Diagnosis of dry eye:

Corneal nerves:

Tear secretion after LASIK:
cuts through sub-basal Laser in situ keratomileusis (LASIK): School of Medicine, Miami, FL
ogy and Charlotte Breyer Rodgers Distinguished Chair, Terrence P. O’Brien, MD, Volume 51, Issue 13 July 7, 2013

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expression of interleukins, MMP-3, and MMP-9 increased; 1 of effects of LASIK found clearance of tears decreased, and hyposensitivity; such patients need obligatory treatment; study associated dry eye may not feel symptoms because of corneal caused more alterations in corneal nerves; patients with LASIK-nerve fibers regenerate and develop microneuromas that cause caused by regeneration (amputation neuromas); resprouting of hinge positions and no dry eye after retreatment with LASIK for years after surgery; studies showed no difference with various dent at hinge; tear production often normal; resolves 6 to 8 mo (TFI) and corneal sensitivity that did not return to baseline for 9 mo; losses greatest at 1 mo

Corneal nerves: provide afferent arm of lacrimal reflex arc and efferent supply of trophic factors; extent of neuronal damage determined by type, depth, and location of injury; dam- age leads to neurotrophic cornea; regeneration aided by nerve growth factor (NGF) and guidance cues; equal numbers of nerves penetrate cornea in all quadrants; many corneas shown not to regain full sensation for 54 mo after LASIK; recovery slower after hyperopic ablations

LASIK-induced neurotrophic epitheliopathy (LINE): seen in patients without previous dry eye; signs adjacent to flap, less evi- dent at hinge; tear production often normal; resolves 6 to 8 mo after surgery; connection between neurotrophic keratopathy and dry eye disputed; high myopes may have symptoms without signs for years after surgery; studies showed no difference with various hinge positions and no dry eye after retreatment with LASIK

Diagnosis of dry eye: no gold standard test; interpretation of tear film osmolarity unclear; matrix metalloproteinase (MMP)-9 potential marker; changes seen in innervation of corneal nerves in age-related and Sjogren syndrome dry eye; multiple fac- tors lead to lacrimal film instability and loss of goblet cells and mucin, epithelial damage, and apoptosis of cells on ocu- lar surface; pain — study (Belmonte, 2007) suggested dry eye and/or neurotrophic keratopathy caused pain; probably caused by regeneration (amputation neuronomas); resprouting of axonal sprouts contribute to hypoaesthesia; sprouts and intact nerve fibers regenerate and develop microneuromas that cause hyperalgesia; study in mice showed dry environment after PRK caused more alterations in corneal nerves; patients with LASIK-associated dry eye may not feel symptoms because of corneal hyposensitivity; such patients need obligatory treatment; study of effects of LASIK found clearance of tears decreased, and expression of interleukins, MMP-3, and MMP-9 increased; 1 yr required for normal levels of fluorescein staining

Effects of suction ring: study showed goblet cell density decreased significantly more after femtosecond laser than mechanical LASIK; effect correlated with suction time

Decreased interblink interval: decreases protection of ocular surface; after patient blinks, tear break-up time (TBUT) acceler- ated and cycle repeats

Risk factors: dryness and inflammation associated with regression of refractive effect; risk factors include high refractive error, ablation depth, low preoperative results from Schirmer test, history of dry eye, female sex, hyperopia, and duration of contact lens wear before surgery

Prevention: identify patients at risk —>40% of patients seek refractive surgery because of dry eye and intolerance of con- tact lenses; use Ocular Surface Disease Index or other surveys; measure TBUT to evaluate evaporative tear loss; perform slit lamp examination for associated or comorbid inflammation of eyelid margin; important to use lissamine green staining (fluor- escene shows only later stages of disease); tear film osmolarity (absolute value of test limited unless extreme hyperosmolarity present); optimize ocular surface before surgery — avoid use of contact lenses; use preservative-free artificial tears; use pulse of topical corticosteroid (4 to 6 wk); eyelid hygiene; punctal plugs; topical azithromycin or tetracycline; course of cyclosporine for some patients (6 to 8 wk); omega-3 essential fatty acids (EFA) supplements; autologous serum tears in some; repeat testing for laser vision correction after pretreatment; all tests (eg, wave front analysis, topography, refraction) affected by unstable ocular surface; intraoperatively — avoid excessive use of agents toxic to ocular surface; minimize use of anesthetic (just-in-time anesthesia); use lubricants with low coefficient of friction (eg, hyaluronate, carboxymethylcellulose, carbomers); postopera- tively — tape eyes closed and have patients rest for ≤15 min; use topical corticosteroids, eyelid hygiene, autologous serum or plasma; consider NGF for severe dry eye

