Update on Eyes in systemic health and systemic diseases

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Disclosures

Has a relevant financial relationship with

Sanofi Speaker
Innova Research
SmartLens consultant
EyePromise Employee
Thea Consultant

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"All relevant financial relationships have been mitigated"

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Talking about systemic diseases

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"Diabetes"

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Impact of Diabetes

Total Cost = 327 Billion Dollars

- Direct Medical Costs
  - 237 Billion Dollars
  - (medical expenses)
- Indirect Medical Costs
  - 90 Billion Dollars
  - (disability, work loss, premature death)

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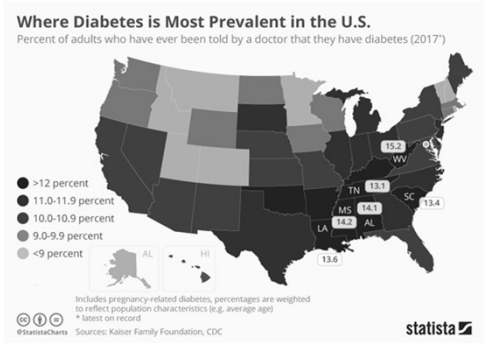

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Statistics – United States

- 34.2 million people of all ages or 10.5% of the US population, have diabetes mellitus.
- 27.2% with DM (over the age of 18) do NOT know they have diabetes mellitus.
- 88.1 million Americans 18 yo or older have prediabetes
  - More men than Women
  - Prevalence of prediabetes was similar among all racial/ethnic groups and education levels
- 4.4% of the US has some level of diabetic retinopathy

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Percent of people aged 18 years or older with DM by race/ethnicity and gender (males / females) in the U.S.

- Non-Hispanic Whites 8.6 / 6.6
- Asian Americans 10.0 / 8.5
- Hispanics 13.7 / 11.6
- Non-Hispanic Blacks 11.4 / 12.0
- American Indians/Alaska Natives 14.5/14.8

*2017-2018

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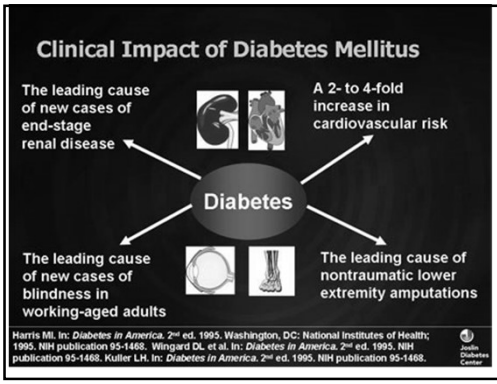

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Types of Diabetes

- Type I – bodies immune system destroys pancreatic beta cells (autoimmune condition)
- Type II – begins as insulin resistance and then gradually the pancreas loses its' ability to produce insulin.
- Gestational
  - Form of glucose intolerance during the 2nd or 3rd trimester
  - 5-10% dx'd with DM
  - 50% chance of development of DM in 5-10 years

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Rare forms of Diabetes

- Monogenic forms of DM
  - Mutation from 1 gene (vs polygenic)
    - Mutation is genetic and sporadic
- Account for 1-5% of DM in younger patients
- Most reduce the body's ability to produce insulin
  - Neonatal Diabetes Mellitus
    - Occurs in first 6 months of life
  - Mature Onset of Diabetes of the Young
    - Occurs in early adolescence

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Role of Insulin

Helps muscle, fat, and liver cells absorb glucose from the bloodstream (inability for this to occur causes insulin resistance)

Stimulates the liver and muscle tissue to store excess glucose (as glycogen)

Insulin also lowers blood glucose by reducing glucose production in the liver

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Diabetes and Obesity

- Type II DM appears to be rising parallel with global trends towards obesity.
- Weight gain of 10-15 pounds can increase the risk of DM by 50%.
  - Especially in women
  - Seeing prevalence of metabolic syndrome also rise in women.
- 65% of Americans are over-weight or obese

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Type II DM

- Associated with obesity, older age, family hx, impaired glucose metabolism, physical inactivity, and race/ethnicity
- African Americans, Hispanics, Native Americans, Asian Americans, and Pacific Islanders
- Seeing it more frequently dx'd in children

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Diagnosing DM

	A1C (%)	Fasting Plasma Glucose (mg/dl)	Oral Glucose Tolerance Test (mg/dl)
Diabetes	6.5 or above	126 or above	200mg/dl or above
Pre-diabetes	5.7 to 6.4	100 to 125	140 to 199
Normal	About 5	99 or below	139 or below

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Pre- diabetes as an entity

- A1c 5.7 to 6.5, fasting 100-125 mg /dl, OGTT- 140-199 mg/dl
- Middle aged individuals with this diagnosis are 20 times at risk of developing diabetes
- Older age group 75 years or greater …. This diagnosis is not as robust diagnostic entity as in Middle Aged individuals
  - Patients often regress to normoglycemic levels
  - Death

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Diabetic eye disease

- Retina takes a good 10-15 years of beating
- Elevated blood glucose is the culprit
- Metabolic control is a must
- Furthermore there is a big body of literature that MPOD is depleted in diabetics
- Can we do anything with nutritional supplements without changing A1c?

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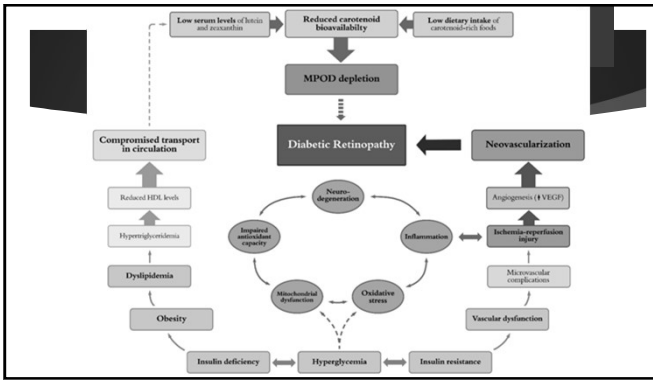

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nutrients

Review

A Systematic Review of Carotenoids in the Management of Diabetic Retinopathy

Drake W. Lem [1,†], Dennis L. Gierhart [2] and Pinakin Gunvant Davey [1,*,†]

of DR, specifically in patients with type 2 or poorly managed type 1 diabetes. Meanwhile, early interventional trials with dietary carotenoid supplementation show promise in improving their levels in serum and macular pigments concomitant with benefits in visual performance. These findings provide a strong molecular basis and a line of evidence that suggests carotenoid vitamin therapy may offer enhanced neuroprotective effects with therapeutic potential to function as an adjunct nutraceutical strategy for management of diabetic retinopathy.

