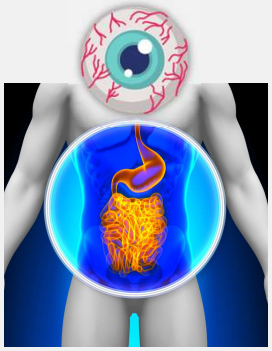
FROM THE GUT

HOW DIET IS LINKED TO DRY EYE AND OCULAR SURFACE DISEASE



Presented by :

JOSEPH J. ALLEN, OD, FAAO, DIPL ABO

Doctor Eye Health

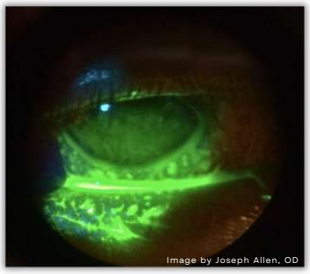
Dr Eye Health Podcast

1

Case 1

- 78 YO Female
- CC: Dry, red, irritated eyes, for 20+ years
  - Tried every OTC eye drop
  - Tried cyclosporine, lifitigrast, IPL, thermopulsation, topical steroids
- BCVA 20/50 (variable), OD/OS

2



Slit Lamp

- Irregular eyelid margins OD/OS
- 3+MGD OD/OS
- 4+ corneal SPK (diffuse)
- 3+ conj staining

3

VITAMIN A

Vitamin A

- Key component of rhodopsin - involved in visual processing
- Involved in Immune regulation & metabolism
- Maintaining the integrity and function of skin and **mucosal** cells (like in the gut and respiratory tract)

Markoulli M, et al.. Ocul Surf. 2023 Jul;29:226-271.

4

VITAMIN A

- Differentiation of corneal epithelium
- Stimulates Mucin 4 on conj epithelial cells
- Down regulated androgen expression on ocular surface

Markoulli M, et al.. Ocul Surf. 2023 Jul;29:226-271.

5

Vitamin A Deficiency (VAD)

Ifwat A, et al. Xerophthalmia in Picky Eater Children. Cureus. 2022 Mar 4;14(3):e22846

Song A, Mousa HM, Soifer M, Perez VL. Recognizing vitamin A deficiency: special considerations in low-prevalence areas. Curr Opin Pediatr. 2022 Apr 1;34(2):241-247.

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Vitamin A Deficiency (VAD)

Results in Xerophthalmia
- Night Blindness
- Bitot Spots
- Corneal & Conj Xerosis
- Ulceration
- Necrosis

Refer for testing

Serum Vitamin A values below 0.70 µmol/l indicating VAD

Song A, Mousa HM, Soifer M, Perez VL. Recognizing vitamin A deficiency: special considerations in low-prevalence areas. Curr Opin Pediatr. 2022 Apr 1;34(2):241-247.

Ifwat A, et al. Xerophthalmia in Picky Eater Children. Cureus. 2022 Mar 4;14(3):e22846

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VITAMIN A DEFICIENCY (VAD)

Risk for VAD

Developing Nations
- Malnutrition
  - (Pregnant women and young children)
- Malaria (chronic diarrhea)

Developed Countries
- Bariatric surgery
- Restrictive Diets
- Liver & Pancreatic disease
  - Anything limiting fat absorption
- Intestinal inflammation

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VITAMIN A DEFICIENCY (VAD)

Risk for VAD

Medical Conditions
- Cystic Fibrosis
- Celiac disease
- Crohn's Disease

Medications
- Orlistat
  - Obesity drug (inhibits fat absorption)
- Cholestyromine
  - Cholesterol med

9

VITAMIN A DEFICIENCY (VAD)

Pediatric Chalazion
- Low serum vitamin A was significantly associated with chalazion in children

Cheng Het al. Optom Vis Sci. 2022 Jun 1;99(6):540-543.
Malekahmadi M, et al. Med Hypothesis Discov Innov Ophthalmol. 2017 Fall;6(3):63-66

10

VITAMIN A DEFICIENCY (VAD)

VAD TREATMENT

Systemic Vitamin A Supplementation
- Depends on age
- Usually treated by advanced healthcare teams
  - Primary care physicians, dietitians, pharmacists

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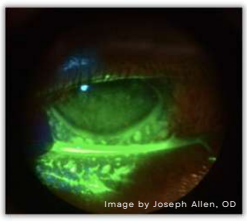
VITAMIN A DEFICIENCY (VAD)

VAD TREATMENT

Xerophthalmia
- Swab for microbial analysis
- Broad spectrum antibiotic
- Preservative Free Artificial Tears
- Topical Vit A?



12

Hypervitaminosis

The UL of vitamin A for adults is ~3000 mcg/ 9000 IUs

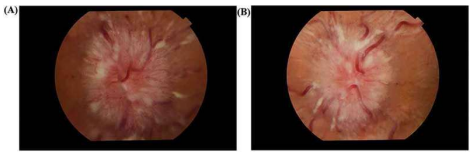
hypervitaminosis A

- nausea
- vomiting
- headache
- dizziness
- irritability
- blurred vision
- **dry eyes**
- hair loss
- hypothyroidism
- bone & joint pain

Olson JM, Ameer MA, Goyal A. Vitamin A Toxicity. 2023 Sep 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.

13

Pseudotumor cerebri

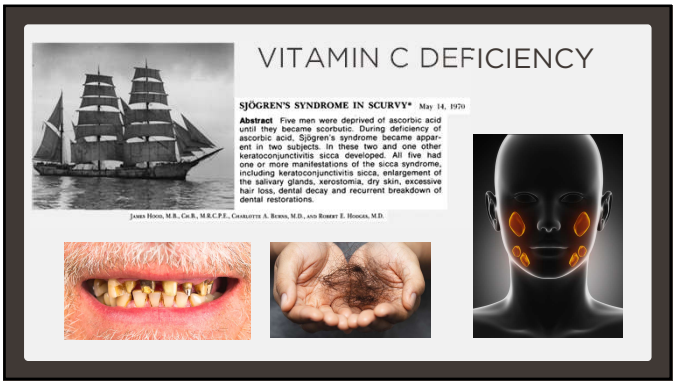


- patient had been taking a weight loss supplement, containing 1500 IU of vitamin A per capsule, twice daily for a year
- but resolved with discontinuation within 6 months

- **non-obese pseudotumor cerebri patients**
  - **Question on diet/supplementation**

Chisholm JT, et al. Neuroophthalmology. 2017 Sep 1;42(3):169-175.

14



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VITAMIN C

AKA L-ascorbic acid

- **Is a water-soluble vitamin that your body needs but can't make on its own**
- **Function: iron absorption, wound healing, collagen formation**
- **Cofactor for collagen-stabilizing enzymes**
- **Helps generate vitamin E**
- **Strong Antioxidant Capacity**

Table 1: Recommended Dietary Allowances (RDAs) for Vitamin C in Milligrams (mg) [8]

Age	Male	Female	Pregnancy	Lactation
0–6 months	40 mg*	40 mg*		
7–12 months	50 mg*	50 mg*		
1–3 years	15 mg	15 mg		
4–8 years	25 mg	25 mg		
9–13 years	45 mg	45 mg		
14–18 years	75 mg	65 mg	80 mg	115 mg
19+ years	90 mg	75 mg	85 mg	120 mg
People who smoke	Individuals who smoke require 35 mg/day more vitamin C than poeple who do not smoke.			

Vitamin C Health Professional Fact Sheet National Institutes of Health (NIH) Office of Dietary Supplements (ODS), July 2025

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VITAMIN C

Deficiency Can Lead to Scurvy

- Deficiency Timeline:
  - Prolonged low intake (<10 mg/day)
  - Can develop in 1-3 months
- Prevalence: ~7% of U.S. Population
- Risk Factors: **chronic alcohol use, poor diet, obesity**
- Symptoms
  - hemorrhagic symptoms (gum disease)
  - poor wound healing
  - anemia
  - fatigue

17

VITAMIN C

Pereira A, Adekunle RD, Zaman M, Wan MJ. Association Between Vitamin Deficiencies and Ophthalmological Conditions. Clin Ophthalmol. 2023 Jul 19;17:2045-2062.

