Ocular Disease: Part I

Presented by MBKU | SCCO

Live Interactive CE Webinar | Day One | AM Session

Saturday | July 10, 2021 | 8:00 a.m. - 11:50 a.m.

Marshall B.
KETCHUM UNIVERSITY
Southern California College of Optometry

Department of Continuing Education

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Ocular Disease: Part II

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry
Department of Continuing Education

Saturday, July 10

Pacific Time Zone | Live Webinar | COPE-Approved

8:00AM - 9:50AM
Comanaging Corneal Transplants: MD & OD Perspective
Presented by Lisa Wahl, OD & Asha Balakrishman, MD

10:00AM - 10:55AM
Thyroid Eye Disease: An Update on Clinical Management and Assessment
Presented by Jessica Yuen, OD

10:55AM - 11:50AM
Marine Omega-3s in Dry Eye Disease: Uncovering the Facts, Dispelling the Myths
Presented by Mark Roark, OD

11:50AM- 12:10PM
Lunch Break

12:10PM - 1:05PM
Evidence-Based Management of Retinal Artery Occlusions
Presented by Edward Chu, OD

1:05PM - 2:00PM
Neurotropic Keratitis: Rare, or Hiding in Plain Sight?
Presented by Douglas Devries, OD

2:10PM - 3:05PM
Anterior Segment Cases: OMD vs OD
Presented by David Sendrowski, OD & John Maher, MD

3:05PM - 4:00PM
Update on Cataract Work Up and Use of Multifocal IOLs
Presented by John Maher, MD & David Sendrowski, OD

Sunday, July 11

Pacific Time Zone | Live Webinar | COPE-Approved

8:00AM - 9:50AM
Oral Pharmaceuticals in Anterior Segment Disease
Presented by Blair Lonsberry, OD, MS, ME

10:00AM - 11:50AM
Legends of the Posterior Segment
Presented by Blair Lonsberry, OD, MS, ME

11:50AM- 12:10PM
Lunch Break

12:10PM - 1:05PM
Un-Nerved Conundrums of the Optic Disc
Presented by Mark Sawamura, OD

1:05PM - 2:00PM
PAMM, Plagues, and RAM: Uncommon Retinal Manifestations from Common Systemic Diseases
Presented by Xiao Xi Yu, OD

2:10PM - 3:05PM
Stargardt's Macular Dystrophy: A Family Affair
Presented by Ashley Deemer, OD

3:05PM - 4:00PM
Minimally Invasive Glaucoma Surgery (MIGS) Updates and Options
Presented by Igor Bussel, MD

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Instructor Biographies

Lisa Wahl, OD

Assistant Professor, MBKU | SCCO
Clinic Co-Director, UECLA, MBKU | SCCO

Dr. Lisa Wahl is an optometrist practicing in Los Angeles, California and is an assistant professor at Marshall B. Ketchum University. She is the coordinator of Cornea and Contact Lens Services at University Eye Center Los Angeles and works predominately in clinical care with fourth-year optometry interns. Dr. Wahl graduated from UCLA with a B.S. in Biology and a minor in English Literature. She received her doctorate at Southern California College of Optometry, graduating Summa Cum Laude, and completed residency training in ocular disease at VA Los Angeles Ambulatory Care Center. Thereafter, she worked a prominent ophthalmology practice in Los Angeles, providing pre and postoperative care for patients undergoing refractive, cataract and corneal surgery. Her areas of interest are medically necessary contact lenses, dry eye and ocular pathology. She is an investigator in several research studies at Marshall B. Ketchum University and frequently lectures at continuing education seminars. In her free time, she enjoys lifting weights, traveling and exploring the local restaurant scene.

Asha Balakrishnan, MD

Surgeon, Dougherty Laser Vision

Dr. Asha Balakrishnan ("Bala") is a cataract, cornea, and refractive surgeon and a board-certified ophthalmologist. She joins DLV after having served as the Director of the Cornea and Refractive Surgery service and an Associate Professor of Ophthalmology at the University of Louisville. She was in private practice in the Los Angeles area prior to joining the DLV team. Dr. Balakrishnan specializes in all forms of cataract surgery, including manual & laser-assisted cataract surgery and premium intraocular lens implantation. She holds multiple certifications for a range of femtosecond laser platforms for cataract surgery. In addition to premium cataract surgery, Dr. Balakrishnan also has extensive experience in complex cataract surgery, sutured intraocular lens implantation, and intraocular lens exchanges. Dr. Balakrishnan is dedicated to providing the highest level of medical and surgical care to every patient.

Jessica Yuen, OD

Assistant Professor, MBKU | SCCO

Dr. Jessica Yuen graduated from the University of California, Berkeley with a Bachelor of Arts in Public Health and minor in Molecular Toxicology. She later returned to Berkeley to complete her Doctorate of Optometry. After receiving her OD degree, she completed a residency in Primary Care/Ocular Disease at the San Francisco VA Medical Center where she worked closely with UCSF ophthalmology in various sub-specialties including oculoplastics, cornea, glaucoma, and retina. In 2020, she joined the Southern California College of Optometry at Marshall B. Ketchum University as a full-time faculty with clinical and laboratory teaching responsibilities in the Primary Eye Care and Ocular Disease service. Dr. Yuen is a fellow of the American Academy of Optometry and member of the American Optometric Association and California Optometric Association.

Mark Roark, OD

Private Practice, Allisonville Eye Care Center

Dr. Mark Roark enjoys full-scope optometry utilizing advanced technology and has extensive experience in the management of ocular conditions including Macular Degeneration and Dry Eye Disease. He has a special interest in ocular nutrition and has lectured frequently to other Eye Care Professionals, both nationally and internationally, on the importance of macular nutrition in reducing the risk of ocular disease and enhancing visual performance, especially contrast sensitivity. Dr. Roark was honored to speak at the 2018 Brain and Ocular Nutrition Conference at Cambridge University and recently co-authored a peer-reviewed article published in a special edition of the Molecular Nutrition and Food Research journal on "Nutrition for the Eye and Brain".

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Instructor Biographies

Edward Chu, OD

Staff Optometrist | Residency Coordinator, Long Beach VA Medical Center

Dr. Edward Chu has worked in the VA system his entire career. After graduating from Berkeley Optometry in 2008, he completed a residency in Primary Care at the San Francisco VA Hospital. After residency, he accepted a staff optometrist position at the Salisbury VA in North Carolina, where he spent 5 years. In April 2014, Edward moved back to Southern California where he began his new job at the Long Beach VA serving as the residency and externship coordinator.

Douglas K. Devries, OD

Co-Founder, Eye Care Associates of Nevada

Dr. Douglas Devries co-founded Eye Care Associates of Nevada in 1992 and since that point has limited his practice to diseases of the eye and surgical co-management. His specific area of interest has been in ocular surface disease, which makes up the majority of his clinical practice. He is the director of the optometric residency program and is an Associate Clinical Professor of Optometry. Dr. Devries graduated with a degree in financial management from the University of Nevada and received his doctor of optometry degree from Pacific University. He has served as President of the Nevada Optometric Association as well as the Great Western Counsel of Optometry. He lectures nationally and internationally on anterior segment eye disease.

David Sendrowski, OD

Professor, MBKU | SCCO
Chief, Opthalmology Consultation & Special Testing Service, Ketchum Health

Dr. Sendrowski is a Professor at the Southern California College of Optometry. He is presently the Chief of the Ophthalmology Consultation and Special Testing Service at the University Eye Center at Ketchum Health. He was residency trained in the area of Hospital-based primary care optometry in 1986 and he has lectured extensively in the area of ocular disease diagnosis and management at the college and continuing education venues. He has co-authored a textbook called “Differential Diagnosis in Primary Eye Care” as well as the Thyroid Chapter is the last four editions of “Clinical Ocular Pharmacology” by Bartlett and Jaanus. He has also published several papers in the area of ocular disease and is a fellow in the American Academy of Optometry. Dr. Sendrowski is a member of the Prospect Medical Group surgical consultation board. He also has consulted for the California Optometric Association Legislative and Education Committees. Dr. Sendrowski is a speaker for Alcon and Allergan Pharmaceuticals. He works toward the advancement of the profession and practice of Optometry.

John Maher, MD

Adjunct Faculty, MBKU | SCCO

John Maher entered medical school with a case of nearsightedness. Although he originally intended to study internal medicine, after being fitted for glasses – and later for contact lenses – he was filled with fascination for the human eye. He took a part time job in the ophthalmology clinic, introducing him to what he came to see as the most fascinating and beautiful part of the human body. In 1981, Dr. Maher graduated from Loyola University, Chicago, Illinois where he completed his residency in ophthalmology. Upon achievement of his medical degree, Dr. Maher returned to California where he accomplished his fellowship training at the University of California, San Diego. He began his practice in ophthalmology in Torrance, California in 1986. Today, Dr. Maher is a board-certified ophthalmologist with fellowship training in Cornea and External Diseases. He maintains memberships in Loyola University’s Foreign Ophthalmologic Care from the United States, the Los Angeles County Medical Association, the California Medical Association, the Los Angeles Society of Ophthalmology and the Orange County Society of Ophthalmology.

Comanaging Corneal Transplants: MD & OD Perspective

Presented by Lisa Wahl, OD & Asha Balakrishman, MD

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Corneal Transplants: OD/MD Perspectives

Asha Balakrishnan, MD

Associate, Dougherty Laser Vision

Cataract, Cornea and Refractive Surgeon

Lisa Wahl, OD FAAO

Assistant Professor, MBKU

Co-Clinic Director, University Eye Center Los Angeles

Coordinator, Cornea and Contact Lenses, University Eye Center Los Angeles

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Financial Disclosures

- None!

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Course Outline/Objectives

- Review various types of corneal transplants including full and partial thickness
- Review common indications for corneal transplantation
- Discussion of surgical cases
- Discussion of vision correction and routine eyecare after surgery
- OD/MD Q+A

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Case

- 15yo Hispanic male
- Cc: “My vision in the right eye is blurry though my lens. It’s gotten a lot worse over the last 6 months.”
- Secondary Cc: Photophobia when outside, getting worse. Glare in both eyes, especially at night.
- LEE: 2yrs year ago
- Medical History: Seasonal allergies
- Ocular History: Keratoconus, RGPsx 3 yrs

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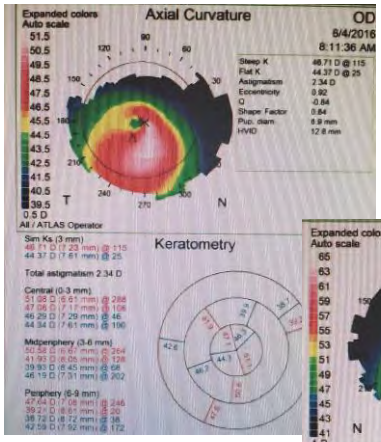

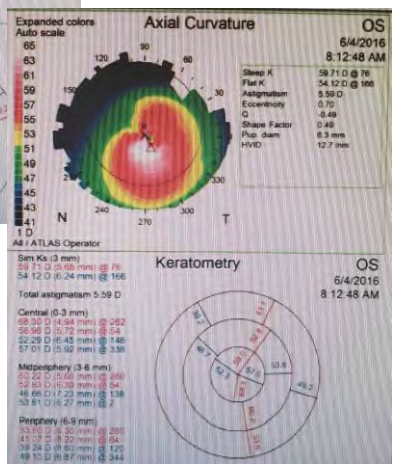

DVA (thru RGPs)
OD: 20/25 PH20/20
OS: 20/200 PH 20/150

EOMs: FULL
Pupils: PERRLA (-)APD

MR
OD: -5.25 -2.75 x 030 20/60
OS: -8.00 -7.50 x 120 20/400

Slit Lamp/Topo: See photos

DFE: Unremarkable OD; Lattice @6o'c OD

Assessment:
1. Severe Progressive Keratoconus with central scarring OS>OD
   -suspect episode of hydrops

Plan:
1. Refer for K-transplant OS

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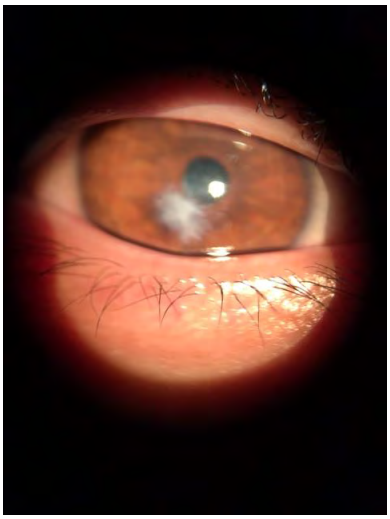

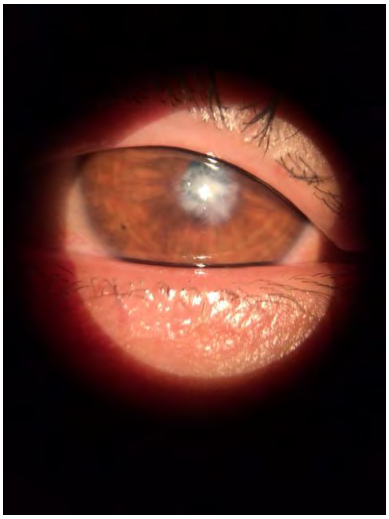

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Corneal Transplants: The OD's Role

- Make the appropriate referral at the right time
  - BCVA
  - Effect on ADLs
  - Timeline/Urgency
- Educate the patient and set expectations
  - Recovery time
  - Visual expectations
  - Vision correction after surgery
- Choose an excellent surgeon

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Corneal Transplants: The OD's Role

- Provide pertinent referral data to the surgeon
  - Ocular History, effect on ADLs
  - BCVA
  - Have you exhausted vision correction options?
- Be an active participant in postoperative care
  - Be ready to provide vision correction as soon as the patient is ready
  - Communicate with the surgeon
- Be aware of postoperative complications
  - Reduce risk of postoperative complications
- Be well versed in the signs and symptoms of graft rejection

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Indications for Corneal Transplantation

- Fuch's Dystrophy
- Bullous Keratopathy
- Graft Failure
- Corneal Ectasia (Keratoconus/Pellucid/Post Refractive)
- Infection
- Corneal Dystrophy
- Trauma
- Other Corneal Scarring

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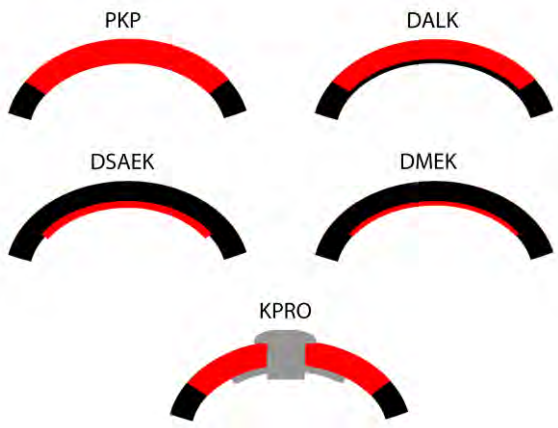
Types of Corneal Transplants

- Penetrating Keratoplasty (PK)
- Deep Anterior Lamellar Keratoplasty (DALK)
- Descemet Stripping Automated Endothelial Keratoplasty (DSAEK)
- Descemet Membrane Endothelial Keratoplasty (DMEK)
- Keratoprothesis



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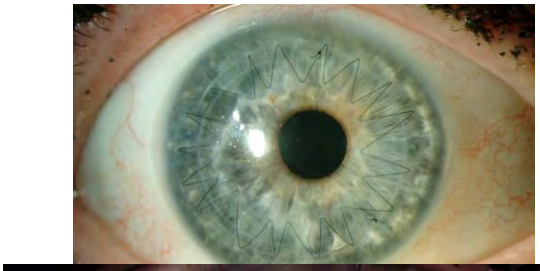
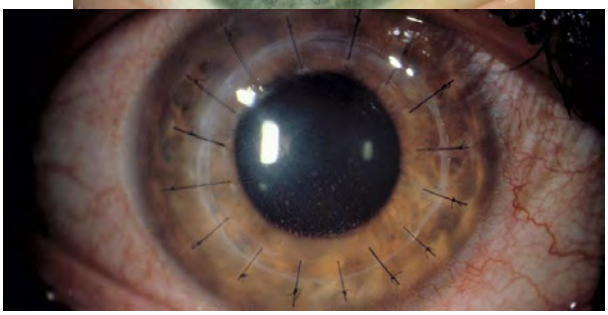
Penetrating Keratoplasty (PK)

- Full thickness transplant
- Performed when anterior and posterior layers are affected
- Entire host cornea replaced with healthy donor tissue
- Interrupted or Continuous Sutures used to hold graft in place
- "Open Sky" Procedure
- Longer recovery
- More unpredictable post op refraction
- Likelihood of high post op astigmatism
- Higher risk of rejection





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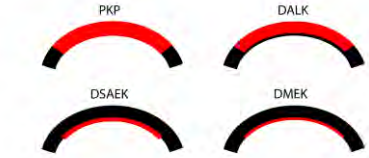
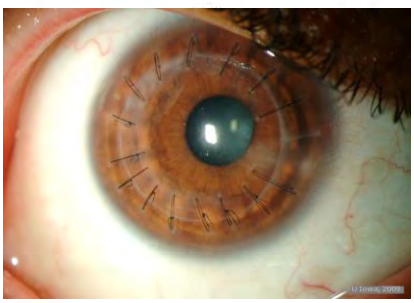
Deep Anterior Lamellar Keratoplasty (DALK)

- Partial thickness transplant from stroma to Descemet's
- Performed when anterior layers are affected
  - Preserves host Descemet's and endothelium
  - Treats pathology with corneal epithelium, Bowman's and stroma
- Interrupted or Continuous Sutures used to hold graft in place
- Common indications
  - Corneal Ectasias (Keratoconus)
  - Corneal Scarring
  - Stromal dystrophies
- Less risk of rejection
- Faster healing time
- Visual outcome compared to PK--??
  - Risk of scarring/opacification at host/donor tissue interface
- Steeper learning curve





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Laser Assisted Corneal Transplant (IEK/FLAK)

- Can be done for PK or DALK
- IEK = Intralase Enabled Keratoplasty
- FLAK = Femtosecond Laser Assisted Keratoplasty
- "Bladeless" or done without trephine
- Host and Donor tissue both cut with a laser
- Possible advantages?
  - More optimal fit, more accurate
  - Faster recovery
  - Better visual outcome

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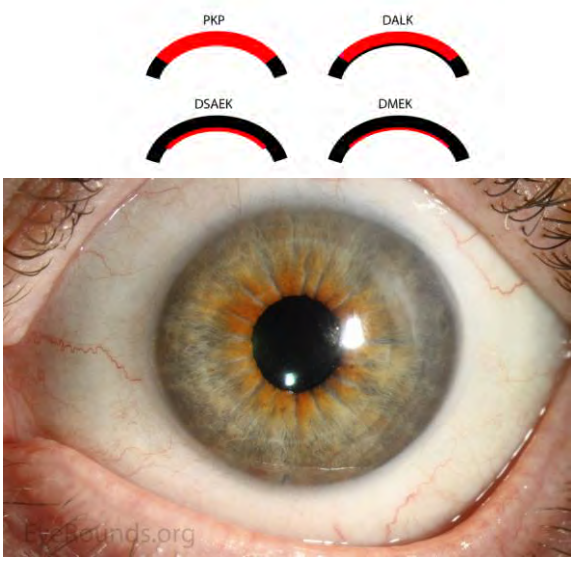
Descemet Membrane Endothelial Keratoplasty (DMEK)

- Partial thickness transplant from Descemet's to endothelium
- Performed when posterior layers affected
- Host Descemet's and endothelium replaced with donor tissue WITHOUT additional stromal tissue
- Graft = 10-15 MICRONS thick
- General Procedure:
  - Incision made into host cornea
  - Host Descemet's and endothelium removed
  - Donor Descemet's and endothelium inserted
- Common indications
  - Fuch's, PPMD, bullous keratopathy, ICE
- Generally very good outcomes
  - Rapid visual recovery!
  - Excellent visual acuity
  - Lower risk of rejection



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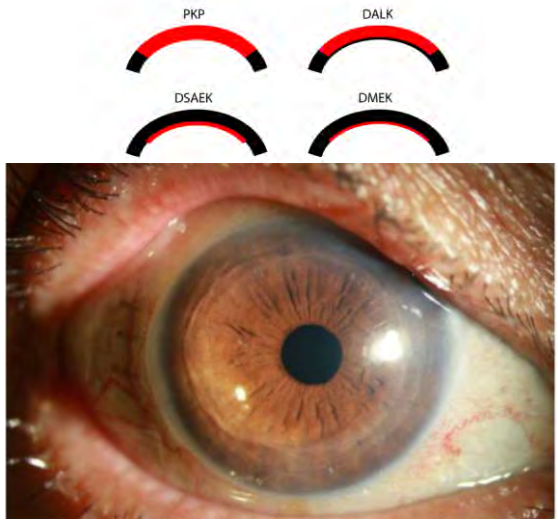
Descemet Stripping Automated Endothelial Keratoplasty (DSAEK)

- Partial thickness transplant from Descemet's to endothelium
- Performed when posterior layers affected
- Host Descemet's and endothelium replaced with donor tissue WITH additional stromal tissue
- Graft = 100-200 MICRONS thick
- General Procedure:
  - Incision made into host cornea
  - Host Descemet's and endothelium removed
  - Donor Descemet's and endothelium inserted (with some stroma
- Generally good outcomes
  - Rapid visual recovery!
  - Excellent visual acuity
  - Lower risk of rejection
- Slightly higher risk of detachment compared to DMEK
- Ultrathin DSAEK (UT-DSAEK)
  - Almost as good outcome as DMEK by most studies



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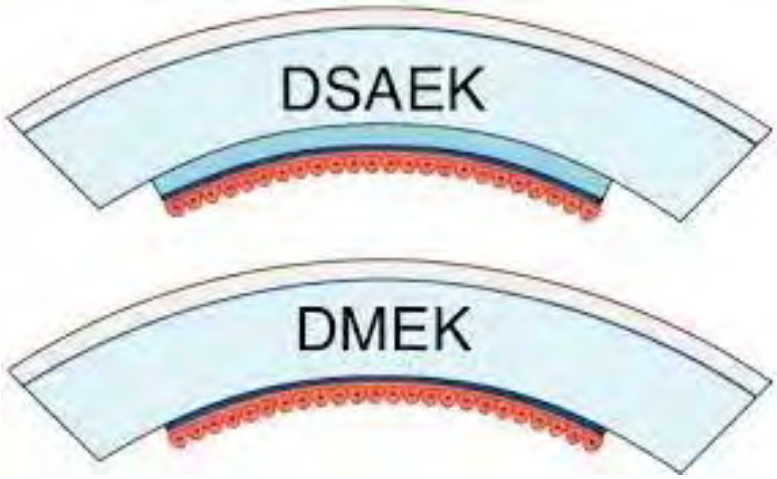
DMEK vs DSAEK

- Smaller tissue
  - More predictable
  - Lower rejection rate
  - Fewer detachments
  - Faster recovery
  - Better visual outcome (less HOAs)



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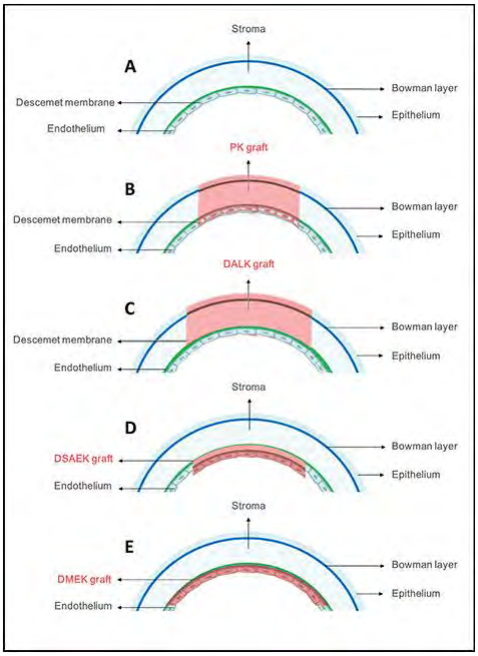

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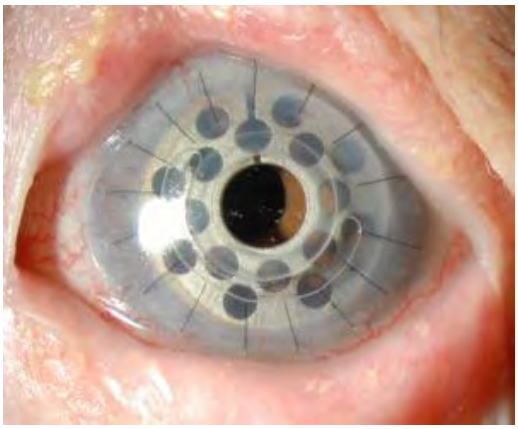
Keratoprosthesis

- Boston Keratoprosthesis = Kpro
- Artificial cornea
- Indications: for corneal conditions in which PKP cannot be used/severe disease
  - Repeated graft failure
  - Steven's Johnson
  - Ocular citricial pemphigoid
  - Chemical burns
  - Aniridia
- General procedure
  - Host tissue removed
  - Donor corneal graft positioned in front + back plate of device and sutured into place
  - Lens removed due to inevitable cataract
- Risk of retroprosthetic membrane, endophthalmitis, glaucoma, RD, vitritis/vit heme



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General Reminders

- The cornea is avascular→ Immune privilege
- Lowest rejection rate of all human organs
- Technology has improved visual outcomes substantially
- Shift from full thickness to partial thickness transplants, when possible, lowers risk of graft rejection
- Can be combined with other ocular surgeries including CE/IOL and retinal surgeries