Nutrients 2021, *13*, 2441. https://doi.org/10.3390/nu13072441

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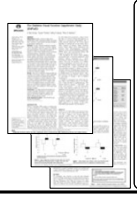
The Diabetes Visual Function Supplement Study (DiVFuSS)

The Diabetes Visual Function Supplement Study (DiVFuSS) was designed to test the effects of a novel, multi-component nutritional supplement on visual function. Participants included patients with both type 1 and type 2 diabetes.

- six-months
- placebo controlled



CLINICAL STUDY RESULTS WITH DVS

Randomized, placebo-controlled study demonstrated:

- 21% improvement in color vision**
- 19% improvement in contrast sensitivity (easier to read ink on an newspaper)**
- 12% improvement in central and peripheral vision**

**improvements were made without significantly affecting blood glucose levels

- 2016 *British Journal of Ophthalmology*

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Ocular Complications

Refractive Changes

- Due to increased glucose levels in the lens
- 21% also demonstrate transient "paralysis" of accommodation
- 40% have dry eyes

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Ocular Complications

Dry Eyes

Reduced corneal sensitivity	• Reduce reflex tearing
Goblet cell density	• Produce mucin (stability)
Affect on lacrimal gland	• Correlated to length of DM
Tear Protein Patterns	• Lactoferrin, sIgA, albumin, lipocalin and lysozyme

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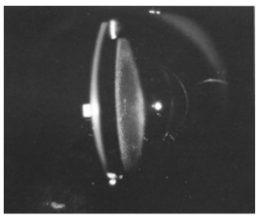
Ocular Complications

"Snowflake" cataract



- Common in uncontrolled Type I diabetic patients
- Sorbitol accumulates in the lens fibers. Water enters to correct the osmotic imbalance
- Lens fibers swell / rupture

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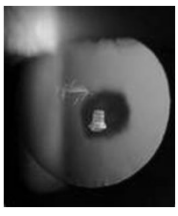
Ocular Complications

Posterior Subcapsular Cataract



- Earlier onset of age-related cataracts
- Due to binding of sugars to lens proteins
- Osmotic imbalance can also increase cortical changes

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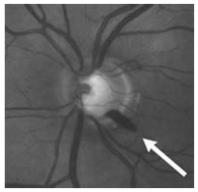
Ocular Complications

Glaucoma



- LALES found 40% higher prevalence in Type II diabetic Latino pt's
- Neovascular glc
  - VEGF-induced neovascularization of the iris and angle
- Normotensive glc

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Ocular Complications

Sixth Nerve Palsy

50%

- Sudden onset
- Absence of other neurologic involvement
- Resolves in 3-6 months.

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Cranial Nerve Palsies

CN III Palsy (45%)

CN IV Palsy (5%)

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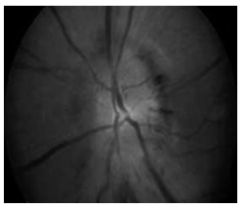
Optic Neuropathy

Diabetic Papillopathy



- Can be unilateral or bilateral
- Minimal affect on VA
- Resolved in 2-10 months
- If bilateral, need to r/o papilledema (imaging or LP)

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- What is a "typical" chief complaint from a diabetic patient?
- Questions to ask:
  - Type of DM
  - Duration of DM
  - Blood sugars (Fasting / Post-prandial)
  - A1C
  - Medications (compliance)
  - Who do they see / How often
  - Hypertension/ BP
  - Other medical Heart, Kidney, Legs
- Does the pt smoke (increase progression)/ drink (excess = non-compliance)

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TABLE 1 DIABETIC RETINOPATHY DISEASE SEVERITY SCALE AND INTERNATIONAL CLINICAL DIABETIC RETINOPATHY DISEASE SEVERITY SCALE

Disease Severity Level		Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy		No abnormalities
Mild NPDR (see Glossary)		Microaneurysms only
Moderate NPDR (see Glossary)		More than just microaneurysms but less than severe NPDR
Severe NPDR		
	U.S. Definition	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: • Severe intraretinal hemorrhages and microaneurysms in each of **four** quadrants • Definite venous beading in **two** or more quadrants • Moderate IRMA in **one** or more quadrants
	International Definition	Any of the following and **no** signs of proliferative retinopathy: • More than 20 intraretinal hemorrhages in each of **four** quadrants • Definite venous beading in **two** or more quadrants • Prominent IRMA in **one** or more quadrants
PDR		One or both of the following: • Neovascularization • Vitreous/preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

NOTE:

- Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR.

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Classifications of Diabetic Retinopathy

Non-Proliferative Diabetic Retinopathy (NPDR)

- Mild
- Moderate
- Severe
- Very Severe

Proliferative

- High risk
- Low risk

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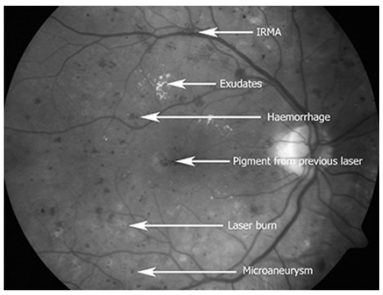

- Diabetic Retinopathy

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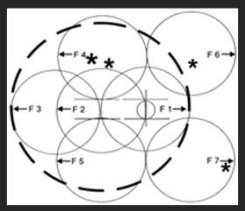
Documentation/Testing



- Baseline Fundus Photography
  - Seven Standard Diabetic Photographic Fields
    - ONH centered, Macula centered, Temporal to macula, Superotemporally, Inferotemporally
    - Superonasally and Inferonasally
    - (*all exclude ONH except for #1)

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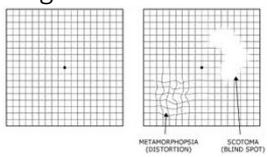
Documentation/Testing

- Amsler Grid



- OCT
- Fluorescein Angiography – assessing vascular integrity

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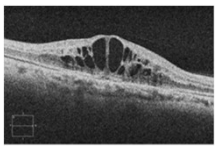
OCT



- CPT: 92133 (ONH) / 92134 (Retina)
- Requires Interpretation and Report
- Reimbursement ~ $50
- Unilateral or Bilateral
- Cannot do same day as DFE/Fundus Photos (*if billing)
- 4x's per year unless acute condition

- Diabetic Macular Edema

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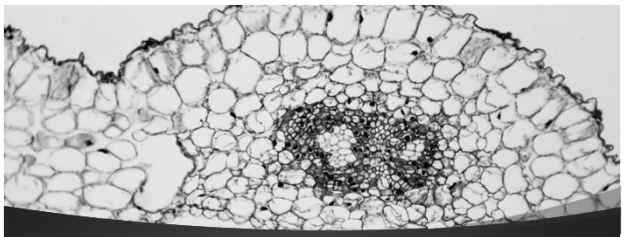

