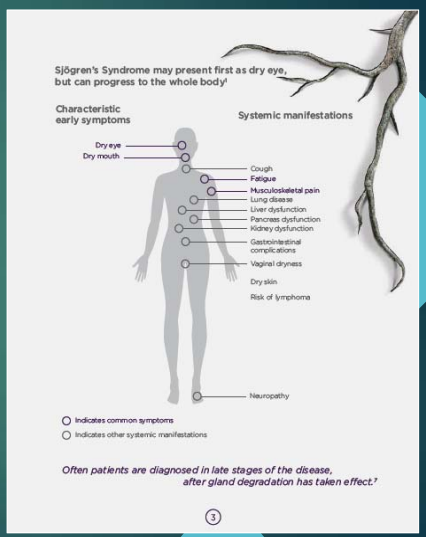
Currently, there is an average delay of 4.7 years for patients to receive an accurate diagnosis for Sjögren's Syndrome.[1]

The early symptoms of Sjögren's Syndrome commonly present as routine dry eye[2]

- Dry eye is a common early symptom of Sjögren's Syndrome and is considered a hallmark of the condition[1,2]
  - *Minor symptoms caused by systemic conditions such as Sjögren's Syndrome are often first addressed by an eye care professional (ECP)[4]
- Because the disease is most common in middle-aged women, dry eye symptoms caused by Sjögren's Syndrome are often attributed to menopause[2]
- The clinical presentation of Sjögren's Syndrome can be broad and nonspecific[2]

As many as 1 in 10 dry eye patients also have Sjögren's Syndrome.[5]

②



Sjögren's Syndrome may present first as dry eye, but can progress to the whole body[1]

Characteristic early symptoms

Dry eye
Dry mouth

Systemic manifestations

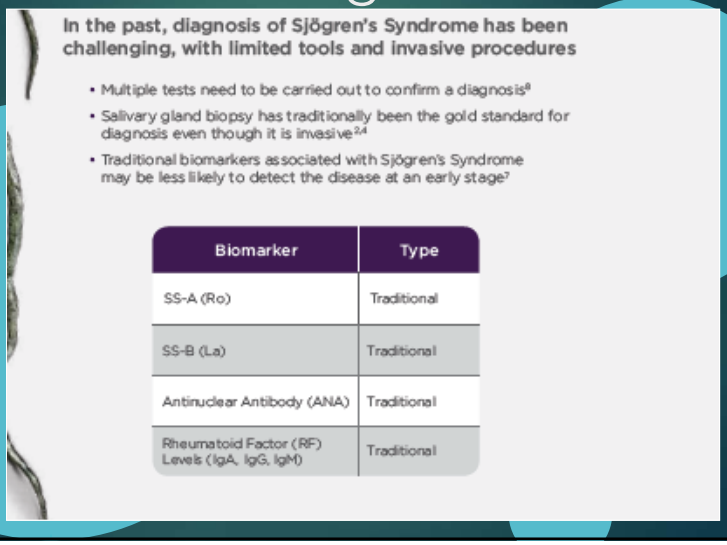
Cough
Fatigue
Musculoskeletal pain
Lung disease
Liver dysfunction
Pancreas dysfunction
Kidney dysfunction
Gastrointestinal complications
Vaginal dryness
Dry skin
Risk of lymphoma
Neuropathy

○ Indicates common symptoms
○ Indicates other systemic manifestations

Often patients are diagnosed in late stages of the disease, after gland degradation has taken effect.[1]

③

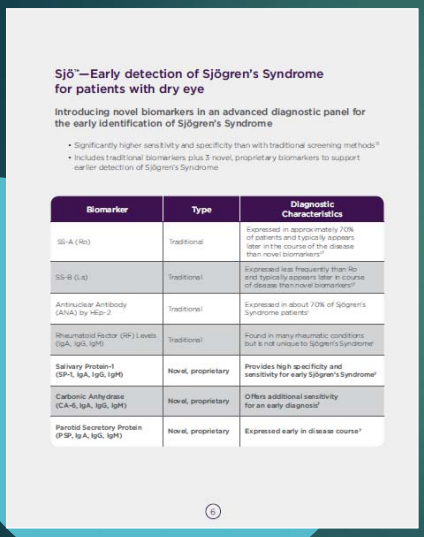
Sjö Diagnostic Testing Traditional testing



Sjö Diagnostic Testing New early detection testing

Biomarker	Type	Diagnostic Characteristics
SS-A (Ro)	Traditional	Expressed in approximately 70% of patients and typically appears later in the course of the disease than novel biomarkers[17]
SS-B (La)	Traditional	Expressed less frequently than Ro and typically appears later in course of disease than novel biomarkers[17]
Antinuclear Antibody (ANA) by HEp-2	Traditional	Expressed in about 70% of Sjögren's Syndrome patients[1]
Rheumatoid Factor (RF) Levels (IgA, IgG, IgM)	Traditional	Found in many rheumatic conditions but is not unique to Sjögren's Syndrome[1]
Salivary Protein-1 (SP-1, IgA, IgG, IgM)	Novel, proprietary	Provides high specificity and sensitivity for early Sjögren's Syndrome[7]
Carbonic Anhydrase (CA-6, IgA, IgG, IgM)	Novel, proprietary	Offers additional sensitivity for an early diagnosis[7]
Parotid Secretory Protein (PSP, IgA, IgG, IgM)	Novel, proprietary	Expressed early in disease course[7]

Sjö Diagnostic Test



Sjö™—Early detection of Sjögren's Syndrome for patients with dry eye

Introducing novel biomarkers in an advanced diagnostic panel for the early identification of Sjögren's Syndrome

- Significantly higher sensitivity and specificity than with traditional screening methods[1]
- Includes traditional biomarkers plus 3 novel, proprietary biomarkers to support earlier detection of Sjögren's Syndrome

Biomarker	Type	Diagnostic Characteristics
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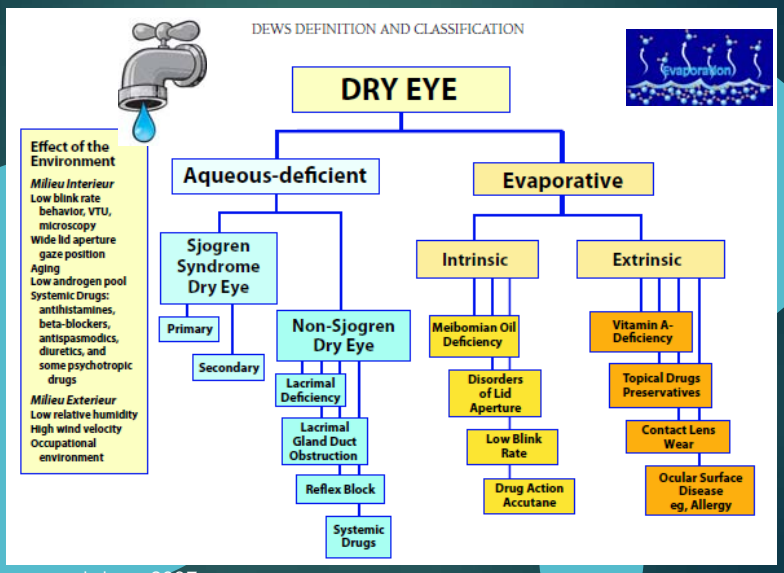
6

- SJO testing recently acquired by Valeant (B&L)
- Testing becoming widely available by local major laboratories
- Now covered by insurance In many cases
- Cash price ~$1000 (US)

Turning to the Most Common Form of Dry Eye

DEWS Workshop Classification



Dry eye workshop 2007

Etiologic Classification of Dry Eye

Evaporative—

86% of Dry Eye Patients have Evaporative Component!

Etiologic Classification of Dry Eye

Evaporative—excessive water evaporation in presence of normal aqueous production

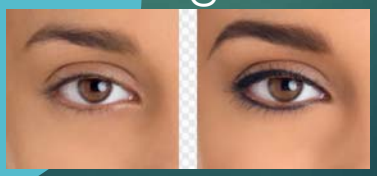
- **Intrinsic** (regulation of evaporation is directly affected)
  - Meibomian gland deficiency (posterior blepharitis)
    - Most common form

Table 4. Meibomian gland diseases causing evaporative dry eye

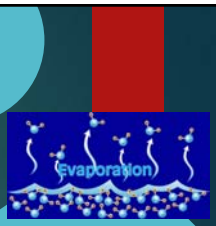
Category	Disease	References
Reduced number	Congenital deficiency Acquired—MGD	Bron et al[137]
Replacement	Dystichiasis	Bron et al[137]
	Dystichiasis lymphedema syndrome	Brooks et al[138] Kiederman et al[139]
	Metaplasia	
Meibomian Gland Dysfunction		
Hypersecretory	Meibomian seborrhoea	Gifford[140] Cowper[141]
Hyposecretory MGD	Retinoid therapy	Mathers et al[142]
Obstructive MGD	Primary or secondary	Bron et al[143]
	Focal or diffuse	Bron et al[143]
	Simple or cicatricial	Foulks and Bron[134]
	Atrophic or inflammatory— note association with dermatoses	Pflugfelder et al[144]
Simple MGD: Primary, or Secondary to:		
Local disease	Anterior blepharitis	
Systemic disease	Acne rosacea; seborrhoeic dermatitis; atopy; icthyosis; psoriasis;	McCulley Dougherty[145] McCulley[146]
Syndromes	Anhydrotic ectodermal dysplasia; ectrodactyly syndrome; Turner syndrome	Baum et al[147] Mondino et al[148]
Systemic toxicity	13-cis retinoic acid	Mathers et al[142] Lambert and Smith[149,150]
	Polychlorinated biphenyls	Ikui[151] Ohnishi et al[152,153]
	Epinephrine (rabbit)	Jester et al[154]
Cicatricial MGD: Primary, or Secondary to:		
Local disease	Chemical burns; trachoma; pemphigoid; erythema multiforme; acne rosacea; VKC and AKC	

Could eyelid tattooing induce Meibomian gland loss?

- Your patient asks: "since I cannot wear makeup due to my dry eyes, can I have eyelid tattooing?"



Does eyelid tattooing induce Meibomian gland loss?