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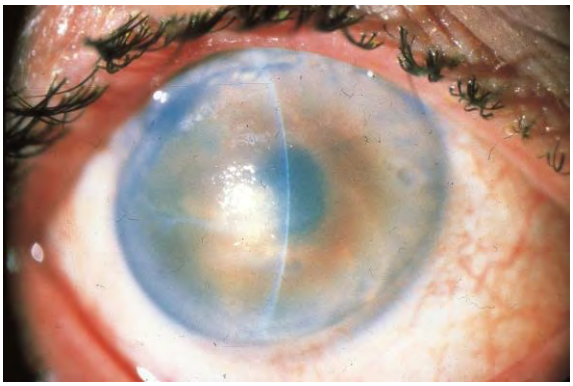
When to Refer

- When the patient has reduced BCVA that affects quality of life or ADLs
  - 20/40?
- When there is risk of severe/debilitating disease (like perforation)
- When pathologic corneal pain cannot be managed (like bullous keratopathy or infection)



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Pertinent Data for Referral

- Ocular History
  - Previous successful and failed treatment
- BCVA
  - Were RGPs or sclerals tried?
- Topography?
- Pachymetry?
- Urgency of referral

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The OD's Role in Preop

- Make a good referral!
- Pick a good surgeon!
- Counsel patients on general surgical procedure
- Emphasize importance of adherence to post op schedule and meds
- Counsel patients on recovery time
- Discuss visual expectations in immediate post op and long term
- Remind patients that routine eyecare is important even (and especially) after surgery

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Surgery Case 1

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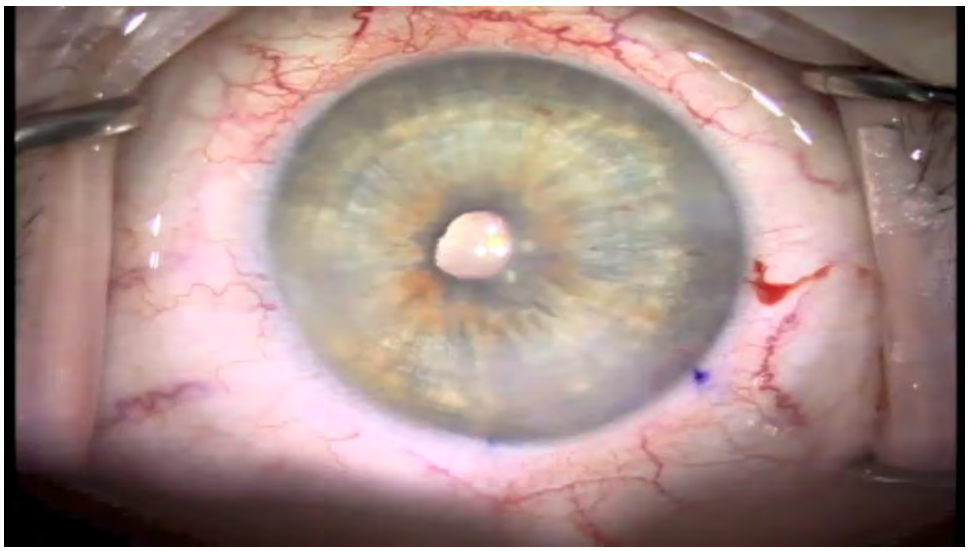

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Surgery Case 2

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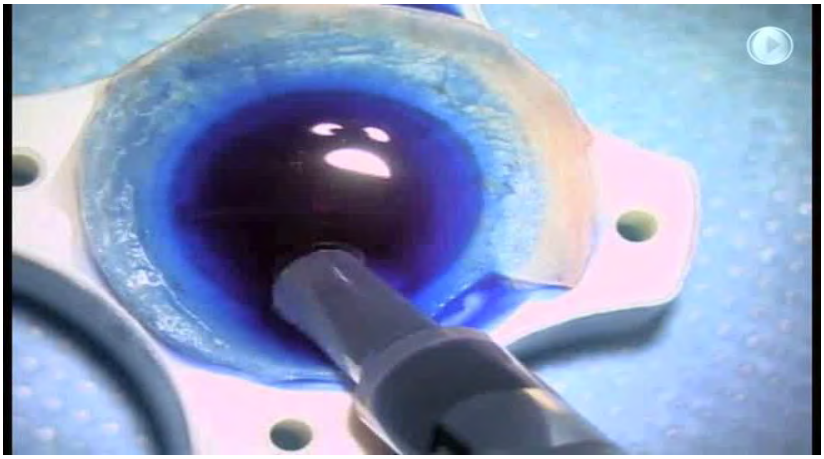

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Surgery Case 3

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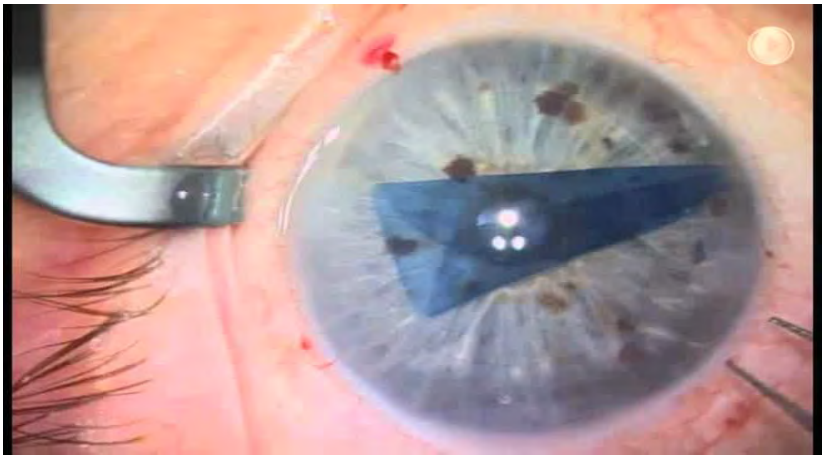

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Case

- 22 year old female presents with worsening vision and a history of keratoconus
- VAsc OD 20/200 VAsc OS 20/80
- VAcc OD 20/80 VAcc OS 20/20
- SLE: Cones OU, central apical scarring OD

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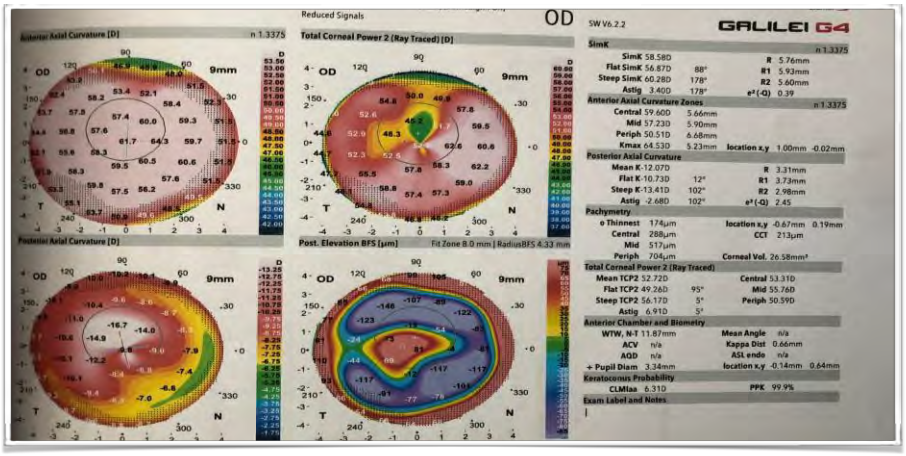

Ks 56.87, 60.28 @ 178
Central Pachymetry 288 um

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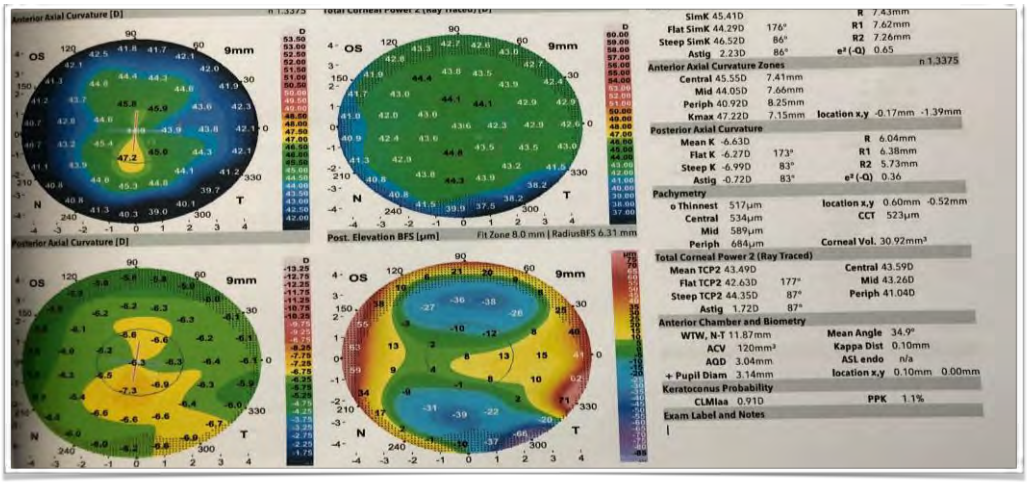

Ks 44.29, 46.52 @ 86
Central Pachymetry 534 um

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What to do?

- A. Refit RGP or Scleral CTLs
- B. Refer for Crosslinking Evaluation OD, Transplant Evaluation OS
- C. Refer for Transplant Evaluation OD, Crosslinking Evaluation OS
- D. Observation

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What to do?

- A. Refit RGP or Scleral CTLs
- B. Refer for Crosslinking Evaluation OD, Transplant Evaluation OS
- **C. Refer for Transplant Evaluation OD, Crosslinking Evaluation OS**
- D. Observation

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Keratoconus Management

- Visual Rehabilitation
  - RGP or Scleral Lens
- Serial Topography Scans
  - q4-6 months

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When to Send?

- Steep K's
- Worsening on Topography
- Inability to tolerate CTLs
- Worsening Vision
- Increasing Cylinder on Refraction

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What can we do?

- Crosslinking
- INTACS
- Transplant
  - DALK or PK

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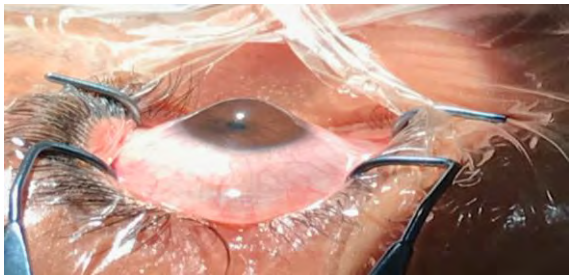
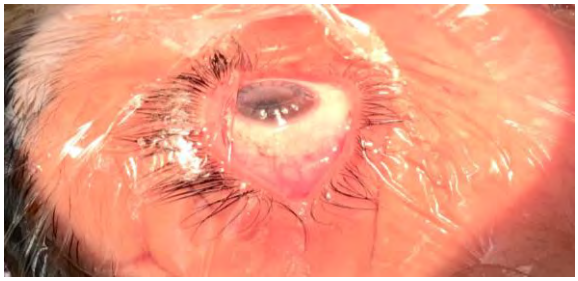


Preop VA OD 20/200



POD0 after PK
POM1 VA OD: 20/40

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Different Strokes for Different Folks…

Technique	Major Indications
DSEK/DMEK	Fuchs Dystrophy Pseudophakic Bullous Keratopathy Corneal Decompensation
DALK/PK	Keratoconus Corneal Scarring Trauma Endothelial Graft Failure

38

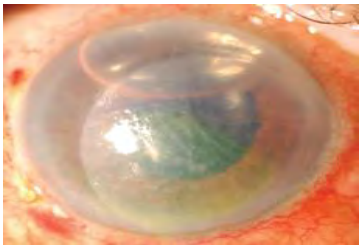
What to Expect

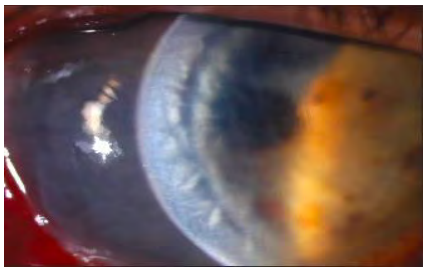
- Air bubble remains in eye for 24-48 hours
- Patient should remain flat and face-up for 50 minutes of every hour for first 1-2 days after surgery
- Key to success = graft attachment

39

Postoperative Complications

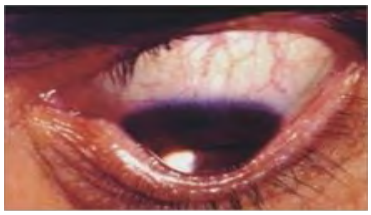
- Pupil block
- Graft dislocation
- Epithelial ingrowth
- Graft failure
- Endothelial cell loss

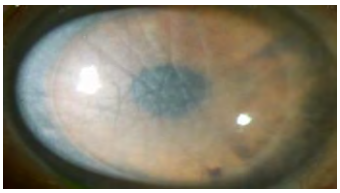




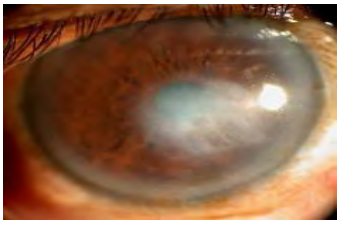
40

Most Common Indications



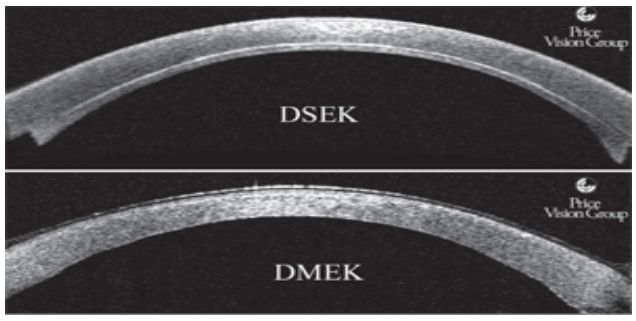


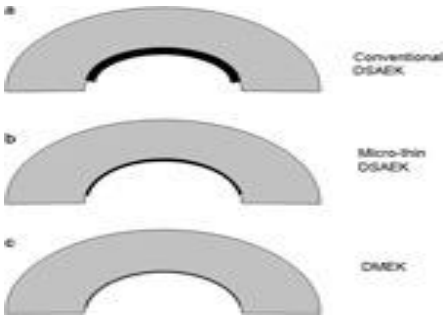
- Fuchs Dystrophy
- Keratoconus
- Pseudophakic Bullous Keratopathy
  - Non-resolving corneal edema after cataract surgery
- Corneal Scar
- Failure of Prior Corneal Transplant



41

Endothelial Keratoplasty: DSEK/DSAEK vs DMEK





- DSAEK = Endothelium + Descemet's Membrane + Posterior Stroma
- DMEK= Endothelium + Descemet's Membrane
- Thickness: 60-120 um (DSAEK) vs. 20 um (DMEK)

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Vision Trends after Surgery

- PK: high astigmatism, corneal flattening, will likely need specialty lens
- DALK: high astigmatism, corneal flattening, will likely need specialty lens
- DMEK/DSAEK: hyperopic shift ~ 1D, likely correctable with glasses or nonspecialty lenses

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Vision Correction Options after PK/DALK

- Spectacles: if ametropia, anisometropia and aniseikonia are minimal
- Soft CLs: if HOAs are low
  - Choose high DK to minimize hypoxia, neovascularization and graft rejection
- Corneal GPs: if HOAs are high
  - Larger diameter to reduce mechanical stress
  - Avoid tight fits—could cause chronic hypoxia and graft rejection
  - Piggy-back with high DK SCL
    - Possibly less GP bearing, but double barrier to oxygen transmission
- Hybrids: if HOAs are high and patient intolerant to GPs
  - Dehydration of soft skirt and low clearance at hard/soft lens junction could cause mechanical stress on cornea
- Sclerals: if HOAs are high, arguably the best option (but with some caveats…)

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Scleral Lenses after Transplant

Contact Lens SPECTRUM

- Advantage: full corneal clearance and lens stability
- Ideal central vault: 200 microns
- Ideal limbal vault: 50 microns
- Use lens with highest oxygen permeability

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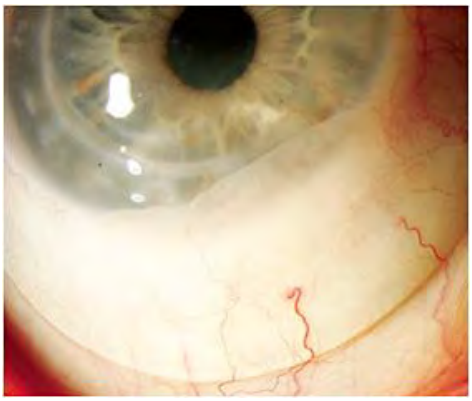
Scleral Lenses after Transplant

Contact Lens SPECTRUM

- Cautions:
  - Too much vault can cause hypoxia
  - Hypoxia threatens endothelial cells
  - Recommend ECC>1000cells/mm2
  - Poor clearance over limbus could cause mechanical trauma to graft
  - Be wary of preexisting neovascular growth and conjunctival prolapse (document)
  - Conjunctival prolapse may cause hypoxia or limbal stem cell deficiency



46

Post OP Case 1

- 29 yo Hispanic Male returning for CL fitting
- s/p PKP OU

- UCVA
  - OD: 20/30 PH 20/20
  - OS: 20/60 PH 20/25

- MR
  - OD: -0.75 -3.25 x 055 20/20
  - OS: +3.00 -5.75 x 023 20/20-

47

Post Op Case 1

- Plan:
  - Order Biofinity Toric XR SCLs 8.7/14/5:
    - OD: -0.75 -3.25 x 055
    - OS: +3.00 -5.75 x 025

- DK = 128

48

Post Op Case 1

- CL Dispense: Biofinity Toric XR 8.7/14.5
  - OD: -0.75 -3.25 x 055
    - DVA: 20/20
    - OR: -0.25 DS 20/20
    - Fit: Good coverage, centration, 0.50 MOB, no rotation
  - OS: +3.00 -5.75 x 025
    - DVA: 20/25
    - OR: +0.25 -0.50 x 040 20/20-3
    - Fit: Good coverage, centration, 0.50 MOB, 3 degrees rotation right

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Post Op Case 1

- SCLs CAN be fit in post corneal transplant patients
- Good VAs on MR
- Regular Astigmatism in central topo
- Optimize oxygen transmissibility by going with high DK lens
- Avoid hydrogel/quarterly replacement if possible due to lower DK

50

Post Op Case 2

- 29 yo Hispanic Male returning for CL fitting
- s/p PKP OU

- UCVA
  - OD: 20/50 PH 20/25
  - OS: 20/80 PH 20/25

- MR
  - OD: +3.00 -5.50 x 025 20/30
  - OS: +2.00 -5.75 x 130 20/40

51

Post Op Case 2

- Plan: Order Scleral Lenses based on diagnostic fitting

  - OD: Zenlens / Oblate / 4250 sag / 16.0 / 9.50 / +6.25 DS / 0.50 / 1 steep
  - OS: Zenlens/ Oblate / 4400 sag / 16.0 / 9.50 / +5.25 / 0.50 / 2 steep

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Post Op Case 2

- CL Dispense:
  - OD: Zenlens / Oblate / 4250 sag / 16.0 / 9.50 / +6.25 DS / 0.50 / 1 steep
    - DVA: 20/20-
    - OR: +0.50 -0.75 x 030 20/20
    - Fit: 200 micron vault/ limbal clearance/ no blanching
  - OS: Zenlens/ Oblate / 4400 sag / 16.0 / 9.50 / +5.25 / 0.50 / 2 steep
    - DVA: 20/20-2
    - OR: -0.50 DS 20/20-
    - Fit: 250 micron vault/ limbal clearance/ no blanching
- Plan: Dispense Lenses and RTC x 1 week (wear lenses at least 4 hours before appt)

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Post Op Case 2

- CL follow up
- CC: “My right lens is great but my left lens is blurry after 2 hours”
- Current scleral lens wear time: 4 hours
  - OD: Zenlens / Oblate / 4250 sag / 16.0 / 9.50 / +6.25 DS / 0.50 / 1 steep
    - DVA: 20/20
    - OR: +0.50 -0.50 x 030 20/20
    - Fit: 150 micron vault/ limbal clearance/ no blanching
  - OS: Zenlens/ Oblate / 4400 sag / 16.0 / 9.50 / +5.25 / 0.50 / 2 steep
    - DVA: 20/20-2
    - OR: -0.50 DS 20/20-
    - Fit: 200 micron vault/ limbal clearance/ no blanching

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Post Op Case 2

- What is going in on in the left eye?!

55

- Plan: Order new OS lens with reduced vault:
  - OS: Zenlens / Oblate / 4350 sag / 16.0 / 9.50 / +4.75 / 0.50 / 2 steep
  - Reduced vault from 4400 → 4350
  - Changed power from +5.25 → +4.75

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Post Op Case 2

- CL Dispense:
  - Presenting Lenses
  - OD: Zenlens / Oblate / 4250 sag / 16.0 / 9.50 / +6.25 DS / 0.50 / 1 steep
    - DVA: 20/20-
    - OR: plano 20/20
    - Fit: 150 micron vault/ limbal clearance/ no blanching
  - OS: Zenlens/ Oblate / 4350 sag / 16.0 / 9.50 / +4.75 / 0.50 / 2 steep
    - DVA: 20/20-2
    - OR: +0.25 -0.50 x 130
    - Fit: 250 micron vault/ limbal clearance/ no blanching
- Dispense:
- OS: Zenlens / Oblate / 4350 sag / 16.0 / 9.50 / +4.75 / 0.50 / 2 steep
    - DVA: 20/20-
    - OR: plano DS 20/20-
    - Fit: 175 micron vault/ limbal clearance/ no blanching

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Post Op Case 2

- CL Follow Up: No more fogging!

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Tips to reduce fogging in sclerals

- Lower vault/corneal clearance
- Switch to buffered scleral lens solution
- Use cocktail of high viscosity preservative free tear and scleral lens solution
- Manage OSD
- Adjust landing zone

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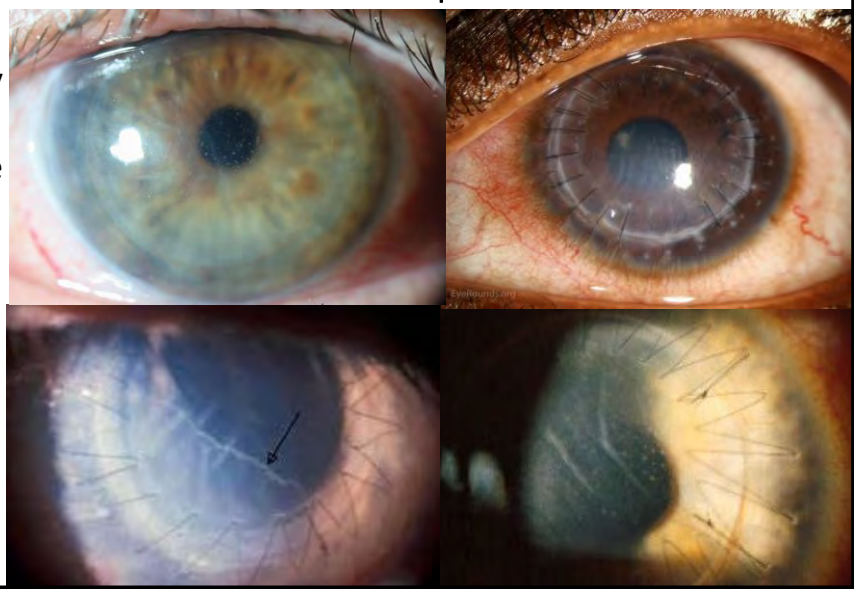
Routine Care after Corneal Transplantation

- Monitor at least annually
- Recognize signs and symptoms of graft failure
  - Symptoms:
    - Redness, loss of vision, discomfort/pain, photophobia
  - Signs:
    - Ciliary flush, corneal edema, linear KPs (Khodadoust line), conjunctival injection



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OD/MD Q+A Session

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The End!

- Questions?

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Thyroid Eye Disease: An Update on Clinical Management and Assessment

Presented by Jessica Yuen, OD

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Thyroid Eye Disease:
An Update on Clinical Management and Assessment

Jessica Yuen, OD, FAAO
Assistant Professor
Jarnagin Center for Primary Eye Care and Ocular Disease
University Eye Center at Ketchum Health

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1

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I have no financial disclosures.

2

Case: 40 y/o Korean Female

CC: Referred by endocrinologist for "hyperthyroidism in the right eye"

Endocrinologist was concerned for exophthalmos and was considering radioactive iodine treatment

Denied diplopia in central gaze, pain on eye movement
Symptoms of dryness in both eyes x1 yr

Personal Medical Systemic History:
Recently diagnosed with hyperthyroidism

Currently on no other medications

Entering VA

OD: -0.50 -0.75 x020	20/20
OS: -0.25 DS	20/20
Add: +0.75	20/20 OU

3

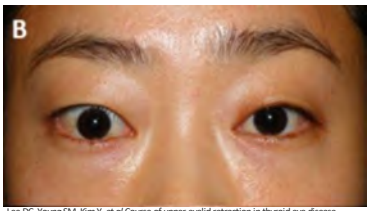
Case: 40 y/o Korean Female

	Slit Lamp Exam	
MRD1: 7mm MRD2: 5mm **superior scleral show**	Lids	MRD1: 5mm MRD2: 5mm
2+ diffuse hyperemia	Conjunctiva	White and quiet
2-3+ inferior SPK	Cornea	1+ inferior SPK
Open	Ant Chamber	Open
Flat, brown	Iris	Flat, brown
Clear	Lens	Clear

EOMs:
-1 restriction in ST gaze OD
Symptoms of diplopia and mild pain on upgaze

Cover Test:
Orthophoria at distance
6^ exophoria at near

(+) Von Graefe's sign OD
(+) Increased retropulsion OD
(-) Lagophthalmos



Lee DC, Young SM, Kim Y, *et al* Course of upper eyelid retraction in thyroid eye disease *British Journal of Ophthalmology* 2020;**104**:254-259.