Thyroid Eye Disease

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Thyroid Eye Disease (TED)

	Men	Women
Incidence rate	2.9 cases per 100,000	16 cases per 100,000
Peak age range	45 to 49 years and 65 to 69 years[1]	40 to 44 years and 60 to 64 years[1]

TED vs. Graves' Disease

- TED and Graves' Disease are not synonymous. TED may coexist, precede, or follow Graves' Disease[2]
- TED can exist without hyperthyroidism[1,2,3]

Hyperthyroidism, TED & Graves' Disease

- TED not directly related to high serum thyroid concentrations[4]
- However, euthyroid patients with Graves' Disease tend to have less severe TED[4]

Risk factors for the development and progression of TED[2]

Nonmodifiable Factors

Age
- Advanced Aging

Gender
- Women (more frequent)
- Men (more severe)

Genetics

Modifiable Factors

Environment
- Smoking
- Radioactive Iodine Therapy

Thyroid Dysfunction
- Hypothyroidism
- Hyperthyroidism

Bartley, G.B. *Trans Am Ophthalmal Soc.* 1994. 92: p. 477-588. 2. Eckstein AK *et al. Br J Ophthalmol.* 2009. 93(8): p. 1052-1056. 3. Leo M *et al. Thyroid.* 2015. 25(3): p. 347-351. 4. Gwinup G *et al. JAMA.* 1982. 247(15): p. 2135-2138

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Thyroid secretion

- Excessive thyroid secretion
  - Fast pulse
  - Palpitations
  - Profuse sweating
  - High blood pressure
  - Irritability/ fatigue/ heat intolerance
  - Weight loss
  - Loss of hair/ changes in hair quality
- Decreased thyroid secretion
  - Weight gain
  - Hoarse voice
  - Thinning hair
  - Tiredness
  - Weight gain/ puffy face
  - Slow heart rate
  - Depression/ memory problems

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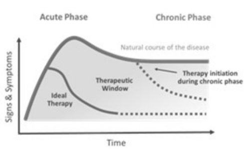
The Natural History of TED



Refined understanding of TED natural course

Acute (active) Stage

- Characterized by inflammation including periorbital chemosis, orbital congestion, and tissue expansion associated with eyelid retraction, proptosis, and diplopia for a variable period up to three years[1-3]

Chronic (inactive) Disease

- Inflammation will subside but the changes may remain and result in permanent damage

1. Bhatti MT, et al. *J Neuroophthalmol.* 2014;34(2):186-197. 2. Bothun ED, et al. *Clin Ophthalmol.* 2009; 3:543-551. 3. Bartalena L, et al. *Endocr Rev.* 2000; 21(2):168-199.

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Clinical Presentation of TED

Conjunctiva and Cornea[1-4]

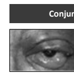


Figure adapted from Briceño CA, et al. *Int Ophthalmol Clin.* 2013; 53(3): 93-101.

- Chemosis
- Conjunctival redness
- Tearing
- Photophobia
- Foreign body sensation

Eyelid[1-4]

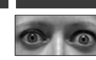
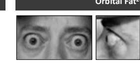


Figure adapted from Briceño CA, et al. *Int Ophthalmol Clin.* 2013; 53(3): 93-101.

- **Upper eyelid retraction 91%**[8]
- Eyelid swelling
- Pain
- Lagophthalmos
- Exposure keratopathy

Orbital Fat[2-3]



- **Proptosis 60%**[8]
- Pain
- Disfigurement
- Exposure keratopathy
- Vision loss

Extraocular Muscle[2-3]

- Restricted ocular motility
- **Diplopia 51%**[9]
- Pain
- Decreased vision & depth perception

Optic nerve[5-7]

- **Compressive Optic Neuropathy 6-9%**[8]
- Loss of vision
- Impairment of color vision
- Optic disc swelling
- Visual field defect

1. Liaboe C *et al. Thyroid eye disease: an introductory tutorial and overview of disease.* EyeRounds.org. https://webeye.ophth.uiowa.edu/eyeforum/tutorials/thyroid-eye-disease/_Thyroid-Eye-Disease.pdf Published November 18, 2016. Accessed January 10, 2022. 2. Bothun ED *et al. Clin Ophthalmol.* 2009;3:543-551. 3. Bahn RS. *N Engl J Med.* 2010;362(8):726-738. 4. Briceño CA et al. *Int Ophthalmol Clin.* 2013;53(3):93-101. 5. Neigel JM et al. *Ophthalmology.* 1988;95(11):1515-1521. 6. McKeag D et al. *J Ophthalmol.* 2007;91:455-458. 7. Fernandez E et al. *Ann Thyroid Res.* 2016;2:63-65. 8. Bartley GB et al. *Am J Ophthalmol.* 1996;121(4):426-434. 9. Terwee C et al. *Eur J Endocrinol.* 2002;146(6):751-757

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TED Is an Autoimmune Inflammatory Eye Disease

Healthy Eye and Orbital Tissue[3]

In Presence of Moderate to Severe TED[3]

While the exact autoimmune triggers for TED are unknown, autoantibody activation leads to inflammation and tissue expansion/remodeling in the eye[1,2]

Multifactorial causes:

- IGF-1R is overexpressed in TED orbital fibroblasts[4]
- Autoantibodies activate the IGF-1R and TSHR-signaling complex, which stimulates orbital fibroblasts[1] and leads to the release of inflammatory cytokines and hyaluronan production[5-7]
- Once activated, orbital fibroblasts cause[4] inflammation and expansion of tissue, muscle, and fat cells behind the eye[7,8]

1. Smith TJ et al. *Front Endocrinol (Lausanne).* 2016; 7:167. 2. Wang Y et al. *Invest Ophthalmol Vis Sci.* 2014; 55(3): 1735-1748. 3. Horizon Pharma. Events & presentations. https://ir.horizontherapeutics.com/static-files/c153d2c9-fae6-4e3b-ab18-7e8485e2c2d4. Accessed January 10, 2022. 4. Tsui S, et al. J Immunol. 2008;181:4397-4405. 5. Pritchard J, et al. J Immunol. 2003;170:6348-6354. 6. Smith TJ, et al. J Clin Endocrinol Metab. 2004;89:5076-5080. 7. Wang Y, et al. Ther Clin Risk Manag. 2019;15:1305-1318. 8. Patel A, et al. Am J Ophthalmol. 2019;208:281-288.