Treatment: therapeutic algorithm — artificial tears with different viscosities; combination of steroids and cyclosporine; aggressive treatment of eyelid disease; punctal plugs; autologous serum

Treatment of pain: low dose of preservative-free topical lido- caine plus autologous serum possibly helpful; pregabalin (Lyr- ica) starting at 150 mg per day and increasing to maximum of 600 mg per day; duloxetine (Cymbalta) starting at 30 mg per day, increasing to 120 mg per day; evaluate at 2 mo

Other considerations: blepharitis reported to increase risk for peripheral corneal infiltrates and infectious keratitis; epithelial basement membrane dystrophies associated with recurrent corneal erosions, epithelial ingrowth, regression of effect, and visual alterations after LASIK; systemic diseases — patients with rheumatoid arthritis or systemic lupus erythematosus can

Educational Objectives

The goal of this program is to improve the diagnosis and treat- ment of dry eye and blepharitis. After hearing and assimilating this program, the clinician will be better able to:

1. Elaborate on the effects of laser in situ keratomileusis (LASIK) on corneal nerves and tear production.
2. Identify patients at increased risk and adopt practices to reduce the likelihood of developing dry eye after LASIK.
3. Diagnose and treat anterior and posterior blepharitis.
4. Recognize the signs and symptoms of ocular involvement in graft-versus-host disease (GVHD).
5. Diagnose and manage dry eye in GVHD.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio-Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the following has been disclosed: Dr. O’Brien is a consultant for Alcon, Allergan, Bausch & Lomb, NicOx, Rapid Patho- gen Screening (RPS), and Santen Pharmaceutical Co. Dr. Mian has received research grant support from Bausch & Lomb. The planning committee reported nothing to disclose. In his lecture, Dr. Mian presents information related to the off-label or investiga- tional use of a therapy, product, or device.
Blepharitis

Dr. O’Brian

Prevalence: study found ocular discomfort in ≥1,000 consecutive patients caused by posterior eyelid margin disease in ≥25%, dry eye in ≥20%, and anterior blepharitis in ≥12%; ≥33% of dry eye caused by blepharitis (evaporative tear loss secondary)

Eyelid inflammation: dermatoblepharitis — caused by infection, allergy, connective tissue disease, or other dermatologic disease; eyelid margin disease — anterior inflammation caused by bacterial, viral, or parasitic infection; posterior inflammation caused by disorders of lipid biochemistry

Anterior blepharitis: caused by excessive colonization with bacteria; release of toxins into tear film causes discomfort, irritation, and burning; biofilms contribute to resistance (may form on punctal plugs); bacteria include gram-positive coagulase-negative staphylococci (57%) or Staphylococcus aureus and other gram-positive bacteria; rarely caused by gram-negative bacteria; signs and symptoms — morning crusting; madarosis; collarettes (scales that encircle lash); redness of eyelid margin and conjunctiva; tests — quantitative microbial culture to determine pathogen load; susceptibility testing in recalcitrant cases

Sequela: some cases with intense inflammation have corneal involvement; study showed cell wall toxin of staphylococci (α-ribitol teichoic acid) caused reaction in peripheral cornea (type III immune-mediated reaction seen with staphylococcal hypersensitivity); intervening clear zone often appears between limbus and infiltrate

Treatment: avoid frequent use of scrubs containing detergent that breaks down meibum into free fatty acids and soaps; use commercial lid scrubs only ≥3 times per week; Sterilid contains natural tea tree oil derivative (linalool) with antimicrobial and anti-inflammatory activity; effective even against methicillin-resistant staphylococci

Other causes: angular blepharitis not always caused by Moraxella; cylindrical dandruff pathognomonic for blepharitis caused by Demodex folliculorum or Demodex brevis

Posterior disease: pathogenesis of meibomian gland dysfunction (MGD) unclear; bacteria may cause internal hordeolum and chronic MGD because secreted lipases break down meibum; obstructive MGD caused by epithelial hyperplasia, thickened secretions, and cicatricial changes; hypersecretory MGD associated with seborrhea or rosacea; sequelae of chronic inflammation include scarring, loss of goblet cells, and chronic dry eye; telangiectatic vessels appear in eyelid margin; soaps along eyelid margin or lateral or medial canthal areas pathognomonic; meibomian glands highly disordered in severe disease; obstruction caused by deposition of keratin with lipogranulomatous inflammation