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VITAMIN C

May Help Slow AMD Progression
- Vitamin C is part of the AREDS and AREDS2

May Help Prevent Glaucoma / Increased IOP
- Vitamin deficiency associated with glaucoma progression
  - Oxidative stress causes damage to trabecular meshwork
  - Lower Vitamin C levels in patients with glaucoma vs normal controls

Paterson C.A, et al. Vitamin C Levels in Human Tears. Arch. Ophthalmol. 1987;105:376–377
Office of Dietary Supplements. (2022, March 26). Vitamin C - Health professional fact sheet. National Institutes of Health.
Pereira A, et al. Clin Ophthalmol. 2023 Jul 19;17:2045-2062.

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VITAMIN C

Cold Symptom Duration, Not Prevention

- ≥200 mg/day can reduce cold duration by 8% in adults and 14% in children.
- Benefits are greater in those under physical stress (e.g., athletes, soldiers) and in cold weather.
- Possibly due to antihistamine effects of high dose Vit C

Johnston CS. Subcell Biochem 1996;25:189-213.
Office of Dietary Supplements. (2022, March 26). Vitamin C - Health professional fact sheet. National Institutes of Health.

20

VITAMIN C

- Corneal wound healing
  - proliferation of corneal epithelial cells
    - from aqueous humor
  - Collagen synthesis
  - Inhibits VEGF, MMPs and corneal neovascularization
  - Synthesis of ECM in keratocytes
  - Anti-oxidant (found natural in tears)

Chen J, et al. Stem Cells Transl Med. 2017;6(5):1356-65.
Yoo EH, et al. Sensors (Basel). 2010;10(5):4558-76.
Doseděl M, et al. Nutrients. 2021;13(2):615.

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VITAMIN C

High-dose vitamin C
- oral 3g/day or IV 20g/day
associated with reduced corneal opacity in patients with infectious keratitis.

At least 2g/day or 10% eye drops soln for chemical burns.

Also consider in
- Contact lens related ulcers
- Photokeratitis

Caution: Doses >1g/day may increase the risk of kidney stones.

High doses may also falsely elevate blood glucose readings.

Chen J, et al. Stem Cells Transl Med. 2017;6(5):1356-65.
Yoo EH, et al. Sensors (Basel). 2010;10(5):4558-76.
Doseděl M, et al. Nutrients. 2021;13(2):615.

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VITAMIN C

- Vitamin C Treatment Protocol (scurvy – based guidance)
  - Indication: Ocular hemorrhages related to vit deficiency
  - Loading dose: 1-2 g daily for 3 days
  - Short term: 500mg daily for 1 week
  - Maintenance dose: 100 mg daily for 3 months

Table 2: Vitamin C Content of Selected Foods [13]

Food	Milligrams (mg) per serving	Percent (%) DV*
Red pepper, sweet, raw, ½ cup	95	106
Orange juice, ¾ cup	93	103
Orange, 1 medium	70	78
Grapefruit juice, ¾ cup	70	78
Kiwifruit, 1 medium	64	71
Green pepper, sweet, raw, ½ cup	60	67
Broccoli, cooked, ½ cup	51	57
Strawberries, fresh, sliced, ½ cup	49	54
Brussels sprouts, cooked, ½ cup	48	53
Grapefruit, ½ medium	39	43
Broccoli, raw, ½ cup	39	43
Tomato juice, ¾ cup	33	37
Cantaloupe, ½ cup	29	32
Cabbage, cooked, ½ cup	28	31
Cauliflower, raw, ½ cup	26	29
Potato, baked, 1 medium	17	19
Tomato, raw, 1 medium	17	19
Spinach, cooked, ½ cup	9	10
Green peas, frozen, cooked, ½ cup	8	9

Vitamin C Health Professional Fact Sheet National Institutes of Health (NIH) Office of Dietary Supplements (ODS), July 2025

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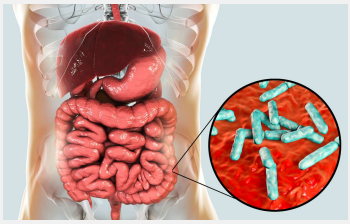
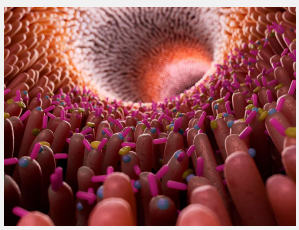
GUT MICROBIOME





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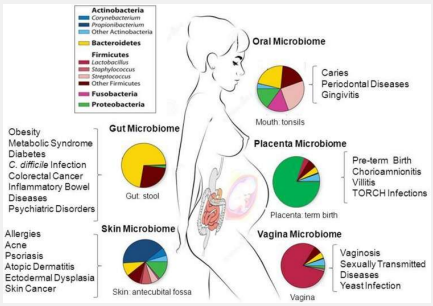
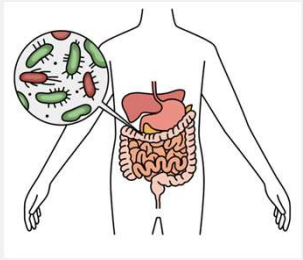
WHAT ARE MICROBIOMES?



Belizário JE, Napolitano M. Front Microbiol. 2015 Oct 6;6:1050.

25

GUT MICROBIOME



Micro-organisms
- bacteria
- fungi
- archaea
- viruses

- Maintains gut epithelium
- Regulates metabolism
- Aids with nutrient absorption
- Resistance to pathogens
- Immune functions
- **Influenced by pharmaceuticals**

Zysset-Burri DC, Morandi S, Herzog EL, Berger LE, Zinkernagel MS. The role of the gut microbiome in eye diseases. Prog Retin Eye Res. 2023 Jan;92:101117.

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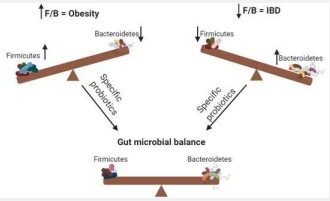
GUT MICROBIOME

Gut Dysbiosis?



Gut microbiome belongs to four phyla:
- Firmicutes
- Bacteroidetes
- Actinobacteria
- Proteobacteria

- Bacteroidetes
  - includes approximately 7000 different species of Gram-negative bacteria associated with lipopolysaccharide (LPS) and immune function
- Firmicutes
  - Gram-positive bacteria that play a key role in host's metabolism through short-chain fatty acid synthesis

Stojanov, S.; Berlec, A.; Štrukelj, B. Microorganisms 2020, 8, 1715.

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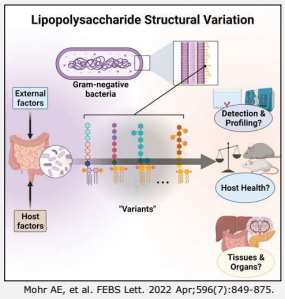
Lipopolysaccharides (LPSs)

- surface glycolipids, produced by Gram-negative bacteria
  - can trigger acute & chronic inflammation
- Gut Microbiome and gut-associated lymphoid tissue (GALT) are influenced by LPS and shift towards an inflammatory pattern
- gut-associated lymphoid tissue (GALT) T regulatory (Tregs) lymphocytes
  - Th17 lymphocytes
  - Th1 lymphocytes
- Damages intestinal epithelial wall
- Triggers Innate Immune response
  - toll-like receptor (TLR)-4



Mohr AE, et al. FEBS Lett. 2022 Apr;596(7):849-875.

Candelli M, et al. Int J Mol Sci. 2021 Jun 10;22(12):6242.
Mohr AE, et al. FEBS Lett. 2022 Apr;596(7):849-875.