Exophthalmometry:
Base: 102 mm, OD: 19mm, OS: 17mm

FDT:
Clear OD/OS

4

Case: 40 y/o Korean Female

	Fundus	
Pink and healthy, (-) edema/pallor	Optic Disc	Pink and healthy, (-) edema/pallor
0.25/0.25 H/V	C/D	0.25/0.25 H/V
Flat, avascular	Macula	Flat, avascular
Normal, A/V ratio: 2/3	Vessels	Normal, A/V ratio: 2/3
No breaks/detachments 360	Periphery	No breaks/detachments 360
Clear	Vitreous	Clear

Mild Inactive Thyroid Eye Disease OD

- **Mild right eye proptosis, upper lid retraction OD, and mild EOM restriction OD**
- Sent exam results to endocrinologist
- Counseled on dry eye therapy
- Return in 3 months for thyroid eye disease follow-up

5

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Thyroid Eye Disease (TED)

Also known as:

- **Thyroid associated ophthalmopathy (TAO)**
- **Graves' ophthalmopathy**
- **Thyroid orbitopathy**

6

Thyroid Eye Disease (TED)

Most common autoimmune inflammatory disorder within orbit
Most common cause of unilateral and bilateral proptosis in adults

May precede or follow endocrinologic manifestations
Typically presents within 18 months of each other

Affects orbital fat, extraocular muscles, and lacrimal gland

Can occur at <u>any</u> thyroid state
90% hyperthyroidism, 5% hypothyroidism, 5% euthyroid

Bartley GB. Trans Am Ophthalmol Soc 1994; 92:477–588.
Smith TJ, Hegedüs L. N Engl J Med 2016; 375: 1552-65.

7

TED Epidemiology

Incidence of 1.9 cases per 10,000 people per year

Who:
Women > Men
Age: 30-50 years
Occurs in all races and ages

90% pts with TED have a current or past history of abnormal systemic thyroid hormone levels

25-50% of pts with immune thyroid disease develop orbital involvement
25-50% of patients with Graves' disease
33% of patients with Hashimoto's thyroiditis

Bartley GB. Trans Am Ophthalmol Soc 1994; 92:477–588.
Lazarus JH. Best Pract Res Clin Endocrinol Metab 2012; 26:273–279.

8

TED Pathogenesis

Orbital fibroblast cross-reaction of thyroid autoantibodies towards:

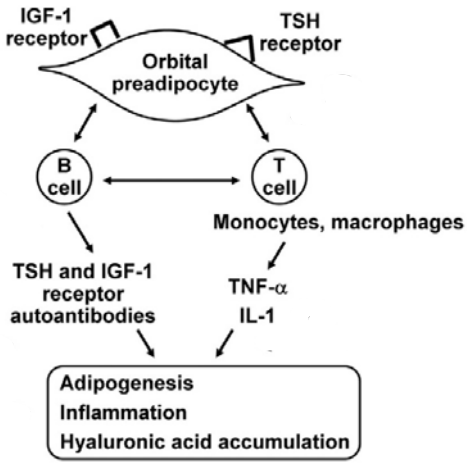
Thyrotropin receptor (TSHR)
Insulin-like growth factor 1 receptor (IGF-1R)

Triggers B cell and T cell activation

Inflammatory response
Increases cytokine release
Activation of orbital fibroblasts

Initiates:

Myofibroblast proliferation
Adipocyte proliferation (adipogenesis)
Secretion of hyaluronic acid



Garrity JA, Bahn RS. Am J Ophthalmol. 2006 Jul;142(1):147-153.
Khong JJ et al. Br J Ophthalmol 2016;100:142–150.

9

Non-Modifiable Risk Factors

Demographics	History	Anatomy
Increasing age	Rapid onset of orbitopathy	Orbital anatomy
Women vs. men Women: more frequent Men: more severe	(+) FHx of orbitopathy	Orbital contour or venous/lymphatic vessels
Caucasian > Asian	H/o radioactive iodine for Graves' Disease	High myopia

Stan MN et al. Thyroid 2010; 20:777–783.
Brand, O. J et al. Mol. Cell. Endocrinol. 2010; 322, 135–143.

10

Modifiable Risk Factors

Environmental	Health
Smoking *Increase in reactive oxygen species* Stress	Selenium deficiency High serum cholesterol Pregnancy Diabetics Iodine intake

Burch HB et al. Exp Eye Res 1997;65:311–316.
Prummel MF et al. JAMA 1993;269:479–82.

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Image source: business.insider.com

Image source: webeye.ophth.uiowa.edu

Linked secondary autoimmune diseases

1. **Superior limbic keratitis (SLK)**
2. **Myasthenia Gravis**
3. **Diabetes mellitus**
4. **Alopecia**
5. **Vitiligo**
6. **Sjogren's Disease**

Bartley GB. Trans Am Ophthalmol Soc. 1994;92: 477– 588.
Cruz AA et al. Ophthal Plast Reconstr Surg. 2007;23(2):104– 8.

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TED's Clinical Course

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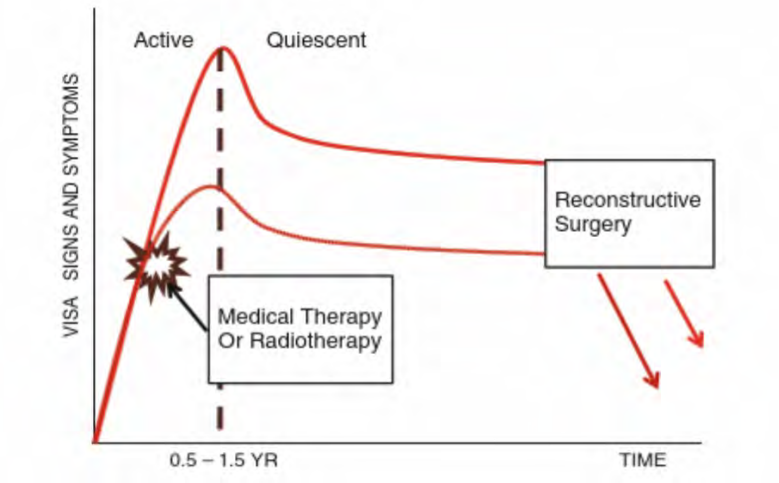
Rundle's Curve



Rundle FF et al. Clin Sci 1945; 5: 177-94.
Thyroid Eye Disease, edited by Raymond S. Douglas, et al., Springer New York, 2014.

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TED's Clinical Features

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Clinical Signs

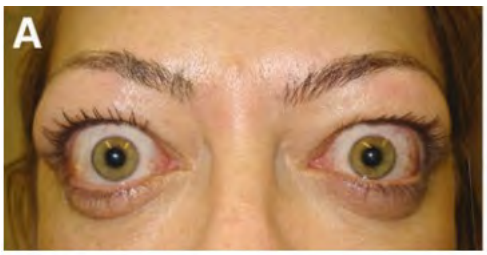

Image source: morancore.Utah.edu

Appearance and Anterior Segment	
Sign	**Diagnostic**
Upper lid retraction (Dalrymple's sign Thyroid stare)	MRD1, MRD2, interpalpebral height Increased superior scleral show
Lid lag in down gaze (Von Graefe's sign)	
Proptosis	Exophthalmometry CT/MRI B-scan/A-scan ultrasonography
Lower lid retraction	MRD1, MRD2, interpalpebral height Increased inferior scleral show *Associated with proptosis*

Anderton LC et al. Plastic and Reconstructive Surgery, Paris; 2000; 107.
Kendler DL et al. Arch Ophthalmol. 1993;111:197– 201.
Regensburg NI et al. Ophthal Plast Reconstr Surg. 2011;27(4):236– 40.
Dolman et al. *Ophthalmic plastic and reconstructive surgery* vol. 34,4S Suppl 1 (2018): S34-S40.

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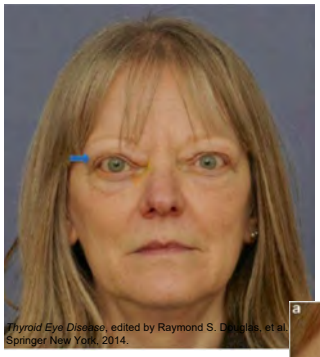
Clinical Signs



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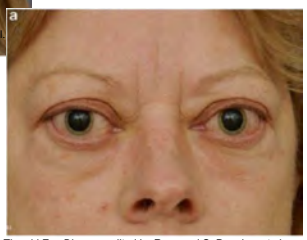

Thyroid Eye Disease, edited by Raymond S. Douglas, et al., Springer New York, 2014.

Appearance and Anterior Segment	
Sign	**Diagnostic**
Crowding of the Eyebrow/Lid Complex	
Exposure keratopathy *Corneal epithelial erosions* *Corneal abrasions* *Corneal ulcerations/perforations*	Lagophthalmos Fluorescein Staining Rose Bengal Lissamine Green
Lacrimal gland inflammation	Prolapse causing tender fullness around superotemporal orbital rim

Anderton LC et al. Plastic and Reconstructive Surgery, Paris; 2000; 107.
Kendler DL et al. Arch Ophthalmol. 1993;111:197– 201.
Regensburg NI et al. Ophthal Plast Reconstr Surg. 2011;27(4):236– 40.
Dolman et al. *Ophthalmic plastic and reconstructive surgery* vol. 34,4S Suppl 1 (2018): S34-S40.

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Inflammatory Signs

Periorbital soft tissue inflammation and congestion

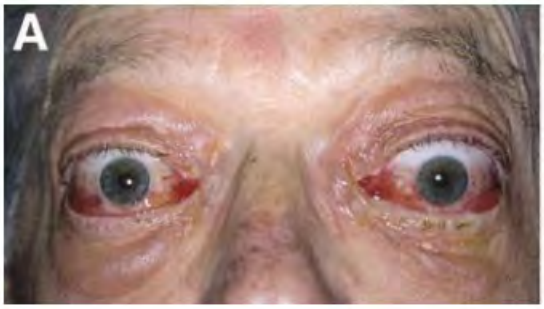
Conjunctival and caruncular injection and edema (Goldzeiher's sign)

Eyelid redness and edema

Diurnal variation
(worse with head position while sleeping)

Elevated IOP in upgaze from inferior rectus restriction or orbital congestion

Topical drops not effective because mechanical cause of elevation



Anderton LC et al. Plastic and Reconstructive Surgery, Paris; 2000; 107.
Kendler DL et al. Arch Ophthalmol. 1993;111:197– 201.
Regensburg NI et al. Ophthal Plast Reconstr Surg. 2011;27(4):236– 40.
Dolman et al. *Ophthalmic plastic and reconstructive surgery* vol. 34,4S Suppl 1 (2018): S34-S40.

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Strabismus Signs

15-51% develop strabismus from restricted ocular motility and fibrotic changes

Order of affected EOM: Inferior, medial, superior, levator, lateral rectus and obliques

Typically hypotropia and esotropia but can be variable

Exotropia should raise concerns for separate entity (i.e. Myasthenia gravis)

May improve spontaneously or with corticosteroid/orbital irradiation therapy

Strabismus	
Early Signs	Ocular discomfort Injection over muscle insertion sites Exophthalmos
Active Phase	Progressive motility restriction (Intermittent or in certain gazes)
Quiescent phase	Stable Secondary to fibrosis

Anderton LC et al. Plastic and Reconstructive Surgery, Paris; 2000; 107.
Kendler DL et al. Arch Ophthalmol. 1993;111:197– 201.
Regensburg NI et al. Ophthal Plast Reconstr Surg. 2011;27(4):236– 40.

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Posterior Segment Signs

Dysthyroid Optic Neuropathy (DON)

(also known as compressive optic neuropathy)

90% secondary to EOM enlargement

10% due to stretching of optic nerve w/o compression

Reversible in 5-7% of all cases of TED

Typically presents during active phase

Risk factors

Male, older, diabetic, smoker

Associated with EOM enlargement, diplopia and motility restriction, choroidal folds

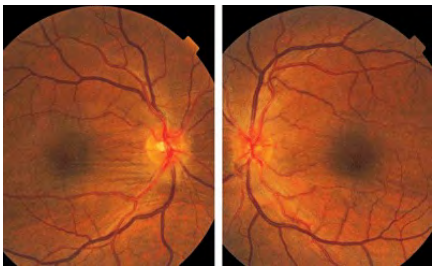

Image source: reviewofoptometry.com

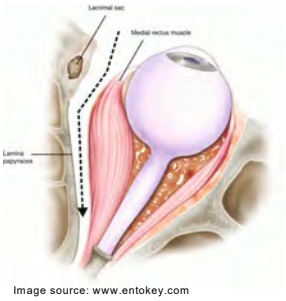

Image source: www.entokey.com

Regensburg NI et al. Ophthal Plast Reconstr Surg. 2011;27(4):236– 40.
Dolman PJ. Et al. J Endocrinol Invest. 2021 Mar;44(3):421-429.

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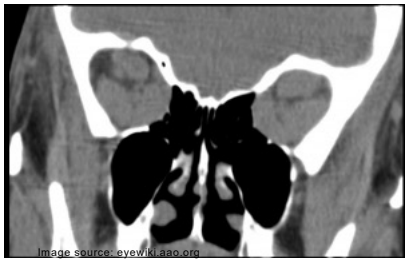
Posterior Segment Signs

Dysthyroid Optic Neuropathy (DON)

- **Color vision (HRR)**
- **(+) Relative Afferent Pupillary Defect**
  - May not be present in 50% because of symmetric loss of vision
- **Central vision**
  - Not sensitive
- **Coronal CT**
  - Enlarged EOM crowding ON at orbital apex
- **Humphrey Visual Field**
  - Paracentral scotomas
  - Generalized depression (~70% of DON cases)
- **Disc edema/pallor**
  - Absent in 40% of patients
- **Visually evoked potentials (VEP)**
  - Abnormal latency in ~75% of DON cases



Regensburg NI et al. Ophthal Plast Reconstr Surg. 2011;27(4):236– 40.
Dolman PJ. Et al. J Endocrinol Invest. 2021 Mar;44(3):421-429.

21

TED Symptoms

Irritation, grittiness, photophobia
Dry eye syndrome
Secondary to lid retraction and proptosis
Epiphora worse with exposure to cold, air, wind or bright lights
Orbital ache at rest or movement
Retroocular discomfort or pain
Diplopia
Desaturation of colors
Blurring of central vision

Kendler DL et al. Arch Ophthalmol. 1993;111:197– 201.
Roos JCP et al. Curr Opin Ophthalmol. 2019

22

Differentials

Orbital pseudotumor
Caroticocavernous fistula
Inflammatory orbitopathy
Orbital myositis
Orbital tumors
IgG4 tumors
Cranial nerve palsies
Myasthenia Gravis (especially with ptosis)
Chronic progressive external ophthalmoplegia (CPEO)

23

Lab testing

Detect thyroid dysfunction
Thyroid stimulating immunoglobulin (TSI)
Thyroid stimulating hormone (TSH)

Can help support diagnosis
Thyroid hormonal tests
1. T3
2. Free T4

Thyroid specific antibodies
1. Anti-thyroglobulin
2. Anti-thyroid peroxidase
3. Anti-TSH receptor

Hyperthyroidism	Low TSH, high T4/T3
Euthyroidism	High serum thyroid autoantibody concentrations or thyroid specific T cells
Hypothyrodisim	High TSH, low T4 (+) TSHR antibodies

24

Imaging

B-scan and A-scan Ultrasonography

- Screening for increase in thickness of EOM

Computed Tomography (CT) w/o contrast

- Extraocular muscle enlargement and orbital fat expansion
- Used for planning orbital decompression surgery (imaging of orbital apex)

Magnetic Resonance Imagining (MRI) w/ fat saturation and gadolinium

- Better for assessing disease activity and imaging soft tissues
- Differentiates non-compressive neuropathy and predicts response of medical therapy

Garrity JA, Bahn RS. Am J Ophthalmol. 2006 Jul;142(1):147-153.
Thyroid Eye Disease, edited by Raymond S. Douglas, et al., Springer New York, 2014.

25

B-scan/A-scan Ultrasonography

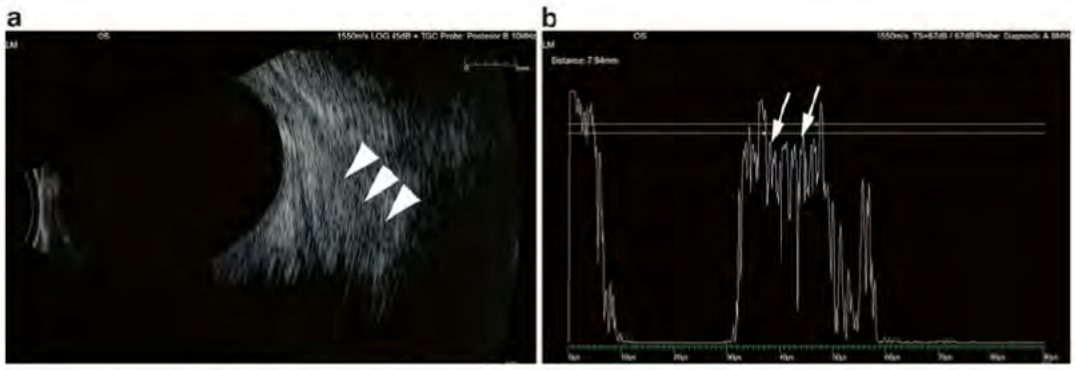


Fig. 10.4 Echographic findings. (**a**) B-scan ultrasound image shows enlarged EOM in retrobulbar space (*arrowhead*). (**b**) A-scan demonstrates high internal reflectivity (*arrows*) characteristic of thyroid ophthalmopathy

Thyroid Eye Disease, edited by Raymond S. Douglas, et al., Springer New York, 2014.

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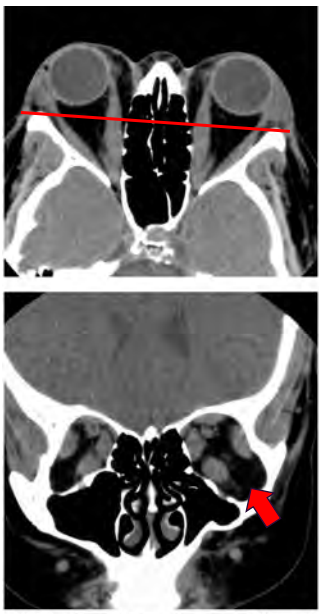
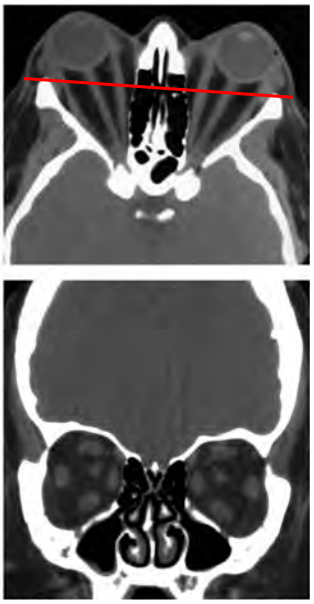
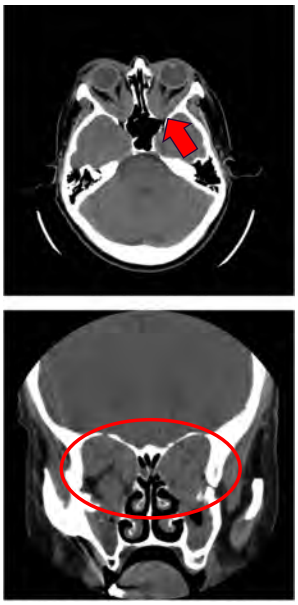
CT



Proptosis from EOM enlargement & orbital fat expansion



Marked proptosis from orbital fat expansion



EOM enlargement and apical muscle compression

Garrity JA, Bahn RS. Am J Ophthalmol. 2006 Jul;142(1):147-153.

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MRI

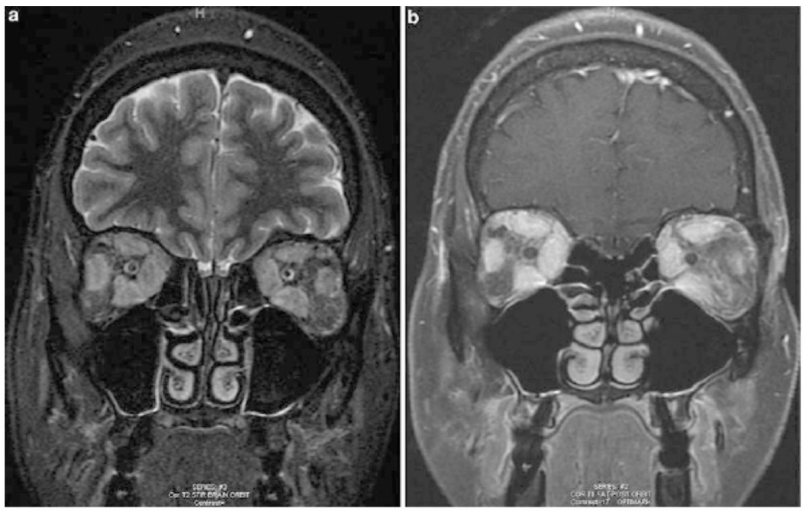

Fig. 10.2 Magnetic resonance imaging of orbit in a patient with strabismus. (**a**) Coronal T2 STIR, (**b**) Coronal T1 fat suppression postcontrast MRI, marked enlargement of the extraocular muscles bilaterally, with greatest involvement of the superior, medial, and inferior recti. There is heterogeneity within the orbital fat

Thyroid Eye Disease, edited by Raymond S. Douglas, et al., Springer New York, 2014.

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Retinal Imaging

Optical Coherence Tomography

OCT- Angiography

Decrease in peripapillary and macular vascular density in active TED

1. Secondary to hypoxia and resultant ischemia from edema in orbital soft tissues
2. Reduction in ocular blood flow in patients with thyroid orbitopathy

OCT- Enhanced Depth Imaging (EDI)

Increased choroidal thickness

1. Orbital venous congestion and increase intraorbital pressure from expanded orbital tissues
2. Mechanical pressure applied directly to eyeball
3. Inflammatory cells increasing vascular leakage/exudates and changes in orbital blood flow

Dave TV et al. Orbit. 2020 Nov 17:1-8.
Zhang T et al. . Invest Ophthalmol Vis Sci. 2019;60:1863–1869.
Tehrani JM et al. Graefes Arch Clin Exp Ophthalmol. 2019;257:2533–2540.
Kim J et al. BMC Ophthalmol. 2021 Jan 12;21(1):32.

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Marshall B.
KETCHUM UNIVERSITY
Southern California College of Optometry

Classification

NO-SPECS
European Group on Graves Orbitopathy Severity Scale
Clinical Activity Score
VISA (ITEDS)

30

NO-SPECS

First introduced in 1969 by the American Thyroid Association
Loosely defined and based on 1 variable

Class	Description
0	**N**o symptoms or signs
1	**O**nly signs, no symptom (upper eyelid retraction, stare, eyelid lag, proptosis up to 22mm)
2	**S**oft tissue involvement (symptoms and signs, RELIEF)
3	**P**roptosis (>22mm, even without symptoms)
4	**E**xtraocular muscle involvement
5	**C**orneal involvement
6	**S**light loss (optic nerve involvement)

Werner SC J Clin Endocrinol Metab 1969;29:982-984.

31

Clinical Activity Score (CAS)

Identifies active TED patients who will respond to immunosuppressive therapy (based on Rundle's curve)

Binary scale

Soft-tissue inflammatory symptoms and signs as surrogate markers

Cons:

Does not correlate with risk of developing significant complications

Assumes each clinical feature is equivalent in nature

Dolman, Peter J. *Ophthalmic plastic and reconstructive surgery* vol. 34,4S Suppl 1 (2018): S34-S40.
Mourits MP et al. Clin Endocrinol (Oxf). 1997; 47: 9–14.

32

Clinical Activity Score (CAS)

	TED Activity
1	Spontaneous retrobulbar pain
2	Pain on attempted upward or downward gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Swelling of caruncle or plica
6	Swelling of eyelids
7	Swelling of conjunctiva (chemosis)
	Follow-up additional points (1-3 months)
1	Increased proptosis ≥2mm
2	Decrease ocular motility (8° or more)
3	Decreased visual acuity over previous 3 months

Case: 40 y/o Korean female
- CAS: 2
- Inactive

Criteria:
- Inactive TED = CAS <3
- Active TED = CAS ≥ 4
  - ≥4 = 80% predictive value in predicting response to corticosteroid therapy

Mourits MP et al. Clin Endocrinol (Oxf). 1997; 47: 9–14.

33

European Group of Graves' Orbitopathy (EUGOGO)

Separates disease into management categories

Implies disease follows rank and order

May not correspond with patient's perception of disease

Stage	Characteristics
Mild (one or more of following) minor impact on daily life	Mild soft tissue involvement (i.e. minimal eyelid swelling) Minor lid retraction (<2mm) Proptosis <3mm over norms for race/gender Little or no EOM dysfunction
Moderate to severe sufficient impact on daily life	Active disease with or without EOM dysfunction w/ diplopia and inflammatory signs Lid retraction ≥2mm Moderate or severe soft-tissue involvement Proptosis ≥3mm over norms for race/gender
Very severe	Sight threatening conditions • Dysthyroid optic neuropathy (DON), corneal ulceration Requires surgical intervention

Bartalena L. et al. European Journal of Endocrinology 2008; 158(3): 273–285.