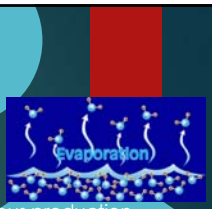


Study: 10 tattoo subjects, 30 controls

- Distance between eyelid tattoo and MG's measured; correl. Meibography & Meiboscore
- Results:
  - TBUT tattoo: 4.3 sec. vs 11.0 control $p<0.001$)
  - Fluorescein staining: worse tattoo ($p<0.001$)
  - MG loss: 3.4 vs 0.9 control ($p<0.001$)

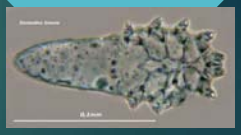
Lee, Kim, Hyon et al Cornea 2015; 34(7):750-755

Etiologic Classification of Dry Eye



Evaporative—excessive water evaporation in presence of normal aqueous production

- **Intrinsic** (regulation of evaporation is directly affected)
  - Meibomian gland deficiency (posterior blepharitis)
    - Most common form
    - Consider Demodex brevis (demodicosis)
      - Recurrent chalazia



  - Disorders of lid aperture
  - Low blink rate/ incomplete blinks
  - Drug action (e.g. retinoids such as Accutane)

Etiologic Classification of Dry Eye

Evaporative (cont)

- **Intrinsic** conditions (cont)
  - Meibomian oil deficiency
  - Low blink rate/ incomplete blinking

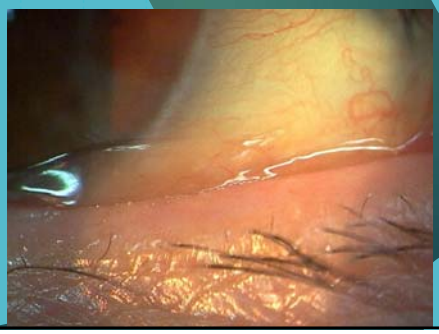
  - Wide lid aperture
  - Conjunctivochalasis

  - Aging/ low androgen pool
  - Systemic drugs

Etiologic Classification of Dry Eye

Evaporative (cont)

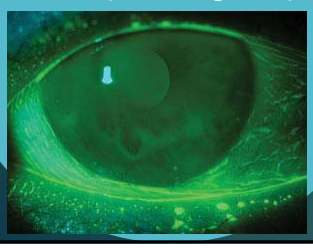
- Conjunctivochalasis:
  - Loss of Tenon's capsule; redundant conj.
  - Reduces tear film reservoir



Etiologic Classification of Dry Eye

Evaporative (cont)

- Conjunctivochalasis:
  - Blue light and fluorescein shows redundant conjunctiva above lid margin
  - Tip of iceberg: shortens inferior fornix
  - Repair surgically



Etiologic Classification of Dry Eye

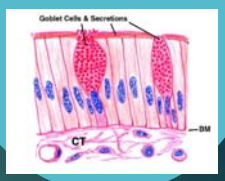
Evaporative (cont)

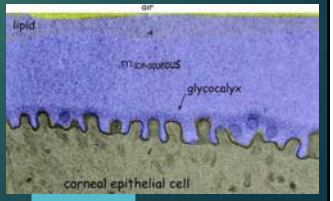
- Intrinsic conditions
  - Low blink rate/ incomplete blinking
  - Wide lid aperture
  - Aging
  - Conjunctivochalasis
  - Low androgen pool
  - Systemic drugs (antihistamines, B-blockers, antispasmodics, diuretics, psychotropic drugs)

Etiologic Classification of Dry Eye

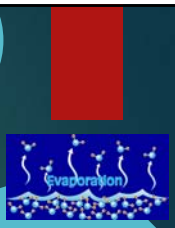
Evaporative (cont)

- **Extrinsic** (increase evaporation by pathological effects on the ocular surface)
  - Vitamin A deficiency
    - Reduced goblet cells/ glycocalyx





Etiologic Classification of Dry Eye



Evaporative (cont)

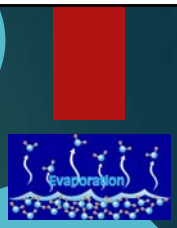
- **Extrinsic** (cont)
  - Contact lens wear
    - (62% women; 40% men)
    - ⇩ Aqueous tear film and lipid layer

Etiologic Classification of Dry Eye

Evaporative (cont)

- **Extrinsic** (cont)
  - Ocular surface disease (OSD)
    - e.g. **allergy**; inflammatory goblet cell reduction (mucin)
    - Topical preservatives;
      - **BAK**
    - drugs e.g. **glaucoma drugs** (OSD 30-70%), antimetabolites
      - inherent drug toxicity + preservative effect

Etiologic Classification of Dry Eye



Evaporative (cont)

- **Glaucoma Drugs**
- Cross-sectional study 109 patients , 79 on topical preserved glaucoma medication
- Results: Drug group
  - Shorter TBUT ($p<0.03$)
  - Greater fluorescein staining ($p<0.001$)
  - Higher impression cytology OSD score ($p<0.001$)
  - More drops caused worse FL staining & shorter TBUT
  - OSDI symptoms **NOT** different between groups

Cvenkel, et al Clin Ophthalmol 2015 Apr 8;9:625-31

Etiologic Classification of Dry Eye

Evaporative (cont)

- Extrinsic/ environmental conditions
  - Low relative humidity
  - High wind velocity
  - Occupational environment
  - Prolonged computer use

Etiologic Classification of Dry Eye

Evaporative (cont)

- Occupational environment
- Prolonged computer/ cell use

Vision Council finds ~95% of Americans spend 2 or more hours daily on digital devices.

--at risk for digital eye strain

--redness, irritation or dry eyes, blurred vision, back & neck pain, headaches

--concerns of blue light overexposure

CRST News Jan 2015

Healthy Tear Film Components

The Healthy Tear Film: A Delicate Balance

Lipid, aqueous & mucin components

Outer **lipid** layer prevents evaporation

- Secreted by meibomian glands

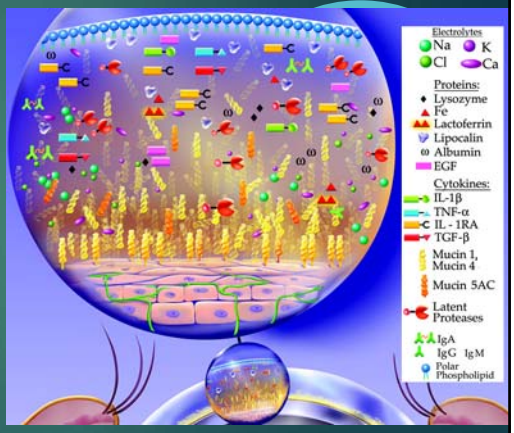
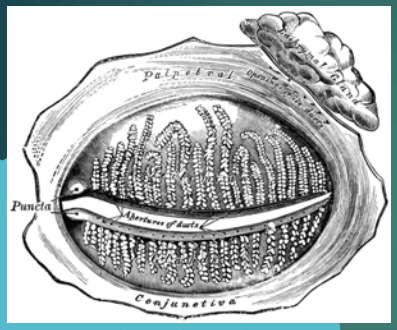


Image from *Dry Eye and Ocular Surface Disorders*, 2004

Lipid Secretion: Meibomian Glands



(WC Posey, *Diseases of the Eye*, 1902)

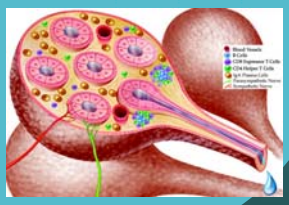
Transillumination of meibomian glands

- The lipid layer
  - Restricts evaporation to 5-10% of tear flow
  - Facilitate tear film spreading over the ocular surface
  - Prevents skin FA's from entering/disrupting tear film

(Transillumination image from Mathers; *Dry Eye and Ocular Surface Disorders*, 2004)

The Healthy Tear Film: A Delicate Balance

- **Aqueous** component – a complex mixture of proteins, mucins, electrolytes
  - Secreted by main & accessory lacrimal glands



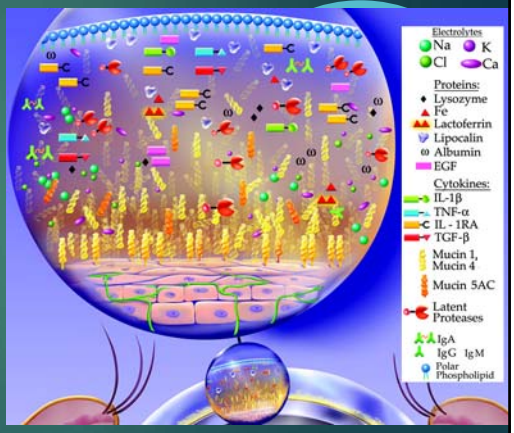


Image from *Dry Eye and Ocular Surface Disorders*, 2004

Aqueous Secretion: Lacrimal Glands

- Lacrimal glands secrete:
  - Aqueous component
  - Most tear proteins
- Similar architecture for main and accessory glands
- Androgens important for glandular homeostasis (Sullivan et al, 1998)

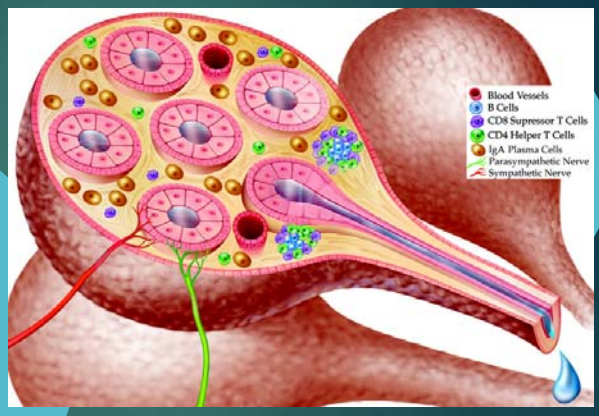
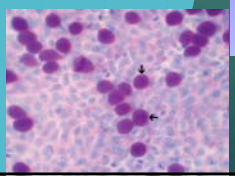


Image from *Dry Eye and Ocular Surface Disorders*, 2004

The Healthy Tear Film: A Delicate Balance

Mucins

- Provide viscosity & stability during blink cycle (gel-like)
- Gel decreases in density toward tear film surface



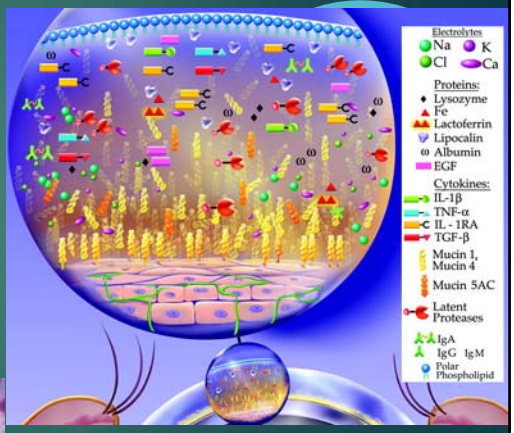
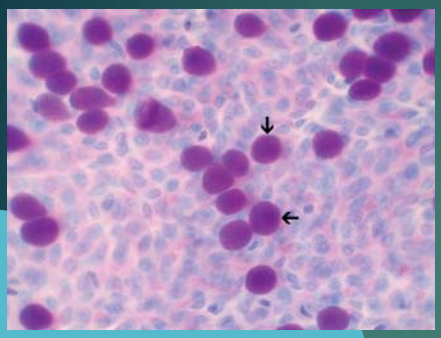
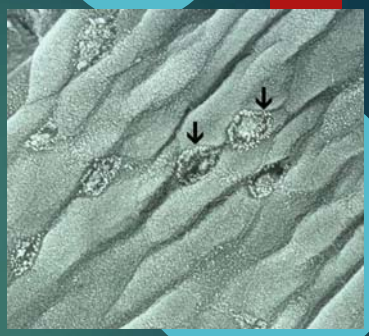


Image from *Dry Eye and Ocular Surface Disorders*, 2004

Mucin Secretion: Goblet Cells





- 5-20% of conjunctival epithelial cells are mucin-producing goblet cells
- Soluble mucins - essential for viscosity of the normal tear film--Helps resist thin spots and tear break-up
- Tear film is somewhat like a mucin/aqueous gel
- Inflammation causes loss of goblet cells (apoptosis)

Image from *Dry Eye and Ocular Surface Disorders*, 2004

Healthy Tears

- A complex mixture of proteins, mucin, and electrolytes
- Antimicrobial proteins: Lysozyme, lactoferrin
- Growth factors & suppressors of inflammation: EGF, IL-1RA
- Soluble mucin 5AC secreted by goblet cells provides viscosity
  - Membrane-bound mucins 1 & 4 help stabilize tear film
- Electrolytes for proper osmolarity

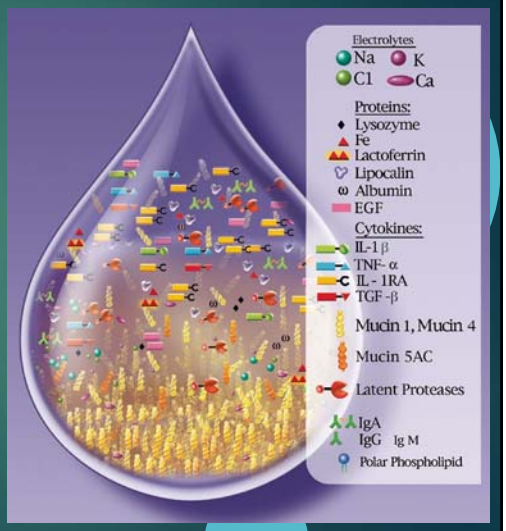


Image from *Dry Eye and Ocular Surface Disorders*, 2004

Tears in Chronic Dry Eye (CDE)