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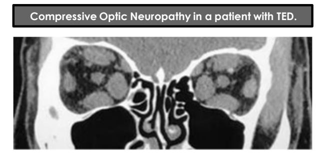
Compressive Optic Neuropathy (CON) Can Result in Irreversible Vision Loss

- Compressive Optic Neuropathy (CON) is a rare, serious complication of TED, affecting 4 to 8% of patients with TED[1-3]
- Caused by compression of optic nerve due to enlargement of rectus muscles and increased volume of periorbital tissue[3]
- May require urgent treatment with medical or surgical decompression to avoid permanent or progressive vision loss[3]
- Clinical features include[3,4]:
  - Slow, progressive loss of vision
  - Impairment of color vision
  - Optic disc swelling
  - Radiologic evidence of apical optic nerve compression
  - Relative afferent pupillary defect
  - Visual field defect
  - Optic atrophy (or edema)

Compressive Optic Neuropathy in a patient with TED.



EOM, extraocular muscle; MRI, magnetic resonance imaging.
1. Bartley GB. *Trans Am Ophthalmol Soc.* 1994; 92:477-588. 2. Bartley GB, et al. *Am J Ophthalmol.* 1996; 121(3):284-290. 3. Neigel JM, et al. *Ophthalmology.* 1988; 95(11):1515-1521. 4. McKeag D, et al. *J Ophthalmol.* 2007; 91:455-458. 5. Fernandez E, et al. *Ann Thyroid Res.* 2016; 2:63-65

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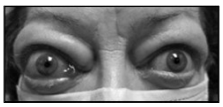
TED Has Broad Implications for Patients' Lives

Diminished Quality of Life

TED impacts the way patients see, the way they look, and the way they feel.[1-3]

In a study of 41 TED patients, **75.6% had altered visual function.**[4]



In a study of 41 TED patients, **95.1% perceived a disturbance in their appearance.**[4]

In another study with 102 TED patients, **45% had anxiety and/or depression.**[3]

1. Bothun ED et al. *Clin Ophthalmol.* 2009; 3:543-551. 2. Barrio-Barrio J et al. *J Ophthalmol.* 2015; 2015:249125. 3. Kahaly GJ et al. *Clin Endocrinol.* 2005; 63:395-402. 4. Delfino LC, et al. *Arch Endocrinol Metab.* 2017;61(4):374-381

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The Palpebral Fissure

- Normally 8-11 mm wide (vertically) and 27-30 mm long (horizontally)
- Large eye with shallow orbit = prominent globe with a wider fissure
- Forward displacement of globe= widening of palpebral fissure
- Abnormal recession of the globe into the orbit results in narrowing of the palpebral fissure

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Exophthalmos

- Seen in Thyroid Disease
- Retraction of the upper eyelids causes a widening of the palpebral fissure
- Thyroid eye disease: Exophthalmometry measurements are remarkably similar to normal patients
- Vertical fissure measurements are better

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Measuring Protrusion

- the amount of protrusion of the normal eye can be important clinical marker
- protrusion is typically measured from the deepest part of the lateral orbital rim to the corneal apex
- Hertel exophthalmometer- most accurate
- Even a simple ruler can be used- screening

http://www.spkplentiesstar.com/Products/examination_instruments/image/K-0161.jpg

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Slideshare Ramachandra Hendge

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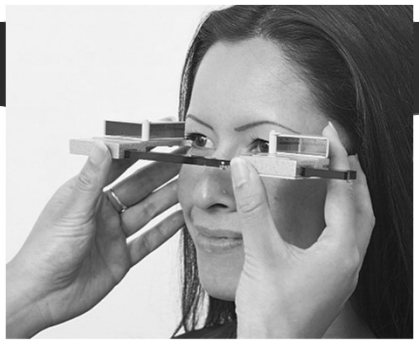

AAO.org Expphthalmometry

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Exophthalmometry measurement

- Measurements range from 12 to 21 mm -normal subjects
- mean of 16 mm
- thyroid eye disease yield values ranging from 12 to 24 mm
- mean of 18 mm.
- Measurements of greater than 19 mm however, were found in only about 5% of normals, while 32% of those with thyroid eye disease fell above this level.
- Lot of ethnic variations

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Proptosis Is Quantified With an Exophthalmometer

- Exophthalmometer is a noninvasive tool designed to measure the forward protrusion of the eye[1,2]
- Normal ocular protrusion as measured from the lateral orbital rim to corneal apex has traditionally been considered ≤21 mm in adults[2]
  - Protrusion >21mm or a 2-mm difference unilaterally or between the two eyes is considered abnormal
- However, proptosis upper limits of normal varies by age, sex, and race[2,3]

Upper Limits of Normal (Proptosis)[3]

Race	Female	Male
African American	23 mm	24 mm
White	19 mm	21 mm
Asian	16 mm	17 mm (Thai) or 18.6 mm (Chinese)

Gorman Bahn Diplopia Scale[4]

Diplopia Score
0. No diplopia
1. Intermittent, i.e., diplopia in primary position of gaze, when tired or when first awakening
2. Inconstant, i.e., diplopia at extremes of gaze
3. Constant, i.e., continuous diplopia in primary or reading position

1. Bothun ED et al. *Clin Ophthalmol.* 2009; 3:543-551. 2. Barrio-Barrio J et al. *J Ophthalmol.* 2015; 2015:249125. 3. Kahaly GJ et al. *Clin Endocrinol.* 2005; 63:395-402. 4. Delfino LC, et al. *Arch Endocrinol Metab.* 2017; 61(4):374-381.

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Thyrotoxicosis

- Dalrymple's Sign

  Retraction of the upper lid(s)

- Von Grafe's Sign
  - Delay of movement of the upper lid when shifting gaze from up to down; causes a staring expression

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Clinical Activity Score Is a Measurement of TED Activity

For initial CAS, only score items 1-7	
1	Spontaneous orbital pain
2	Gaze-evoked orbital pain
3	Eyelid swelling that is considered to be due to active TED
4	Eyelid erythema
5	Conjunctival redness considered to be due to active TED
6	Chemosis
7	Inflammation of caruncle OR plica
Patients assessed after follow-up (1-3 months) can be scored out of 10 by including items 8-10	
8	Increase of ≥2 mm in proptosis
9	Decrease in uniocular excursion in any one direction of ≥5°
10	Decrease of acuity equivalent to ≥1 Snellen line

7-component scale commonly used to assess changes in disease activity in clinical trial settings.