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VISA
(Vision, Inflammation, Strabismus, Appearance)

International Thyroid Eye Disease Society (ITEDS)

Based on clinical severity AND activity in 4 sections

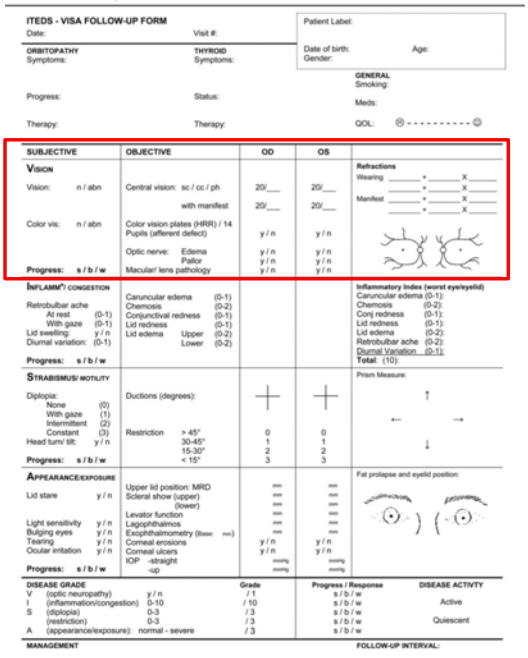
Subjective and objective

Each section has progress row based on interval changes

Not on rank order of clinical features

Dolman PJ, Rootman J. Ophthal Plast Reconstr Surg. 2006;22(5):319– 24.

35



ITEDS - VISA FOLLOW-UP FORM

Date: Visit #:

Patient Label:

ORBITOPATHY Symptoms: THYROID Symptoms: Date of birth: Age: Gender:

GENERAL Smoking:

Progress: Status: Meds:

Therapy: Therapy: QOL: ☹ ---------- ☺

SUBJECTIVE	OBJECTIVE	OD	OS	
VISION				Refractions
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___	Wearing ___ * ___ X ___
	with manifest	20/___	20/___	Manifest ___ * ___ X ___
Color vis: n / abn	Color vision plates (HRR) / 14			___ * ___ X ___
	Pupils (afferent defect)	y / n	y / n	
	Optic nerve: Edema	y / n	y / n	
	Pallor	y / n	y / n	
Progress: s / b / w	Macular/ lens pathology	y / n	y / n	
INFLAMM[n] CONGESTION				Inflammatory Index (worst eye/eyelid)
Retrobulbar ache	Caruncular edema (0-1)			Caruncular edema (0-1):
At rest (0-1)	Chemosis (0-2)			Chemosis (0-2):
With gaze (0-1)	Conjunctival redness (0-1)			Conj redness (0-1):
Lid swelling: y / n	Lid redness (0-1)			Lid redness (0-1):
Diurnal variation: (0-1)	Lid edema Upper (0-2)			Lid edema (0-2):
	Lower (0-2)			Retrobulbar ache (0-2):
Progress: s / b / w				Diurnal Variation (0-1):
				Total (10):
STRABISMUS/ MOTILITY				Prism Measure:
Diplopia:	Ductions (degrees):			
None (0)				
With gaze (1)				
Intermittent (2)				
Constant (3)	Restriction > 45°	0	0	
Head turn/ tilt: y / n	30-45°	1	1	
	15-30°	2	2	
Progress: s / b / w	< 15°	3	3	
APPEARANCE/EXPOSURE				Fat prolapse and eyelid position:
Lid stare y / n	Upper lid position: MRD	mm	mm	
	Scleral show (upper)	mm	mm	
	(lower)	mm	mm	
	Levator function	mm	mm	
Light sensitivity y / n	Lagophthalmos	mm	mm	
Bulging eyes y / n	Exophthalmometry (Base: mm)	mm	mm	
Tearing y / n	Corneal erosions	y / n	y / n	
Ocular irritation y / n	Corneal ulcers	y / n	y / n	
Progress: s / b / w	IOP -straight	mmHg	mmHg	
	-up	mmHg	mmHg	

DISEASE GRADE		Grade	Progress / Response	DISEASE ACTIVITY
V (optic neuropathy)	y / n	/ 1	s / b / w	
I (inflammation/congestion)	0-10	/ 10	s / b / w	Active
S (diplopia)	0-3	/ 3	s / b / w	
(restriction)	0-3	/ 3	s / b / w	Quiescent
A (appearance/exposure):	normal - severe	/ 3	s / b / w	

MANAGEMENT FOLLOW-UP INTERVAL:

http://thyroideyedisease.org/downloads/

Vision

Presence or absence of dysthyroid optic neuropathy (DON)

Severity and response to therapy within individual objective measurements

Includes HVF, VEP, and OCT

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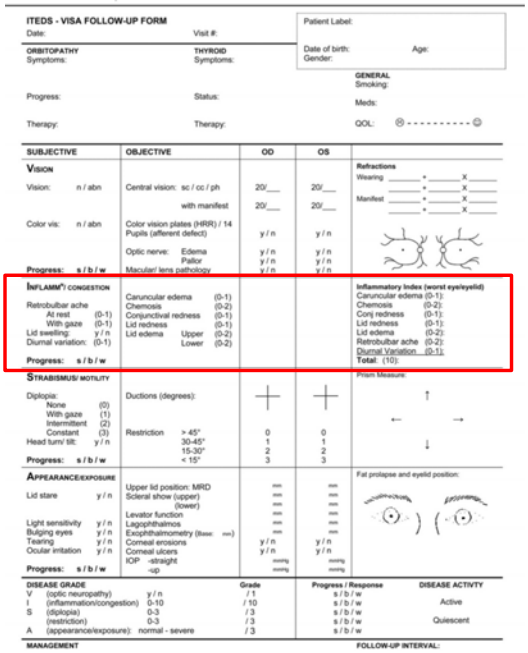
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Date: Visit #:

Patient Label:

ORBITOPATHY Symptoms: THYROID Symptoms: Date of birth: Age: Gender:

GENERAL Smoking:

Progress: Status: Meds:

Therapy: Therapy: QOL:

SUBJECTIVE	OBJECTIVE	OD	OS
VISION			
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___
	with manifest	20/___	20/___
Color vis: n / abn	Color vision plates (HRR) / 14		
	Pupils (afferent defect)	y / n	y / n
	Optic nerve: Edema	y / n	y / n
	Pallor	y / n	y / n
Progress: s / b / w	Macular/ lens pathology	y / n	y / n
INFLAMM[n] CONGESTION			
Retrobulbar ache	Caruncular edema (0-1)		
At rest (0-1)	Chemosis (0-2)		
With gaze (0-1)	Conjunctival redness (0-1)		
Lid swelling: y / n	Lid redness (0-1)		
Diurnal variation: (0-1)	Lid edema Upper (0-2)		
Progress: s / b / w	Lower (0-2)		
STRABISMUS/ MOTILITY			
Diplopia:	Ductions (degrees):		
None (0)			
With gaze (1)			
Intermittent (2)			
Constant (3)	Restriction > 45°	0	0
Head turn/ tilt: y / n	30-45°	1	1
	15-30°	2	2
Progress: s / b / w	< 15°	3	3
APPEARANCE/EXPOSURE			
Lid stare y / n	Upper lid position: MRD	mm	mm
	Scleral show (upper)	mm	mm
	(lower)	mm	mm
	Levator function	mm	mm
Light sensitivity y / n	Lagophthalmos	mm	mm
Bulging eyes y / n	Exophthalmometry (Base: mm)	mm	mm
Tearing y / n	Corneal erosions	y / n	y / n
Ocular irritation y / n	Corneal ulcers	y / n	y / n
Progress: s / b / w	IOP -straight	mmHg	mmHg
	-up	mmHg	mmHg

DISEASE GRADE		Grade	Progress / Response	DISEASE ACTIVITY
V (optic neuropathy)	y / n	/ 1	s / b / w	
I (inflammation/congestion)	0-10	/ 10	s / b / w	Active
S (diplopia)	0-3	/ 3	s / b / w	
(restriction)	0-3	/ 3	s / b / w	Quiescent
A (appearance/exposure):	normal - severe	/ 3	s / b / w	

MANAGEMENT FOLLOW-UP INTERVAL:

Refractions: Wearing ____ * ____ X ____; Manifest ____ * ____ X ____; ____ * ____ X ____

Inflammatory Index (worst eye/eyelid): Caruncular edema (0-1): Chemosis (0-2): Conj redness (0-1): Lid redness (0-1): Lid edema (0-2): Retrobulbar ache (0-2): Diurnal Variation (0-1): Total (10):

Prism Measure:

Fat prolapse and eyelid position:

http://thyroideyedisease.org/downloads/

Inflammation

Orbital soft tissue inflammation or congestion

Based on the worst score for either eye or eyelid

Orbital ache at rest or with movement/diurnal variation

Ocular surface or eyelid injection/edema

Progress: change of ≥2 or more on inflammatory score

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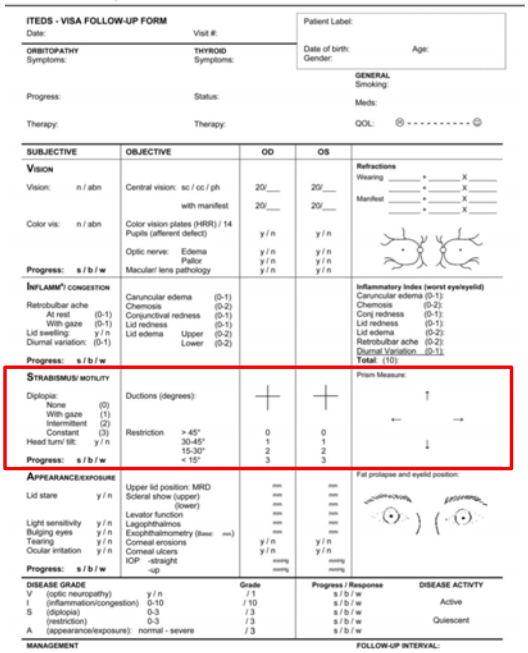
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Patient Label:

ORBITOPATHY Symptoms: THYROID Symptoms: Date of birth: Age: Gender:

GENERAL Smoking:

Progress: Status: Meds:

Therapy: Therapy: QOL:

SUBJECTIVE	OBJECTIVE	OD	OS
VISION			
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___
	with manifest	20/___	20/___
Color vis: n / abn	Color vision plates (HRR) / 14		
	Pupils (afferent defect)	y / n	y / n
	Optic nerve: Edema	y / n	y / n
	Pallor	y / n	y / n
Progress: s / b / w	Macular/ lens pathology	y / n	y / n
INFLAMM[n] CONGESTION			
Retrobulbar ache	Caruncular edema (0-1)		
At rest (0-1)	Chemosis (0-2)		
With gaze (0-1)	Conjunctival redness (0-1)		
Lid swelling: y / n	Lid redness (0-1)		
Diurnal variation: (0-1)	Lid edema Upper (0-2)		
Progress: s / b / w	Lower (0-2)		
STRABISMUS/ MOTILITY			
Diplopia:	Ductions (degrees):		
None (0)			
With gaze (1)			
Intermittent (2)			
Constant (3)	Restriction > 45°	0	0
Head turn/ tilt: y / n	30-45°	1	1
	15-30°	2	2
Progress: s / b / w	< 15°	3	3
APPEARANCE/EXPOSURE			
Lid stare y / n	Upper lid position: MRD	mm	mm
	Scleral show (upper)	mm	mm
	(lower)	mm	mm
	Levator function	mm	mm
Light sensitivity y / n	Lagophthalmos	mm	mm
Bulging eyes y / n	Exophthalmometry (Base: mm)	mm	mm
Tearing y / n	Corneal erosions	y / n	y / n
Ocular irritation y / n	Corneal ulcers	y / n	y / n
Progress: s / b / w	IOP -straight	mmHg	mmHg
	-up	mmHg	mmHg

DISEASE GRADE		Grade	Progress / Response	DISEASE ACTIVITY
V (optic neuropathy)	y / n	/ 1	s / b / w	
I (inflammation/congestion)	0-10	/ 10	s / b / w	Active
S (diplopia)	0-3	/ 3	s / b / w	
(restriction)	0-3	/ 3	s / b / w	Quiescent
A (appearance/exposure):	normal - severe	/ 3	s / b / w	

MANAGEMENT FOLLOW-UP INTERVAL:

Refractions: Wearing ____ * ____ X ____; Manifest ____ * ____ X ____; ____ * ____ X ____

Inflammatory Index (worst eye/eyelid): Caruncular edema (0-1): Chemosis (0-2): Conj redness (0-1): Lid redness (0-1): Lid edema (0-2): Retrobulbar ache (0-2): Diurnal Variation (0-1): Total (10):

Prism Measure:

Fat prolapse and eyelid position:

http://thyroideyedisease.org/downloads/

Strabismus

Diplopia

Bahn-Gorman scale

- 0= no diplopia
- I = intermittent diplopia (present w/ fatigue)
- II = inconstant diplopia (w/ vertical or horizontal gaze)
- III = constant diplopia in straight gaze, correctable with prisms
- IV = constant diplopia, not correctable with prisms

Ocular ductions/restrictions

Hirschberg technique

Ocular posture

Alternating cover test in 4 gazes to plan for surgical alignment

Progress: 12º change in ocular ductions

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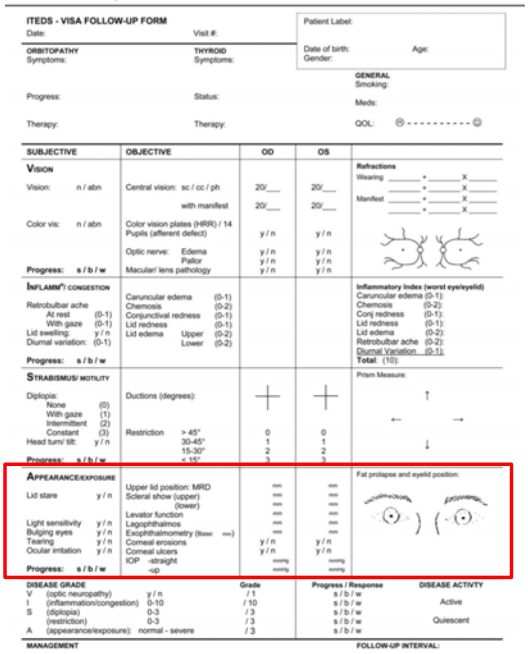

ITEDS - VISA FOLLOW-UP FORM

Date: Visit #:

Patient Label:

ORBITOPATHY Symptoms: THYROID Symptoms:

Date of birth: Age: Gender:

GENERAL Smoking:

Progress: Status: Meds:

Therapy: Therapy: QOL:

SUBJECTIVE	OBJECTIVE	OD	OS
VISION			
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___
	with manifest	20/___	20/___
Color vis: n / abn	Color vision plates (HRR) / 14		
	Pupils (afferent defect)	y / n	y / n
	Optic nerve: Edema	y / n	y / n
	Pallor	y / n	y / n
Progress: s / b / w	Macular/ lens pathology	y / n	y / n
INFLAMM*) CONGESTION			
Retrobulbar ache	Caruncular edema (0-1)		
At rest (0-1)	Chemosis (0-2)		
With gaze (0-1)	Conjunctival redness (0-1)		
Lid swelling: y / n	Lid redness (0-1)		
Diurnal variation: (0-1)	Lid edema Upper (0-2)		
	Lower (0-2)		
Progress: s / b / w			
STRABISMUS/ MOTILITY			
Diplopia:	Ductions (degrees):		
None (0)			
With gaze (1)			
Intermittent (2)			
Constant (3)	Restriction > 45°	0	0
Head turn/ tilt: y / n	30-45°	1	1
	15-30°	2	2
Progress: s / b / w	< 15°	3	3
APPEARANCE/EXPOSURE			
Lid stare y / n	Upper lid position: MRD	mm	mm
	Scleral show (upper)	mm	mm
	(lower)	mm	mm
	Levator function	mm	mm
Light sensitivity y / n	Lagophthalmos	mm	mm
Bulging eyes y / n	Exophthalmometry (Base: mm)	mm	mm
Tearing y / n	Corneal erosions	y / n	y / n
Ocular irritation y / n	Corneal ulcers	y / n	y / n
Progress: s / b / w	IOP -straight	mmHg	mmHg
	-up	mmHg	mmHg

DISEASE GRADE		Grade	Progress / Response	DISEASE ACTIVITY
V (optic neuropathy)	y / n	/ 1	s / b / w	
I (inflammation/congestion)	0-10	/ 10	s / b / w	Active
S (diplopia)	0-3	/ 3	s / b / w	
(restriction)	0-3	/ 3	s / b / w	Quiescent
A (appearance/exposure):	normal - severe	/ 3	s / b / w	

MANAGEMENT FOLLOW-UP INTERVAL:

Refractions Wearing Manifest

Inflammatory Index (worst eye/eyelid)
Caruncular edema (0-1):
Chemosis (0-2):
Conj redness (0-1):
Lid redness (0-1):
Lid edema (0-2):
Retrobulbar ache (0-2):
Diurnal Variation (0-1):
Total (10):

Prism Measure:

Fat prolapse and eyelid position:

http://thyroideyedisease.org/downloads/

Appearance

Relating to adnexa and exposure

Photograph to document appearance changes

Progress:
≥2mm change in proptosis

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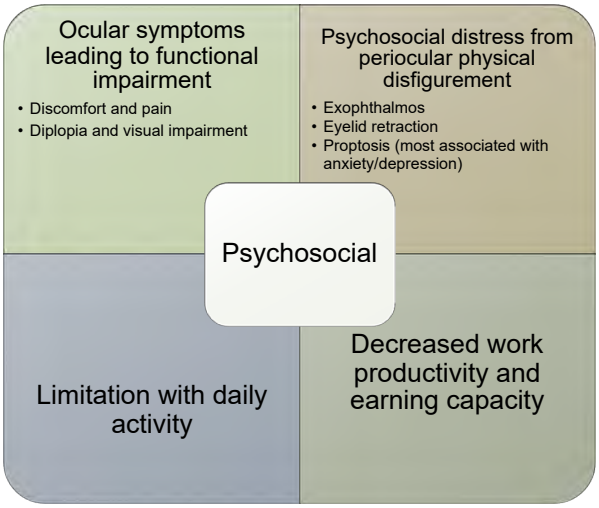
Psychological Disturbances

Almost ½ patients suffer from symptoms of anxiety and/or depression

As high as 90% patients with TED have appearance related concerns

Emotional effects do not have to be correlated with duration, severity, or activity of TED

Physicians may view TED as self-limiting or inactive, while only 2% of patients consider themselves to be recovered



Terwee CB, et al. *British Journal of Ophthalmology* 1998;**82**:773-779
Carta MG, et al. BMC Psychiatry. 2004;4:25.
Sabini E et al. Eur Thyroid J 2017; 6:263–270.

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Quality of Life (QoL)

Patients with TED have lower QoL than the healthy American population

Should determine the thresholds for various interventions: medical, orbital radiation, or surgery

Types

1. *General health related*
2. *Disease-specific QOL questionnaires*
   - GO-QOL questionnaire (multiple item questionnaire)
   - Graves ophthalmopathy quality of life scale (GO-QLS)
   - TED-QOL questionnaire (single-item questionnaire)
   - Singapore TED-QOL
3. *Vision-specific questionnaires*
4. *Semi-structured interviews*

Gerding MN et al. Thyroid 1997;7:885–9.
Terwee Cbet al. Clin Endocrinol (Oxf). 2001 Mar;54(3):391-8.
Lee, Tze et al. *Ophthalmic plastic and reconstructive surgery* vol. 36,2 (2020): 118-126.

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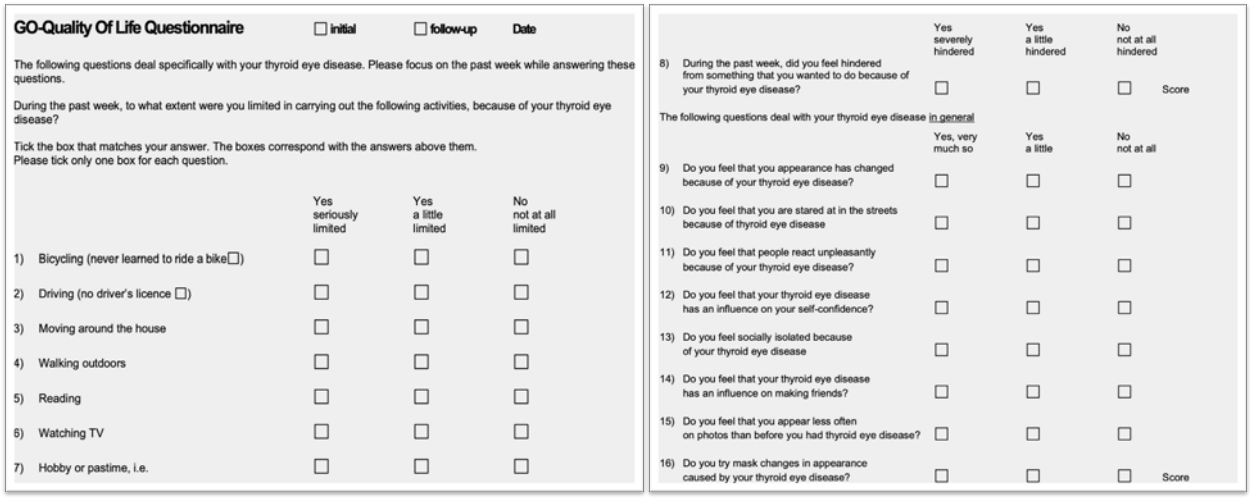
GO-QoL



GO-Quality Of Life Questionnaire ☐ initial ☐ follow-up Date

The following questions deal specifically with your thyroid eye disease. Please focus on the past week while answering these questions.

During the past week, to what extent were you limited in carrying out the following activities, because of your thyroid eye disease?

Tick the box that matches your answer. The boxes correspond with the answers above them. Please tick only one box for each question.

	Yes seriously limited	Yes a little limited	No not at all limited
1) Bicycling (never learned to ride a bike☐)	☐	☐	☐
2) Driving (no driver's licence ☐)	☐	☐	☐
3) Moving around the house	☐	☐	☐
4) Walking outdoors	☐	☐	☐
5) Reading	☐	☐	☐
6) Watching TV	☐	☐	☐
7) Hobby or pastime, i.e.	☐	☐	☐

	Yes severely hindered	Yes a little hindered	No not at all hindered	
8) During the past week, did you feel hindered from something that you wanted to do because of your thyroid eye disease?	☐	☐	☐	Score

The following questions deal with your thyroid eye disease in general

	Yes, very much so	Yes a little	No not at all	
9) Do you feel that you appearance has changed because of your thyroid eye disease?	☐	☐	☐	
10) Do you feel that you are stared at in the streets because of thyroid eye disease	☐	☐	☐	
11) Do you feel that people react unpleasantly because of your thyroid eye disease?	☐	☐	☐	
12) Do you feel that your thyroid eye disease has an influence on your self-confidence?	☐	☐	☐	
13) Do you feel socially isolated because of your thyroid eye disease	☐	☐	☐	
14) Do you feel that your thyroid eye disease has an influence on making friends?	☐	☐	☐	
15) Do you feel that you appear less often on photos than before you had thyroid eye disease?	☐	☐	☐	
16) Do you try mask changes in appearance caused by your thyroid eye disease?	☐	☐	☐	Score

www.eugogo.eu

Terwee CB, et al. *British Journal of Ophthalmology* 1998;**82**:773-779

42

Which Grading Criteria Should We Use?

VISA offers an easy-to-use grading sheet online that follows progress of patient in the 4 sections

EUGOGO Severity Scale still widely used in clinic and research

CAS is straightforward and quick
Used in research and clinical settings

Be aware of each test's strengths and weaknesses

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Ophthalmic Management

44

All patients with TED

1) Maintain or restore euthyroidism

2) Smoking cessation

- Have more severe TED than non-smokers
- Show progression or de novo occurrence after radioiodine treatment
- Worsens or delays outcome with immunosuppressive Tx
- Cessation = better outcome

3) May refer to specialist at various stages of mild, moderate to severe, and sight threatening (DON) stages

45

All patients with TED
- Maintain and restore euthyroidism
- Smoking cessation
- Adjust modifiable RF
- Refer to specialists when necessary

Mild Active TED

46

Mild active TED

Mixed dry eye syndrome (evaporative and aqueous)

1. Non-preserved artificial tears with long retention time; ointment or gel at nighttime

47

Mild active TED

Mixed dry eye syndrome (evaporative and aqueous)

Selenium supplementation

1. 100-300 ug sodium selenite daily for ~6 mos
2. Increase intake of selenium rich foods
   (i.e. pork, beef, turkey, chicken, eggs, brazil nuts)
3. Improves ocular manifestations, QoL and prevents GO progression to severe forms

Selenium supplementation for patients with Graves' hyperthyroidism (the GRASS trial): study protocol for a randomized controlled trial

Torquil Watt[1*], Per Cramon[1], Jakob Bue Bjorner[2,3], Steen Joop Bonnema[4], Ulla Feldt-Rasmussen[1], Christian Gluud[5], Jeppe Gram[6], Jane Lindschou Hansen[5], Laszlo Hegedus[4], Nils Knudsen[7], Pernille Bach-Mortensen[8], Kuna Nolsoe[9], Birte Nygaard[10], Flemming Pociot[11], Marla Skoog[12], Pei Winkel[5] and Åse Krogh Rasmussen[1]

Study done in Europe where selenium deficiency is common

Duntas LH et al. J Clin Endocrinol Metab 2010, 95:5180–5188.
Watt T et al. Trials. 2013 Apr 30;14:119.