- Lesser concentrations of many proteins in CDE
  - *e.g.* antimicrobial proteins
- Growth factor concentrations decreased
- Cytokine balance shifted, promotes inflammation
- Soluble mucin 5AC greatly decreased
  - Due to loss of goblet cells
  - Impacts viscosity of tear film
- Activated proteases
  - Degrade extracellular matrix & tight junctions
- Increased electrolytes/ hyperosmolar

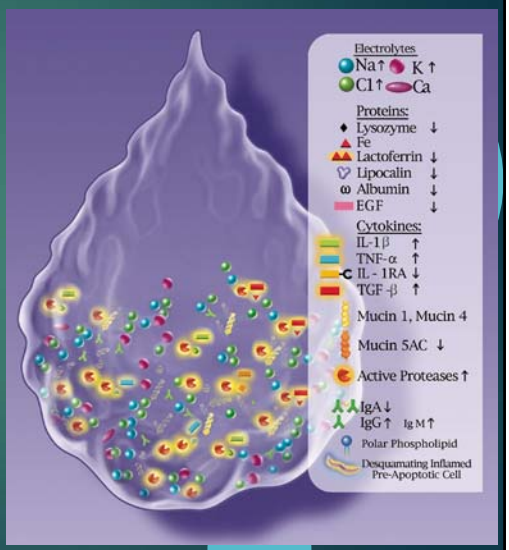


Image from *Dry Eye and Ocular Surface Disorders*, 2004

Overall, Who Is Most Likely to Have Dry Eye? (abbreviated epidemiology)

- Women aged 50 or older[1]
- Women using postmenopausal hormone replacement therapy[2]
- Those with ocular comorbidities[3]
- Contact lens wearers[3]
- Users of artificial tears ≥ 3 times/day

1. Schaumberg et al. *Am J Ophthalmol*. 2003; 2. Schaumberg et al. *JAMA*. 2001; 3. Lemp. *CLAO J*. 1995

Diagnosis of DES

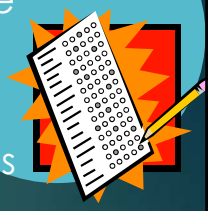
Diagnosis

- *Until recently*, no reliable sensitive test to diagnose dry eyes
- If relatively severe, diagnosis made based on clinical exam +/- Schirmer's testing
- Milder cases: establishment of diagnosis is often difficult and is based *more on symptoms*

—Recent exceptions: MGD testing, Osmolarity & MMP-9?

Diagnosis: Questionnaires

- Currently, symptom questionnaires are among most repeatable of the commonly used diagnostic tests

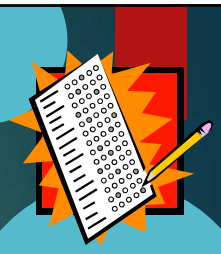


- ~14 commonly used questionnaires
- Signs and symptoms often don't correlate with moderate & severe disease
- Useful to monitor response to therapy

Diagnosis

Osaka study (2015)

672 Japanese office VDT users



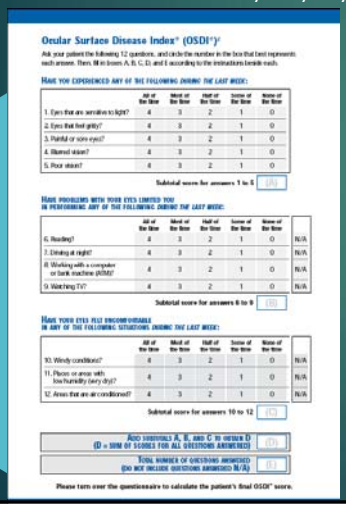
- Found subjective happiness (subjective happiness scale) inversely correlated with dry eye symptoms score (Happy = fewer symptoms)
- Happiness Scale did not correlate with objective findings
- **Worst** symptoms with **no objective findings** found in **unhappiest patients**

PLoS One. 2015 Apr 1;10(4)

Diagnosis

Example symptom questionnaire:

OSDI for inflammatory dry eye

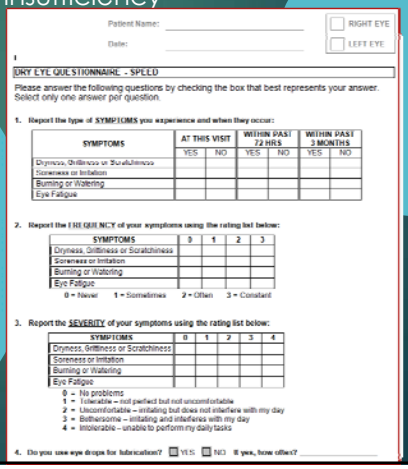


Diagnosis

Example symptom questionnaire:

SPEED test

--for evaporative tear film insufficiency



Patient Name: _____ RIGHT EYE

Date: _____ LEFT EYE

DRY EYE QUESTIONNAIRE - SPEED

Please answer the following questions by checking the box that best represents your answer. Select only one answer per question.

1. Report the type of SYMPTOMS you experience and when they occur:

SYMPTOMS	AT THIS VISIT		WITHIN PAST 72 HRS		WITHIN PAST 3 MONTHS	
	YES	NO	YES	NO	YES	NO
Dryness, Grittiness or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

2. Report the FREQUENCY of your symptoms using the rating list below:

SYMPTOMS	0	1	2	3
Dryness, Grittiness or Scratchiness				
Soreness or Irritation				
Burning or Watering				
Eye Fatigue				

0 = Never 1 = Sometimes 2 = Often 3 = Constant

3. Report the SEVERITY of your symptoms using the rating list below:

SYMPTOMS	0	1	2	3	4
Dryness, Grittiness or Scratchiness					
Soreness or Irritation					
Burning or Watering					
Eye Fatigue					

0 = No problems
1 = Tolerable – not perfect but not uncomfortable
2 = Uncomfortable – irritating but does not interfere with my day
3 = Bothersome – irritating and interferes with my day
4 = Intolerable – unable to perform my daily tasks

4. Do you use eye drops for lubrication? ☐ YES ☐ NO If yes, how often? _____

Diagnosis

91 subject study of ***mild to moderate*** dry eye, correlating symptoms and common tests

- Aqueous deficiency tests (Phenol red thread, tear film break up time, slit lamp evaluation and impression cytology of goblet cells): ***no correlation with Dry Eye Questionnaire (McMonnie's)***
- Only lipid/ mucous deficiency tests correlated with symptoms ***(MG pathology, reduced goblet cell density and TBUT correlated with Dry eye questionnaire)***

Moore, Graham, Goodall et al BJO **2009**:93:66-72

Diagnosis Questionnaires caveat

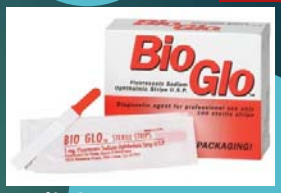
- Recent studies have shown <60% of DED subjects with objective dry eye have symptoms
- Using symptoms alone likely to miss significant % of patients with DED, particularly with early/mild disease (e.g. anticipating cataract, refractive sx)

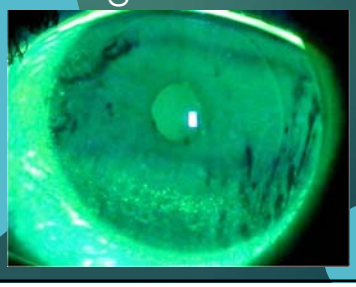
Bron, Tomlinson, Foulks, Pepose, Baudouin, Geerling, Nichols, Lemp: Ocul Surf 2014 Apr;12(2 Suppl):S1-31.

Common Tests for Dry Eye

Diagnosis: common tests

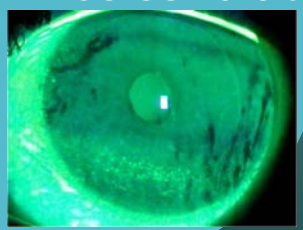
- Fluorescein staining
  - Conjunctival staining in milder cases
  - Corneal staining in more severe cases





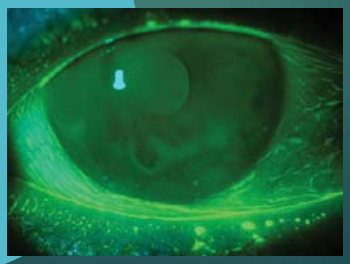
Diagnosis: common tests

- Fluorescein staining
  - Conjunctival staining in milder cases
  - Corneal staining in more severe cases
  - Deep yellow filter (Wratten #12)
  - Evaluate after 1-2 minutes to detect late staining



Diagnosis: common tests

- Fluorescein staining
  - Conjunctival staining in milder cases
  - Corneal staining in more severe cases
  - Deep yellow filter (Wratten #12)
  - Evaluate after 1-2 minutes to detect late staining
  - Look for conjunctivochalasis folds

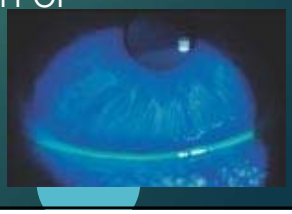


Diagnosis: common tests

- Tear breakup time
  - Good aid for diagnosing meibomian gland dysfunction in presence of adequate aqueous layer
  - Fluorescein instilled, blink several times to distribute
  - Do before any anesthetic administration
  - Patient looks straight ahead without blinking

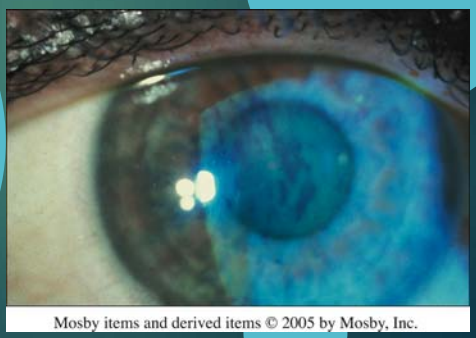
Diagnosis: Other tests

- Fluorescein Dilution/ Disappearance
  - Measures decrease of fluorescence by production of new tears
  - Drop fluorescein instilled and fluorescence measured over time with stop watch or photometer
  - Confounded by punctal occlusion



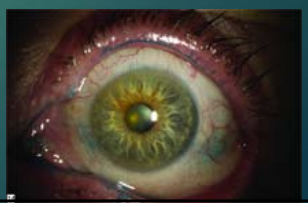
Diagnosis: common tests

- Tear breakup time
  - Observe with cobalt blue light for black islands or streaks in the green film
  - <10 seconds abnormal



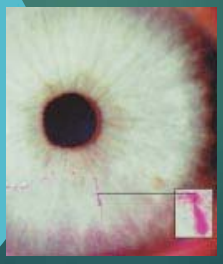
Diagnosis: common tests

- Rose bengal or lissamine green staining
  - --Stains cells lacking protection by precorneal tear film and mucus
  - --interpalpebral pattern on conjunctiva and cornea
  - Milder cases staining limited to the conjunctiva

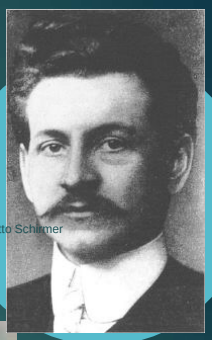
Diagnosis: common tests

- Rose bengal or lissamine green staining
  - -- LG is more comfortable
  - --Severest cases: most of cornea stains; mucus filaments may be present; SLK-like staining


Diagnosis: common tests

Schirmer's Testing (1903)


Otto Schirmer

Schirmer's I

- Measures total reflex and basic tear secretion
- Unanesthetized
- Should not be <10 mm