- Clinical Activity Score (CAS) is based on four classical signs of inflammation: pain, redness, swelling and impaired function[1-3]
  - One point for each item, weight for each item is the same
  - Total CAS may range from 0 to 7 or 0 to 10
  - CAS ≥ 3 out of 7 on initial visit or CAS ≥ 4 out of 10 at follow-up visit implies active inflammatory stage of TED*
- Validated as a predictor of response to immunosuppression[1]
- ATA Guidelines and European Thyroid Association/EUGOGO recommend CAS to determine TED activity[2,3]

ATA, American Thyroid Association; EUGOGO, European Group of Graves' Orbitopathy.
*≥ 3 at initial visit and ≥ 4 at follow-up visit.
1. Mourits MP et al. *Br J Ophthalmol.* 1989; 73(8):639-644. 2. Ross DS et al. *Thyroid.* 2016; 26(10):1343-1421. 3. Bartalena L et al. *Eur Thyroid J.* 2016; 5(1):9-26. 4. Barrio-Barrio J et al. *J Ophthalmol.* 2015; 2015:249125.

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American Thyroid Association
TED Severity Grades

Mild TED†: Patients whose features of TED have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment.

Moderate-to-Severe TED: Patients without sight-threatening TED whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).

Sight-Threatening TED: Patients with optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.

Grade†	Lid retraction	Soft tissues	Proptosis†	Diplopia	Corneal exposure	Optic nerve status
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	≥2 mm	Moderate involvement	≥3 mm	Inconstant	Mild	Normal
Severe	≥2 mm	Severe involvement	≥3 mm	Constant	Mild	Normal
Sight threatening	—	—	—	—	Severe	Compression

The European Thyroid Association has similar severity grades with one exception. The severity grades of moderate and severe are combined to be Moderate/Severe. All of the signs and symptoms for ATA and ETA are the same[2]

†Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient's baseline, if available.
1. Ross DS et al. Thyroid. 2016; 26(10):1343-1421. 2. Bartalena, Luigi, et al. "The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy." *European Journal of Endocrinology* 185.4 (2021): G43-G67.

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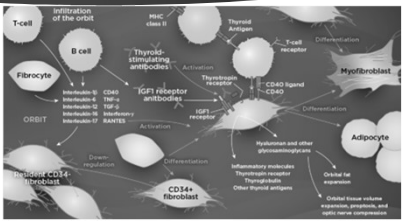
IGF-1R/TSHR Signaling Complex Activation Triggers Inflammatory Response Leading to Tissue Expansion and Remodeling

- Orbital fibroblasts (OFs) are the principal cells that drive the inflammation and expansion of orbital soft tissues[1-4]
- OFs from patients with TED are more prone to activation, leading to proliferation, differentiation into adipocytes and increased hyaluronan secretion than OFs from healthy controls[1,3,4]
- IGF-1R and TSHR are co-localized and form a signaling complex[5]



IGF-1R, insulin-like growth factor-1 receptor; TSHR, thyroid-stimulating hormone receptor.
1. Smith TJ, et al. *Thyroid.* 2008;18(9):983-988. 2. Smith T. *Pharmacological Rev.* 2015;67(1):99-136. 3. Bahn RS. *N Engl J Med.* 2010;362(8):726-738. 4. Khan SU, et al. *J Neuroophthalmol.* 2016;36(2):177-185. 5. Tsui S et al. *J Immunol.* 2008;181:4397-4405.

54

Historically, Treatment Options for TED Selected Based on Disease Activity and Severity[1,2]

	Disease Severity: Mild	Moderate-to-severe	Sight-threatening
Acute Stage	• Local measures* • Oral steroids if acute stage or decreased QoL	• IV steroids • Off-label biologics (TOCI, RTX) • Orbital radiation • Orbital decompression surgery or clinical trial enrollment	• IV steroids + urgent orbital decompression surgery
Chronic Disease	• Local measures	• Surgical intervention after ≥3 months observation (as needed)	• Surgical intervention

IV, intravenous; N/A, not applicable; QoL, quality of life; TOCI, tocilizumab, RTX, rituximab
*With or without selenium supplementation.
1. Ross DS et al. *Thyroid.* 2016; 26(10):1343-1421. 2. Bartalena L et al. *Eur Thyroid J.* 2016; 5(1):9-26.

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Teprotumumab-trbw Overview

FDA Indication
- **Teprotumumab is indicated for the treatment of Thyroid Eye Disease**
- Approved January 21, 2020[1]

Mechanism of Action
- Teprotumumab-trbw is a fully human monoclonal antibody[1] that binds to IGF-1R and blocks its activation and signaling

Administration
- One infusion every 3 weeks across 21 weeks (8 total infusions)[1]
- First infusion of 10 mg/kg followed by 7 infusions of 20 mg/kg[1]

IGF-1R, insulin-like growth factor-1 receptor;
1. Horizon Pharma USA, Inc. Treatment of Graves' orbitopathy (thyroid eye disease) to reduce proptosis with teprotumumab-trbw infusions in a randomized, placebo-controlled, clinical study (OPTIC). https://www.clinicaltrials.gov/ct2/show/NCT03298867. Accessed November 15, 2018.

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Mechanism of Action of Teprotumumab-trbw for TED

Pathophysiology of TED
- The body attacks its own orbital cells which overexpress IGF-1R.[1,2]
- IGF-1R and TSHR are co-localized and form a signaling complex.[2]
- This leads to severe inflammation and expansion of tissue, muscle and fat cells behind the eye.[1,3]
- May cause proptosis (bulging of the eyes) and optic nerve compression.[1,3]

Teprotumumab-trbw Mechanism of Action[3]
- Fully human monoclonal antibody inhibitor of IGF-1R.
- Blocks IGF-1R and turns off signaling complex at the source of the disease.
- Intended to reduce inflammation and prevent excessive cell growth behind the eye.

1. Bahn RS. *N Engl J Med.* 2010; 362:726-738. 2. Tsui S, et al. *J Immunol.* 2008; 181:4397-4405. 3. Smith TJ, et al. *N Engl J Med.* 2016; 375:1552-1565.