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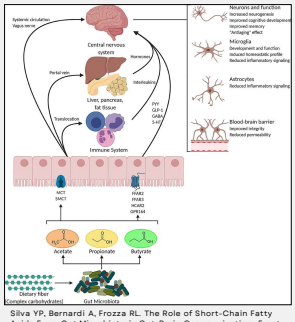
Short-Chain Fatty Acids (SCFAs)

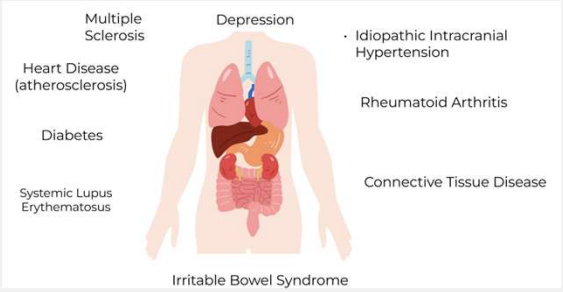
- Fermentation of dietary fibers and resistant starches leads to metabolites
  - acetate
  - propionate
  - butyrate
- Improve Gut Health and Barrier Integrity
  - promote mucus production
  - associated with reduced risk of colorectal cancer.
- Receptor-Mediated Signaling
  - bind G protein/ Free - Fatty Acid Receptors
  - influencing
    - glucagon-like peptide1 (GLP-1)
    - peptide YY (PYY)
- Immune System Modulation
  - Regulation of T cells (Tregs) and helps control inflammation.
- linked to regulating
  - brown fat activation
  - liver mitochondrial function
  - appetite
  - sleep
  - CNS signaling



Silva YP, Bernardi A, Frozza RL. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. Front Endocrinol (Lausanne). 2020 Jan

29

GUT MICROBIOME



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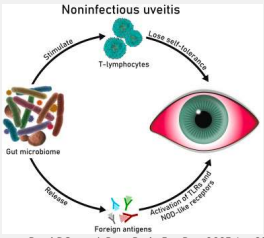
GUT MICROBIOME

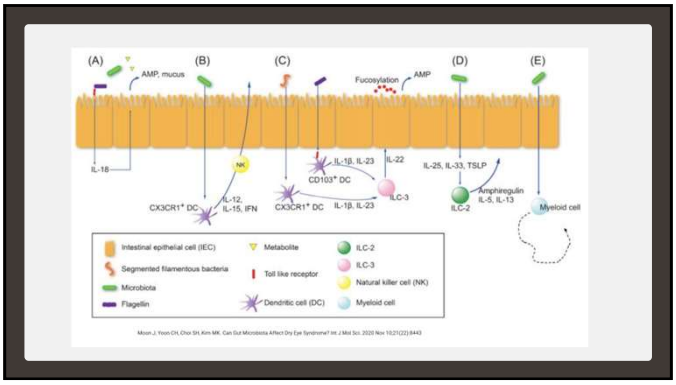
Associated with ocular disease
- Non-infectious Uveitis
- Age-related macular degeneration
- Diabetic Retinopathy
- Retinal artery occlusion
- Central serous chorioretinopathy
- Glaucoma
- Ocular surface disease / dry eye



Zysset-Burri DC, et al. Prog Retin Eye Res. 2023 Jan;92:101117

Xue W, et al. Front Cell Infect Microbiol. 2021 Oct 21;11:759333.
Cai Y, et al. Biomed Pharmacother. 2023 Aug;164:114994.
Markoulli M, et al. TFOS Lifestyle: Impact of nutrition on the ocular surface. Ocul Surf. 2023 Jul;29:226-271.

31



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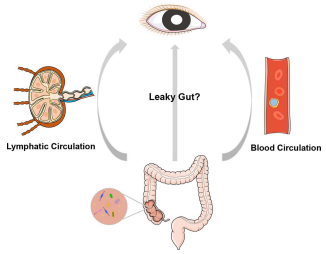
GUT-EYE AXIS?

1. Mucosal barrier dysfunction and bacterial translocation
   - (and their metabolites)
   - Activation of pro-inflammatory cytokines
     - Alterations in b and T cells

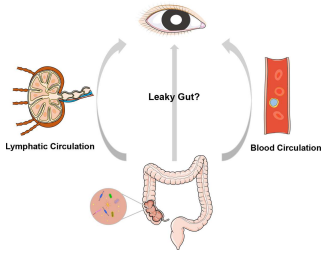


Xue W, et al. Front Cell Infect Microbiol. 2021 Oct 21;11:759333.

33

GUT-EYE AXIS?

2. Dysbiosis causes Immune system dysregulation
   - non-specific inflammation
   - increase of pro-inflammatory cytokines and ROS



Xue W, et al. Front Cell Infect Microbiol. 2021 Oct 21;11:759333.

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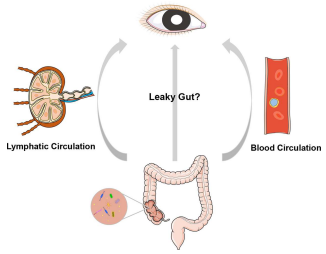
GUT-EYE AXIS?

3. Alteration in vitamin / nutrient absorption
   - influence on dietary nutrients
   - AREDS supplementation etc.



Xue W, et al. Front Cell Infect Microbiol. 2021 Oct 21;11:759333.

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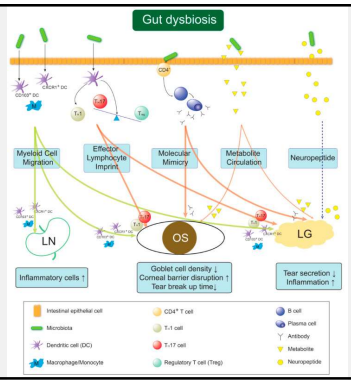
Gut Dysbiosis–Ocular Surface–Lacrimal Gland Axis

Immune Cell Migration
- Activated dendritic cells and monocytes/macrophages (e.g., CD103+, CXCR1+), migrate to the ocular surface and lacrimal gland to prime T cells or secrete pro-inflammatory cytokines.

Effector T Cell Imprinting & Regulatory Imbalance
- TH1 and TH17 cells may migrate to the eyes, while circulating regulatory T cells (Tregs) may be reduced, contributing to inflammation.

Molecular Mimicry & Autoimmunity
- Microbial antigens can activate autoreactive CD4+ T cells, leading to B-cell-driven autoantibody production.

Metabolite & Neuropeptide Signaling Disruption
- Reduced gut-derived metabolites (e.g., short-chain fatty acids) and neuropeptides may impair tear production and increase ocular surface inflammation.



Moon J, et al. Int J Mol Sci. 2020 Nov 10;21(22):8443

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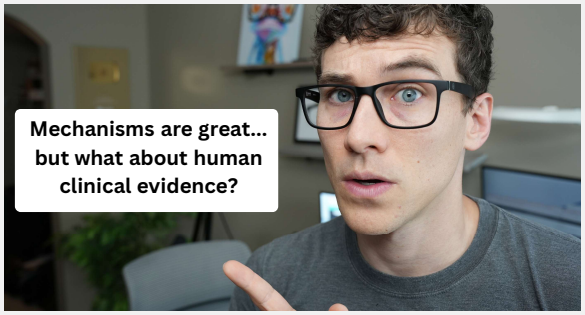

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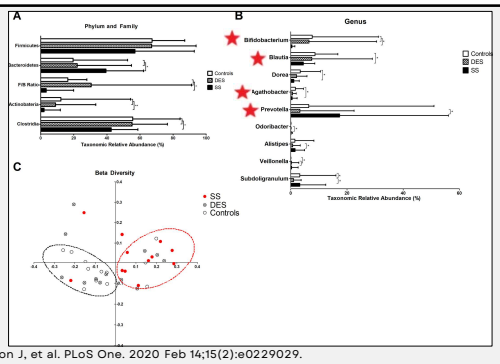

Moon J, et al. PLoS One. 2020 Feb 14;15(2):e0229029.

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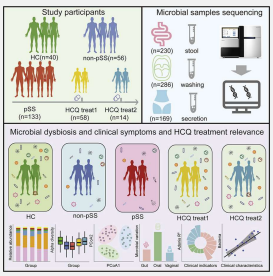
> Cell Rep. 2022 Sep 13;40(11):111352. doi: 10.1016/j.celrep.2022.111352.

Microbiota dysbiosis in primary Sjögren's syndrome and the ameliorative effect of hydroxychloroquine

Xiaobing Wang [1], Kun Pang [2], Jinfeng Wang [3], Bing Zhang [4], Zhenwei Liu [5], Saisai Lu [6], Xin Xu [5], Lingxiao Zhu [6], Zihao Zhou [5], Miaomiao Niu [5], Jianxia Gao [5], Jianmin Li [7], Fangqing Zhao [8], Jinyu Wu [9]

- **Sjögren's syndrome (pSS)**
  - linked to gut microbiota dysbiosis
  - **Lower Firmicutes/Bacteroidota** ratio
- **Non-Sjögren's dry eye (non-pSS) individuals showed similar gut microbiota to pSS**
- Healthy controls showed greater gut microbial diversity and lower prevalence of inflammatory/pathobiont species



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> Int J Gen Med. 2023 May 9:16:1735-1746. doi: 10.2147/IJGM.S405225. eCollection 2023.