Diagnosis: common tests

- Basic Secretion Test
  - Instill topical anesthetic (wait 3-4 minutes)
  - Dry cul-de-sac
  - Insert Schirmer strips
  - Wait 5 minutes
  - Abnormal: <3mm
  - False negatives frequent due to incomplete anesthesia

Diagnosis: common tests

Schirmer's Testing

- Schirmer's II (measures reflex secretion)
  - Rarely used
  - Instill topical anesthetic
  - Rub nasal mucosa with cotton swab
  - Measure wetting after 2 minutes
  - Wetting <15 mm = failure of reflex secretion

Diagnosis: common tests

Phenol red thread test

- Less invasive
- 70mm cotton thread
- Wetting with tears 15 seconds
- Changes yellow red
- 9-20mm normal

Less Used Tests for Dry Eye

- Tear lysozyme
- Tear lactoferrin
- Impression cytology (conjunctival)
- Tear film osmolality

Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- MGD Analysis
  - Physical inspection
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
  - MG expressibility (Korb MGE)
  - Tear film lipid layer thickness--interferometry

Newer Tests for Dry Eye

- **Tear Film Osmolarity**
- Tear Film Thickness
- MMP-9
- MGD Analysis
  - Physical inspection
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
  - MG expressibility (Korb MGE)
  - Tear film lipid layer thickness--interferometry

Diagnosis: Newer tests

- Tear Film Osmolarity
  - Relatively sensitive for diagnosis
  - Tear Lab

DEWS Definition of Dry Eye Disease

Dry eye is a multifactorial disease of the tears and ocular surface… It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

Testing for osmolarity is a good place to start

Note: the definition was updated 2 years prior to TearLab approval and based on 40+ years of research using tear osmometers requiring 500 to 1000 times the volume now needed (50 nanoliter sample)

International Dry Eye Workshop (DEWS). The definition & classification of dry eye disease. Ocul Surf 2007.

Two Numbers Crucial to Understand Osmolarity

The MAXIMUM of the two eyes:

Tears higher than 300 mOsm/L demonstrate loss of homeostasis and likely become pathogenic > **308**.

The DIFFERENCE b/w two eyes:

This shows the stability of the tear film. Normal tears are stable and < 300 mOsm/L bilaterally. A difference of > 8 mOsm/L is a hallmark of tear instability.

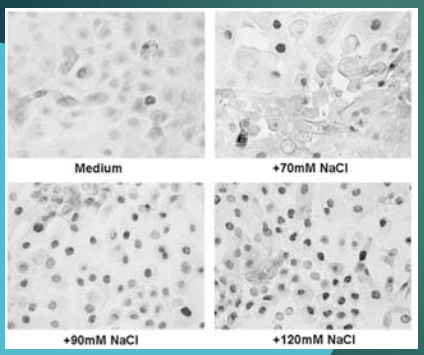
Non-DED Patients are Low and Stable - DED Patients are Elevated and Unstable

	Mild/Moderate Dry Eye Patient OSDI = 22.92		Normal Patient OSDI = 4.17	
	Right Eye	**Left Eye**	**Right Eye**	**Left Eye**
Day 1				
1 min	311	326	286	288
2 min	304	324	285	289
3 min	308	308	281	281
4 min	337	334	287	286
Day 2				
1 min	315	321	296	284
2 min	305	313	296	291
3 min	315	323	285	291
4 min	297	343	291	287
Day 3				
1 min	308	307	290	292
2 min	320	312	287	291
3 min	307	309	286	286
4 min	333	332	292	295
Mean	**313**	**321**	**289**	**288**
Stdev	**11.8**	**11.5**	**4.6**	**3.9**

Keech A, et al. Curr Eye Res 2013 Apr;38(4) 428-36

Hyperosmolarity-Induced Apoptosis in Human Corneal Epithelial Cells Is Mediated by Cytochrome c and MAPK Pathways

Lihui Luo, MD,†‡ De-Quan Li, MD, PhD,* and Stephen C. Pflugfelder, MD**



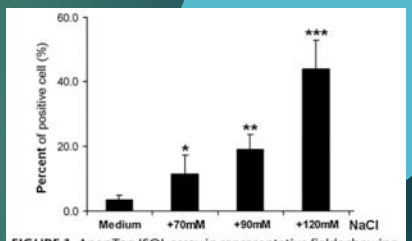


FIGURE 1. ApopTag ISOL assay in representative fields showing the increased ISOL-positive apoptotic cells in corneal epithelial cultures exposed to high-osmolarity saline–added media (+70, 90, or 120 mM NaCl) for 24 hours, compared with cells cultured in normal medium. The percentage of positive cells in each group ($n = 5$) is shown in the graph. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ compared with control medium.

Luo L, *Cornea*. 2007 May;26(4):452-60.

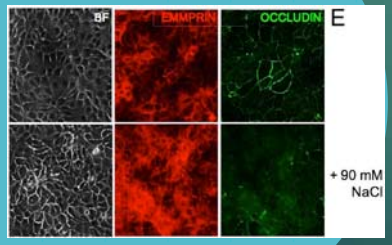
Hyperosmolarity Upregulates EMMPRIN/MMP-9

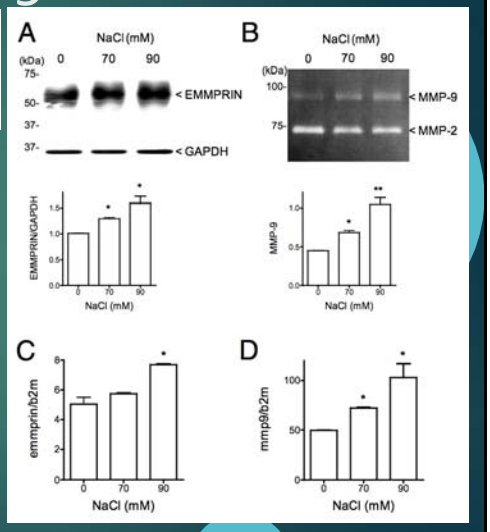
High Osmolarity Increases EMMPRIN Expression in Human Corneal Epithelial Cells and Is Associated with an Increase in MMP-9 and a Loss of Epithelial Cell–Cell Junctions

Eric Huet,*† Benoit Vallée,* Jean Delbé,*† Samia Mourah,† Virginie Prulière-Escabasse,§ Magali Tremouilleres,† Kenji Kadomatsu,¶ Serge Doan,‖ Christophe Baudouin,‖** Suzanne Menashi,* and Eric E. Gabison‖*†††

The American Journal of Pathology, Vol. 179, No. 3, September 2011

DOI: 10.1016/j.ajpath.2011.05.036





Cell remodeling, spk, surgery, ulceration

Huet E et al. *Am J Pathol*. 2011;179.

Hyperosmolarity Upregulates
--inflammatory cytokines
e.g. interleukins, metalloproteinases
--cycle of inflammation with apoptosis, T-cell infiltration
--symptoms of dryness, irritation

Huet E et al. *Am J Pathol*. 2011;179.

Why Measure Tear Osmolarity?

Measuring osmolarity allows us to evaluate an actual **physiologic marker** rather than a "sign" of the disease such as staining or tear break up time.

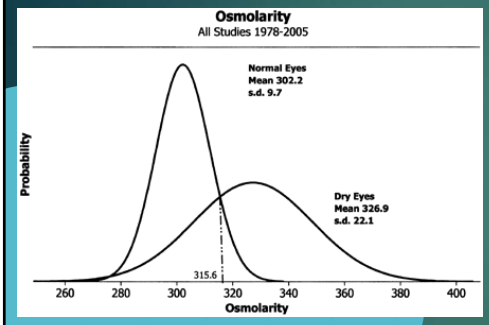
Like BP or serum glucose!

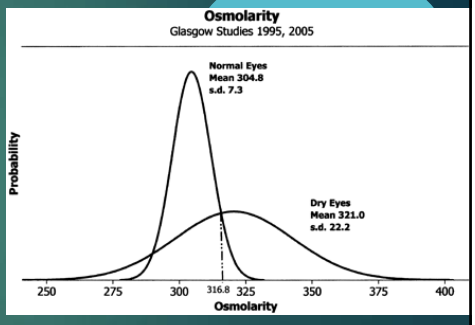
Abstract Title: Measuring Tear Film Osmolarity in Dry Eye Disease: A Review of the Literature

Christopher J. Rapuano , Rick Potvin (ASCRS 2015 Poster)

- Purpose: To analyze the role of objectively measuring tear film osmolarity in the diagnosis of dry eye disease, based on a review of the peer-reviewed literature.
- Methods: A literature search of all peer-reviewed articles associated with tear film osmolarity was conducted. Identified studies were graded into four categories: very low, low, moderate and high quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE
- Results: 164 peer-reviewed study articles relevant to tear osmolarity and dry eye disease were identified. Of these, 72% indicated that tear film osmolarity was a useful diagnostic tool, while 7% suggested no utility to the test. Thirty percent of studies were rated as 'moderate' to 'high' quality based on study design. In this subgroup 73% supported the use of objective tear osmolarity measurement in dry eye diagnosis, 18% were neutral regarding the test and 10% suggested no utility.
- Conclusion: Tear film osmolarity has been identified as a central mechanism related to dry eye disease by the Dry Eye Workshop (DEWS) report. Peer-reviewed literature indicates that an objective evaluation of tear film osmolarity is valuable in the diagnosis of dry eye disease.

Tear Osmolarity: various studies





Tear Osmolarity: various studies

- What is the value of incorporating tear film measurement in assessing patient response to therapy in DED?
  - Single institution study
  - 186 patients w/ DED
  - 2 visits: Tear Osm (Tear Lab) vs OSDI symptoms & fluorescein staining (mod Oxford scheme)

Results

Fluorescein staining and symptoms modest correlation

No correlation between change in OSM and symptoms

*Change in Tear OSM didn't correlate significantly with changes in symptoms or corneal fluorescein staining between **2 visits***

Amparo, Dana et al AJO 2013: Sept 20 Epub

Tear Osmolarity: various studies

Recent NHS (UK) study:
--596 patients
Osm ➡ highest positive ***predictive value*** of dry eye disease compared with other routine diagnostic tests (no Schirmer's testing)
% DED by Osm 72.3%, in good agreement with DEWS scores (78%)

Wong K, Din N, Ansari E, et al. Tear osmolarity prevalence in general NHS ophthalmic clinics and relationtoclinical examination of dry eye. Poster presented at: XXXII Congress of the ESCRS, London, UK, Sept 13-17, 2014

Besides the science, why Measure Tear Osmolarity?

Patients may not think they have dry eye (e.g. down-regulated nerves).