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OPTIC Study

Patient Criteria
- Active TED
- 18-80 years
- CAS ≥4
- <9 months since active TED onset with no prior treatment
- FT4 and FT3 <50% above or below normal limits

Screening / Randomization

Week 0 → Week 24

- Teprotumumab: 8 infusions (Q3W)
- Placebo: 8 infusions (Q3W)

Primary endpoint at Week 24
Percentage of participants with ≥2mm reduction in proptosis

Off-Treatment Follow-up Period

Douglas RS, et al. *N Engl J Med.* 2020;382(4):341–352

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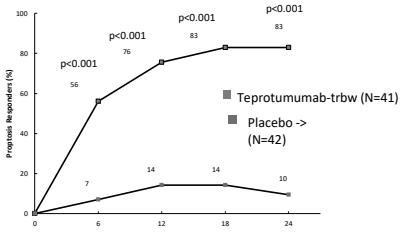
Proptosis Responders (≥ 2 mm reduction)



Douglas RS, et al. *N Engl J Med.* 2020;382(4):341–352

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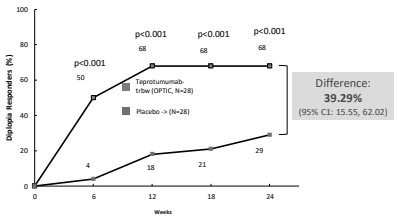
Diplopia Responders (≥ 1 grade improvement)



Douglas RS, et al. *N Engl J Med.* 2020;382(4):341–352

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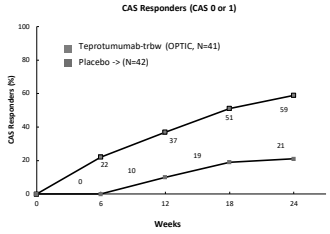
CAS score responders



Douglas RS, et al. *N Engl J Med.* 2020;382(4):341–352

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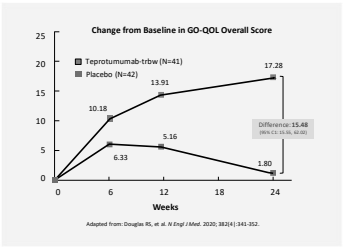
GO-QoL Improvements Overall



Adapted from: Douglas RS, et al. *N Engl J Med.* 2020; 382(4):341-352.

Drivers of decreased QoL:

- TED activity[1-4] and ocular pain[1,5]
- Disease severity[2-4,6,7]:
  - Proptosis[4,8-10] and asymmetric proptosis (≥2 mm difference between eyes)[4]
  - Diplopia[1,3-5,11]
  - Blurred vision[1]

MMRM ANCOVA model with an unstructured covariance matrix, including the following terms: baseline score, tobacco use status (non-user, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions; least square mean +/- standard error.

1. Kahaly GJ, et al. *Clin Endocrinol (Oxf).* 2005; 63:395-402. 2. Chan YJ, et al. *Eye (Lond).* 2012; 26:544-551. 3. Lin IC, et al. *J Formos Med Assoc.* 2015; 114:1047-1054. 4. Villagelin D, et al. *Front Endocrinol (Lausanne).* 2019; 10:592. 5. Kahaly GJ, et al. *Thyroid.* 2002; 12:207-208. 6. Park SJ, et al. *Br J Ophthalmol.* 2004; 88:75-78. 7. Delfino LC, et al. *Arch Endocrinol Metab.* 2017; 61:374-381. 8. Bartalena L, et al. *Endocr Rev.* 2000; 21:168-199. 9. Gerding MN, et al. *Thyroid.* 1997; 7:885-889. 10. Tehrani M, et al. *Eur J Ophthalmol.* 2004; 14:193-199. 11. Bradley EA, et al. *Ophthalmology.* 2006; 113:1650-1654.

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Warnings, Precautions, and Special Populations

Infusion Reactions

- Teprotumumab-trbw may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with teprotumumab-trbw

Exacerbation of Preexisting Inflammatory Bowel Disease

- Teprotumumab-trbw may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of teprotumumab-trbw

Hyperglycemia

- Hyperglycemia or increased blood glucose may occur in patients treated with teprotumumab-trbw. In clinical trials, 10% of patients (two thirds of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary
- Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with teprotumumab-trbw. Ensure patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving teprotumumab-trbw

Special Population

- Teprotumumab-trbw should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment, and for 6 months following the last dose of teprotumumab-trbw

TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon

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Adverse Reactions

Adverse Reactions Occurring in ≥5% of Patients Treated With Teprotumumab and Greater Incidence Than Placebo

Adverse Reactions	Teprotumumab (n=84), n (%)	Placebo (n=86), n (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue	10 (12%)	6 (7%)
Hyperglycemia	8 (10%)	1 (1%)
Hearing impairment	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0
Weight decreased	5 (6%)	0
Nail disorder	4 (5%)	0

Menstrual disorders like amenorrhea, metrorrhagia, and dysmenorrhea were reported in approximately 23% (5 of 22 patients) of menstruating women treated with teprotumumab-trbw compared to 4% (1 of 25 patients) treated with placebo in clinical trials.

1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon.

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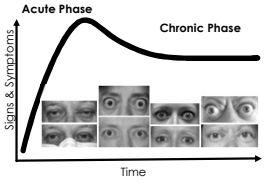
Evolving TED disease state understanding



"This treatment has the potential to alter the course of the disease, potentially sparing patients from needing multiple invasive surgeries by providing an alternative, nonsurgical treatment option."

- Wiley Chambers, M.D., Deputy Director of the Division of Transplant and Ophthalmology Products in the FDA's Center for Drug Evaluation and Research

Source: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-thyroid-eye-disease

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Efficacy and Safety of Teprotumumab in Patients With Thyroid Eye Disease of Long Duration and Low Disease Activity

Raymond S. Douglas,[1] Steven Couch,[2] Sara T. Wester,[3] Brian T. Fowler,[4] Catherine Y. Liu,[5] Prem S. Subramanian,[6,7] Rosa Tang,[8] Quang T. Nguyen,[9] Robi N. Maamari,[2] Shoaib Ugradar,[1] Kate Hsu,[10] Michael Karon,[10] and Marius N. Stan[11]

Context: Early inflammatory thyroid eye disease (TED) can lead to symptomatic chronic disease, including disabling proptosis. Teprotumumab, an insulin-like growth factor-1 receptor (IGF-1R) inhibitor, previously demonstrated efficacy in acute, high-inflammation TED trials.

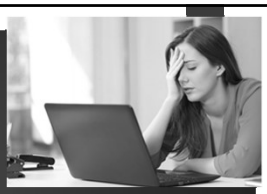
Objective: We present data from the first placebo-controlled trial with teprotumumab in chronic/low disease activity TED.

42 Tx vs 20 Placebo
-2.41 vs 0.92 Proptosis
AE similar between groups

Conclusion: Teprotumumab significantly improved proptosis vs placebo in longstanding/low inflammation TED, demonstrating efficacy regardless of disease duration/activity. The safety profile was comparable to that previously reported.

The Journal of Clinical Endocrinology & Metabolism, 2024, **109**, 25–35
https://doi.org/10.1210/clinem/dgad637
Advance access publication 31 October 2023
Clinical Research Article

66



Screen time stress, cortisol and cognitive performance

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Carotenoids and health ?

- Carotenoids in macula improves vision and decreases ocular fatigue- easy sell
- But not so straightforward….