Anxiety Disorders and Gut Dysbiosis in Primary Sjögren's Syndrome-Mediated Dry Eye Patients

Yiting Zhang [1], Meiqi Gan [1], Yuqin He [1], Tingting Liu [1], Mei Xu [1]

- **Bidirectional Relationship**
  - About 30.4% of patients with pSS-mediated dry eye exhibited anxiety disorders

Microbiome Differences

- **Lower Firmicutes/Bacteroidetes** (F/B) ratio in anxious patients.
- Higher abundance of Bacteroides, Odoribacter, and Bifidobacterium in anxiety group.
- Lower abundance of Prevotella and Actinobacteria in the anxiety group.
- Prevotella positively correlated with dry eye severity (OSDI scores).
- Odoribacter negatively correlated with pSS activity.
- Bacteroidetes positively correlated with pSS activity.

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OTHER RELATED CONDITONS

- Systemic Lupus Erythematosus
- Rheumatoid Arthritis
- B27-related disorders
- Inflammatory Bowel Disease
- Graft-Versus-Host Disease
- Atopic Disease

Moon J, et al. PLoS One. 2020 Feb 14;15(2):e0229029.
Trujillo-Vargas CM, et al. Ocul Surf. 2020 Apr;18(2):335-344.
Cavuoto KM, et al. Ocul Surf. 2019 Jul;17(3):384-392.
Baim AD, et al. Exp Biol Med (Maywood). 2019 Apr;244(6):419-429.
Belkaid Y, et al. Cell. 2014 Mar 27;157(1):121-41.

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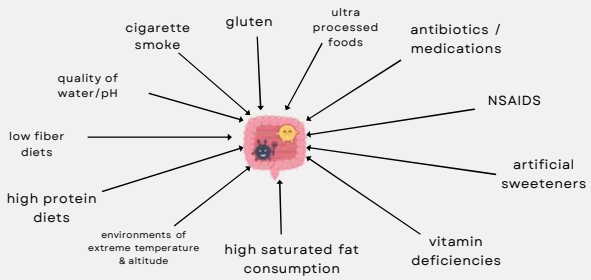
What Causes Gut Dysbiosis



O. Bajinka, et al. Amb Express, 10 (2020), p. 130
C.W. Lees. Nat Rev Gastroenterol Hepatol, 17 (2020), pp. 715-716

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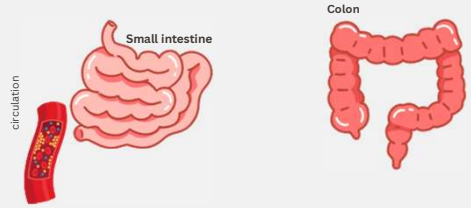
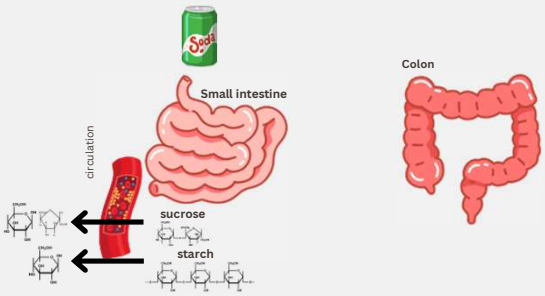
GUT MICROBIOME & FIBER



Sean Spencer, MD, PhD. Feeding Your Microbiome: Dietary Strategies for Wellness and Disease Prevention. University of California Television. 11/22/2024

43

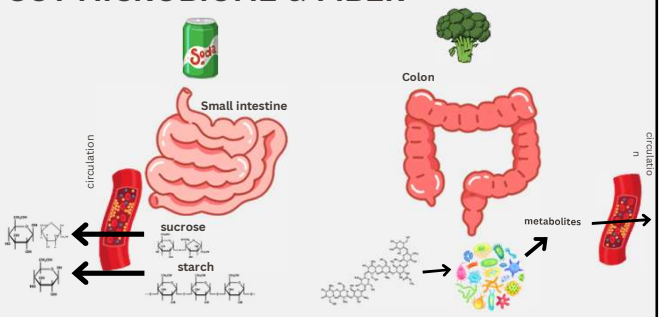
GUT MICROBIOME & FIBER



Sean Spencer, MD, PhD. Feeding Your Microbiome: Dietary Strategies for Wellness and Disease Prevention. University of California Television. 11/22/2024

44

GUT MICROBIOME & FIBER



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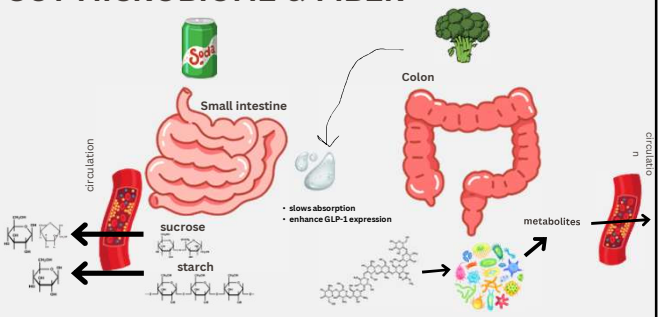
45

GUT MICROBIOME & FIBER



Sean Spencer, MD, PhD. Feeding Your Microbiome: Dietary Strategies for Wellness and Disease Prevention. University of California Television. 11/22/2024

46

Do we get enough fiber?

- USDA and IOM suggest ~26-38 grams of fiber/day
  - ~5% of men and 9% of women meet this recommendation
- Avg fiber consumption in USA ~10-15 grams
  - 2019 meta-analysis found 15-30% decrease in all-cause mortality with sufficient fiber intake (25-29g.day)

Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Energy, Carbohydrates, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids. Washington, DC: National Academies Press; 2005
US Department of Agriculture; Agricultural Research Service. What We Eat in America: Nutrient intakes from food by gender and age. National Health and Nutrition Examination Survey (NHANES) 2009-10.
Quagliani D, et al. Am J Lifestyle Med. 2016 Jul 7;11(1):80-85.
Reynolds A, et al. Lancet. 2019 Feb 2;393(10170):434-445

47

Foods and Diets for Dry Dye

Mediterranean Diet & Eye Health

- High intake of olive oil, legumes, whole grains, fruits, vegetables
- Moderate fish, dairy (yogurt, cheese); low red/processed meats and sugars
  - Rich in monounsaturated fats (oleic acid), antioxidants, and fiber
- Associated with lower all-cause mortality and chronic inflammation
- Linked to lower risk of primary Sjögren syndrome

RCT: Mediterranean diet (with olive oil & nuts) improved OSDI, TBUT, Schirmer, and staining scores

- Greater improvements in those following hypocaloric diet plus exercise
- note: patients were obese with metabolic syndrome

Molina-Leyva I, et al. Nutrients. 2020 May 1;12(5):1289.

48

Foods and Diets for Dry Dye

Randomized Controlled Trial > Nutrients. 2020 May 1;12(5):1289. doi: 10.3390/nu12051289.

Effectiveness of Mediterranean Diet Implementation in Dry Eye Parameters: A Study of PREDIMED-PLUS Trial

Ignacio Molina-Leyva [1], Alejandro Molina-Leyva [2,3], Blanca Riquelme-Gallego [4,3], Naomi Cano-Ibáñez [4,3], Laura García-Molina [4,3], Aurora Bueno-Cavanillas [4,3]

Mediterranean diet (with olive oil & nuts) improved
- OSDI
- TBUT
- Schirmer
- staining scores

- Greater improvements in those following hypocaloric diet **plus** exercise
- note: patients were obese with metabolic syndrome

Molina-Leyva I, et al. Nutrients. 2020 May 1;12(5):1289.

49

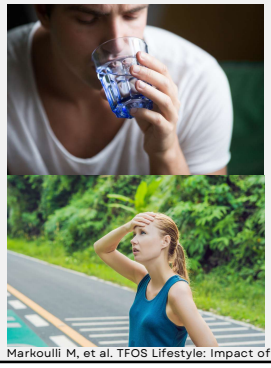
Foods and Diets for Dry Dye

Anti-inflammatory diets recommended by leading dry eye specialists

Toyos Dry Eye Diet. Rolando Toyos,MD
- Whole Food Plant-Based / Vegan Diet

The Whole30. Melissa & Dallas Hartwig
- Restrictive diet with slow introduction

50



Dehydration
- Research on hydration is limited and non-conclusive
  - A few small studies are showing an association

Food and Nutrition Board of the Institute of Medicine
- recommends that adult males consume 3.0L and adult females consume 2.2 L of water per day
  - (includes water from food)

Not just WATER
- Electrolytes!