48

Mild active TED

Mixed dry eye syndrome (evaporative and aqueous)

Selenium supplementation

Lid retraction

Botulinum toxin injections
Hyaluronic acid injection into levator plane and/or lower lid
Triamcinolone injections
Upper eyelid weights

Control modifiable risk factors

Close monitoring depending on pt history, symptoms, and psychological state

Duntas LH et al. J Clin Endocrinol Metab 2010, 95:5180–5188.
Grisolia ABD et al. Br J Ophthalmol 2017.
Xu D et al. Can J Ophthalmol 2012; 47:34–41.
Watt T et al. Trials. 2013 Apr 30;14:119.
Zamani M et al. Arch Ophthalmol 2008; 126:1157–1159.

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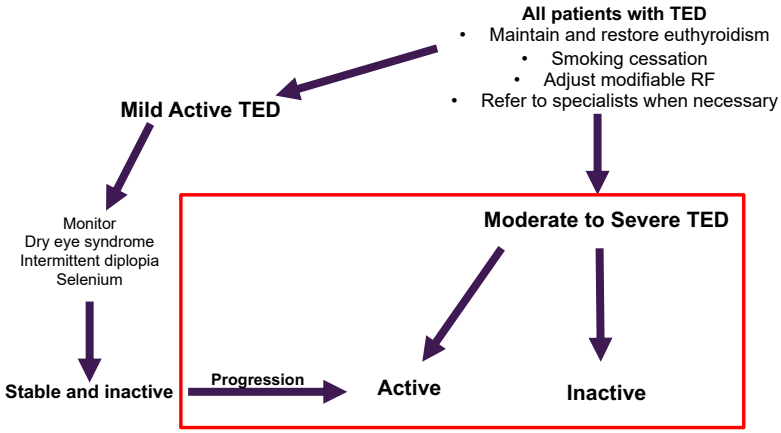
All patients with TED
- Maintain and restore euthyroidism
- Smoking cessation
- Adjust modifiable RF
- Refer to specialists when necessary

Mild Active TED

Monitor
Dry eye syndrome
Intermittent diplopia
Selenium

Stable and inactive

50



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Active moderate to severe TED

Immunosuppressants

Systemic glucocorticoids (Intravenous preferred)

IV glucocorticoids (high dose, dose dependent)
Moderate: 500 mg x 6 wks, 250 mg x6 wks
Severe: 750 mg x 6 wks, 500mg x6 weeks
Total dose of should not exceed 8g; can cause hepatic failure

Oral glucocorticoids
If IV unable, oral 3-day course of 50 mg for any improvement
Oral can be used as adjunct therapy with 2nd line Tx

Kahaly GJ, et al. J Clin Endocrinol Metab 2005;**90**:5234–40
Rajendram R et al. Lancet Diabetes Endocrinol 2018; 6:299–309.

52

Active moderate to severe TED

Immunosuppressants

Systemic glucocorticoids (Intravenous preferred)

Steroid sparing (adjuvant)

- Methotrexate
- Mycophenolate
- Azathioprine
- Cyclosporine

Kahaly GJ et al. Lancet Diabetes Endocrinol 2018; 6:287–298.
Rajendram R et al. Lancet Diabetes Endocrinol 2018; 6:299–309.
Ye X et al. Clin Endocrinol 2017;86:247–55.

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Active moderate to severe TED

Immunosuppressants

Systemic glucocorticoids (Intravenous preferred)

Steroid sparing (adjuvant)

Orbital irradiation therapy + glucocorticoids

Avoid surgical decompression in 94% of patients and elective decompression in 86% of TED-DON cases

Ongoing multicenter studies *(prospectively efficacy of combination radiotherapy and steroid)*

CRI-SEPTED: Combined radiotherapy and intravenous steroid for early progressive thyroid eye disease
CRISDON: Combined radiotherapy and intravenous steroid for dysthyroid optic neuropathy

Not recommended for young patients and diabetics

(worsening of retinal microvascular abnormalities)

Gold KG et al. Ophthalmic Plast Reconstr Surg 2018; 34:172–177.

54

Active moderate to severe TED

Immunosuppressants

Systemic glucocorticoids (Intravenous preferred)

Steroid sparing (adjuvant)

Orbital irradiation therapy + glucocorticoids

Diplopia: Fresnel prisms, monocular occlusion, botulinum toxin injection

May last months to years, can also self-improve

Strabismus surgery only performed during inactive phase

Bartalena L, et al. *Eur Thyroid J.* 2016;5:9-26.
Gold KG et al. Ophthalmic Plast Reconstr Surg 2018; 34:172–177.

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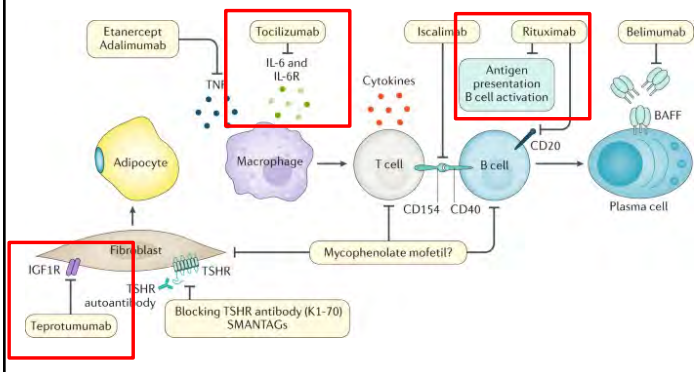

Biologics

Rituximab

Tocilizumab

Teprotumumab

Davies, T.F*et al. Nat Rev Dis Primers; 2000:* **6,** 52.
Salvi, M. Curr Opin Endocrinol Diabetes Obes 2014; 21(5): 409–414

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Biologics

Rituximab

B-cell depleting anti CD-20

Possible Uses: 2nd or 3rd line treatment

IV Low doses (100 mg) + steroid + 2nd line steroid-sparing agent
IV Moderate doses (400 mg) when steroid + radiotherapy has failed

Contradictory randomized controlled trial results

Not a large effect on proptosis, lid fissure width, and eye motility

No more efficacious than IV methylprednisolone

Treating severe steroid resistant TED? Need more large clinical trials

Insull EA et al. Clin Endocrinol (Oxf) 2019; 91:179–186
Du Pasquier-Fediaevsky L et al. Ocul Immunol Inflamm 2018; 1–7.

Biologics

Tocilizumab

Monoclonal antibody targeting IL-6

Use: Treat active severe TED non-responsive or minimal effect with steroid Tx

One double masked randomized control trial (2018)

Moderate to severe corticosteroid resistant graves orbitopathy
Results:
- Improved CAS score of 2 or more (93% treated vs 59% placebo)
- Disease inactivation higher (86.7% treated vs 35.2% placebo)
- Minimal proptosis reduction
- No difference in QoL @ 40 wks
- No reactivation

Need more clinical studies for:

Treating DON
Reproducibility of efficacy for active, moderate to severe TED

Canas CA et al. Endocr Metab Immune Disord Drug Targets 2018; 18:665–667.
Maldiney T et al. Ocul Immunol Inflamm 2018; 1–4
Copperman T et al. Ophthalmic Plast Reconstr Surg 2019.
Perez- Moreiras JV et al. Am J Ophthalmol 2018;195:181–90.

Biologics

Teprotumumab (TEPEZZA™)

Human monoclonal antibody as IGF-IR inhibitor
FDA approved as the first immunomodulator for TED in 2020

Teprotumumab for the Treatment of Active Thyroid Eye Disease

R.S. Douglas, G.J. Kahaly, A. Patel, S. Sile, E.H.Z. Thompson, R. Perdok, J.C. Fleming, B.T. Fowler, C. Marcocci, M. Marinò, A. Antonelli, R. Dailey, G.J. Harris, A. Eckstein, J. Schiffman, R. Tang, C. Nelson, M. Salvi, S. Wester, J.W. Sherman, T. Vescio, R.J. Holt, and T.J. Smith

Douglas, Raymond S et al. *The New England journal of medicine 2020;* 382 (4): 341-352.
Smith TJ, Kahaly GJ et al. N Engl J Med 2017; 376:1748–1761.

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Biologics

Teprotumumab (TEPEZZA™)

OPTIC Trial (2020): Randomized, double-masked, placebo-controlled phase 3 multicenter trial

Treatment: TED intravenous infusions of this every 3 wks for 21 wks (analysis at wk 24)
18-80 y/o, moderate to severe TED w/ Sx developing within last 9 mos, CAS ≥4, euthyroid

Outcome: Clinically meaningful proptosis reduction, CAS, diplopia, and QoL

Results:
Improvement in Proptosis: 83% teprotumumab vs 10% placebo
Number to treat: 1.36
Mean change ~-2.82 mm vs -0.52mm
Diplopia response (68% vs 29%)
CAS of 0 or 1 (59% vs 21%)
GO-QOL mean change (13.79 pts vs 4.43 pts)
Rapid improvement as early as week 6 and continued through to 24 weeks

Serious events uncommon

Douglas, Raymond S et al. *The New England journal of medicine 2020;* 382 (4): 341-352.
Smith TJ, Kahaly GJ et al. N Engl J Med 2017; 376:1748–1761.

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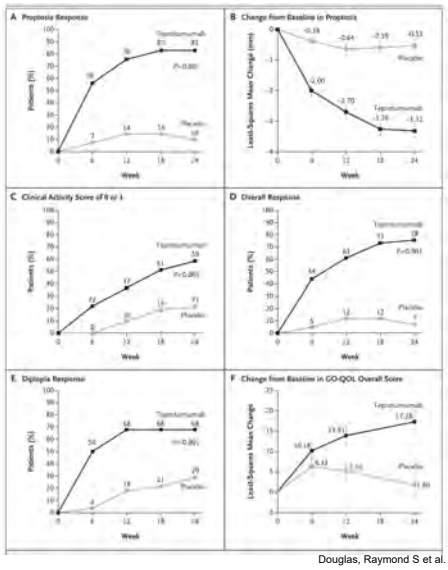

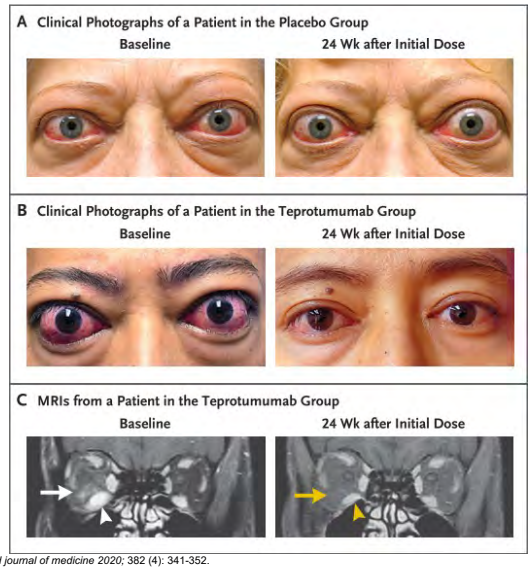

Douglas, Raymond S et al. *The New England journal of medicine 2020;* 382 (4): 341-352.

Cost without insurance: ~$14,900 per vial, 23 vials over 6 month course = ~$343,000

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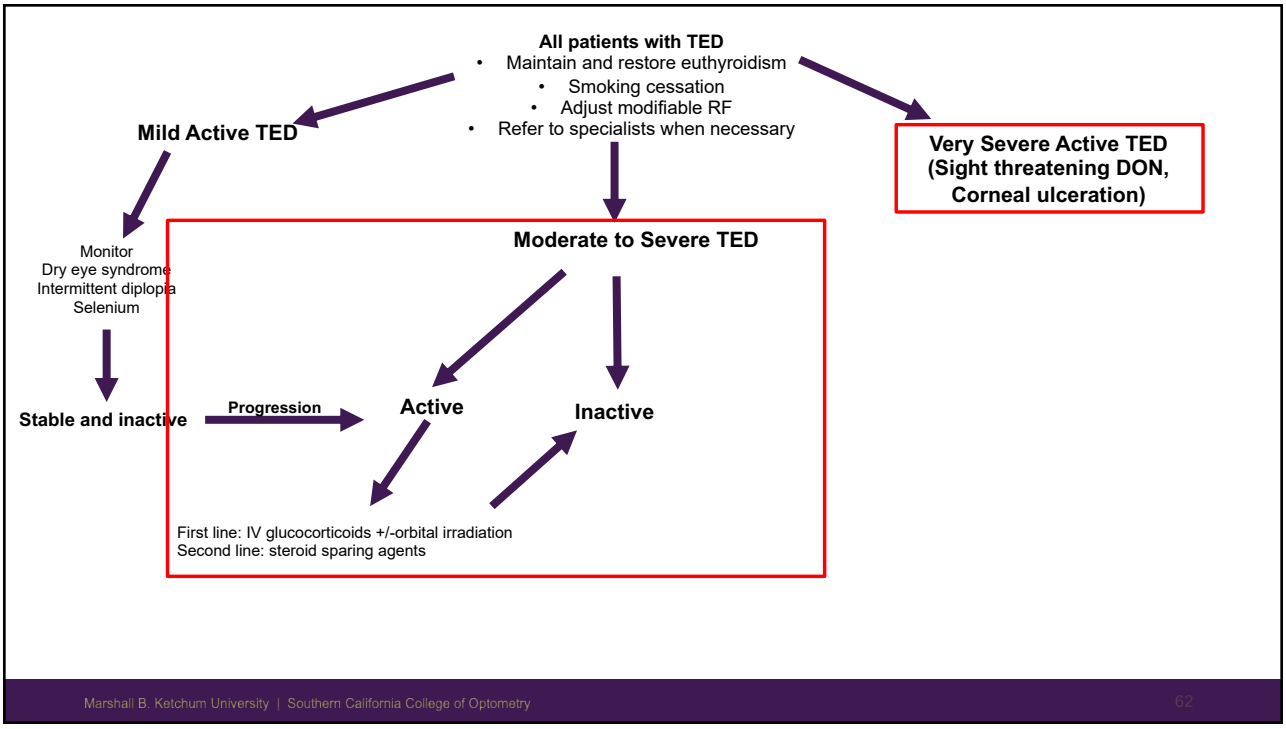

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Active Very Severe TED (Sight threatening)

High dose pulsed intravenous glucocorticoids

500-1000 mg for 3 consecutive days and repeated after 1 week

Orbital Decompression

If no improvement with IV glucocorticoids within 2 weeks
May be put on second round of IV glucocorticoids after completion of orbital decompression

Tarsorrhaphy

Corneal ulceration or perforation

Liang QW et al. Medicine (Baltimore) 2019; 98:e14162.80.
Tooley AA et al. Eye (Lond) 2019; 33:206–211

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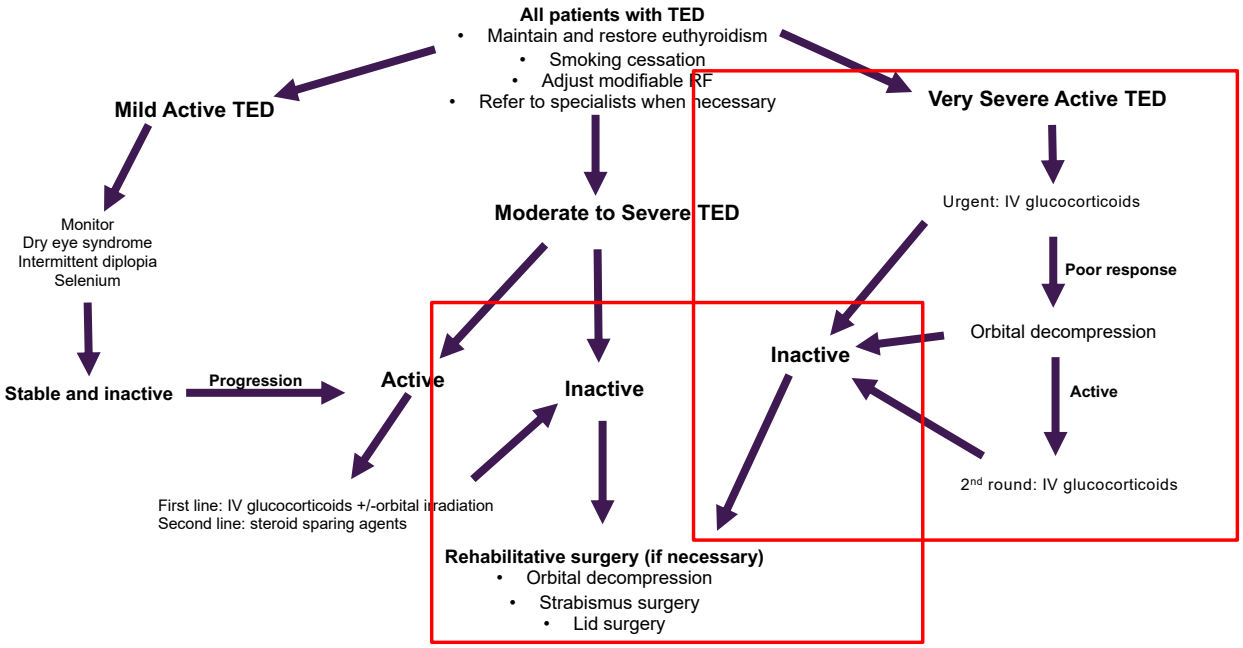

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Rehabilitative Surgery
Inactive TED Surgical Treatment

Orbital Wall Decompression

Typically done to reduce proptosis and ocular discomfort

When: Completed once stable

More durable and predictable results when goals limited to proptosis reduction

Strabismus Surgery

Goal = single binocular vision in primary & down gaze position

When: completed after in static phase and stable for 6 months

Eyelid Repair

Classical retractor recessions (levator recession)

Graded muller muscle resection

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Psychological Support

1. **Multidisciplinary care team**
   Including mental health professional for psychological counseling

2. **Refer patients to support groups and organizations**
   Graves' Disease and Thyroid Foundation (www.gdatf.org)

3. **Lower threshold for surgical intervention if altered appearance is significant and QoL is affected**

4. **Include QoL questionnaires alongside severity scoring in clinical practice**

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Clinical Pearls

1. Thyroid eye disease follows a biphasic course and no matter the stage smoking is the most important risk factor for ocular sequalae
2. TED signs and symptoms are not linear and thus there are no current fool-proof grading systems for clinical activity and severity
3. Numerous new medical treatments are being heavily researched for better management of TED
4. Dysthyroid optic neuropathy is a vision threatening sign and should be urgently referred to neuro-ophthalmology for initiation of therapy
5. Psychological disturbances can occur at any severity level, duration, or stage of the disease

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References

1. Anderton LC, Neoh C, Walshaw D, Dickinson AJ. Reproducibility of clinical assessment in thyroid eye disease. In: Abstract of the European Society of Ophthalmic, Plastic and Reconstructive Surgery, Paris; 2000. p. 107.
2. Bartley GB. The epidemiologic characteristics and clinical course of ophthal- mopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. Trans Am Ophthalmol Soc 1994; 92:477–588.
3. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M, Wiersinga WM; European Group on Graves' Orbitopathy (EUGOGO). The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016 Mar;5(1):9-26.
4. Canas CA, Bonilla-Abadia F, Vallejo K, et al. Successful treatment for severe thyroid-associated ophthalmopathy with tocilizumab. Endocr Metab Immune Disord Drug Targets 2018; 18:665–667.
5. Carta MG, Loviselli A, Hardoy MC, Massa S, Cadeddu M, Sardu C, et al. The link between thyroid autoimmunity (antithyroid peroxidase autoantibodies) with anxiety and mood disorders in the community: a field of interest for public health in the future. BMC Psychiatry. 2004;4:25.
6. Copperman T, Idowu OO, Kersten RC, Vagefi MR. Subcutaneous tocilizumab for thyroid eye disease: simplified dosing and delivery. Ophthalmic Plast Reconstr Surg 2019.
7. Bartalena L , Baldeschi L , Dickinson A et al., "Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) onmanagement ofGO," European Journal ofEndo- crinology,vol.158,no. 3, pp.273–285,2008.
8. Brand, O. J. & Gough, S. C. L. Genetics of thyroid autoimmunity and the role of the TSHR. Mol. Cell. Endocrinol. 2010; 322, 135–143.
9. Burch HB, Lahiri S, Bahn RS, Barnes S. Superoxide radical production stimuates retroocular fibroblast proliferation in Graves ophthalmopathy. Exp Eye Res 1997;65:311–316.
10. Dave TV, Laghmisetty S, Krishnamurthy G, Bejjanki K, Ganguly A, Jonnadula GB, Dave VP, Reddy Pappuru R. Retinal vascularity, nerve fiber, and ganglion cell layer thickness in thyroid eye disease on optical coherence tomography angiography. Orbit. 2020 Nov 17:1-8.
11. Davies, T.F., Andersen, S., Latif, R. *et al.* Graves' disease. *Nat Rev Dis Primers* 6, 52 (2020)
12. Dolman, Peter J. "Grading Severity and Activity in Thyroid Eye Disease." *Ophthalmic plastic and reconstructive surgery* vol. 34,4S Suppl 1 (2018): S34-S40.
13. Dolman PJ. Dysthyroid optic neuropathy: evaluation and management. J Endocrinol Invest. 2021 Mar;44(3):421-429.
14. Dolman PJ, Rootman J. VISA classification for Graves' orbitopathy. Ophthal Plast Reconstr Surg. 2006;22(5):319– 24.
15. Douglas, Raymond S et al. "Teprotumumab for the Treatment of Active Thyroid Eye Disease." *The New England journal of medicine* vol. 382,4 (2020): 341-352.
16. Du Pasquier-Fediaevsky L, Andrei S, Berche M, et al. Low-dose rituximab for active moderate-to-severe Graves' orbitopathy resistant to conventional treat- ment. Ocul Immunol Inflamm 2018; 1–7
17. Duntas LH: Selenium and the thyroid: a close-knit connection. J Clin Endocrinol Metab 2010, 95:5180–5188.
18. Cruz AA, Akaishi PM, Vargas MA, et al. Association between thyroid autoimmune dysfunction and nonthyroid autoimmune diseases. Ophthal Plast Reconstr Surg. 2007;23(2):104– 8.
19. Garrity JA, Bahn RS. Pathogenesis of graves ophthalmopathy: implications for prediction, prevention, and treatment. Am J Ophthalmol. 2006 Jul;142(1):147-153.
20. Gold KG, Scofield S, Isaacson SR, et al. Orbital radiotherapy combined with & corticosteroid treatment for thyroid eye disease-compressive optic neuro- pathy. Ophthalmic Plast Reconstr Surg 2018; 34:172–177.

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References

21. Gerding MN, Terwee CB, Dekker FW, et al. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. Thyroid 1997;7:885-9.
22. Grisolia ABD, Couso RC, Matayoshi S, et al. Nonsurgical treatment for eyelid retraction in thyroid eye disease (TED). Br J Ophthalmol 2017.
23. Insull EA, Sipkova Z, David J, et al. Early low-dose rituximab for active thyroid eye disease: an effective and well tolerated treatment. Clin Endocrinol (Oxf) 2019; 91:179–186
24. Kahaly GJ, Pitz S, Hommel G , *et al*. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 2005;90:5234–40
25. Kahaly GJ, Riedl M, Ko¨nig J, et al., European Group on Graves' Orbitopathy (EUGOGO). Mycophenolate plus methylprednisolone versus methylpredni- solone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol 2018; 6:287–296.
26. Kendler DL, Lippa J, Rootman J. The initial clinical characteristics of Graves' orbitopathy vary with age and sex. Arch Ophthalmol. 1993;111:197– 201.
27. Khong JJ, McNab AA, Ebeling PR, et al. Pathogenesis of thyroid eye disease: review and update o molecular mechanisms. Br J Ophthalmol 2016;100:142–150.
28. Kim J, Yoon S, Baek S. Increase of central foveal and temporal choroidal thickness in patients with inactive thyroid eye disease. BMC Ophthalmol. 2021 Jan 12;21(1):32.
29. Lee, Tze Howe Brandon, and Gangadhara Sundar. "Quality of Life in Thyroid Eye Disease: A Systematic Review." *Ophthalmic plastic and reconstructive surgery* vol. 36,2 (2020): 118-126
30. Lazarus JH. Epidemiology of Graves' orbitopathy (GO) and relationship with thyroid disease. Best Pract Res Clin Endocrinol Metab 2012; 26:273–279.
31. Liang QW, Yang H, Luo W, et al. Effect of orbital decompression on dysthyroid optic neuropathy: a retrospective case series. Medicine (Balti- more) 2019; 98:e14162.80.
32. Maldiney T, Deschasse C, Bielefeld P. Tocilizumab for the management of corticosteroid-resistant mild to severe Graves' ophthalmopathy, a report of three cases. Ocul Immunol Inflamm 2018; 1–4
33. Mourits MP, Prummel MF, Wiersinga WM,Koornneef L: Clinical activity score as a guidein the management of patients with Graves'ophthalmopathy. Clin Endocrinol (Oxf). 1997; 47: 9–14.
34. Perez- Moreiras JV, Gomez- Reino JJ, Maneiro JR, et al. Efficacy of tocilizumab in patients with moderate- to- severe corticosteroid- resistant Graves orbitopathy: a randomized clinical trial. Am J Ophthalmol 2018;195:181–90.
35. Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. JAMA 1993;269:479–82.
36. Regensburg NI, Wiersinga WM, Berendschot TT, et al. Densities of orbital fat and extraocular muscles in graves orbitopathy patients and controls. Ophthal Plast Reconstr Surg. 2011;27(4):236– 40.
37. Roos JCP, Murthy R. Update on the clinical assessment and management of thyroid eye disease. Curr Opin Ophthalmol. 2019
38. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthal- moplegia in Graves' disease with special reference to the effect of thyroidectomy. Clin Sci 1945; 5: 177-94.
39. Rajendram R, Taylor PN, Wilson VJ, et al. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre, 2 ? 2 factorial, double-blind, randomised controlled trial. Lancet Diabetes Endocrinol 2018; 6:299–309.
40. Salvi, M. Immunotherapy for Graves' ophthalmopathy. Curr Opin Endocrinol Diabetes Obes 2014; 21(5): 409–414
41. Sabini E, Leo M, Mazzi B, et al. Does Graves' orbitopathy ever disappear Answers to an old question. Eur Thyroid J 2017; 6:263–270.
42. Smith TJ, Hegedüs L. Graves' disease. N Engl J Med 2016; 375: 1552-65.
43. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated &ophthalmopathy. N Engl J Med 2017; 376:1748–1761.