Osm = Objective number

- "This test shows that the Osm of your tear film is XX points above normal which indicates you have dry eye"—end of discussion
- Patients become aware of this number as something they want to work to lower, just like blood pressure or cholesterol levels
- Encourages compliance

M. McDonald, MD

Confounding variables of tear film osmolarity

- Time from most recent eye drops (2 h minimum)
- Environmental conditions
- Patient just drive to clinic?
- Other disease process e.g. allergy, blepharitis
- Blepharitis average Osm approaches 305 cut off ----304 mOsm/L JAMA Ophthalmol 2015 Mar 26
- Dry eye variability of 8 mOsm is typical; between visits—makes it hard to interpret response to therapy

Tear Osmolarity Can Be Used To Follow The Response To Treatment

- Objective way to determine if patient is responding to treatment
- Do at each follow up visit, like BP measurement
- If Osm improving, can reassure patient they are improving even if symptoms (or signs) haven't improved yet
- Don't rely on single day's measurement

DED Can Affect Surgical Outcomes

Hyperosmolarity Can Decrease Visual Acuity and/or Quality of Vision including post-operatively

DED frequent cause of failure of premium lenses

Osm & Contact Lenses

- Diagnosing hyperosmolarity in potential contact lens patients, particularly past failed CL wear can signal need for aggressive therapy with Omega 3's, MGD TX, plugs, Restasis…
- Once the hyperosmolarity is controlled, patients can be ***more likely to wear contacts successfully***
- Studies are now showing hyperosmolarity responds well with Omega 3 supplements @ 2 months and this can be monitored over time
- Punctal occlusion has been shown in studies to reduce osmolarity in patients NOT having significant inflammation

Newer Tests for Dry Eye

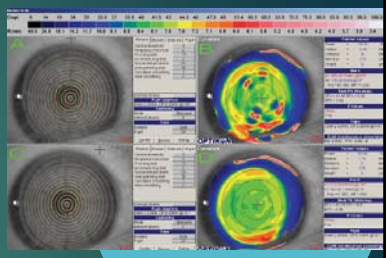
- Tear Film Osmolarity
- **Tear Film Thickness**
- MMP-9
- MGD Analysis
  - Physical inspection
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
  - MG expressibility (Korb MGE)
  - Tear film lipid layer thickness--interferometry

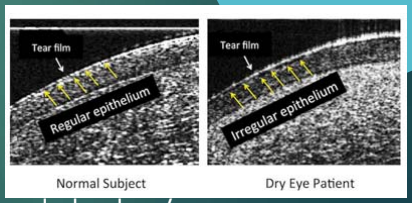
Diagnosis: Other tests

Tear Film thickness

Corneal topography

O.C.T.





Tear film thickness correlated w/ subjective symptoms Schmidt et al IOVS 2015 Feb 3;56(3):1467-72

Newer Tests for Dry Eye

- Tear Film Osmolarity
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- **MMP-9**
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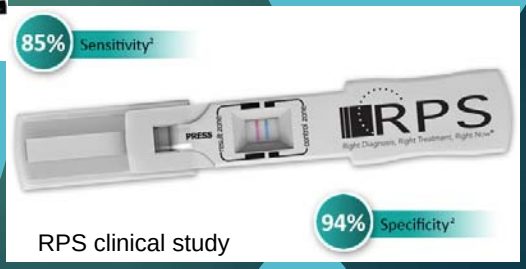
Diagnosis: Other tests

MMP-9 testing

RPS clinical study

Diagnosis: Other tests

MMP-9 testing—InflammaDry (CLIA waved)



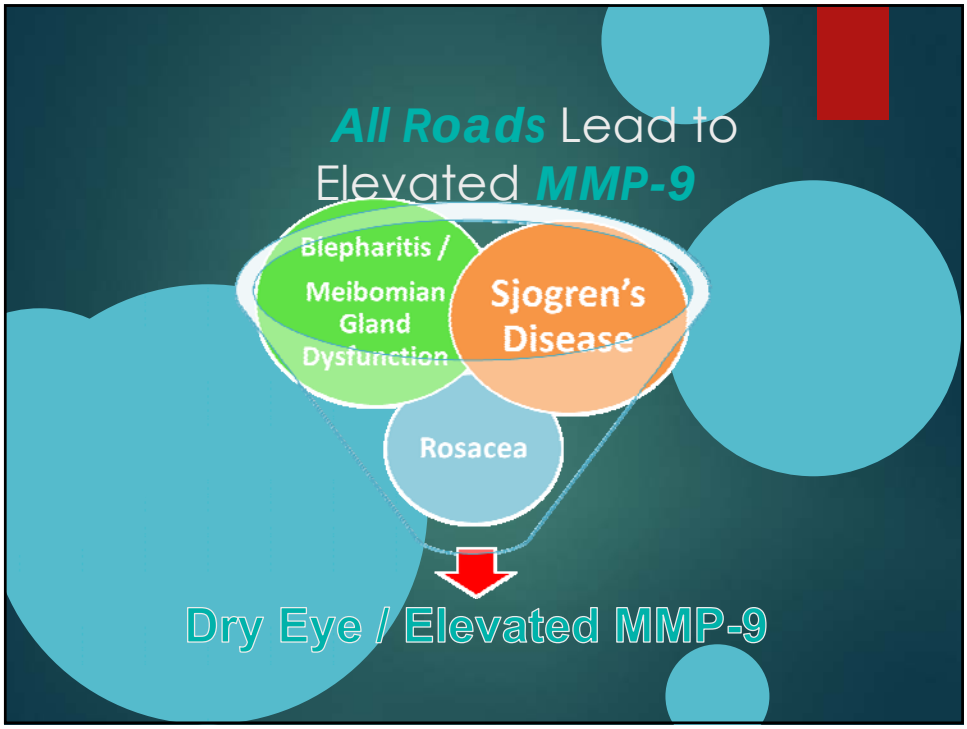
RPS clinical study

Dry Eye Disease and *MMP-9*

Matrix metalloproteinases (MMP) are proteolytic enzymes that are produced by stressed epithelial cells on the ocular surface[1]

- MMP-9 in Tears
  - Non-specific inflammatory marker
  - Normal range between 3-41 ng/ml
  - Correlates with clinical exam findings[1]
  - Ocular surface disease (dry eye) demonstrates elevated levels of MMP-9 in tears[1]

[1] Chotikavanich S, de Paiva CS, Li de Q, et al. Production and activity of matrix metalloproteinase-9 on the ocular surface increase in dysfunctional tear syndrome. Invest Ophthalmol Vis Sci. 2009 Jul;50(7):3203-9.



Diagnosis: Other tests

MMP-9 testing—InflammaDry

- More sensitive marker than clinical signs
  Chotikanovich, Pflugfelder et al IOVS 2009 Jul50(7):3203-9
- Reflects inflammation present before clinical signs
  Sambursky, O'Brien Curr Opin Ophthalmol 2011 Jul:22(4):294-303

Diagnosis: Other tests

MMP-9 testing—InflammaDry

- 15 minute in office test

Diagnosis: Other tests

MMP-9 testing—InflammaDry

237 patient study, 4 trial sites

Tbut, Schirmer, Staining, +/- OSDI

81-86% **positive** agreement for DES

If MMP-9 **negative**, 97-98% agreement not dry eye

Sambursky R et al Cornea 2014 Aug; 33(8): 812-8

InflammaDry Compared to TearLab Osm

- Osmolarity is associated with variability[1-3]
  - Osmolarity levels vary greatly throughout the day[3]
  - Reflex tearing may dilute osmolarity levels in the tear sample, causing further variability
- MMP-9 is produced by the entire lacrimal system
  - Reliable biomarker for inflammation, consistently elevated in the tears of patients with ocular surface disease[4]
  - **Reflex tearing** does not affect test result

[1] Yagci A, Gurdal C. The role and treatment of inflammation in dry eye disease. Int Ophthalmol. 2014 Dec;34(6):1291-301. [2] Eldridge DC, Sullivan BD, Berg MD, et al. (2010) Longitudinal variability of tear film osmolarity in normal and dry eye patients. Investig Ophthalmol Vis Sci 51(5):3379–3381 [3] Fuerst N, Massaro-Giordano M, McCabe B, et al. Variability of tear osmolarity in dry eye patients and controls. Abstract submitted for publication (May 2014): The Association for Research in Vision and Ophthalmology. [4] Chotiakavanich S, de Paiva CS, Li de Quan, et al. Invest Ophthalmol Vis Sci 2009; 50(7):

Key Clinical Results[1]

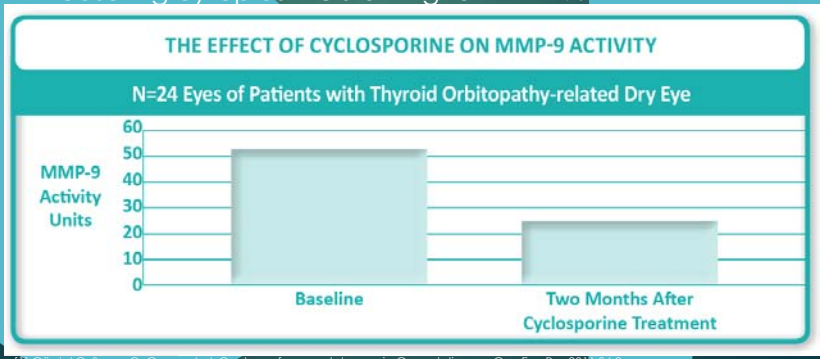
- N=237 *symptomatic* patients
  - 61% (146/237) confirmed dry eye by TBUT, Schirmer, staining ***or*** OSDI
    - Of the 61% ***confirmed*** dry eye, ***InflammaDry*** was ***positive 81%*** of the time
    - Of all ***symptomatic*** patients, ***InflammaDry*** was ***positive 53%*** of the time
  - 39% (80/237) confirmed negative by TBUT, Schirmer, staining ***and*** OSDI
    - Of the 39% ***confirmed*** negative, ***InflammaDry*** was also ***negative 98%*** of the time

In patients having symptoms consistent with dry eye disease, *InflammaDry* is expected to be *POSITIVE* approximately *50%* of the time.

[1] Sambursky R, Davitt WF 3rd, Friedberg M, Tauber S. Prospective, multicenter, clinical evaluation of point-of-care matrix metalloproteinase-9 test for confirming dry eye disease. Cornea. 2014 Aug;33(8):812-8.

Cyclosporine and MMP-9[1]

- MMP-9 expression was evaluated by immuno-histochemistry. The mean percentage of MMP-9 expression of the conjunctival epithelial cells was significantly decreased.
- MMP-9 expression was evaluated semi-quantitatively by measuring cytoplasmic staining for MMP-9.



[1] Gürdal C, Saraç O, Genç, et al. Ocular surface and dry eye in Graves' disease. Curr Eye Res.2011;36:8-13.

Punctal *Occlusion*

- Punctal occlusion has been shown to improve objective and subjective measures of dry eye to and to ***exacerbate ocular surface inflammation*** in subjects with overt clinical inflammation[1]
- The Delphi treatment guidelines for ocular surface disorders recommends that ***inflammatory conditions be treated before punctal occlusion***[2]

[1] Pflugfelder SC. Antiinflammatory therapy for dry eye. Am J Ophthalmol. 2004 Feb;137(2):337-42. [2] Behrens A, Doyle JJ, Stern L, et al. The Dysfunctional Tear Syndrome Study Group. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. *Cornea. 2006;25:900-907.*

Example: Importance of Identifying MMP-9

- Dry eye frequently leads to ***contact lens intolerance***
  - **InflammaDry POSITIVE** patients will benefit from the following management plan:
    - Daily disposable contact lens use
    - Cyclosporine
    - Omega 3 fatty acids
    - Punctal occlusion after inflammation controlled
  - **InflammaDry NEGATIVE** symptomatic patients will benefit from the following management plan:
    - Daily disposable contact lens use
    - Omega 3 fatty acids
    - Punctal occlusion

OK, I can only add Osm or MMP-9 for DES

- Which one should I choose?

OK, I can only add **Osm** or **MMP-9** for DED: *Which One?*

- Direct comparative study, *EARLY* DED
- 20 patients >60 y.o. to r/o DED
- T Osm , MMP-9 (incl InflammaDry), Schirmer, TBut, OSDI, Fluorescein staining, LG staining

Results: **MMP-9** positive: 1/9 symptomatic and 2/14 suspected mild DED

T Osm positive: 6/9 symptomatic, 9/14 suspected mild DED

Thus: **T Osm** tends to be a more frequent early indicator (***n*** was too small for adeq. P values)

Schargus, et al Cornea 2015 Apr 23

Newer Tests for Dry Eye

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- Tear Film Thickness
- MMP-9
- **MGD Analysis**
  - Physical inspection
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
  - MG expressibility (Korb MGE)
  - Tear film lipid layer thickness--interferometry

Diagnosis: other tests

Meibomian gland analysis

Diagnosis: other tests

Meibomian Gland Analysis

Why Do This?