Markoulli M, et al. TFOS Lifestyle: Impact of nutrition on the ocular surface. Ocul Surf. 2023 Jul;29:226-

51

Pre-Biotics & Pro-Biotics

Pre-Biotics

Chicory Root
Leeks
Onions
garlic
asparagus
Apples
Whole Oats
Omega-3s?
Polyphenols

Pro-biotics

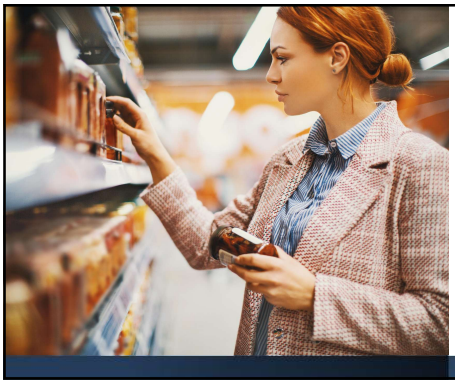
Supplements?

fermented foods
kimchi
sauerkraut
tempeh
dairy and non-dairy yogurt

Sourdough & Kombucha?

Tavakoli A, Flanagan JL. Antibiotics (Basel). 2019 Jun 30;8(3):88.

52



- What about Probiotic Supplements?
- Are they good? Bad?

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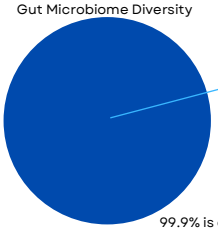
What is in most Probiotic supplements?

Most contain Bifidobacterium and lactobacillus

Gut Microbiome Diversity



~0.01% Bifidobacterium and lactobacillus

99.9% is other human microbiota

Sean Spencer, MD, PhD. Feeding Your Microbiome: Dietary Strategies for Wellness and Disease Prevention. University of California Television. 11/22/2024

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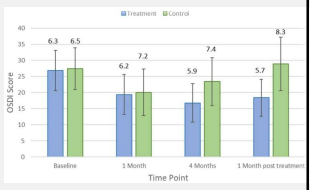
Probiotics & Prebiotics in Dry Eye

Probiotic + Prebiotic Mixture for 4 months N=41

- Probiotic
  - MULTIBIOTIC™ Probiotics
  - (**21.075 billlon** CFU of bacteria per capsule, including Streptococcus, Lactobacillus, and Bifidobacterium species)
- Prebiotic
  - NutriKane D (contains sugarcane fiber and red sorghum flour)

Significant improvement in OSDI scores compared to controls after 4 months (16.8 vs. 23.4; p < 0.001).

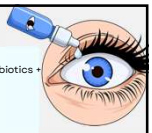
- In contrast, the control group experienced a significant worsening in tear stability (NIKBUT) and TMH, while these remained stable in the treatment group



Tavakoli A,. J Clin Med. 2022 Aug 20;11(16):4889.

55

Probiotics in Dry Eye - Topical VS Oral Probiotics?



Chisari et al. 2017 - two studies - one used Topical Probiotics in Artificial tears, Other used oral probiotics + artificial tears

- Probiotics
  - Saccharomyces boulardii MUCL 53837 and Enterococcus faecium LMG S-28935
- Significant improvement in Schirmers, TBUT and Symptoms (p< 0.001)

Heydari et al. (2023)
Randomized, Placebo-controlled, and Triple-masking Clinical Trial (n=40)

- Probiotics
  - Topical: Bacterial lysate of Lactobacillus sakei, hydroxypropylmethylcellulose (HPMC), boric acid, sodium chloride, purified water.
  - Oral: Live Lactobacillus sakei (5 billion cfus) in hydroxypropylmethylcellulose hard capsule, with maltodextrin excipient
- both methods were safe, topical administration was more effective at reducing inflammation (inhibition of inflammatory factors such as IL-6, TNF-α, and Interferon-gamma) and improving tear stability
  - OSDI, TBUT, Shirmer I test significant improvement (p<0.0001).

Chisari G, Chisari EM, Borzi AM, Chisari CG. Aging eye microbiota in dry eye syndrome in patients treated with Enterococcus faecium and Saccharomyces boulardii. Curr Clin Pharmacol. 2017;12(2):99-105.
Chisari G, Chisari EM, Francaviglia A, Chisari CG. The mixture of Bifidobacterium associated with fructo-oligosaccharides reduces the damage of the ocular surface. Clin Ter. 2017;168(3):e181-e185.
Heydari M, Kalani M, Ghasemi Y, Nejabat M. The Effect of Ophthalmic and Systemic Formulations of Latilactobacillus sakei on Clinical and Immunological Outcomes of Patients With Dry Eye Disease: A Factorial, Randomized, Placebo-controlled, and Triple-masking Clinical Trial. Probiotics Antimicrob Proteins. 2024 Jun;16(3):1026-1035

56

Probiotics for Lids and OSD

Chalazion

Significantly faster resolution of chalazion with probiotic supplement + standard therapy vs standard therapy alone

- Standard therapy: (warm compress, lid hygiene, topical antibiotic + steroid ung) for 20 days
- Probiotic: ≥ 1 × 10^9 live cells of Streptococcus thermophilus ST10 (DSM 25246), ≥ 1 × 10^9 live cells of Lactococcus lactis LCC02 (DSM 29536) and ≥ 1 × 10^9 live cells of Lactobacillus delbrueckii subsp

Filippelli M, dell'Omo R, Amoruso A, Paiano I, Pane M, Napolitano P, Bartollino S, Costagliola C. Intestinal microbiome: a new target for chalaziosis treatment in children? Eur J Pediatr. 2021 Apr;180(4):1293-1298.

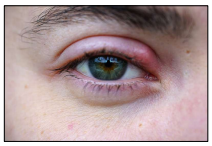
57

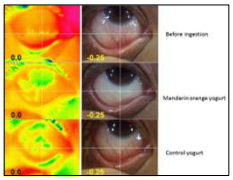
Probiotics for Lids and OSD

Allergic Conjunctivitis

Significantly lower redness, chemosis, itching and eyelid temperature after diet with mandarin orange yogurt for 2 weeks vs controls.

- Second study found **mandarin yogurt** was superior to yogurt without mandarin.
- Bacteria in yogurt studied:
  - Lactobacillus delbrueckii subsp. bulgaricus, Streptococcus themophillius, Lactobacillus acidophilus (LA-5), and Bifidobacterium lactis BB-12.

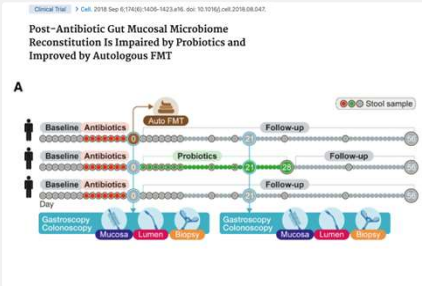




Filippelli M, dell'Omo R, Amoruso A, Paiano I, Pane M, Napolitano P, Bartollino S, Costagliola C. Intestinal microbiome: a new target for chalaziosis treatment in children? Eur J Pediatr. 2021 Apr;180(4):1293-1298.
Hara Y, Shiraishi A, Sakane Y, Takezawa Y, Kamao T, Ohashi Y, Yasunaga S, Sugahara T. Effect of Mandarin Orange Yogurt on Allergic Conjunctivitis Induced by Conjunctival Allergen Challenge. Invest Ophthalmol Vis Sci. 2017 Jun 1;58(7):2922-2929.

58

Pro-Biotics Supplements After Antibiotics?



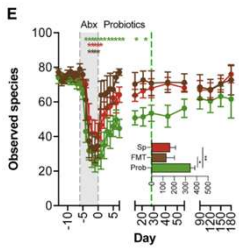
Probiotic used

Lactobacillus acidophilus (LAC), L. casei (LCA), L. casei sbsp. paracasei (LPA), L. plantarum (LPL), L. rhamnosus (LRH), Bifidobacterium longum (BLO), B. bifidum (BBI), B. breve (BBR), B. longum sbsp. infantis (BIN), Lactococcus lactis (LLA), Streptococcus thermophilus (STH)

Suez J, et al. Cell. 2018 Sep 6;174(6):1406-1423.e16.