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References

44. Stan MN, Bahn RS. Risk factors for development or deterioration of Graves' ophthalmopathy. Thyroid 2010; 20:777–783.
45. Terwee CB, Dekker FW, Mourits MP, Gerding MN, Baldeschi L, Kalmann R, Prummel MF, Wiersinga WM. Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. Clin Endocrinol (Oxf). 2001 Mar;54(3):391-8.
46. Tehrani JM, Mahdizad Z, Kasaei A, Fard MA. Early macular and peripapillary vasculature dropout in active thyroid eye disease. Graefes Arch Clin Exp Ophthalmol. 2019;257:2533–2540.
47. *Thyroid Eye Disease*, edited by Raymond S. Douglas, et al., Springer New York, 2014. *ProQuest Ebook Central*,
48. Tooley AA, Godfrey KJ, Kazim M. Evolution of thyroid eye disease decompression-dysthyroid optic neuropathy. Eye (Lond) 2019; 33:206–211
49. Watt T, Cramon P, Bjorner JB, Bonnema SJ, Feldt-Rasmussen U, Gluud C, Gram J, Hansen JL, Hegedüs L, Knudsen N, Bach-Mortensen P, Nolsøe R, Nygaard B, Pociot F, Skoog M, Winkel P, Rasmussen AK. Selenium supplementation for patients with Graves' hyperthyroidism (the GRASS trial): study protocol for a randomized controlled trial. Trials. 2013 Apr 30;14:119.
50. Werner SC: Classification of the eye changes of Graves' disease. (Letter) J Clin Endo-critnol Metab 1969;29:982-984.
51. Xu D, Liu Y, Xu H, et al. Repeated triamcinolone acetonide injection in the treatment of upper-lid retraction in patients with thyroid-associated ophthalmopathy. Can J Ophthalmol 2012; 47:34–41.
52. Ye X, Bo X, Hu X, et al. Efficacy and safety of mycophenolate mofetil in patients with active moderate- to- severe Graves' orbitopathy. Clin Endocrinol 2017;86:247–55.
53. Zamani M, Thyagarajan S, Olver JM. Functional use of hyaluronic acid gel in lower eyelid retraction. Arch Ophthalmol 2008; 126:1157–1159.
54. Zhang T, Xiao W, Ye H, Chen R, Mao Y, Yang H. Peripapillary and macular vascular density in dysthyr- oid optic neuropathy: an optical coherence tomography angiography study. Invest Ophthalmol Vis Sci. 2019;60:1863–1869.

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Marine Omega-3s in Dry Eye Disease: Uncovering the Facts, Dispelling the Myths

Presented by Mark Roark, OD

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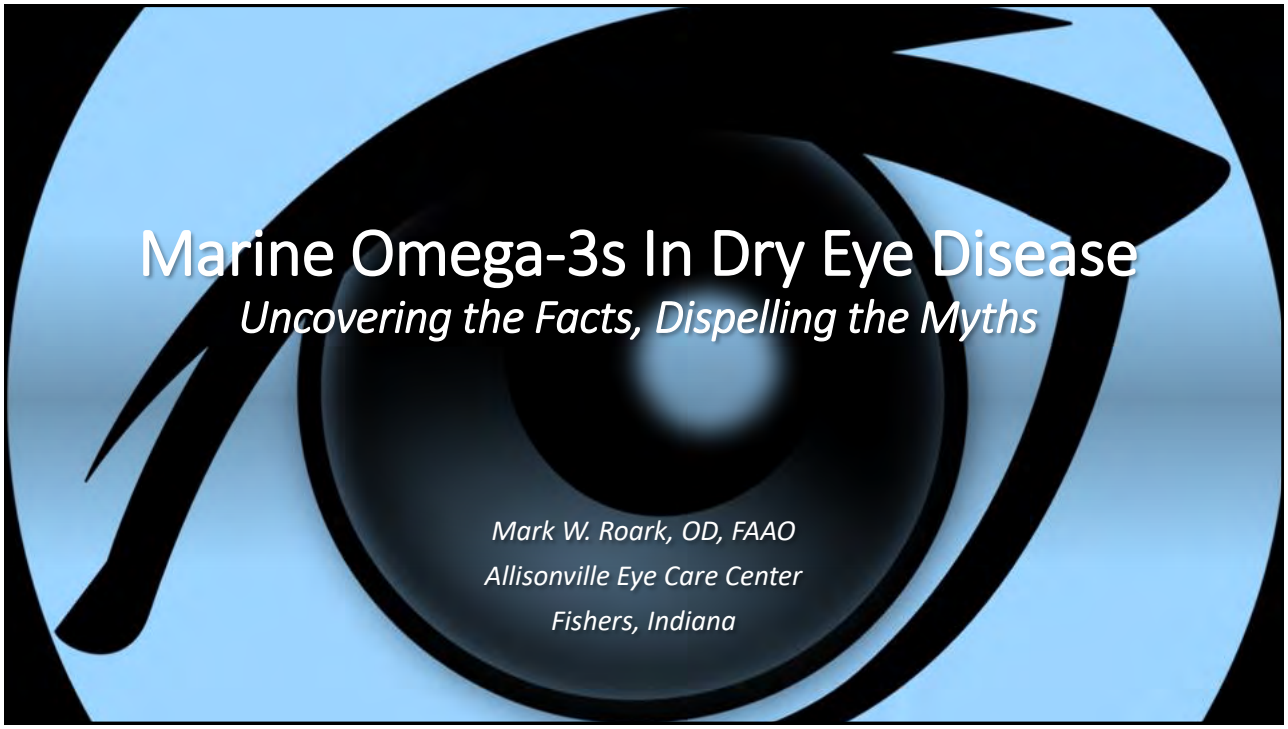

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RELEVANT FINANCIAL DISCLOSURES

- ❑ Johnson and Johnson Vision
- ❑ MacuHeath, LLC

2

Allisonville Eye Care Center –Fishers, Indiana

PRACTICE PHILOSOPHY

"We combine our passion for patient care with the latest scientific research to enhance the quality of your life through HEALTHY EYES and BETTER VISION"

3

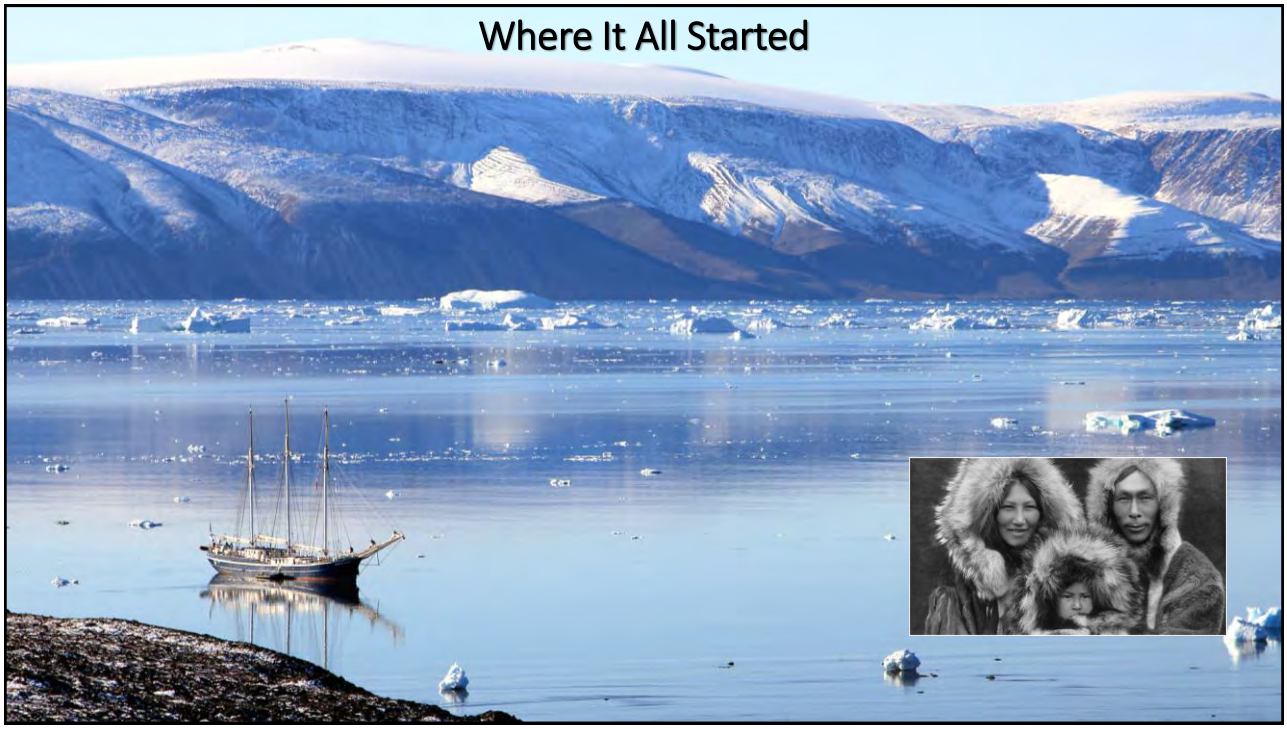
GOALS FOR THIS COURSE

UNDERSTAND:

- The Basic Structure And Function Of Omega-3 Fatty Acids
- The Mechanisms of Action by Which Marine Omega-3s Address Dry Eye Disease
- The Results of Clinical Trials Investigating the Role of Marine Omega-3s in Dry Eye Disease
- An Effective Implementation Strategy to Incorporate Marine Omega-3s in the Care of Dry Eye Disease Patients

4

Where It All Started



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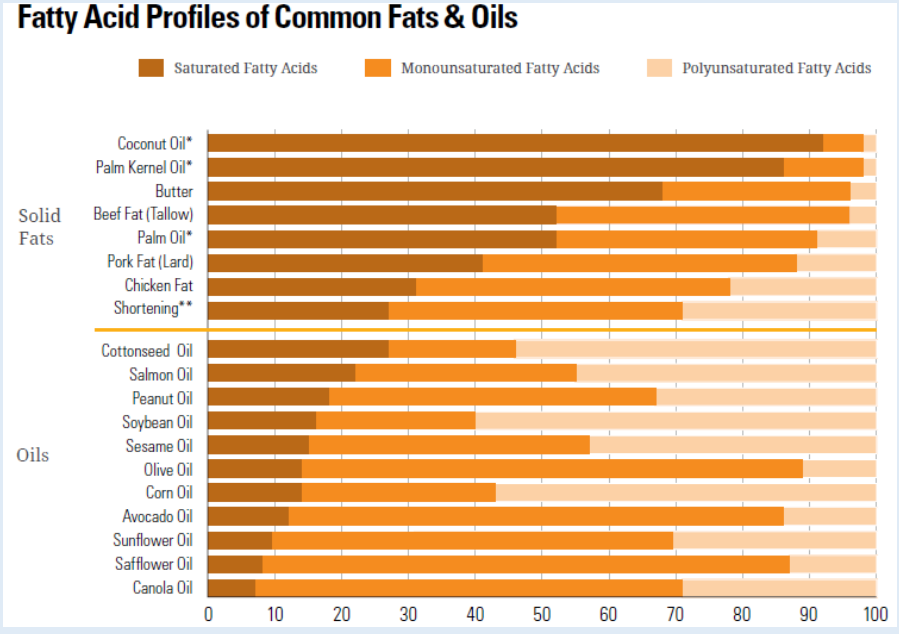
OMEGA-3s: ONE OF SEVERAL FATTY ACIDS



U.S. Department of HHS and U.S.D.A. *2015–2020 Dietary Guidelines for Americans*. 8th Edition. December 2015

6

POLYUNSATURATED FATTY ACIDS (PUFAS)
Essential Fatty Acid Families

Omega-6s

- Corn Oil
- Soybean Oil
- Safflower Oil
- Sunflower Oil

Linoleic Acid* (LA)
18 Carbons

Arachidonic Acid (AA)
20 Carbons

Omega-3s

- Flaxseed Oil
- Canola Oil
- Walnuts

Alpha Linolenic Acid* (ALA)
18 Carbons

PLANT-DERIVED

Eicosapentaenoic Acid (EPA)
20 Carbons

Docosahexaenoic Acid (DHA)
22 Carbons

Long-Chain PUFAS: The Main Components Of Our Cell Membranes

*Conversion to AA and EPA ~ 0.2-0.25% (Hussein et al. J Lipid Res 2005;46:269)

7

ALL OMEGA-3 FATTY ACIDS ARE NOT THE SAME

Omega-3 PUFAs

1) ***EPA***- *eicosapentaenoic acid* (long-chain PUFA)
   Source of **resolvins**- resolve inflammation
2) ***DHA***- *docosahexaenoic acid* (long-chain PUFA)
   Source of **resolvins, protectins, and maresins;** more prevalent than EPA in many cell membranes
3) ***DPA***- *docosapentaenoic acid (long-chain PUFA)*
   Less abundant in fish; source of **resolvins, protectins, and maresins**

Atlantic Bluefin Tuna

4) ***ALA***- *alpha-linolenic acid* (intermediate-chain PUFA)
   Found in plants, does not reduce need for EPA / DHA

Byelashov, Oleksandr A et al. "Dietary sources, current intakes, and nutritional role of omega-3 docosapentaenoic acid." *Lipid technology* vol. 27,4 (2015): 79-82.

8

OMEGA- 6 AND OMEGA-3 FATTY ACID MOLECULAR PATHWAYS

How important is the Omega-6/Omega-3 Ratio?

Omega-6s

LA
↓
GLA
↓
DGLA
↓
AA

Omega-3s

ALA
↓
SDA
↓
ETA
↓
EPA
↓
DHA

"Ratio-thinking distracts from the almost universal need for individuals with a "high" ratio to simply raise their EPA+DHA intake, not lower their n-6 intake."[2]

The conversion rate to the long-chain fatty acids is <1%[1]

Both Omega-6 and Omega-3 fatty acids have been associated with important health benefits. The problem with the Western diet with high rates of chronic disease is not too much LA and AA but too little EPA and DHA as can be measured using RBC membrane analysis.[2]

1. Conversion to AA and EPA ~ 0.2-0.25% (Hussein et al. J Lipid Res 2005;46:269)
2. Harris, William S. "The Omega-6:Omega-3 Ratio: A Critical Appraisal and Possible Successor." *Prostaglandins, Leukotrienes and Essential Fatty Acids*, vol. 132, 2018, pp. 34–40

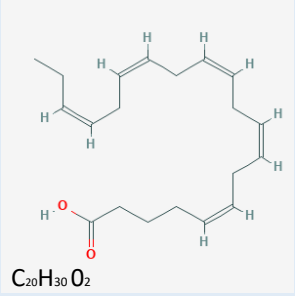
9

EPA AND DHA TERMINOLOGY- BREAKING IT DOWN

Eicosapentaenoic Acid – EPA

20:5n-3

"Eicosa"- means "20"- the number of carbons in the chain
"penta"- indicating "5"- the number of double bonds
"enoic"- indicates a fatty acid
The **"omega" is the** last **or *"nth" carbon*** *(sometimes show as "ω")*
The last double bond is 3 carbons from the nth carbon (so n-3)

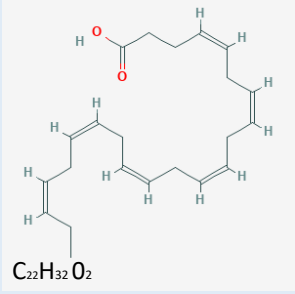


Words of Greek origin

Docosahexaenoic Acid – DHA

22:6n-3

"Docosa"- means "22"- the number of carbons in the chain
"hexa"- indicating "6"- the number of double bonds
"enoic"- indicates a fatty acid
The last double bond is 3 carbons from the nth carbon (so n-3)



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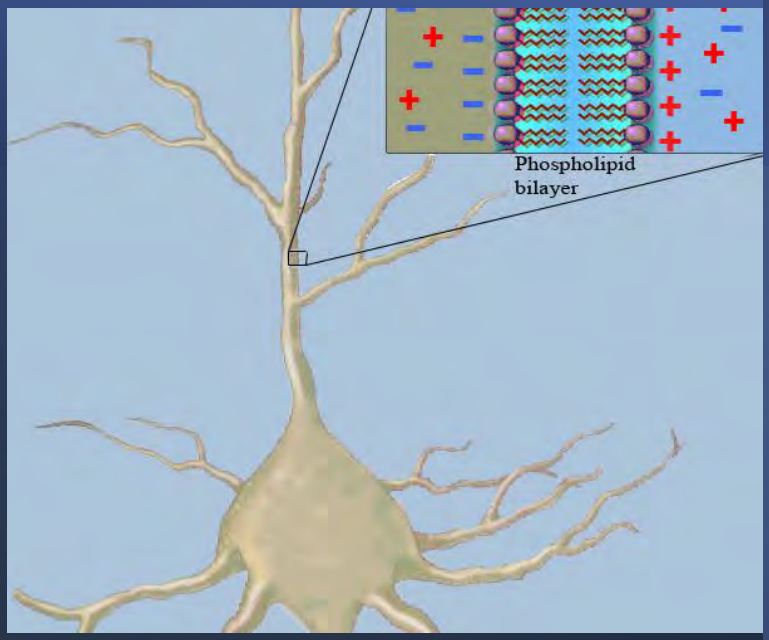


Omega-3s are incorporated into cell membranes in all tissues throughout the body.

Dietary intake of omega-3s can change the composition of the membrane.

11

MEASURING OMEGA-3 FATTY ACIDS LEVELS IN BODY TISSUES

Tests of EPA/DHA Omega-3 FA Blood Levels

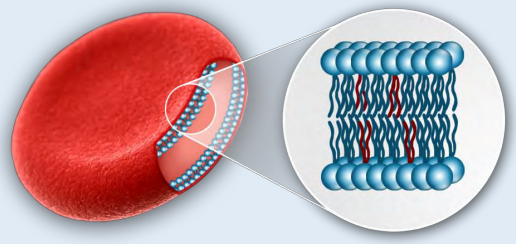
- Wide variation in omega-3 levels with a fixed dose
- Measured in plasma, serum, or RBC membranes
- RBC levels: mean O-3 level over prior 3-4 months
- The "O-3 Index" describes % EPA + DHA in RBCs

The Omega-3 Index is supported by hundreds of studies in the medical and scientific literature.

Superko, H Robert et al. "Omega-3 Fatty Acid Blood Levels Clinical Significance Update." *Current cardiovascular risk reports* vol. 8,11 (2014): 407.

12

The Omega-3 Index: Biomarker and Risk Factor



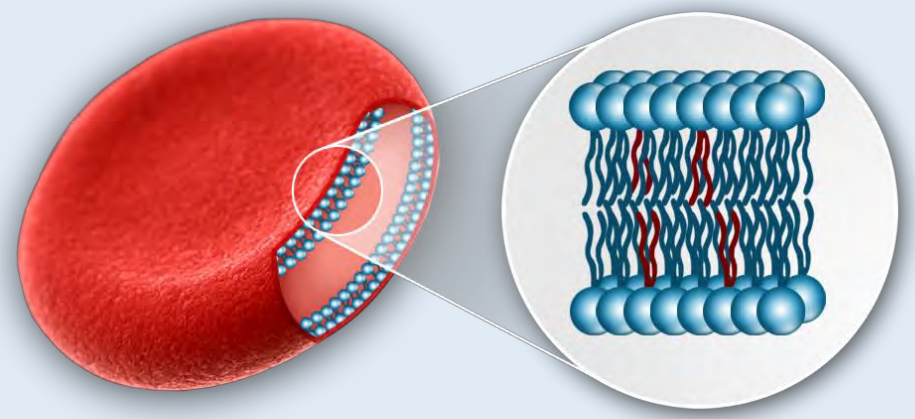
- The Omega-3 Index (EPA+DHA as a % of erythrocyte fatty acids) is a marker of tissue levels of EPA and DHA.

Having an Omega-3 Index in the desirable range (8%-12%) has been associated with improved heart, brain, eye, and joint health.

Harris WS and von Schacky C. *Prev Med* 2004;39:212-220.

13

The Omega-3 Index: Biomarker and Risk Factor



Having an Omega-3 Index in the desirable range (8%-12%) has been associated with improved heart, brain, eye, and joint health.

Harris WS and von Schacky C. *Prev Med* 2004;39:212-220.

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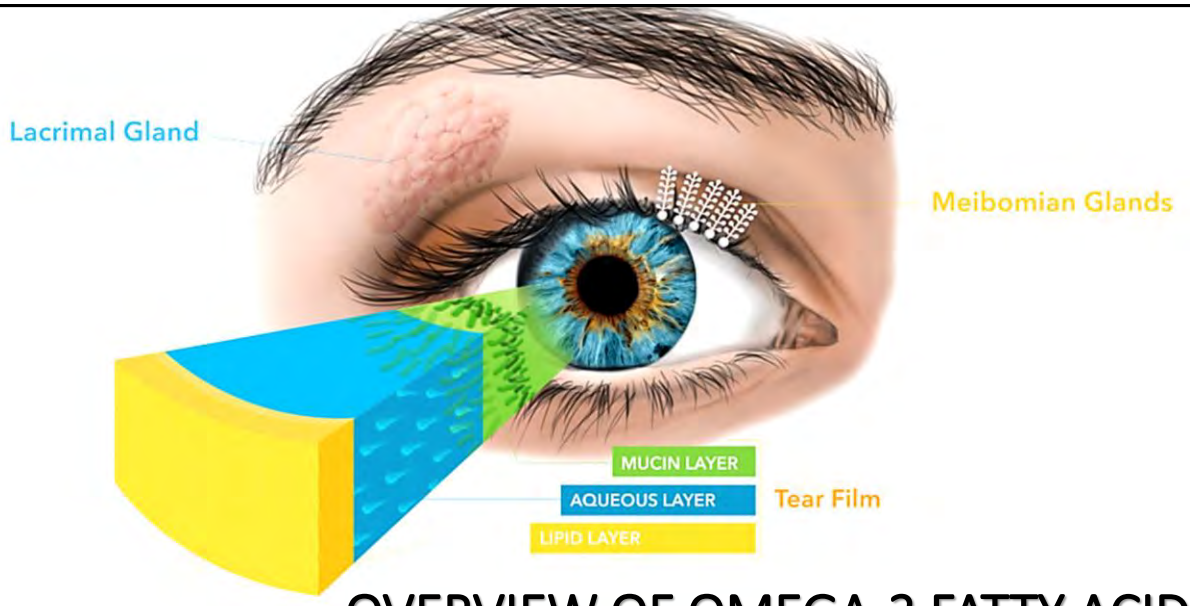

OVERVIEW OF OMEGA-3 FATTY ACIDS IN DRY EYE DISEASE

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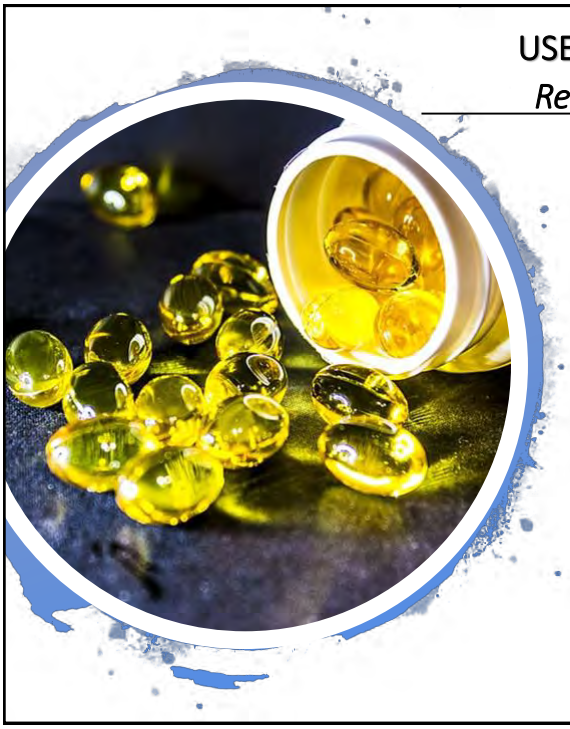
THE TFOS DEWS II DEFINITION OF DRY EYE-2017

*". . . a **multifactorial** disease of the ocular surface characterized by a **loss of homeostasis** of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, **ocular surface inflammation** and damage, and neurosensory abnormalities play etiological roles.*

Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf.* 2017;15(3):276-283

16



USE OF NUTRITIONAL INTERVENTION IN DED

Recommendations of TFOS DEWS II Report

Step 1 in DED treatment:

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- **Education regarding potential dietary modifications (including oral essential fatty acid supplementation)**
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

J.P. Craig et al. / The Ocular Surface 15 (2017) 802e812 811

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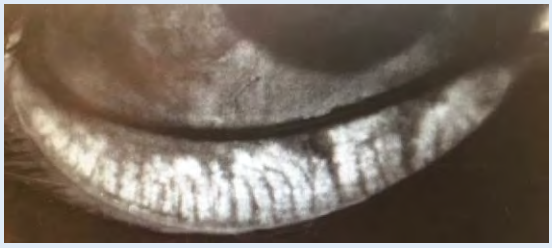
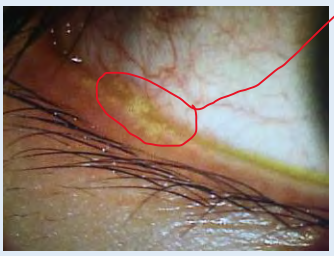
MEIBOMIAN GLAND DYSFUNCTION

The Root Cause of Most Dry Eye Disease

"MGD is perhaps the most underdiagnosed, undertreated, and underappreciated disease in eye care worldwide."