Meibomian Gland Dysfunction

- 2011 Report of the International Workshop on meibomian gland dysfunction
- 2 years to complete

MGD: Leading Underlying Cause of Dry Eye![1-3]

"Meibomian gland dysfunction may well be the leading cause of dry eye disease throughout the world."[4]

—The International Workshop on Meibomian Gland Dysfunction: Executive Summary

1. Lemp MA, Nichols KK. Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment. *Ocul Surf*. 2009;7(2 suppl):S1-S14.
2. Lemp MA, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea*. 2012;31(5):472-478.
3. Shimazaki J, et al. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. *Arch Ophthalmol*. 1995;113(10):1266-1270.
4. Nichols KK, et al. The international workshop on meibomian gland dysfunction: executive summary. *Invest Ophthalmol Vis Sci*. 2011;52(4):1922-1929.

MGD: Underlying Cause of Dry Eye

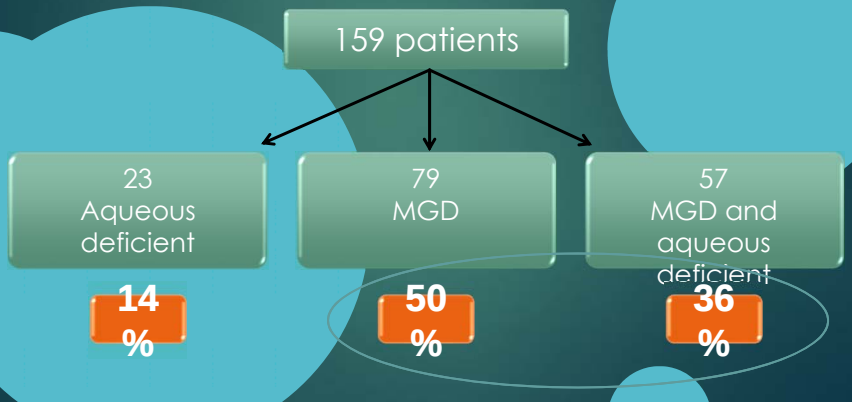
Ocular Surface Inflammation is often linked to meibomian gland inflammation

"*—We propose that the ocular surface and the adnexal meibomian glands should be considered as one unit, i.e. the "meibomian gland and ocular surface (MOS) when encountered in the clinical setting"*

Suzuki T, Teramakai S, Kinoshita S. Ocul Surf 2015 Apr;13(2)133-149

Prevalence of Evaporative Dry Eye

Recent study by Lemp et al reports
86% of patients evaluated had Evaporative Dry Eye



Lemp MA, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea.* 2012;31(5):472-478.

VDT Dry Eye Severity (Computer Vision Syndrome)

Prospective case control study (China)

106 eyes of 53 patients

VDT time >4 h/day vs </= 4 h/day

OSDI, TBut, Fluorescein staining; Schirmer I

3 MGD parameters: lid margin abn; meibum score; meibumian gland dropout

Conclusion: *MGD is associated with dry eye patients in long term VDT workers with higher OSDI scores—yet may have normal tear volume*

Wu, Wang, Dong, Yang, Lin, Shang, Li: PLoS One 2014 Aug 21 e collection

MGD and Daily Soft Contact Lens Use

Study of 41 CL uses vs 31 non-users

- CL wearers statistically worse:
  - Lid margin telangiectasias (OR 6.0)
  - Rounding (OR 9.3)
  - Notching (OR 3.9)
  - Posterior margin hyperemia (OR 4.3)
  - Orifice plugging (OR 4.8)

Greater CL wear duration resulted in greater lid margin abnormalities

MGD is Chronic and Progressive

- Age-standardized prevalence of MGD was **56.3%** in study of 3280[1]
- MGD present in **30.5%** of adults 40 and over[2]
- 155 of 398 patients (**38.9%**) exhibited MGD[3]

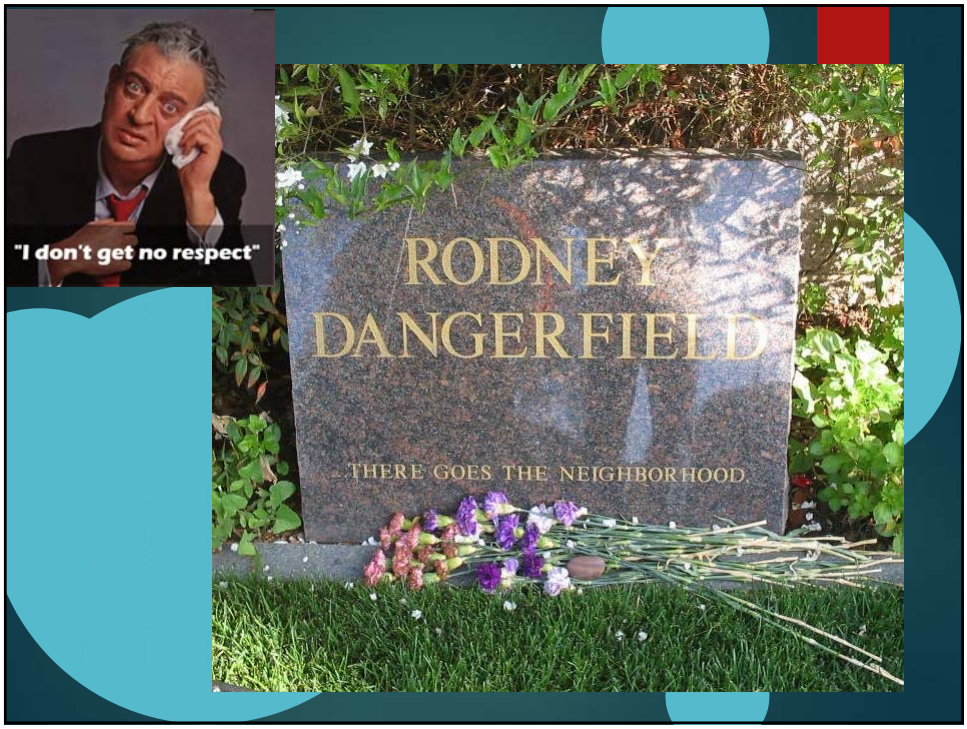
Partial obstruction

Total obstruction

1. Siak JJ, et al. Prevalence and risk factors of meibomian gland dysfunction: the Singapore Malay Eye Study. *Cornea*. 2012;31(11):1223-1228.
2. Viso E, et al. Prevalence of asymptomatic and symptomatic meibomian gland dysfunction in the general population of Spain. *Invest Ophthalmol Vis Sci*. 2012;53(6):2601-2606.
3. Hom MM, et al. Prevalence of meibomian gland dysfunction. *Optom Vis Sci*. 1990;67(9):710-712

133

The Pendulum has Swung!



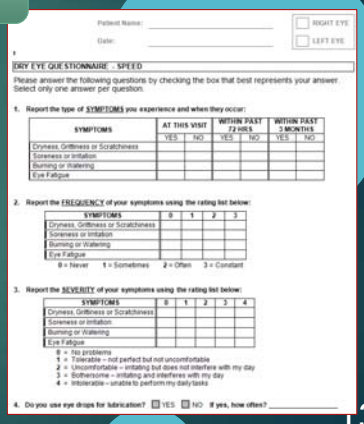
Meibomian Gland Dysfunction

Disease Identification

Standard Patient Evaluation of Eye Dryness **(SPEED)** Questionnaire (Evaporative Tear Film Deficiency Symptoms)

Identify

- Evaluates symptom frequency and severity
- Easy, 2-3 minutes
- Assists to identify symptoms
- **Monitor response to treatment**



DRY EYE QUESTIONNAIRE - SPEED

Please answer the following questions by checking the box that best represents your answer. Select only one answer per question.

1. Report the type of SYMPTOMS you experience and when they occur:

SYMPTOMS	AT THIS VISIT		WITHIN PAST 72 HRS		WITHIN PAST 3 MONTHS	
	YES	NO	YES	NO	YES	NO
Dryness, Grittiness or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

2. Report the FREQUENCY of your symptoms using the rating list below:

SYMPTOMS	0	1	2	3
Dryness, Grittiness or Scratchiness				
Soreness or Irritation				
Burning or Watering				
Eye Fatigue				

0 = Never 1 = Sometimes 2 = Often 3 = Constant

3. Report the SEVERITY of your symptoms using the rating list below:

SYMPTOMS	0	1	2	3	4
Dryness, Grittiness or Scratchiness					
Soreness or Irritation					
Burning or Watering					
Eye Fatigue					

0 = No problems
1 = Tolerable – not perfect but not uncomfortable
2 = Uncomfortable – irritating but does not interfere with my day
3 = Bothersome – irritating and interferes with my day
4 = Intolerable – unable to perform my daily tasks

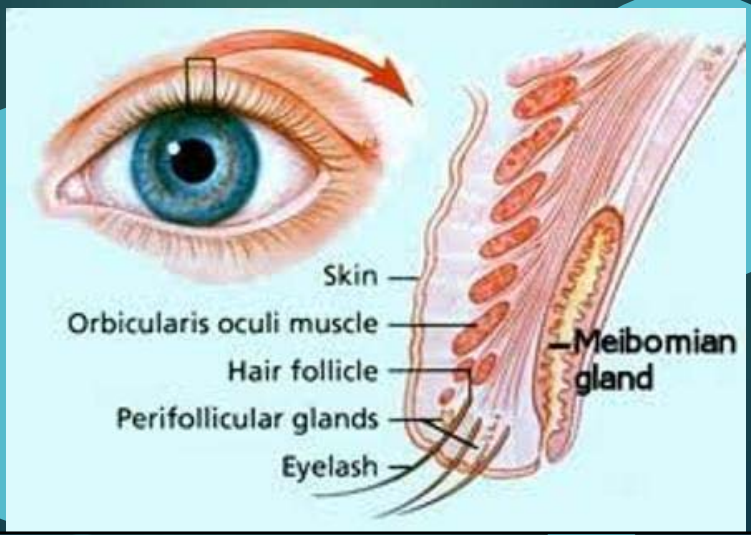
4. Do you use eye drops for lubrication? ☐ YES ☐ NO If yes, how often? _____

13
7

Newer Tests for Dry Eye

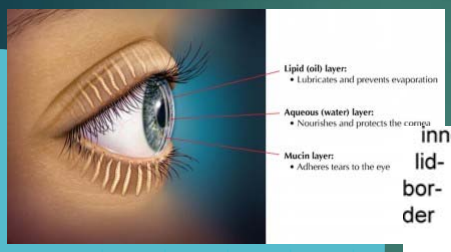
- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- **MGD Analysis**
  - **Physical inspection**
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
  - MG expressibility (Korb MGE)
  - Tear film lipid layer thickness--interferometry

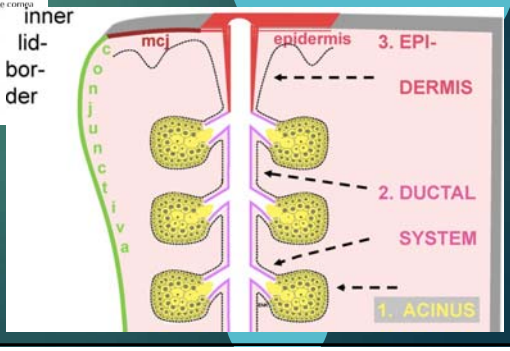
Evaluate Meibomian Glands



Meibomian Gland Evaluation

- Normal Glands





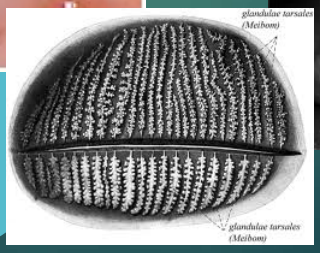
Identify Ocular Rosacea

Ocular Rosacea

- Principal cause of MGD
- Chronic inflammatory condition that affects face, nose, forehead, eyes
- Often affects **eyes only**
- Onset childhood and adults
- More often in fair skinned individuals
- No cure, chronic and progressive if not controlled