59

Pro-Biotics Supplements After Antibiotics?



- Compared to spontaneous post-antibiotic recovery,
  - probiotics induced a markedly delayed and persistently incomplete indigenous stool/mucosal microbiome reconstitution and host transcriptome recovery toward homeostatic configuration
- In contrast, autologous fecal microbiome transplantation (aFMT) induced a rapid and near-complete recovery within days of administration

Suez J, et al. Cell. 2018 Sep 6;174(6):1406-1423.e16.

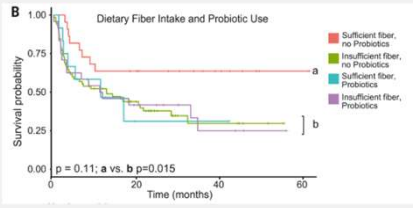
60

Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response

CHRISTINE N. SPENCER, JENNIFER L. MCQUADE, VANCHESWARAN GOPALAKRISHNAN, JOHN A. MCCULLOCH, MARIE VETIZOU, ALEXANDRA P. COGDILL, MD A. RAHAD KHAN, XIAOTAO ZHANG, MICHAEL G. WHITE, [...], AND JENNIFER A. WARGO, +79 authors, Authors Info & Affiliations

SCIENCE · 10 Dec 2021 · Vol 374, Issue 6575 · pp. 1632-1640 · DOI: 10.1126/science.aaz7015

"Higher dietary fiber was associated with significantly improved progression-free survival in 128 patients on ICB, with the most pronounced benefit observed in patients with sufficient dietary fiber intake and no probiotic use"

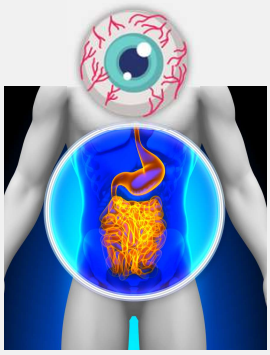


Spencer CN, et al. Science. 2021 Dec 24;374(6575):1632-1640.

61

Take Home Message

- **Changes to the gut microbiome may influence eye disease**
- **Dry eye, particularly autoimmune dry eye may be associated with gut dysbiosis**
- **Encouraging a dietary change to increase fiber and fermented foods may be of benefit (for dry eye and other health outcomes)**



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Take Home Message

Prebiotics / fiber

- Best if whole food
- In general - people need to eat more whole - fibrous foods (and a good variety)

Probiotic

- Purified supplements not recommended at this time
- Probiotic containing foods are good (lower dose) and produce metabolites

Tips

- Increase fiber and fermented foods gradually, don't forget to drink water
- Avoid processed foods and added sugars
- Larger particle size may be better (whole nuts vs nut butter)
  - also whole fruit vs fruit juices/jams
- Beans & Legumes
  - Excellent source of protein, fiber, phytonutrients
    - (improves glycemic control, increase in SCFAs, cardioprotective)

Mullins AP, Nutrients. 2021 Feb 5;13(2):519.

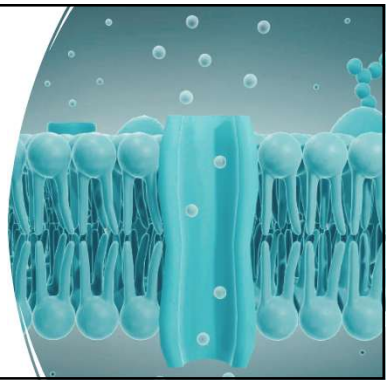
63

Vitamins and Supplements?

64

Roll of Omega 3s in Human Body

- Maintain cell structure (membrane lipid structure)
- Alter blood lipid profiles and Cholesterol metabolism
- Affect eicosanoid biosynthesis
- Cell signaling cascades
- Gene regulation
- Hormonal function
- Energy storage



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Types of Omega-3 Polyunsaturated Fatty Acids (PUFAs)

- ALA - α-linolenic acid
- DHA - Docosahexaenoic acid
- DPA - Docosapentaenoic acid
- EPA - Eicosapentaenoic acid
- SDA – Stearidonic acid

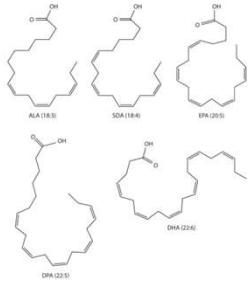


Image from: Shahidi F, Ambigaipalan P. Omega-3 Polyunsaturated Fatty Acids and Their Health Benefits. Annu Rev Food Sci Technol. 2018 Mar 25;9:345-381. doi: 10.1146/annurev-food-111317-095850. PMID: 29350557.

66

Overview of alpha-linolenic acid (ALA)

ALA is an essential fatty acid

- Involved in anti-inflammatory, antioxidant, anticancer, neuroprotection, and gut floral processes.
- Human body cannot synthesize ALA

ALA can be converted to EPA and then DHA (occurs in the liver)

- Limited conversion (<8% of ALA to EPA and <4% of ALA to DHA)
- High intake of omega-6 PUFA linoleic acid (LA) competes with ALA for rate-limiting enzyme Δ6-desaturase
- Omega-6 LA transforms into gamma-linolenic acid (GLA) while blocking ALA into stearidonic acid.

Dietary Sources

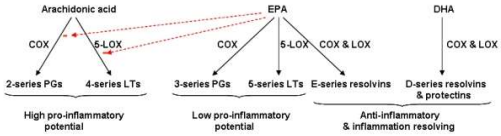
- **Flaxseed Oil, Perilla Oil, Chia Seed Oil, Kiwi Fruit, Purslane,** Walnut, canola, Soybean, Pumpkin Seed Oil, other sources

Burdge GC, et al. Reprod Nutr Dev. 2005 Sep-Oct;45(5):581-97.

67

Overview of Eicosapentaenoic Acid (EPA)

- Human body cannot synthesize EPA
- May have positive effects on coronary heart disease, high triglycerides, high blood pressure, and inflammation.
- Incorporates into all cell membranes changing the viscosity of cell membranes
- EPA competes with Arachidonic acid as a substrate COX/LOX enzymes
- Reduces thromboxane A2 production at platelet level
- Compared to LTB4, LTB_5 is 10- to 100-fold less potent as a neutrophil chemoattractant
- PGD_3 has been found to antagonize PGD_2
  - inhibiting neutrophil migration and reducing inflammation



Calder PC. Nutrients. 2010 Mar;2(3):355-374.
Lazzarin N, et al. Fertil Steril. 2009 Jul;92(1):296-300

68

Overview of Docosahexaenoic Acid (DHA)

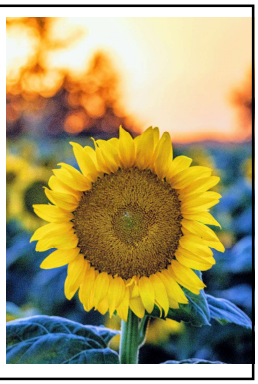
- DHA is a key component of all cell membranes and is found in abundance in the brain and retina.
  - Approximately 40% of total fatty acids in the brain are DHA (mostly gray matter), while <1% are EPA
  - 50-60% of the brain's weight is lipid, 35% of which is omega-3 polyunsaturated fatty acids
  - Accumulates rapidly in the brain during first 18 months of life and earlier stages of pregnancy
    - Important for developmental visual acuity and cognitive growth
- Roles in plasma membrane integrity, cell survival, cell signaling, neuronal morphology, synaptic function, ion channel modulation.
- May have a positive effect on risk for Alzheimer's, retinal disease, cognitive decline, tumor growth, pain, cardiovascular disease, learning disorders, depression and visual processing.

Ohguro H, et al. Int J Mol Sci. 2024 Jul 14;25(14):7717.
Horrocks LA, et al. Pharmacol Res. 1999 Sep;40(3):211-25. doi: 10.1006/phrs.1999.0495.
Petermann A, et al. Int J Mol Sci. 2022 May 12;23(10):5390.