Signs and symptoms: toothpaste-like material expressed; dry eye; thickened eyelid margin; milky or foamy vision; irreversible dragging of meibomian gland orifice posteriorly

Mimics of blepharitis: neoplasia (especially sebaceous cell carcinoma)

Treatment: warm compresses; LipiFlow device available that warms and massages eyelid and has lasting beneficial effect; not all cases caused by infection; among tetracyclines, minocycline most lipophilic, followed by doxycycline and tetracycline; begin treatment with doxycycline; use minocycline for refractory cases; lower doses found to have greater immunomodulatory effect; rotate antibiotic agents or use anti-septics to discourage development of resistance; metronidazole can be used around eye

Antibiotic choice: bacitracin effective against staphylococci and streptococci (only available as ointment); erythromycin ineffective because of resistance; aminoglycosides toxic and delay healing; topical azithromycin — macrolide available for ocular use; concentrated in eyelid; dose, once per night for 6 wk, then every other month; has immunomodulatory and anti-inflammatory effects

Treatment algorithm: topical and systemic antibiotics; corticosteroids; immunomodulatory agents (eg, cyclosporine); grade severity to determine treatment; moderate to severe disease requires multifactorial, protracted approach; omega-3 EFAs help reduce inflammation

Dry Eye in Graft-Versus-Host Disease

Shahzad I. Mian, MD, Associate Professor, Ophthalmology and Visual Sciences; Terry J. Bergstrom Collegiate Professor for Resident Education in Ophthalmology and Visual Sciences, University of Michigan, Kellogg Eye Center, Ann Arbor

Graft-versus-host disease (GVHD): incidence from 10% to 90% (higher with allogeneic tissue and in older recipients); more intense immunosuppressive protocol may increase incidence

Acute GVHD: appears in first 100 days; incidence 35% to 45%; manifestations include maculopapular rash, and involvement of gastrointestinal tract, liver, and (less often) eye; may overlap or recur in chronic stage

Chronic GVHD: incidence 40% to 80%; wider range of organs involved, including eyes; ocular involvement not diagnostic; biopsy diagnosis required or ≥1 diagnostic criterion in another organ

Ocular involvement: features — dry eye, cicatrical conjunctivitis, conjunctivitis sicca, and confluent areas of punctate keratopathy; mild to severe conjunctivitis with membranous features; keratitis with corneal staining; corneal melting with perforation possible in acute and chronic stages; episcleritis, secondary glaucoma, and secondary choroidal detachment reported; chronic phase — may involve external ocular disease, ocular surface disease, and intraocular disease; eyelid margin possibly involved, with MGD, blepharitis, conjunctivitis, and dry eye common; corneal thinning and melting, retinal hemorrhages, cotton wool spots, and nasolacrimal duct obstruction may occur; cataracts develop as result of treatment with steroids

Incidence and risk factors for dry eye disease: incidence >70% to 80% in ocular GVHD; usually occurs after 6 mo; risk factors — condition leading to transplantation; transplantation of allogeneic hematopoietic stem cells; development of systemic disease (especially skin involvement); total body irradiation; aggressive chemotherpay

Pathophysiology: mediated by T,1 helper cells, with infiltration of lacrimal gland and conjunctival surface; destruction of tissue and formation of fibroblasts; altered environment of ocular surface and increased osmolarity; secondary inflammation damages surface further and leads to corneal-epithelial and conjunctival-epithelial irregularities

Diagnosis: history; Ocular Surface Disease Index; measurement of basal production of aqueous tears by Schirmer test (<5 mm indicates dry eye, 6 to 10 mm suggestive of dry eye); corneal fluorescein staining to assess degree of keratitis and detect punctate keratopathy and frank defects; use rose Bengal and lissamine green to evaluate patterns of conjunctival staining; TBUT reduced (because of eyelid margin disease); osmolarity provides additional quantitative measurement (absolute value and change over time within single eye and intereye correlation)

Management: lubrication with unpreserved tears; viscosity of tears important; hypo-osmotic tears if osmolarity high; viscoselastic for severe cases; gels and ointments; use of selective muscarinic agonists limited by systemic side effects; environmental modification to control evaporation important, but humidifiers possibly contraindicated because of susceptibility to bronchial infection; moisture goggles; increased blinking

Treatment of blepharitis: warm compresses and eyelid hygiene; oral tetracycline and azithromycin; LipiFlow (no data available for use

Audio-Digest Ophthalmology 51:13
in GVHD); scleral contact lenses treatment of choice for severe dry eye disease; punctal occlusion with silicon plugs or thermal cautery; smart plugs increase risk for canaliculitis and dacryocystitis