The International Workshop on Meibomian Gland Dysfunction





Geerling, Gerd, et al. "The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Management and Treatment of Meibomian Gland Dysfunction." *Investigative Opthalmology & Visual Science*, vol. 52, no. 4, 2011, p. 2050.

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RESULTS OF RAPID TEAR EVAPORATION

A tear film that lacks proper lipid chemistry evaporates too quickly- leading to Evaporative Dry Eye Disease (EDE)

- Tear hyperosmolarity
- **Increased inflammation**
- Ocular surface irritation
- Visual symptoms and discomfort

EFFECTIVE MANAGEMENT OF DED MUST ADDRESS THE CAUSATIVE FACTORS AND THE RESULTING INFLAMMATION.

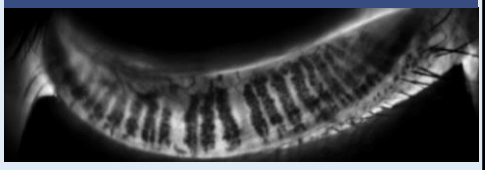
Chhadva, Priyanka et al. "Meibomian Gland Disease: The Role of Gland Dysfunction in Dry Eye Disease." *Ophthalmology* vol. 124,11S (2017): S20-S26

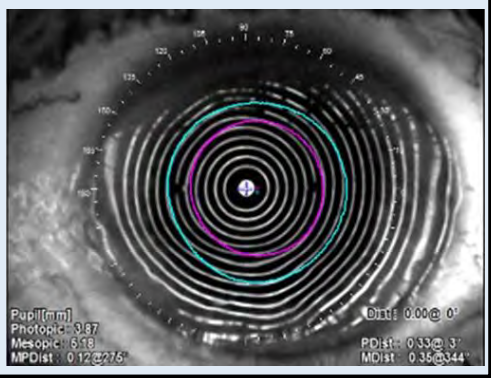
20

DRY EYE DISEASE FINDINGS

Visual fluctuations are common due to unstable tear film
Corneal topography reveals distorted rings

Nearly 90% of DED involves MGD which can lead to gland atrophy





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EVALUATING MEIBOMIAN GLAND SECRETIONS

Meibum Grade	0	1	2	3
Meibum Findings	None	Thick, Turbid	Gel, Turbid	Thin, Clear

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MECHANISMS FOR IMPROVEMENT OF DED WITH OMEGA-3 FATTY ACIDS

① *Improvement in Meibomian Gland Secretions*

8-Week Studies Looking at Meibum Secretions

- **Found DHA in in 14/14 patients after treatment (2-3% of meibum)**
- **Improvements in DED symptoms and signs**
- **Follow-up study: nearly 5x increased meibum omega-3 levels in 80% of participants**

Daily Dose >2g EPA/DHA

Earlier Studies with only ALA or low dose EPA/DHA were not successful

14. https://patents.google.com/patent/US9381183B2/en

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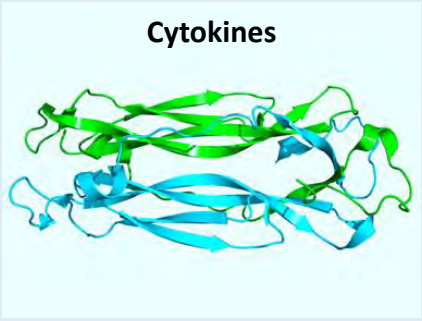
MECHANISMS FOR IMPROVEMENT OF DED WITH OMEGA-3 FATTY ACIDS

② *Control of Inflammation on the Ocular Surface*

The DED Inflammatory Cycle

Key Cytokines

- ❖ **Interleukins (IL)**
- ❖ **Tumor Necrosis Factor (TNF)**
- ❖ **Interferon (IFN)**



EPA and DHA travel through the bloodstream and are incorporated into cell membranes where they suppress release of cytokines and downregulate inflammation

Na, K, et al. "Correlations between Tear Cytokines, Chemokines, and Soluble Receptors and Clinical Severity of Dry Eye Disease. "*Investigative Opthalmology & Visual Science*, vol. 53, no. 9, 2012, p. 5443.//Lam, Helene, et al. "Tear Cytokine Profiles in Dysfunctional Tear Syndrome." *American Journal of Ophthalmology*, vol. 147, no. 2, 2009//Ostermann, Annika I, et al. "Plasma Oxylipins Respond in a Linear Dose-Response Manner with Increased Intake of EPA and DHA: Results from a Randomized Controlled Trial in Healthy Humans." *The American Journal of Clinical Nutrition*, vol. 109, no. 5, 2019, pp. 1251–1263

24

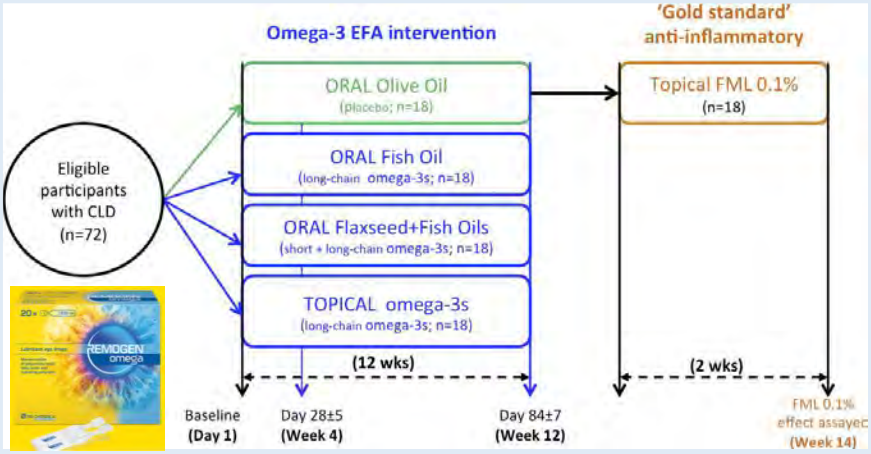
TEAR FILM CYTOKINES

EFFECT OF ORAL AND TOPICAL OMEGA-3s ON TEAR FILM CYTOKINES

Randomized Controlled Trial – Participants with Soft Contact Lens Discomfort

Daily Interventions

- Fish Oil (TG) = 1500mg EPA+DHA
- Flaxseed Oil = 900mg ALA
- Omega-3 PF Ophthalmic Sol = Remogen Omega (Europe) with 0.025% EPA + 0.0025% DHA qid= 30mg EPA/3mg DHA per day
- FML 0.1% tid: for placebo group only, after wk 12 x 2 wks

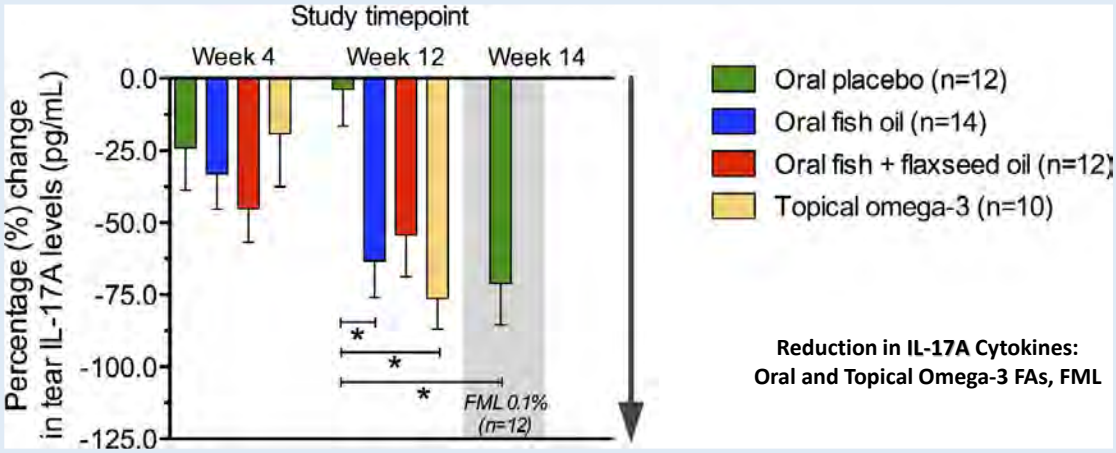


Laura E. Downie, Anne Gad, Chinn Yi Wong, John Henry V. Gray, Weiguang Zeng, David C. Jackson, Algis J. Vingrys; Modulating Contact Lens Discomfort With Anti-Inflammatory Approaches: A Randomized Controlled Trial. *Invest. Ophthalmol. Vis. Sci.* 2018;59(8):3755-3766

25

EFFECT OF ORAL AND TOPICAL OMEGA-3S ON SYMPTOMS AND TEAR FILM CYTOKINES

Significant Outcome Measures After 12 Weeks



Reduction in IL-17A Cytokines: Oral and Topical Omega-3 FAs, FML

" Both oral and topical forms of omega-3 supplements also induced relative reductions in the tear concentration of key proinflammatory cytokines, being similar to the treatment effect of the short-term (2 week) use of a topical corticosteroid…"

Laura E. Downie, Anne Gad, Chinn Yi Wong, John Henry V. Gray, Weiguang Zeng, David C. Jackson, Algis J. Vingrys; Modulating Contact Lens Discomfort With Anti-Inflammatory Approaches: A Randomized Controlled Trial. *Invest. Ophthalmol. Vis. Sci.* 2018;59(8):3755-3766

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MECHANISMS FOR IMPROVEMENT OF DED WITH OMEGA-3 FATTY ACIDS

③ *Reduction of Systemic Inflammation*

Higher Levels Of Circulating Plasma Cytokines Are Found In Primary Sjogren's Syndrome[1]

Include IL-1β, IL-6, and TNF-α

Results were highly statistically significant:
EPA + DHA (2.5g/d) lowered cytokines at both 4-week and 8 weeks time-points[2]

1.Szodoray, P., et al. "Circulating Cytokines in Primary Sjogren's Syndrome Determined by a Multiplex Cytokine Array System." *Scandinavian Journal of Immunology*, vol. 59, no. 6, 2004, pp. 592–599.
2.Tan, Alai et al. "Supplementation with eicosapentaenoic acid and docosahexaenoic acid reduces high levels of circulating proinflammatory cytokines in aging adults: A randomized, controlled study." *Prostaglandins, leukotrienes, and essential fatty acids* vol. 132 (2018): 23-29.

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MECHANISMS FOR MANAGEMENT OF DED WITH OMEGA-3 FATTY ACIDS

③ *Reduction of Systemic Inflammation*

	Baseline	Week 4	Week 8
Log IL-6			
EPA + DHA	**2.45**	**2.15**	**1.90**
Control	1.89	1.96	1.83
Log IL-1ß			
EPA + DHA	**2.52**	**1.78**	**1.39**
Control	1.25	1.34	1.83
Log TNF-α			
EPA + DHA	**3.90**	**3.45**	**3.01**
Control	3.00	2.96	2.96
Est Omega-3 Index			
EPA + DHA	**5.2%**	**9.2%**	**9.6%**
Control	5.2%	5.2%	5.2%

EPA+DHA Of >2g/D Has Led To Decreased Production Of Circulating Cytokines In Several Human Studies[1]

Tan, Alai et al. "Supplementation with eicosapentaenoic acid and docosahexaenoic acid reduces high levels of circulating proinflammatory cytokines in aging adults, A randomized, controlled study." *Prostaglandins, leukotrienes, and essential fatty acids* vol. 132 (2018): 23-29.

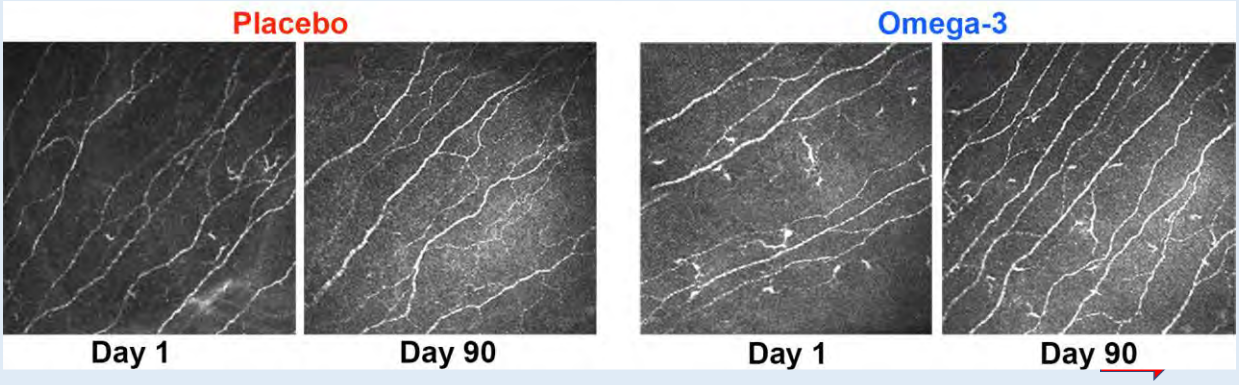
1. Biochemical Society Transactions (2017) 45 1105–1115

28

MECHANISMS FOR MANAGEMENT OF DED WITH OMEGA-3 FATTY ACIDS

④ *Evidence for Corneal Neuroprotection*

A placebo-controlled, double-masked pilot study using ~1500 mg of omega -3 FAs daily for 3 months, showed enhanced nerve branch density in the corneal sub-basal plexus in subjects with mild-to-moderate DED.



Chinnery, Holly R., et al. "Omega-3 Supplementation Is Neuroprotective to Corneal Nerves in Dry Eye Disease: A Pilot Study." *OPHTHALMIC AND PHYSIOLOGICAL OPTICS*, vol. 37, no. 4, pp. 473–481, 2017

29

SUMMARY

Omega-3 fatty acids influence cytokine production and activity, leading to improved tissue health through nutrition.

At therapeutic doses, they suppress key inflammatory pathways at work in DED.

Serhan and Levy. J Clin Invest 2018;128(7):2657-2669
Biochemical Society Transactions (2017) 45 1105–1115

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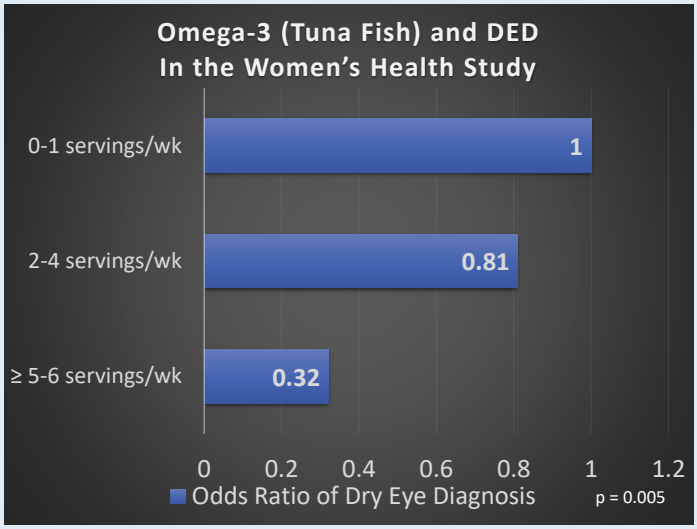
OMEGA-3 FATTY ACIDS AND DRY EYE DISEASE RESEARCH

31

FIRST SYSTEMATIC STUDY SHOWING ROLE OF OMEGA-3 FAs IN DRY EYE DISEASE



This study of over 30,000 women also found an association of total DHA intake with DED. Those in the highest versus the lowest quintiles had a **12% lower risk.**

Miljanovic´ et al. Am J Clin Nutr 2005;82:887-893

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OMEGA-3 FATTY ACID PILOT STUDY- 2011

90-day, placebo-controlled study

- 36 Participants with DED- 21 Active, 15 Placebo
- *70% of the active group became asymptomatic*
- *Average tear production/volume increased*

Conclusion

Omega-3 FAs show positive results despite low dose: 750mg EPA/DHA with 1000mg flaxseed oil

Wojtowicz, Jadwiga Cristina, et al. "Pilot, Prospective, Randomized, Double-Masked, Placebo-Controlled Clinical Trial of an Omega-3 Supplement for Dry Eye." *Cornea*, vol. 30, no. 3, Mar. 2011, pp. 308–314.

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EFFECT OF ORAL RE-ESTERIFIED OMEGA-3 NUTRITIONAL SUPPLEMENTATION ON DRY EYES

CLINICAL SCIENCE

OPEN

Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes

Alice T. Epitropoulos, MD,* Eric D. Donnenfeld, MD,† Zafar A. Shah, MPH,‡ Edward J. Holland, MD,§ Michael Gross, MD,¶ William J. Faulkner, MD,‖ Cynthia Matossian, MD,¶ Stephen S. Lane, MD,‖ Melissa Toyos, MD,** Frank A. Bucci, Jr, MD,†† and Henry D. Perry, MD‡

Cornea • Volume 35, Number 8, September 2016 www.corneajrnl.com | 1185

Multicenter, prospective, interventional, placebo-controlled, double-masked 12-week study

OMEGA-3 (2.3g/d)	ACTIVE (n=54) vs PLACEBO (n=51)	P VALUE
TEAR OSMOLARITY*	-11.1	0.004
TEAR BUT	+2.3 Seconds	0.002
OSDI	-12 Units	0.002
OMEGA-3 INDEX	+2.8%	<0.001

Cornea 2016;35:1185–1191

*Primary Outcome Measure

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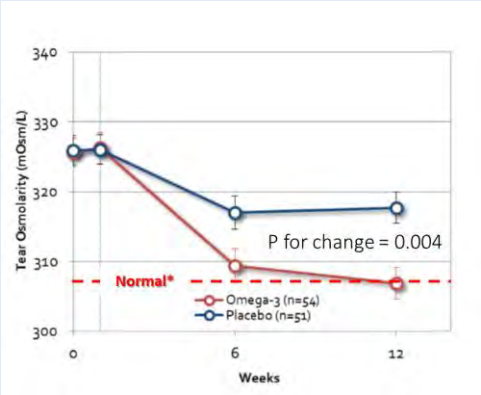
EFFECT OF ORAL RE-ESTERIFIED OMEGA-3 NUTRITIONAL SUPPLEMENTATION ON DRY EYES

Daily dose of 2.3g of TG Omega-3 Fatty Acids SIGNIFICANTLY REDUCED Tear Osmolarity



"Tear osmolarity….may be the most sensitive diagnostic tool for evaluating DED. Further, tear osmolarity has been shown to be significantly correlated to the severity of DED and can effectively track therapeutic response…"

There appears to be a linear relationship between osmolarity and DED severity

Cornea 2016;35:1185–1191

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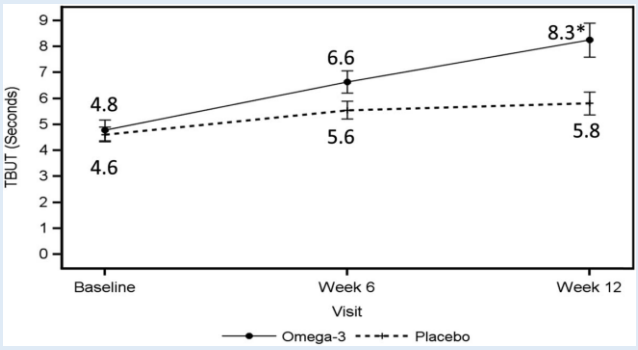
EFFECT OF ORAL RE-ESTERIFIED OMEGA-3 NUTRITIONAL SUPPLEMENTATION ON DRY EYES

SIGNIFICANT IMPROVEMENT IN TEAR BREAK UP TIME



REDUCTION IN INFLAMMATION AS SHOWN BY MMP-9 BIOMARKER

	Baseline	Wk 12	%	*P*-value*
Omega-3 group (n = 54)	28	9	67.9	0.024
Control group (n = 51)	20	13	35	

*χ^2 test.

Cornea 2016;35:1185–1191

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THE DREAM STUDY

The Dry Eye Assessment and Management Study Research Group

Multicenter, 12-month double-blind placebo-controlled trial, sponsored by the NEI

- Looked at the role of omega-3 fatty acids in **moderate-to-severe DED regardless of osmolarity score**
- Patients on drying oral meds, steroids allowed as well as those with Sjogren's, RA, and other inflammatory conditions, and average Schirmer score 9.3-10.2mm in 5minutes

Results

- ***Both groups showed significant improvement in signs and symptoms after 12 months***
- This included OSDI, ocular surface staining, TBUT, but not Schirmer's score

CONCLUSION OF AUTHORS:

"…We found no evidence of a beneficial effect of n−3 fatty acid supplements as compared with placebo supplements among patients with dry eye disease."

BUT… is there a better conclusion?

Asbell, Penny A., et al. "Dry Eye Assessment and Management (DREAM©) Study: Study Design and Baseline Characteristics." *Contemporary Clinical Trials*, vol. 71, 2018, pp. 70–79.

37

PROTOCOL OF THE DREAM STUDY

At least 75% of participants in both groups had a change in their multifaceted treatment regimens (which could include <1200 mg EPA/DHA)

By attempting to mimic "real-world" DED treatment practices, the power of the study to tease out the specific cause(s) of the improvement seen in both groups with an additional year of therapy was greatly diminished.

Asbell, Penny A., et al. "Dry Eye Assessment and Management (DREAM©) Study: Study Design and Baseline Characteristics." *Contemporary Clinical Trials*, vol. 71, 2018, pp. 70–79.

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EFFICACY OF OMEGA-3 FA SUPPLEMENTATION FOR TREATMENT OF DED

2019 META-ANALYSIS

Omega-3 FA Supplements vs Placebo in Randomized Clinical Trials (RCTs)

- Review of **17 RCTs** from 2008-2018 **involving 3393 participants** (included *The Dream Study*)
- Outcome measures: **DED symptoms, TBUT, Schirmer test, corneal fluorescein staining**.

Significant Effects of Omega-3 FAs

- ***Improved dry eye symptoms***
- ***Reduced corneal fluorescein staining***
- ***Increased tear BUT and Schirmer score***

"This meta-analysis provides evidence that omega-3 FA supplementation significantly improves dry eye symptoms and signs in patients with dry eye disease..."

Giannaccare, Giuseppe, et al. "Efficacy of Omega-3 Fatty Acid Supplementation for Treatment of Dry Eye Disease." *Cornea*, vol. 38, no. 5, 2019, pp. 565–573

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Marine Omega-3 Fatty Acids: Anti-Inflammatory Mechanism of Action

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HIGHER OMEGA-3 LEVELS = LOWER INFLAMMATION

"Inappropriate, excessive or uncontrolled inflammation contributes to a range of human diseases."

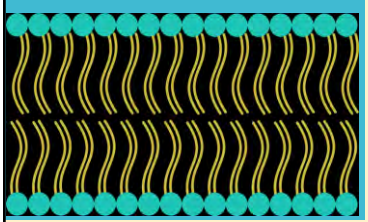
The Framingham Offspring Study began 1971-1975 (n=2724)

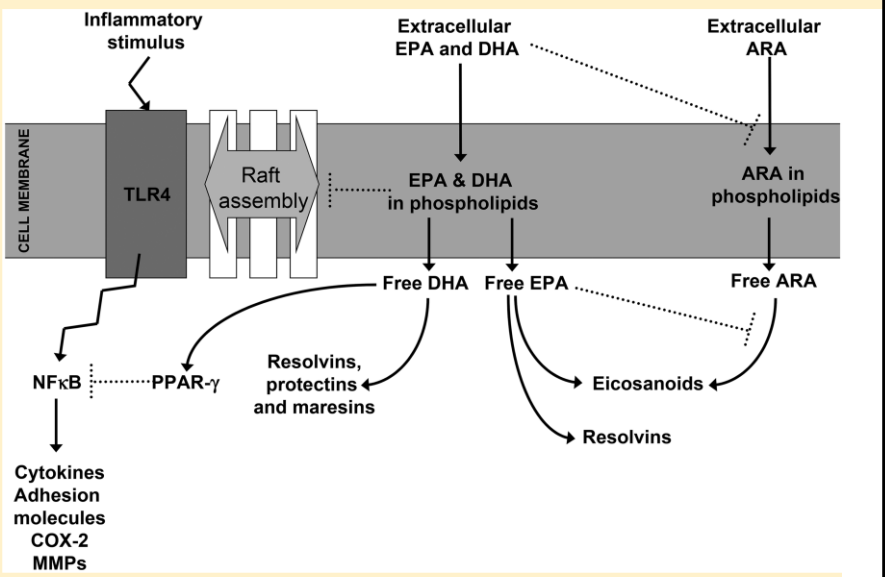
- ❖ Observational study (not interventional)
- ❖ Found **negative** correlations between the omega-3 RBC levels and at least **10** inflammatory biomarkers including:
  - **C-Reactive Protein**
  - **Interlukin-6 (IL-6)**
  - **Intercellular Adhesion Molecule-1 (ICAM-1)**

Fortes J., et al. Atherosclerosis 240 (2015) 431e436

41

Omega-3 Anti-Inflammatory Mechanisms of Action





Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochemical Society Transactions* (2017) 45 1105–1115

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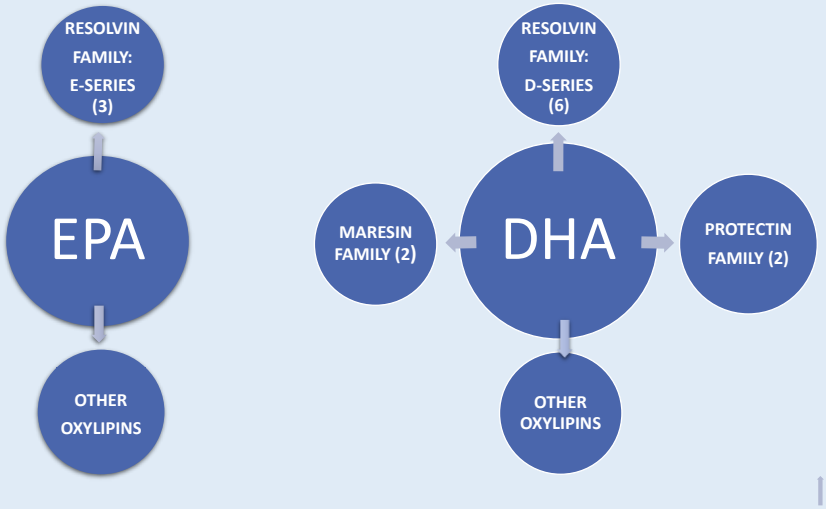
SPECIALIZED PRO-RESOLVING MEDIATORS

Derived Only From Omega-3 Metabolism

Multiple SPMs known as *resolvins, protectins, and maresins* help with the resolution of inflammation and promote healing.