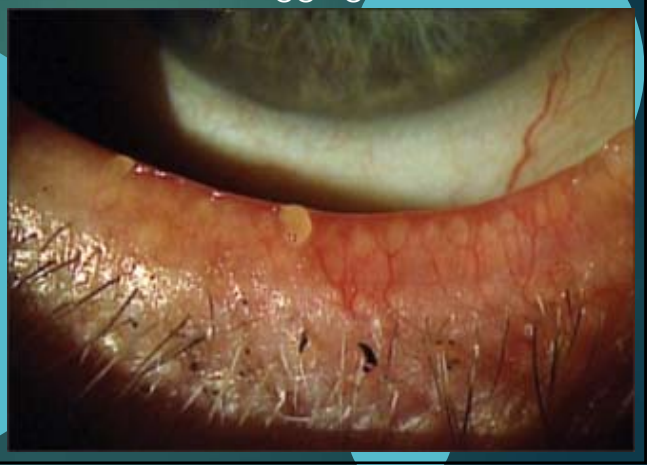
Ocular Rosacea

Meibomian Gland Evaluation



Meibomian Gland Evaluation

- Ocular rosacea, selective clogging



Meibomian Gland Evaluation

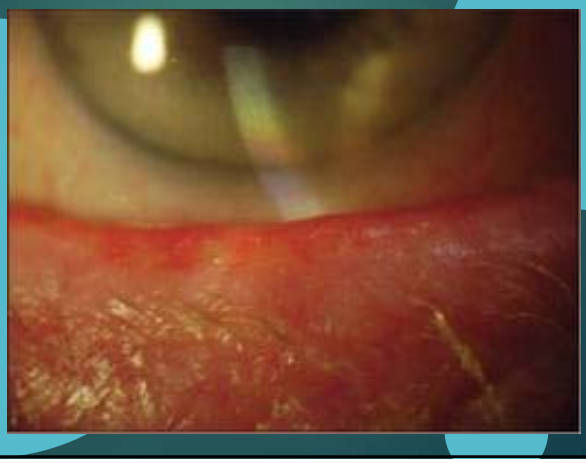
- Moderate clogging

Meibomian Gland Evaluation

- Early gland drop out

Meibomian Gland Evaluation

- Progressive scarring of orifices



Meibomian Gland Evaluation

- More scarring & glandular drop out

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  - Tear film lipid layer thickness--interferometry

Meibomian Gland Evaluation

- Missing gland

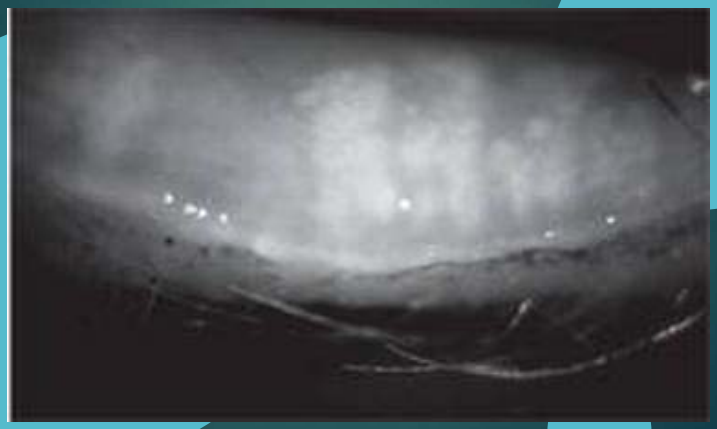
Transillumination

Meibomian Gland Tests

Look for gland truncation or dropout

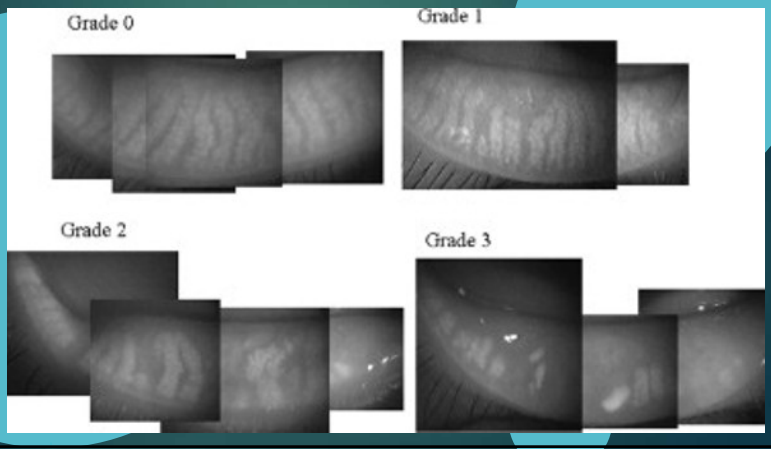
Meibomian Gland Evaluation

- 60% gland loss



Meibomian Gland Evaluation

- Progressive gland drop out (transillumination)



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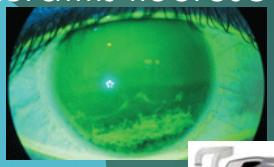
Diagnosis: Lagophthalmos

--**A common cause of dry eye**

- Monitor blinking activity at slit lamp
- Examine for obvious lid scarring
- Exposure keratitis fluorescein pattern



- Lipiview instrument:

—measures number of partial blinks!

Blink Analysis

- Lipiview Videography
  - Automated result
  - Can show patients they don't blink properly

Meibomian Gland Analysis

Complete vs Partial Blinking

Why Measure?

- Partial blinking linked to MGD development
  - 60 patient study with VII nerve palsy for more than 1 week
  - TBUT, fluorescein staining & meibomian gland expression significantly worse w/ incomplete blinkers
  - Subgroup with complete blinking only affected TBUT Wan T et al Current Eye Research 2015 Apr 2:1-7

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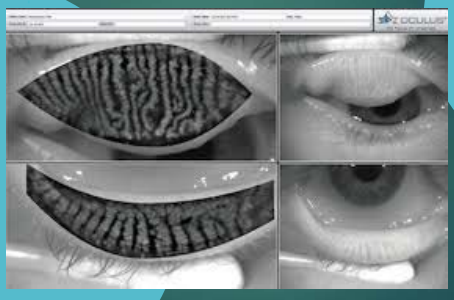
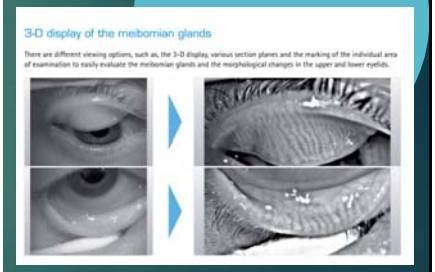
Meibomian Gland Tests

Meibomography



Meibomian Gland Tests

Meibomography: non-contact infrared



Meibomian Gland Tests

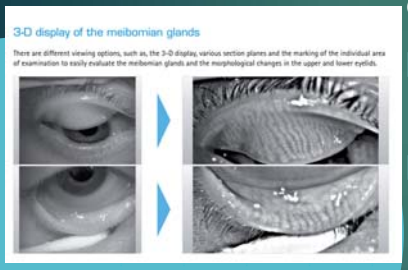
Meibomography

- Oculus 5M infrared meibography study
- 128 patients, retrospective
- Meibomian gland atrophy (meiboscore) vs. expressible glands and TBUT and age
- Meiboscores
  - Worse if poorly expressible p=0.003
  - Worse if lower TBUT p=0.012
  - Worse with age p<.0001
  - Lower lid adequate for evaluation
  - Lower nasal third often more drop out
  - Meibography alone not sufficient for dx of MGD

Finis, Ackermann, Pischel, Konig, Hayajneh, Borrelli, Schrader, Geerling: Curr Eye Res 2014 Oct 20:1-8 Epub

Meibomian Gland Tests

Meibomography



Sjogrens patients vs non-dry eye controls

- SS group 16% dropout vs. 6.7% (p=0.01)
- SS patients also had reduced LLT (lipid layer thickness) and TBUT

Menzies, Srinivasan, Prokopich, Jones
IOVS 2015 Jan8;56(2):836-41

Meibomian Gland Tests

Meibomography: non-contact infrared + transillumination

Lipiview II (Tear Science)

DMI

Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- **MGD Analysis**
  - Physical inspection
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
  - **MG expressibility (Korb MGE)**
  - Tear film lipid layer thickness--interferometry

Meibomian Gland Tests

- Meibomian Gland Evaluator (MGE) (Korb)
  - 0.8-1.2 g/mm2 (moderate pressure)
  - A **physiologic test** like Schirmer & Osm

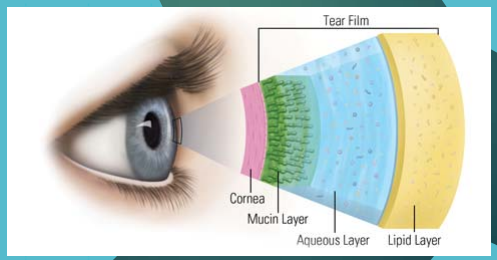
<6 secreting glands: should Rx

Newer Tests for Dry Eye

- Tear Film Osmolarity
- Tear Film Thickness
- MMP-9
- **MGD Analysis**
  - Physical inspection
  - Transillumination
  - Blink Analysis--videography
  - Meibomography
  - MG expressibility (Korb MGE)
  - **Tear film lipid layer thickness--interferometry**

Meibomian gland analysis

Tear Film *Lipid Layer* thickness



LipiView® Ocular Surface Interferometer

Measures Lipid Layer in Nanometers

169

Light source:
The Illuminator

Touch screen
control panel

Chin rest

Camera, computer
and drivers are
housed by the device

Device dimensions:
28" x 17" x 17"

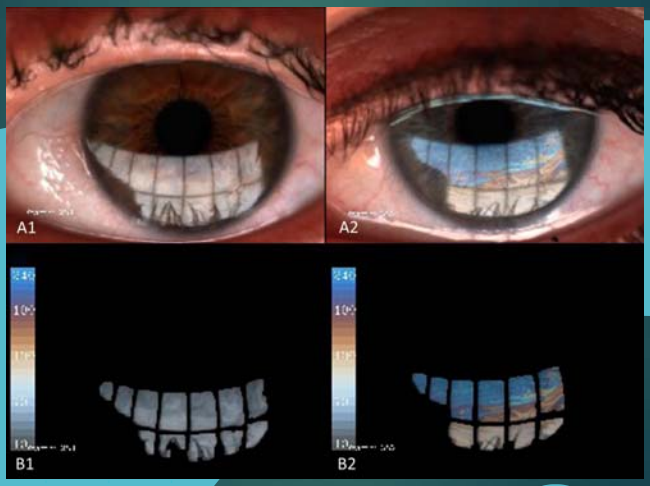
Measurement time:
20 seconds per eye

LipiView® Interferometer

170

Mean 31 nm

Mean >100 nm



Finis, Geerling et al, *Evaluation of Lipid Layer Thickness Measurement of the Tear Film as a Diagnostic Tool for Meibomian Gland Dysfunction*, Cornea 2013, Oct 3 E-pub ahead of print

LipiView® Report

Results are displayed for printout & patient education

- ✓ **Evaluate the lipid layer and blink profile**
- ✓ **Educate patients**
- ✓ **Monitor treatment response**
- ✓ **Predict treatment outcome based on identification of partial blink (PB)**

Diagnosis: Lagophthalmos

--**A common cause of dry eye**

- Monitor blinking activity at slit lamp
- Examine for obvious lid scarring
- Exposure keratitis fluorescein pattern

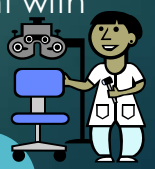
- Lipiview instrument:

—measures number of partial blinks!