**Treatment of ocular surface inflammation:** topical corticosteroids — loteprednol (0.3% or 0.5%) has lower risk for ocular hypertension; fluorometholone (drop or ointment); prednisolone for severe inflammation; cyclosporine for mild to moderate disease (low side effect profile with long-term use); tacrolimus ointment on eyelids may reduce MGD and inflammation; more severe disease — autologous serum drops supply anti-inflammatory mediators and growth factors that improve surface and symptoms; dilution varies (20%-50%); higher concentration increases risk for infection of serum tear drops; topical retinoid acid for keratinization (stings); speaker does not use androgens topically because of limited supporting evidence; mucolytics for filamentary keratitis

**Prophylaxis:** topical cyclosporine (0.5%) before transplantation and continued for ≥6 to 12 mo after transplantation; prophylactic loteprednol under evaluation

**Screening:** perform eye examinations on all patients before bone marrow transplantation and follow up at 3 mo

Acknowledgements

Dr. O’Brien, spoke at the 81st Mid-Winter Clinical Conference: Controversies in Ophthalmology, held February 9, 2013, in Los Angeles, CA, and presented by the Research Study Club of Los Angeles (to learn about the 82nd Mid-Winter Clinical Conference, please visit www.researchstudyclub.com). Dr. Mian addressed the 56th Annual Postgraduate Symposium in Ophthalmology—Advances in Corneal Disease, held March 1 to 2, 2013, in Columbus, OH, and presented by Ohio State University Harven Eye Institute (to learn more about cme activities at Ohio State University, please visit https://ccme.osu.edu. The Audio-Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

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- Take posttest: 10 minutes

The Audio-Digest Ophthalmology 51:13
1. All the following statements about the association between dry eye and laser in situ keratomileusis (LASIK) are correct, except:
   (A) Photorefractive keratectomy (PRK) interferes less with corneal nerves and produces less loss of corneal sensation and tear function than LASIK
   (B) A study found that the reduction in tear function index and corneal sensitivity was greatest at 9 mo after LASIK
   (C) LASIK cuts through the sub-basal plexus of nerves and uncouples the neural reflex arc
   (D) Many corneas do not regain full sensation for 54 mo after LASIK

2. Choose the correct statements about dry eye.
   1. Multiple factors lead to instability of the lacrimal film and loss of goblet cells and mucin
   2. Pain may be caused by regenerating nerve fibers (microneuromas)
   3. Patients with LASIK-associated dry eye may not feel symptoms because of corneal hyposensitivity
   4. Clearance of tears has been shown to decrease after LASIK
   5. Expression of matrix metalloproteinase (MMP)-9 has been shown to decrease after LASIK
      (A) 2,3,4,5  (B) 1,2,3,4 ** (C) 1,2,4,5 (D) 1,3,4,5

3. All the following factors increase a patient’s risk for dry eye after LASIK, except:
   (A) Hyperopia  (C) Male sex **
   (B) High refractive error (D) Ablation depth

4. Which of the following presurgical treatments is(are) useful for prevention of dry eye after LASIK?
   (A) Preservative-free artificial tears  (C) Topical azithromycin or tetracycline
   (B) A 4- to 6-wk pulse of topical corticosteroid (D) A, B, and C

5. Posterior blepharitis is generally caused by which of the following?
   (A) Viral infection  (C) Disorders of lipid biochemistry
   (B) Parasitic infection (D) Connective tissue disease

6. A patient who has morning crusting, madarosis, and collarettes is likely to have anterior blepharitis.
   (A) True ** (B) False

7. When treating blepharitis with tetracycline antibiotics, treatment should begin with ______, reserving ______ for refractory cases.
   (A) Minocycline; doxycycline (B) Doxycycline; minocycline

8. Identify the incorrect statement about graft-versus-host disease (GVHD).
   (A) Incidence higher with allogeneic tissue and in older recipients
   (B) Ocular involvement is diagnostic for GVHD
   (C) Episcleritis, secondary glaucoma, and secondary choroidal detachment have been reported
   (D) Corneal melting with perforation is possible in acute and chronic stages

9. In GVHD, dry eye is mediated by T H1 helper cells that infiltrate the lacrimal gland and conjunctival surface.
   (A) True ** (B) False

10. Which of the following has(have) been shown to protect against dry eye if used before and for 6 to 12 mo after transplantation?
    (A) Topical retinoic acid  (C) Topical cyclosporine
    (B) Autologous serum drops (D) Artificial tears with high viscosity