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Frontiers in nutrition

A Machine Learning Based Dose Prediction of Lutein Supplements for Individuals With Eye Fatigue

Juntao Kan[1†], Ao Li[2†], Hong Zou[2], Liang Chen[1] and Jun Du[1]*

[1] Nutrilite Health Institute, Shanghai, China, [2] Department of Bioinformatics, WuXi NextCODE Genomics, Shanghai, China

November 2020 | Volume 7 | Article 577923

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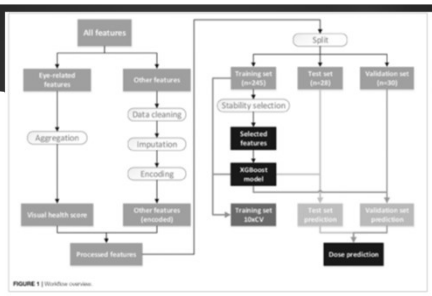

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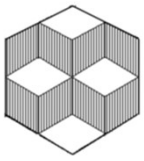

- Visual health score (VHS) was a composite score developed from 4 most correlated/predictive parameters
1. Total score of eye fatigue,
2. Visuognosis persistence,
3. **Macular pigment optical density (most predictive)**
4. Schirmer's test

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Screen time issues- prediction and precision nutrition

- Most individuals 67.24% need high dose of carotenoids – 14 mg lutein equivalent
- 29.31% may take a lower dose – 10 mg lutein equivalent
- 3.45% cannot be helped

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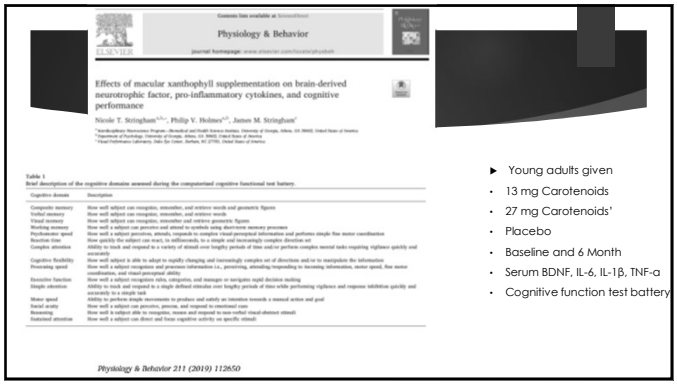

- Young adults given
- 13 mg Carotenoids
- 27 mg Carotenoids'
- Placebo
- Baseline and 6 Month
- Serum BDNF, IL-6, IL-1β, TNF-α
- Cognitive function test battery

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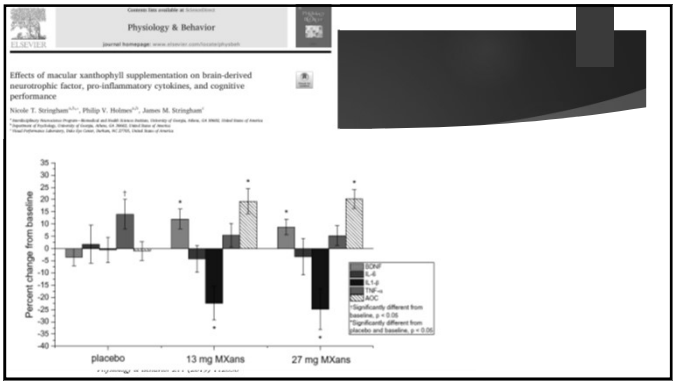

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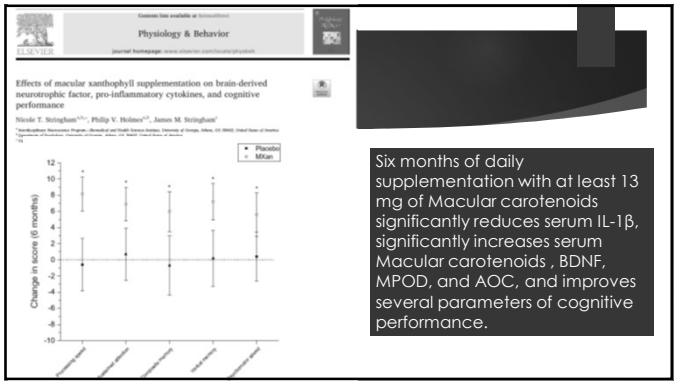
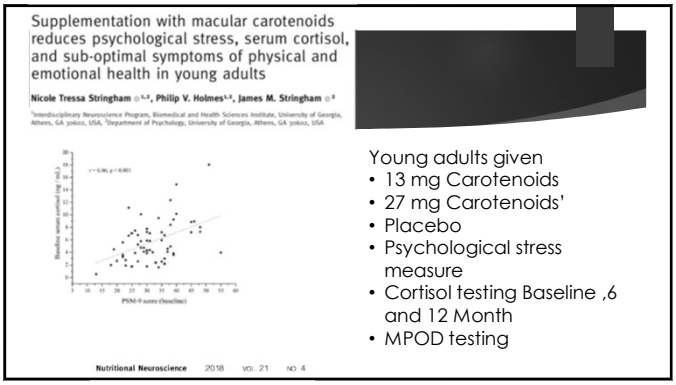


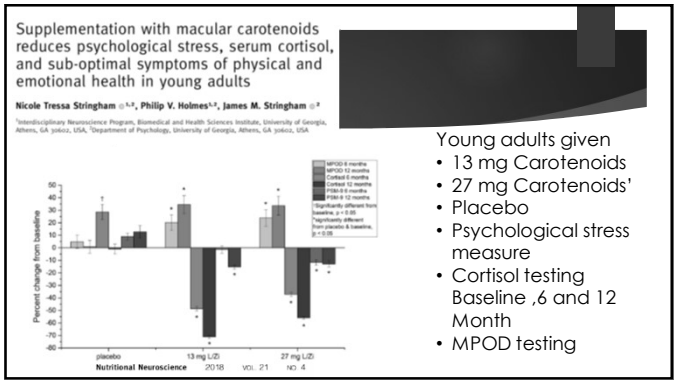
Six months of daily supplementation with at least 13 mg of Macular carotenoids significantly reduces serum IL-1β, significantly increases serum Macular carotenoids , BDNF, MPOD, and AOC, and improves several parameters of cognitive performance.