So, how do I diagnose dry eye?

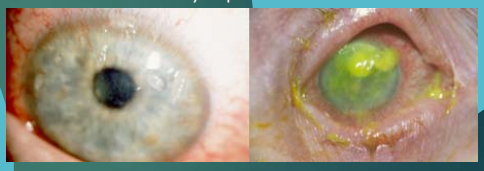
- Pre examination **Intake Questionnaire (SPEED index), Medical History, Ophthalmic history** (CL wear, LVC, cataract surgery, other risk factors)
- Interview: Let the patient **tell their story**

If **symptoms** warrant, examine the patient with high degree of suspicion



So, how do I diagnose dry eye?

- *Severe cases:* easy clinical diagnosis by **signs** +/- tear test
  - *caution: most severe cases often asymptomatic



- *Mild cases:* establishing diagnosis is difficult (Osm or other tests may help);
  - **symptoms** most important feature

So, how do I diagnose dry eye?

Patients should have one ocular ***symptom*** and one ocular ***sign***:

- **Symptoms**:
  - Daily, persistent, troublesome dry eyes for more than 3 months;
  - Recurrent sensation of sand or gravel in eyes or:
  - Use of tear substitutes more than 3x/day

So, how do I diagnose dry eye?

Patients should have one ocular symptom and one ocular sign:

- **Signs**
  - Look for **MGD** (<6 functioning glands per lower lid) (use MGE—Tear Science); entropic orifices, inspissation, telangiectatic vessels
  - Typical **fluorescein** staining pattern (@ 2 minutes)
  - Positive **lissamine green** or **rose bengal** staining, or
  - Positive result on **Schirmer** test, consider **Osm**

So, how do I diagnose dry eye?

Patients should have one ocular symptom and one ocular sign:

- **Signs**
  - If MGD suspected, I schedule patient for Lipiview evaluation
    - Comprises
      - meibum thickness
      - Incomplete blinking analysis
      - MGE: # functioning glands lower lids
      - Meiboscopy (muscle light, soon Lipiview II meibography)

- Once dry eye diagnosed, attempt to determine severity

--Useful for explaining prognosis to the patient

--explain patient has a disease,

--explain risk of not treating disease

My Treatment Paradigm – In a nutshell

- Treat the MGD first (3-4 months)
- MGD treatments generally assist aqueous component, reduces ongoing "fuel to the fire" inflammation (MOS)
- Finish with augmentation of aqueous component if necessary
- Mucus issues generally improve but may require additional interventions

TREATMENT

Dry Eye Treatment

Peter Cushing making a difference

Dry Eye Severity Classification & Treatment Overview

- DEWS Workshop proposed 4 Dry Eye severity levels
- Emphasized early and aggressive treatment appears to
  - improve quality of life
  - Prevent potentially blinding complications

DEWS Workshop Report 2007; Ocular Surface Apr;5(2)

Dry Eye Severity Classification & Treatment Overview

- Adopt strategies that
  - Stimulate natural tear constituents
  - Maintain surface epithelial health/ barrier function
  - Inhibit inflammatory factors that adversely impact ability of ocular surface and glandular epithelia to produce tears

DEWS Workshop Report 2007; Ocular Surface Apr;5(2)

Dry Eye Severity Classification & Treatment Overview

Severity level 1

Mildest signs and symptoms

- Discomfort: mild and/ or episodic occurs under environmental stress
- Visual symptoms: none or episodic
- Conjunctival signs: none to mild
- Corneal/ tear signs: none to mild
- Lid/ meibomian glands: mgd variable (NOMGD)
- Schirmer: variable

DEWS Workshop Report 2007; Ocular Surface Apr;5(2)

Dry Eye Severity Classification & Treatment Overview

Severity level 1 (Mildest signs and symptoms)

Treatment:

- Limit dessicating medications (antihistamines, decongestants
- Environmental strategies (avoid low humidity and air conditioning drafts)
- Lid hygiene/ meibomian gland function treatments e.g. Lipiflow (most wait until level 2!)
- OTC lubricants

DEWS Workshop Report 2007; Ocular Surface Apr;5(2)

Dry Eye Severity Classification & Treatment Overview

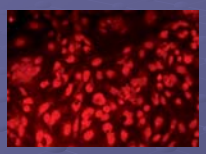
Severity level 1

Treatment (cont):

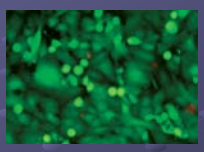
OTC lubricants

- Do not use preserved tears more than 4-6x/day, especially BAK…

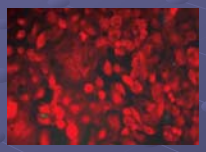
Human corneal epithelial cells toxicity comparisons



A. DEAD CONTROL

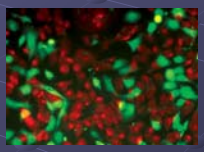


B. LIVE CONTROL

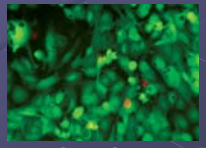


C. GENTAMICIN

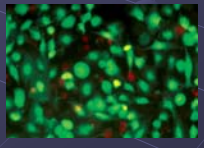
Live cells - green
Dead cells - red



D. LATANOPROST



E. HP-GUAR GELLABLE LUBRICANT EYEDROP SOLUTION



F. TRAVOPROST WITHOUT BAK

Paisley, Yee 2007

Dry Eye Severity Classification & Treatment Overview

Severity level 1 Treatment (cont):

OTC lubricants

- Do not use preserved tears more than 4-6x/day, especially BAK
- Alternative preservatives
  - Chlorbutanol
  - Polyquad
  - EDTA
  - PHMB

Dry Eye Severity Classification & Treatment Overview

Severity level 1 Treatment (cont):

OTC lubricants

- Alternative preservatives (cont)
  - Purite (stabilized oxychloro complex), an oxidizing preservative

    Light exposure: sodium & chlorine free radicals, water and oxygen

    (e.g. Refresh Tears, Alphagan P)
  - Gen Aqua (sodium perborate)

    Catalyzed into H2O2, water, oxygen

    (Genteal)

Dry Eye Severity Classification & Treatment Overview

Severity level 1 Treatment (cont):

OTC lubricants

- Alternative preservatives (cont)
  - SofZia, an oxidizing preservative

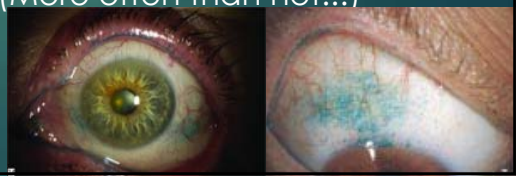
    Exposure to the eye (cations) inactivates the preservative

    (Travatan Z, not yet in tears)

Dry Eye Severity Classification & Treatment Overview

Severity level 2

- Discomfort/severity & frequency: moderate episodic, with or without environmental stress
- Visual symptoms: annoying and/ or activity limiting, episodic
- Conjunctival signs: none to mild
- Corneal staining: variable
- MGD variably present (More often than not!!!)
- Schirmer ≤ 10 mm



Dry Eye Severity Classification & Treatment Overview

Severity level 2 Treatment:

Severity level 1 treatments prove inadequate

- Address the inflammatory component
  - Topical steroids
  - Cyclosporine
- Treat MGD, rosacea (lid hygiene, Lipiflow)
- Punctal plugs AFTER mgd & inflammation controlled
- Moisture chamber spectacles
- Lacriserts select cases

Dry Eye Severity Classification & Treatment Overview

Severity level 2 Treatment (cont):

DRUGS/ Interventions

- Tetracyclines (for meibomitis, rosacea), vs omega 3 fatty acids
- Topical steroids—Loteprednol 0.5% gel, oint. (Lotemax) Fluorometholone 0.1% (FML)
- Topical cyclosporine—Restasis; tacrolimus (FK-506)
- Secretogogues
- Punctal plugs (after inflammation controlled)

Dry Eye Severity Classification & Treatment Overview

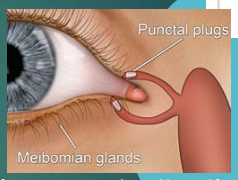
Severity level 2 Treatment (cont):

DRUGS/ Interventions

No secretogogue FDA approved for dry eyes

- Oral
  - Pilocarpine (Salagen)
- Topical
  - Diquafasol (Prolacria-Phase III) (surface cell production of mucin, fluid, ± lipid from MG)
  - Eicosanoid15-(S)-HETE (MUC1 mucus)
  - Ecabet sodium (goblet/ epithelial cell mucus)
  - Rebamipide (mucin)

Dry Eye Severity Classification & Treatment Overview



Severity level 2 Treatment (cont):

DRUGS/ Interventions

- Punctal plugs (after inflammation controlled)
  - Beneficial outcomes reported in 74-86% of patients treated in various studies
  - Postulated feedback mechanism to regulate tear production by lacrimal gland,
    i.e. significant decrease in tear production for up to 2 weeks after plug insertion

Dry Eye Severity Classification & Treatment Overview

Severity level 3

- Discomfort frequently severe, or constant without environmental stress
- Visual symptoms annoying, chronic &/or constant limiting activity
- Conjunctiva: +/- injection; moderate to marked staining
- Cornea: increased tear debris, mucus clumping, filaments
- MGD/ lid problems frequent
- Schirmer ≤ 5 mm

Dry Eye Severity Classification & Treatment Overview

Severity level 3 Treatment (cont):

If level 1 & 2 treatments fail:

- Never use preserved or "disappearing preservative" tears, gels or ointments
- Preservative free tears:
  - Unit dose
  - Spray (mist, liposomes)
  - Multidose silver tip (Visine Tears)
  - VIVA drops with vitamin A (Avitears)
- ASED's

Dry Eye Severity Classification & Treatment Overview

Severity level 3 Treatment (cont):

If level 1 & 2 treatments fail:

- Autologous serum eye drops (20-100%)

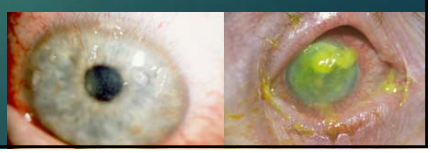
- Permanent punctal occlusion

- Therapeutic contact lenses
  - PROSE, Scleral vaulting contact lenses

Dry Eye Severity Classification & Treatment Overview

Severity level 4

- Severe &/or disabling, constant discomfort
- Visual symptoms constant or disabling
- Conjunctiva: injected, marked staining
- Cornea: severe punctate erosions
- Increased tear debris, mucus clumping, filaments, ulceration
- Lids: keratinization, trichiasis, symblepharon
- Schirmer I: ≤ 2 mm

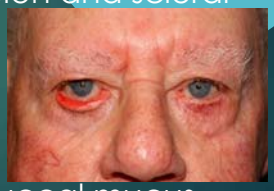


Dry Eye Severity Classification & Treatment Overview

Severity level 4 Treatment:

If level 3 treatments are inadequate:

- Systemic antiinflammatory agents (e.g. Sjogrens tx's)
- Surgery
  - Lid surgery: Tarsorrhaphy, ectropion and scleral show repairs



  - Grafting: amniotic membrane, buccal mucus membrane, salivary gland transplantation

Summary

- "What is dry eye?"
- Etiologic classification
  - Aqueous deficient
  - Evaporative
- "Environmental" contributions
  - Intrinsic/systemic
  - Extrinsic
- Delicate balance of healthy tears
  - Mucus, aqueous & lipid

Summary

- Diagnostic tools
  - Questionnaires
  - Testing
- 4 levels of Dry Eye Severity (DEWS)
- Overview of Treatment Strategies

Next Up

- Current & Future Treatment Options for Dry Eye


Dry Eye: Etiology & Diagnosis
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