69

Omega-6 Fatty Acids

- Family of many PUFAs, Linoleic acid (LA) is most widely consumed
- LA plays a role in **skin health, cholesterol regulation, and cell function**
  - Found primarily in **seed oils** (soybean, sunflower, corn, canola, cottonseed).
  - US Adult Diet:
    - Mixed-grain dishes (12%)
    - Salad dressing (10%)
    - Mixed meat and seafood dishes (10%)
    - Mixed potato dishes (9%)
    - Nuts (7%)
    - Sweet baked goods (7%)
    - Crackers and salty snacks (7%)
    - Poultry (5%)
    - Yeast breads (5%), and quick breads (3%)



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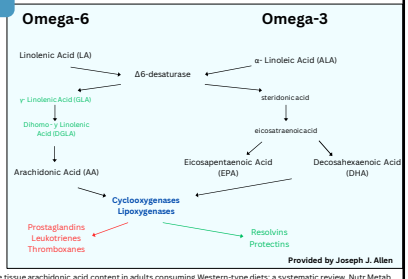
OMEGA-3 FATTY ACIDS (ALA, EPA, DHA)

- **Omega - 3s**
  - α-linolenic acid (ALA)
  - eicosapentaenoic acid (EPA)
  - docosahexaenoic acid (DHA)



Rett BS, Whelan J. Increasing dietary linoleic acid does not increase tissue arachidonic acid content in adults consuming Western-type diets: a systematic review. Nutr Metab (Lond). 2011 Jun 10;8:36.
nnes JK, Calder PC. Omega-6 fatty acids and inflammation. Prostaglandins Leukot Essent Fatty Acids. 2018 May;132:41-48.
Jackson KH, Harris WS, Belury MA, Kris-Etherton PM, Calder PC. Beneficial effects of linoleic acid on cardiometabolic health: an update. Lipids Health Dis. 2024 Sep 12;23(1):296.
Retterstøl K, Rosqvist F. Fat and fatty acids - a scoping review for Nordic Nutrition Recommendations 2023. Food Nutr Res. 2024 Jan 12;68.

71

Clinical Trial > Am J Clin Nutr. 2005 Oct;82(4):887-93. doi: 10.1093/ajcn/82.4.887.

Relation between dietary n−3 and n−6 fatty acids and clinically diagnosed dry eye syndrome in women

Biljana Miljanović [1], Komal A Trivedi, M Reza Dana, Jeffery P Gilbard, Julie E Buring, Debra A Schaumberg

32,470 women health professionals aged 45–84 years
(4.7%) participants reported dry eye diagnosis

- Women in the highest quintile of omega-3 intake had a 17% lower risk of DES compared to the lowest quintile (OR = 0.83; 95% CI: 0.70–0.98; p for trend = 0.04).

Fifth of Dietary Intake (Mean Intake in Group)	n	n with DES	Model 1* OR (95% CI)	Model 2† OR (95% CI)
n-3 Fatty Acids				
Quintile Group 1 (0.92 g)	6473	329	1.0	1.0
Quintile Group 2 (1.17 g)	6396	296	0.89 (0.76-1.05)	0.89 (0.76-1.05)
Quintile Group 3 (1.34 g)	6606	318	0.92 (0.78-1.08)	0.92 (0.78-1.08)
Quintile Group 4 (1.55 g)	6572	314	0.90 (0.76-1.06)	0.90 (0.76-1.05)
Quintile Group 5 (1.99 g)	6423	289	0.83 (0.70-0.98)	0.83 (0.70-0.98)
P for trend			0.03	0.04
n-6 Fatty Acids				
Quintile Group 1 (7.15 g)	6447	329	1.0	1.0
Quintile Group 2 (9.12 g)	6498	304	0.92 (0.78-1.09)	0.93 (0.79-1.09)
Quintile Group 3 (10.50 g)	6512	306	0.95 (0.80-1.12)	0.94 (0.80-1.12)
Quintile Group 4 (12.03 g)	6516	307	0.94 (0.78-1.12)	0.94 (0.79-1.12)
Quintile Group 5 (15.25 g)	6497	300	0.91 (0.75-1.11)	0.92 (0.76-1.12)
P for trend			0.72	0.74

- Fish consumption of tuna reduced DED risk
  - Tuna consumption 5–6 times/week had a 68% lower risk of DES compared to those eating ≤1 serving/week (OR = 0.32; 95% CI: 0.13–0.77).

Pellegrini M, Senni C, Bernabei F, Cicero AFG, Vagge A, Maestri A, Scorcia V, Giannaccare G. The Role of Nutrition and Nutritional Supplements in Ocular Surface Diseases. Nutrients. 2020 Mar 30;12(4):952

72

Omega 3s and Dry Eye

Review > J Clin Med. 2023 Nov 10;12(22):7026. doi: 10.3390/jcm12227026.

Efficacy of Omega-3 Intake in Managing Dry Eye Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Wei-Xiang Wang [1], Mei-Lan Ko [2,3]

- omega-3 FAs effectively reduce DED symptoms
- especially in high doses >2000mg/day
- for a long duration
- with increased **EPA levels**
  - **2:1 or 3:1 ratio**

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Omega 3s and Dry Eye

The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

n-3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease

Author: The Dry Eye Assessment and Management Study Research Group Author Info & Affiliations

Published April 13, 2018 | N Engl J Med 2018;378:1681-1690 | DOI: 10.1056/NEJMoa1709691 | VOL. 378 NO. 18

- 2000mg EPA 1000mg DHA vs 5000mg Olive oil
- "Real world" trial
- 12 months
- No significant difference in symptoms or clinical changes vs Olive Oil

74

43 Patients from omega 3 arm
- 22 patients assigned to continue ω3
- 21 patients assigned to take placebo supplements

Ocul Surf. Author manuscript; available in PMC: 2021 Jan 1.

Published in final edited form as: Ocul Surf. 2019 Aug 16;18(1):47-55. doi: 10.1016/j.jtos.2019.08.002

The Dry Eye Assessment and Management (DREAM) Extension Study - A Randomized Clinical Trial of Withdrawal of Supplementation with Omega-3 Fatty Acid in Patients with Dry Eye Disease

Munira Hussain [1], Roni M Shtein [1], Maxwell Pistilli [2], Maureen G Maguire [2], Marko Oydanich [3], Penny A Asbell [4], DREAM Research Group[‡]

- No significantly worse outcomes for people who stopped omega-3 supplements for an additional 12 months

No significant changes
- corneal, conjunctival staining
- TBUT or Schirmer's score

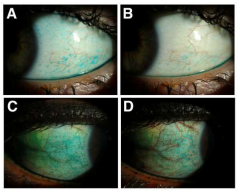
75

Omega 3 & Dry Eye

Cornea. 2024 Feb 22. doi: 10.1097/ICO.0000000000003503. Online ahead of print.

Two-Year Progression of Dry Eye Disease in Dry Eye Assessment and Management Study

Daniel Chein Lee [1], Michelle Guo [2], Yinxi Yu [3], Vatinee Y Bunya [4], Penny Asbell [3], Gui-Shuang Ying [5]



- Probable Placebo Response (3 months)
- Significant Improvement in Conjunctival Staining

Carolyn Begley, et al. Review and analysis of grading scales for ocular surface staining, The Ocular Surface, Volume 17, Issue 2, 2019, Pages 208-220,

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OMEGA-3 AND MEIBOMIAN GLAND DYSFUNCTION (MGD)

- Omega-3s may enhance meibum composition, improving lipid layer function in MGD patients.

A study in isotretinoin users found significantly improved meibum quality with omega-3 supplementation vs punctal plug alone
- 1040 mg/day O3FA for 6 months
- No other significant difference between plugs+O3FA and plugs alone

In patients with mild-to-moderate dry eye and MGD, showed borderline significant improvement in MGD scores and tear breakup time
- omega-3 (600 mg EPA + 1640 mg DHA) for 8 weeks

Elhamaky TR. Eur J Ophthalmol. 2021 Sep;31(5):2339-2345
Jo YJ, Lee JS. Int J Ophthalmol. 2021 Nov 18;14(11):1700-1706..

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OMEGA-3 AND MEIBOMIAN GLAND DYSFUNCTION (MGD)

Review > Ther Adv Ophthalmol. 2020 Oct 16:12:2515841420952188. doi: 10.1177/2515841420952188. eCollection 2020 Jan-Dec.