75



Young adults given
- 13 mg Carotenoids
- 27 mg Carotenoids'
- Placebo
- Psychological stress measure
- Cortisol testing Baseline ,6 and 12 Month
- MPOD testing

76



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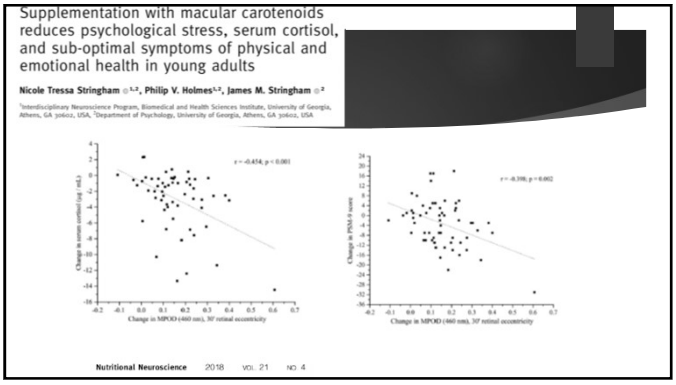
77



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foods
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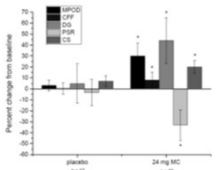
Article

Macular Carotenoid Supplementation Improves Visual Performance, Sleep Quality, and Adverse Physical Symptoms in Those with High Screen Time Exposure

James M. Stringham [1,*], Nicole T. Stringham [2] and Kevin J. O'Brien [3]



48 healthy young adults
6 hours of screen time
Placebo versus Macular carotenoids
- MPOD testing with HFF
- Critical flicker fusion frequency
- Photo stress recovery
- Contrast sensitivity
- Disability Glare

Foods 2017, 6, 47; doi:10.3390/foods6070047

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foods
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Article
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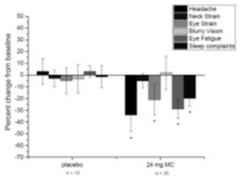

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Increased MPOD significantly improves visual performance and, in turn,improves several undesirable physical outcomes associated with excessive ST. The improvement in sleep quality was not directly related to increases in MPOD, and may be due to systemic reduction in oxidative stress and inflammation.

Foods 2017, 6, 47; doi:10.3390/foods6070047

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48 healthy young

HFF
- Critical flicker fusion frequency
- Photo stress

Foods 2017, 6, 47; doi:10.3390/foods6070047

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Summary

- Carotenoid supplementation has a real role in decreasing stress and betterment.
- Dose matters
- Duration matters -6-12 months effects visible
- Don't turn your computers on unless you have taken your Lutein and Zeaxanthin
- Don't be Lazy; take your LZ (Lutein and Zeaxanthin)

SCAN ME

Nutrients 2022, 14, 4005

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Cognition and MPOD Children and Adults

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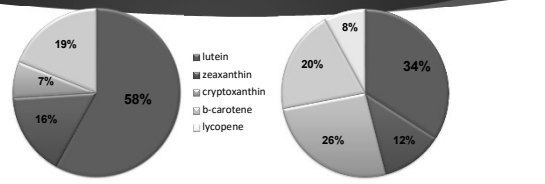
Brain carotenoid profile in infants and centenarians



Vishwanathan et al, 2014 *Johnson EJ et al. 2013*

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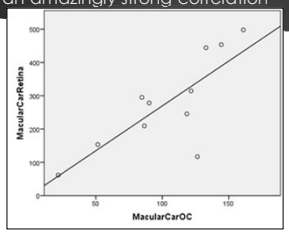
Correlation – Human retina and occipital cortex concentrations of lutein and zeaxanthin. have an amazingly strong correlation



n=11	r	*P* value
Bivariate	0.784	**0.004**
Age & sex adjusted	0.834	**0.010**
Age, sex & cognitive status adjusted	0.887	**0.008**

Macular pigment carotenoids = Lutein (*Meso*-zeaxanthin) + Zeaxanthin in the retina

Vishwanathan R, Schalch W, Johnson E J.Nutr Neurosci. 2016;19(3):95-101

86

Renzi et al., The relation between serum xanthophylls, fatty acids, macular pigment and cognitive function in the Health ABC Study.

FASEB J ;22:877.5.

- n = 118 healthy older subjects in the Memphis, Tennessee area
- ages 76–85 y; equal numbers of men and women, were assessed for serum lutein and zeaxanthin, MP density, and various measures of cognitive function.

MP was related to performance on a variety of indexes designed to assess processing **speed**, **accuracy, and completion ability** (P < 0.05).

87

Hammond BR et al , Effects of lutein/zeaxanthin supplementation on the cognitive function of community dwelling older adults: A Randomized, Double-Masked, Placebo-Controlled Trial,

Front. Aging Neurosci. 9:254, .

- AREDS II carotenoid dosing (12 mg LZ) was evaluated in community dwelling older adults 73.7 +/- 8.2 yrs. of age.
- Participants receiving the active LZ dietary supplement had statistically significant increases in MP (P<0.03)

Improvements in complex attention (p<0.02) and cognitive flexibility domains (p < 0.04) relative to study participants taking the placebo.

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Dietary carotenoids related to risk of incident Alzheimer dementia (AD) and brain AD neuropathology: a community-based cohort of older adults

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927 participants (No AD) were followed up for 7 years- Rush Memory and Ageing project
AD neuropathy was assessed in 508 deceased participants

Results were controlled for Age, sex, education, cognitively stimulating activities, physical activities, Apolipoprotein

Conclusions: Our findings support a beneficial role of total carotenoid consumption, in particular lutein/zeaxanthin, on AD incidence that may be related to the inhibition of brain β-amyloid deposition and fibril formation.

Am J Clin Nutr 2021;113:200–208.

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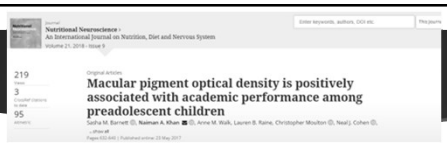

Macular pigment optical density is positively associated with academic performance among preadolescent children

Results: The regression analyses revealed that MPOD improved the model, beyond the covariates, for overall academic achievement ($\Delta R^2 = 0.10$, $P < 0.01$), mathematics ($\Delta R^2 = 0.07$, $P = 0.02$), and written language composite standard scores ($\Delta R^2 = 0.15$, $P < 0.01$).

Discussion: This is the first study to demonstrate that retinal L and Z, measured as MPOD, is positively related to academic achievement in children, even after accounting for the robust effects of IQ and other demographic factors. These findings extend the positive associations observed between MPOD and cognitive abilities to a pediatric population.

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Nutritional Epidemiology

Maternal Intake of Lutein and Zeaxanthin during Pregnancy Is Positively Associated with Offspring Verbal Intelligence and Behavior Regulation in Mid-Childhood in the Project Viva Cohort

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Conclusions: Higher maternal L/Z intake during pregnancy was associated with better offspring verbal intelligence and behavior regulation ability in mid-childhood, suggesting a potential benefit during prenatal development. We did not find a benefit of higher maternal L/Z intake on other child cognitive or behavioral outcomes. Project Viva is registered at clinicaltrials.gov as NCT02820402. *J Nutr* 2021;00:1–13.

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Thank You!

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