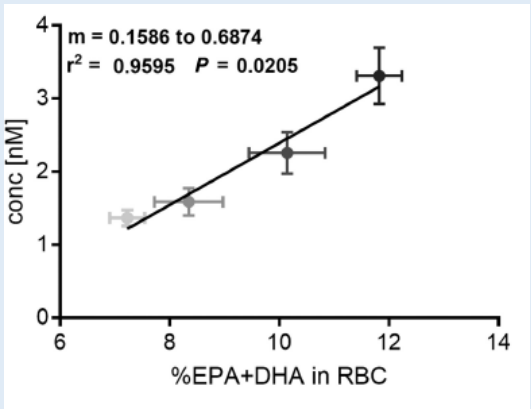
Levels directly related to EPA+DHA RBC levels.



Serhan and Levy. J Clin Invest 2018;128(7):2657-2669.

43

BENEFITS OF A HIGHER DOSAGE OF OMEGA-3 FATTY ACIDS



A LINEAR RELATIONSHIP

"Thus, our findings show that for healthy human subjects consuming a Western diet, the more n–3 PUFAs (i.e., EPA + DHA) consumed with the diet, the higher the plasma concentrations of EPA- and DHA-derived oxylipins."

Oxylipins are found in the blood and all body tissues. They work to suppress inflammation throughout our body.

Ostermann, Annika I, et al. "Plasma Oxylipins Respond in a Linear Dose-Response Manner with Increased Intake of EPA and DHA: Results from a Randomized Controlled Trial in Healthy Humans." *The American Journal of Clinical Nutrition*, vol. 109, no. 5, 2019, pp. 1251–1263

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Omega-3 Fatty Acids: Dietary Intake

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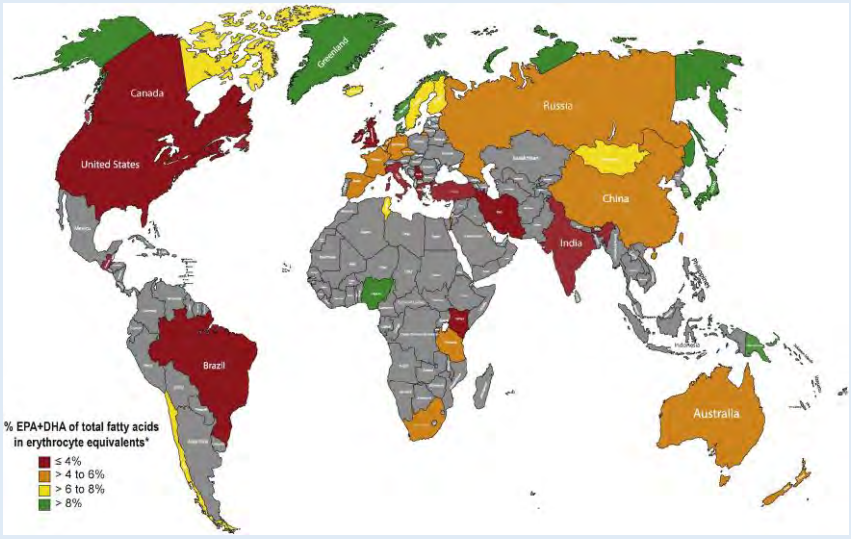
GLOBAL OMEGA-3 INDEX[1]

Circulating EPA+DHA levels taken from:

- 24,129 individual subjects
- 54 countries
- 398 data sets
- Converted to Omega-3 Index equivalents based on Stark et al[2]



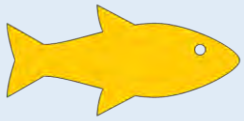
[1] Stark et al. Global survey of the omega-3 fatty acids, DHA and EPA in the blood stream of healthy adults. Prog Lipid Res. 2016;63:132-152.

[2] Stark et al. PLEFA 2016;104:1–10

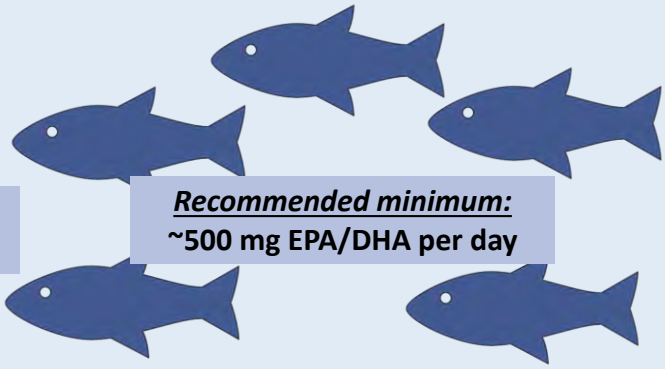
46

OMEGA-3 DIETARY RECOMMENDATIONS

THE AVERAGE AMERICAN IS CONSUMING ONLY ~1/5TH OF THE MINIMUM DIETARY OMEGA-3 RECOMMENDATION



Actual:
~100 mg EPA/DHA per day



Recommended minimum:
~500 mg EPA/DHA per day

ISSFAL. Intake of PUFA in healthy adults. http://www.issfal.org/statements/pufa-recommendations/statement-3. Accessed April 3, 2019

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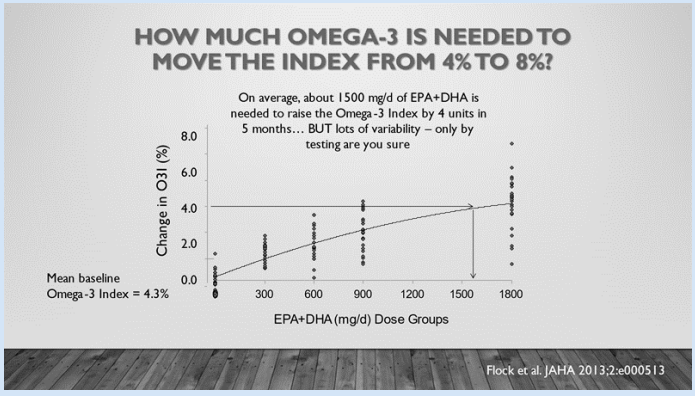
BUT…THERE IS HIGH VARIABILITY IN INDIVIDUAL UPTAKE

FACTORS INCLUDE:

1) Diet
2) Supplement form-TG Vs EE
3) Genetics
4) BMI
5) Smoking habits



Flock, Michael R., et al. "Determinants of Erythrocyte Omega-3 Fatty Acid Content in Response to Fish Oil Supplementation: A Dose–Response Randomized controlled Trial." *Journal of the American Heart Association*, vol. 2, no. 6, 2013.

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WHAT IS THE IDEAL RATIO OF EPA TO DHA IN A SUPPLEMENT?

Many oily fish have more DHA than EPA

FISH (3 OZ COOKED, DRY HEAT)	EPA	DHA	EPA + DHA	% DHA
PACIFIC HERRING	1056	751	1807	**42**
ATLANTIC SALMON (wild)	349	1215	1564	**78**
BLUEFIN TUNA	309	970	1279	**76**
MACKEREL (canned)	369	677	1046	**65**
SOCKEYE SALMON (wild)	451	595	1046	**57**
RAINBOW TROUT (farmed)	284	697	981	**71**
SARDINES (canned)	402	433	835	**52**
ALBACORE TUNA (canned)	198	535	733	**73**
SEA BASS	175	473	648	**73**
TILAPIA	4	111	115	**97**
ORANGE ROUGHY	5	21	26	**81**
STD FISH OIL 1000 MG CAP (EE)	180	120	300	**40**

DHA tends to be more effective than EPA in modulating specific markers of inflammation

Avoid eating fish with potential for the highest levels of mercury contamination.

This includes shark, swordfish, king mackerel, and tilefish

Table adapted from Harris et al. Current Atherosclerosis Reports 2008;10:503-509.
Values based on USDA Nutrient Data Lab values

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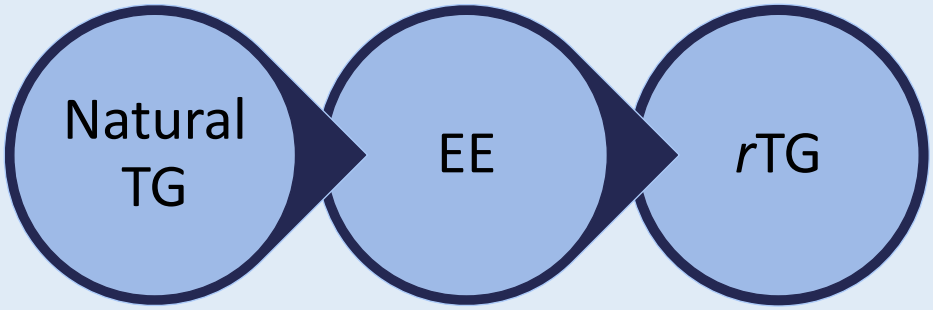
FORMS OF FISH OIL



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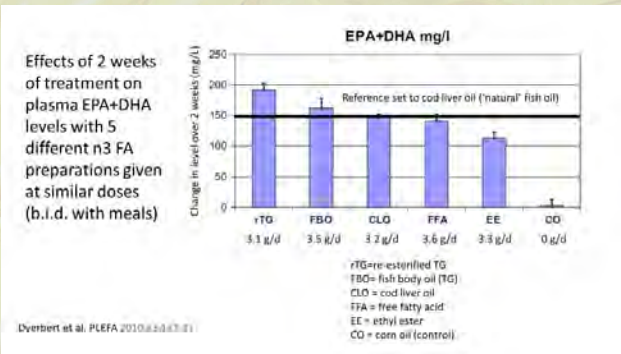
COMPARISON OF FISH OIL SUPPLEMENTS

Advantages of rTG over EE Fish Oil

- **Digestion** within small intestine more easily accomplished with rTG since pancreatic lipase is more effective against glycerol-fatty acid than ethanol-fatty acid chemical bonds[1]
- This leads to superior **bioavailability** of rTG fish oil of 124% vs FBO vs 73% for EE fish oil[2]
- TG is the form of fish oil found in fish, while EE does not occur naturally
- EE absorption may vary from 20% -60% (better with high-fat meal)[3]
- Research shows about **1.5-1.7X** the availability of rTG compared to EE fish oil[3,4]



Even though quality rTG fish oil costs more to produce, actual cost per gram of EPA/DHA may be the same or less when concentration and bioavailability are factored in[1]

1. Alexander L, The slippery facts about fish oil. *Review of Optometry*, vol. 147, no. 5, 2010, p. 35+. Accessed 3 Jan. 2021.
2. Dyerberg, J., et al. "Bioavailability of Marine n-3 Fatty Acid Formulations." *Prostaglandins, Leukotrienes and Essential Fatty Acids*, vol. 83, no. 3, 2010, pp. 137–141
3. Visioli F, Rise P, Barassi MC, et al, Dietary intake of fish vs. formulations leads to higher plasma concentrations of n-3 fatty acids. Lipids. 2003 Apr;38(4):415-8
4. Beckermann B, Beneke M, Seitz I. Comparative bioavailability of eicosapentaenoic acid and docosahexaenoic acid from triglycerides, free fatty acids and ethyl esters in volunteers. Arzneimittelforschung. 1990 Jun;40(6):700-4.

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FISH OIL SUPPLEMENTS

Understanding Labels

Typical Goal: >2000 mg of EPA + DHA per day
Is taking 2 of these 1200 mg capsules enough?

CALCULATION (per 2 capsules):
Fish Oil: 2400mg
EPA: 360mg
DHA: 240mg
600mg (**25% concentration**)

Triglyceride Formulation

Disregard other ingredients (mixture of various unidentified fatty acids)

Actual dose per 2 caps: 600mg total EPA +DHA

Based on this calculation, it would be necessary to
take 7 caps/day to achieve the desired dosage
With EE fish oil, factor in poorer absorption

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EPA AND DHA –SAFE EVEN AT HIGHER DOSES

Safety

- No drug interactions expected
- No contraindications during pregnancy
- Safe for diabetics
- No bleeding concerns

2.

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CLINICIAN'S GUIDE TO DRY EYE DISEASE

FROM MOST COMMON ROOT CAUSE OF MGD: MEIBUM STAGNATION*

Mark W. Roark, OD, FAAO

- **Poor oil quality** *(suboptimal nutrition, hormonal influences)*
- **Poor Lid Closure/ Infrequent Blinks** *(digital device use, lagophthalmos)*
- **Cosmetics** *(mechanical blockage)*
- **Inflammatory skin conditions** *(ocular rosacea)*
- **Medications** *(retinoids)*

MEIBUM STAGNATION

Often asymptomatic

Meibum Stagnation → Bacterial overgrowth ↑Inflammatory enzymes ↑Keratinization

Common Clinical Findings
Positive Korb-Blackie test/Partial blinking
LOM migration toward MG orifices
Frothy tear film /Cylindrical dandruff
Poor MGE scores/Meibum thickening
Lid margin telangiectasias

Typical Treatment Approach
Heat mask/Omega-3s/Nutraceuticals
Sleep mask/ Blinking exercises
Hypochlorous acid/Lid cleansers
Micro-blepharoexfoliation

EVAPORATIVE DED

Visual fluctuations, variable symptoms

Chronic Meibomian Gland Obstruction → Lipid deficiency

Additional Clinical Findings
Rapid TBUT /±Normal tear prism
Ocular surface staining
Hyperosmolarity/±Inflammadry pos
Abnormal meibography/meibum
Irregular lid margins/notching
Increasing lid margin telangiectasias

Additional Treatment Approach
Oil-based artificial tears/ Lubricants
Immunomodulator
Thermal MG Expression
Intense Pulsed LIght/ LLLT
Doxycycline/Azasite

AQUEOUS DEFICIENT DED

Increasingly symptomatic (unless neurotrophic)

Lacrimal Gland Inflammation → Reduced Tear Production

Additional Clinical Findings
Thin tear prism/Abnormal Schirmer/Phenol red test
Increased ocular surface staining
Increased conjunctival injection/tearing
Increased hyperosmolarity/ Inflammadry pos
Possible decreased corneal sensitivity

Additional Treatment Approach
Steroid Pulse –Drops/Ointment/Plug
Serum Tears / Biologics
Trigeminal nerve stimulation
Cryopreserved amniotic membrane
Punctal occlusion (IFD negative)

*Choi, Moonjung, et al. "Meibum Expressibility Improvement as a Therapeutic Target of Intense Pulsed Light Treatment in Meibomian Gland Dysfunction and Its Association with Tear Inflammatory Cytokines." *Scientific Reports*, vol. 9, no. 1, 2019

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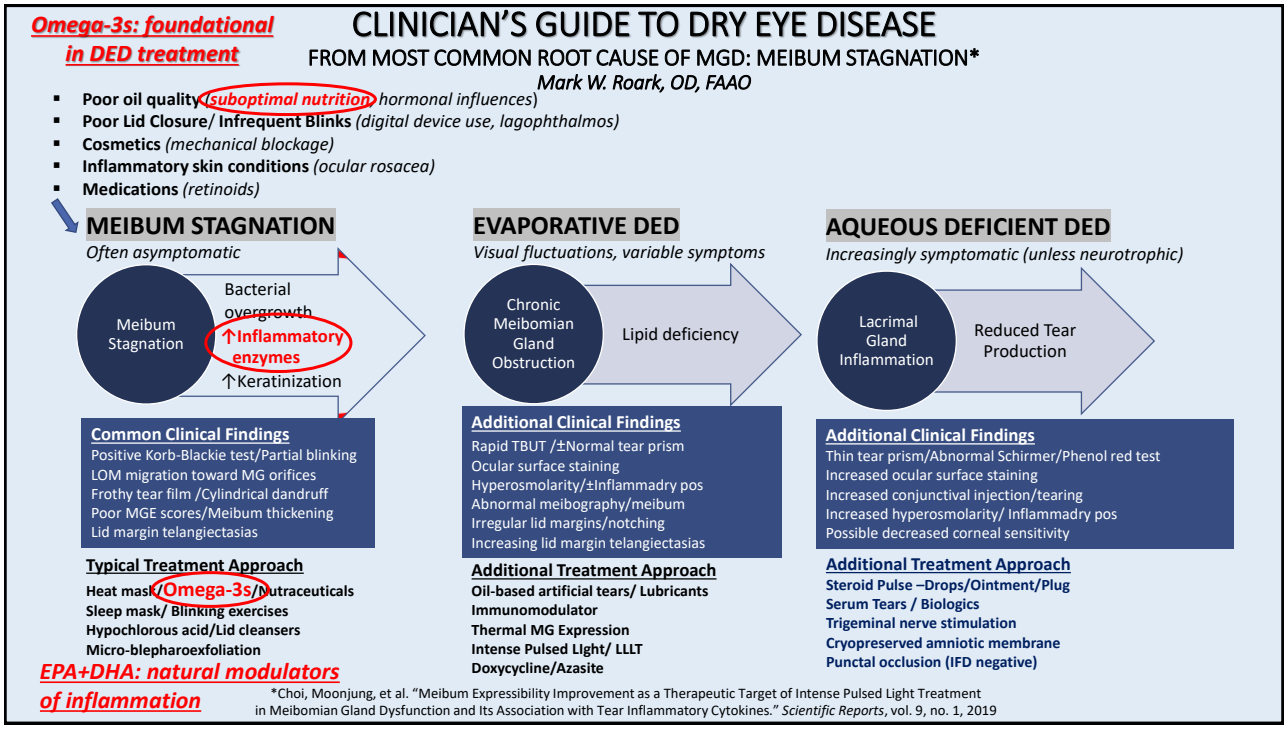

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IMPLEMENTATION: USING EPA + DHA IN THE MANAGEMENT OF DRY EYE DISEASE

- **Prescribe EPA + DHA as foundational treatment to reduce risk of meibum stagnation/EDE**
- **Prescribe EPA + DHA to lower the local and systemic inflammatory component of DED**
- **Use EPA + DHA because they are holistic, safe, and backed by solid research**
- **Recommend a balanced amount of EPA/DHA to mimic what is found in nature**
- **Increase odds of a therapeutic response with a daily EPA + DHA dose of ≥ 2 grams**
- **Improve absorption and potential benefit with a rTG rather than EE formulation**
- **Consider use of Omega-3 Index testing to monitor and achieve goal of >8%**

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Thank You!

markroark.od@gmail.com

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FISH OIL SUPPLEMENTS

Fish Oil Production

- Fish Body Oil **(FBO)** is present in the Triglyceride (TG) chemical form where three fatty acids combine with a molecule of glycerol for stability[1]
- Once the oil is extracted from the fish and purified, the EPA and DHA can be concentrated through the process of **esterification** which replaces the glycerol with an ethanol backbone, thereby creating a semi-synthetic ethyl ester **(EE)** fish oil concentrate[2]
- To restore the TG form, EE fish oil is again esterified to replace the alcohol with a glycerol backbone and create **re-esterified triglyceride (rTG) fish oil**
- The amount of EPA and DHA in the final product can be concentrated from 30% to 90%[3]
- Liquid fish oil products can also be created, and are available only in the TG form since EE is not a palatable product

1. Segura R. Preparation of fatty acid methyl esters by direct reesterification of lipids with aluminum chloride methanol. J Chromatogr. 1988 May 27;441(1):99-113.
2. Saghir M, Werner J, Laposata M. Rapid in vivo hydrolysis of fatty acid ethyl esters, toxic nonoxidative ethanol metabolites. Am J Physiol. 1997 Jul;273(1 Pt 1):G184-90.
3. Dyerberg, J., et al. "Bioavailability of Marine n-3 Fatty Acid Formulations." *Prostaglandins, Leukotrienes and Essential Fatty Acids*, vol. 83, no. 3, 2010, pp. 137–141

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SOUTHERN CALIFORNIA COLLEGE OF OPTOMETRY

CONTINUING EDUCATION COURSE SCHEDULE

2021 COURSE SCHEDULE

DATE	LOCATION	COURSE TOPIC	CE UNITS
July 10 & 11	**SCCO	MBKU** *Live Webinar*	**Ocular Disease Part II** *COPE Approval Pending*	16
September 19	**SCCO	MBKU** *Live Webinar*	**Joint SCCO I USC I VA Symposium** *COPE Approval Pending*	8
December 12	**SCCO	MBKU** *Live Webinar*	**Contemporary Topics in Optometry** *COPE Approval Pending*	8

GENERAL INFORMATION

MBKU CAMPUS LOCATIONS

SCCO I FULLERTON CAMPUS
2575 Yorba Linda Blvd. Fullerton, CA 92831

LEARN MORE & REGISTER *ketchum.edu/ce*

CONTACT US

email: ce@ketchum.edu

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry

Neurotrophic keratitis is a degenerative disease that warrants immediate attention[1]

oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

OXERVATE is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis (NK)[2]

Cenegermin-bkbj, the active ingredient in FDA-approved OXERVATE, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues.[3]

Endogenous NGF is a protein involved in the differentiation and maintenance of neurons and is believed to support corneal integrity through three mechanisms (in preclinical models): corneal innervation, tear secretion, and epithelial cell growth.[3-5]

In clinical studies, with a single 8-week course of therapy:

- Up to **72%** of patients with NK achieved complete corneal healing*†[2]
- **80%** of patients who achieved complete corneal healing remained completely healed at 1 year (REPARO trial)[6]

OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.

Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

Please see additional Important Safety Information on accompanying page and full Prescribing Information, including patient information, at OXERVATE.com/prescribing-information.

You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Dompé at 1-833-366-7387 or Usmedinfo@dompe.com.

TREAT NK TODAY
OXERVATE.com/HCP

*Study NGF0212 (REPARO): 52 patients per group; European patients with NK in one eye; 72% of patients completely healed; key findings were after 8 weeks of treatment; 6 times daily; vehicle response rate 33.3%.[2] Study NGF0214: 24 patients per group; US patients with NK in one or both eyes; 65.2% completely healed; vehicle response rate 16.7%[2,7]

†Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of OXERVATE treatment.[2]

References: 1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579. **2.** OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA: Dompé U.S. Inc.; 2019. **3.** Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320:1309. **4.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **5.** Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29:1163-1168. **6.** Data on file. Dompé U.S. Inc.; 2021. NGF0212. **7.** Pflugfelder SC, Massaro-Giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. *Ophthalmology*. 2020;127:14-26.

Dompé

US-OXE-1900180.02 02/21

oxervate™
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

Clinical Studies Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

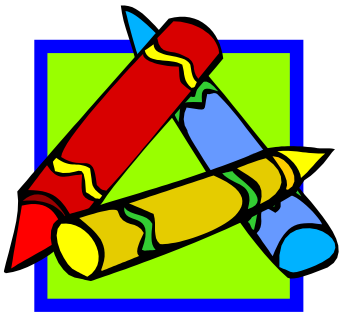
Dompé

Amblyopia Treatment Study

RECRUITMENT UNDERWAY FOR NIH-SPONSORED STUDY

Amblyopia is the most common cause of monocular visual impairment in children. The choice of a sequential approach versus a simultaneous approach to "optical treatment (glasses) plus patching treatment" remains unresolved, with some existing data supporting one approach and some data supporting the other. There is a reasonable rationale for either approach. This unresolved controversy results in a dichotomy of current clinical practice, with some care providers favoring one approach and others favoring the opposite approach. In addition, the influence of adherence to patching on treatment response is not well understood.

The Pediatric Eye Disease Investigator Group (PEDIG) is conducting a clinical trial to evaluate if treating amblyopia with glasses and patching at the same time improves vision as well as treating amblyopia first with glasses and then with patching, if needed. This study will also use occlusion dose monitors (ODMs) to record adherence with prescribed patching treatment, to study dose-response. The study is supported through funding from the National Eye Institute of the U.S. National Institutes of Health and is being coordinated by the Jaeb Center for Health Research in Tampa, Florida.



Study Specifics

- 544 children are expected to be enrolled
- Children must be between 3 to < 13 years old
- Visual acuity in the amblyopic eye must be between 20/40 and 20/200
- Random assignment to either:
  - **Sequential treatment**: full-time glasses first, with subsequent patching for 2 hours per day/7 days per week if there is no further improvement in amblyopic eye visual acuity with glasses alone and there is residual amblyopia, OR
  - **Simultaneous treatment:** full-time glasses and part-time patching for 2 hours per day/7 days per week
- Occlusion dose monitors (ODMs) will be used to record actual patch wear time during prescribed patching
- Follow-up visits every 8 weeks for 56 weeks
- No previous treatment for amblyopia is allowed, including glasses or contact lenses.

How Can You Help?

- Your assistance is needed in referring children who may qualify.
- Referrals can be sent to the investigator listed below, or for more information, visit the PEDIG website at http://pedig.net/ or call the PEDIG Coordinating Center toll free at 1-888-797-3344

National Eye Institute
NATIONAL INSTITUTES OF HEALTH

Susan Parker – Study Coordinator
Ketchum Health
5460 E. La Palma Avenue
Anaheim, CA 92807
(714) 463-7580 sparker@ketchum.edu

Pediatric Eye Disease Investigator Group