A systematic review of the effect of omega-3 supplements on meibomian gland dysfunction

Mashael Al-Namaeh [1]

"A moderate daily dose of omega-3 may be a beneficial therapeutic for MGD"

~1000-2000mg (epa +dha) / day

Precision of noninvasive TBUT (NITBUT) compared with invasive NaFl-TBUT
- NITBUT had higher sensitivity and more precision than invasive NaFl-TBUT

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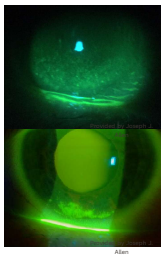
OMEGA-3 AND SCHIRMERS, OSDI, STAINING, OSMOLARITY?

Schirmer Score (Tear Production):
- Modest improvements seen in several RCTs and meta-analyses but not always clinically significant

OSDI Score (Symptoms):
- Inconsistent results–some meta-analyses show benefit
- Large RCT (DREAM trial) showed no significant difference in OSDI vs placebo.

Ocular Surface Staining & Osmolarity:
- Variable findings–some improvement in corneal staining and tear osmolarity reported, but not consistently across all studies.



Allen

Downie LE. Cochrane Database Syst Rev. 2019 Dec 18;12(12):CD011016.
Chi SC, et al. Nutrients. 2019 Apr 26;11(5):942.
Giannaccare G, et al. Cornea. 2019 May;38(5):565-573
Dry Eye Assessment and Management Study Research Group; Asbell PA, Maguire MG, Pistilli M, Ying GS, Szczotka-Flynn LB, Hardten DR, Lin MC, Shtein RM. n-3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease. N Engl J Med. 2018 May 3;378(18):1681-1690.

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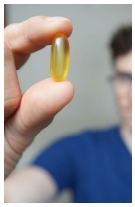
META-ANALYSIS CONCLUSIONS ON OMEGA-3 FOR DRY EYE DISEASE

Cochrane Review (2019):
- Analyzed 34 RCTs (n=4314); Lasting 1-12 months.
- Found low to moderate certainty evidence for omega-3 benefits.
  - Symptoms: Possible reduction, not significant vs placebo.
  - Schirmer score: Small benefit, not clinically meaningful.
- Evidence was judged to be uncertain and inconsistent

J. Clin. Med (2023):
- Analyzed 19 RCTs (n=4246);
  - significant improvements in symptom scores, TBUT, Schirmer test, and tear osmolarity.
  - But not corneal staining
- Greater symptom improvement was correlated with higher daily omega-3 doses, longer treatment durations, and higher EPA content in supplements
  - 3000mg max dose, 12 months duration, higher EPA (80/20 EPA/DHA)
- Omega-3 fatty acids are effective for managing dry eye disease and are recommended in clinical practice, particularly formulations with high EPA and sustained use.



Downie LE, Ng SM, Lindsley KB, Akpek EK. Omega-3 and omega-6 polyunsaturated fatty acids for dry eye disease. Cochrane Database Syst Rev. 2019 Dec 18;12(12)
Wang WX, Ko ML. Efficacy of Omega-3 Intake in Managing Dry Eye Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2023 Nov 10;12(22):7026.

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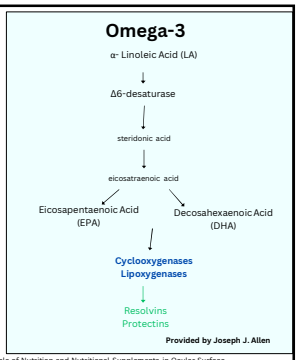
OMEGA-3 FATTY ACIDS (ALA, EPA, DHA)

- 🔬 **Omega - 3s and Dry Eye Mechanisms**
- Resolvins and protectins
  - help limit leukocyte infiltration
  - enhancing macrophage activity
- Resolvins show anti-inflammatory effects on human corneal epithelial cells in vitro.
- Boost tear production, reduce corneal inflammation and preserve corneal intergrity in animal models.
- The cornea produces neuroprotectin D1 (a DHA-derived mediator) via lipooxygenases, which has anti-inflammatory, epitheliotrophic, and neuroprotective properties.



Pellegrini M, Senni C, Bernabei F, Cicero AFG, Vagge A, Maestri A, Scorcia V, Giannaccare G. The Role of Nutrition and Nutritional Supplements in Ocular Surface Diseases. Nutrients. 2020 Mar 30;12(4):952

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OMEGA-6; GAMMA-LINOLENIC ACID(GLA)

- 🔬 **Gamma-Linolenic Acid (GLA) & Inflammation Modulation**
- GLA elevates DGLA, a precursor to anti-inflammatory PGE1
  - shown to increase aqueous tear secretion (lacrimal adrenergic receptors leading to cyclic nucleotide synthesis)
- Negative feedback loop reduces chronic inflammation
- Clinical studies show dietary GLA/LA supplementation provides symptomatic relief in inflammatory conditions (e.g., rheumatoid arthritis)

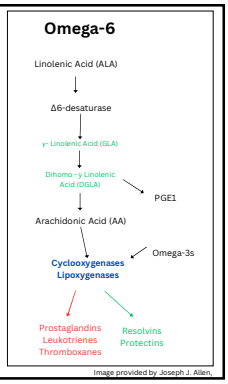

Image provided by Joseph J. Allen,

Belch JJ, Hill A. Evening primrose oil and borage oil in rheumatologic conditions. Am J Clin Nutr. 2000 Jan;71(1 Suppl):352S-6S. doi: 10.1093/ajcn/71.1.352s.

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OMEGA-6; GAMMA-LINOLENIC ACID(GLA)

Randomized Controlled Trial > Cornea. 2013 Oct;32(10):1297-304.
doi: 10.1097/ICO.0b013e318299549c.

Long-term Supplementation With n-6 and n-3 PUFAs Improves Moderate-to-Severe Keratoconjunctivitis Sicca: A Randomized Double-Blind Clinical Trial

John D Sheppard Jr [1], Ruhi Singh, Andrew J McClellan, Mitchell P Weikert, Stephen V Scoper, Thomas J Joly, Walter O Whitley, Ekta Kakkar, Stephen C Pflugfelder

38 Subjects (postmenopausal women) given supplement or placebo for 6 months

Findings at week 24
Significant improvements in
- OSDI (P = 0.05)
- Surface Asymmetry Index (P = 0.005)
- Inhibited conjunctival dendritic cell maturation

Supplement Facts
Serving Size: 4 Softgels
Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Calories	90	
Total Fat	2.5 g	3%
Vitamin A (from retinyl palmitate and cod liver oil)	625 mcg RAE	69%
Vitamin C (as ascorbic acid)	240 mg	267%
Vitamin E (d-alpha tocopherol)	8 mg	53%
Vitamin B6 (from pyridoxal 5-phosphate)	3.4 mg	200%
Magnesium (from magnesium sulfate)	40 mg	10%
Black Currant Seed Oil [15% gamma linolenic acid (GLA); also contains 12-15% alpha linolenic acid (ALA)]	1570 mg	†
Omega-3 Fatty Acids (100 mg EPA, 70 mg DHA from fish oil)	170 mg	†

*Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Other Ingredients: Kosher Bovine Gelatin, Glycerin, Beeswax, Sunflower Lecithin, Water, Lemon Oil, Caramel Color (4-MEI free, from organic sugarcane), and Annatto.

HydroEye® is manufactured under U.S. Patent No. 6,506,412 B2.

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OMEGA-6; GAMMA-LINOLENIC ACID(GLA)

- **Additional Studies**
  - Effect on Meibomian Glands
    - Supplement: (28.5mg linoleic acid and 15mg gamma-linolenic acid) (180 days)
      - Significant reduction in meibomian gland secretion turbidity (P = 0.02)
      - and meibomian gland obstruction (P = 0.0001)
  - Effect on Tear Secretion post refractive surgery (PRK)
    - Supplement: (28.5 mg linoleic acid and 15.1mg gamma-linolenic acid) (30 days)
      - Patients who took an oral supplement after PRK surgery had a slight increase in tear production and tear clearance, while those who did not take the supplement showed a significant decrease.

- Pinna A, et al. Cornea. 2007 Apr;26(3):260-4.
- Macri A, et al. Graefes Arch Clin Exp Ophthalmol. 2003 Jul;241(7):561-566.
- Kokke KH, et al. Cont Lens Anterior Eye. 2008 Jun;31(3):141-6; quiz 170.
- Aragona P, et al. Invest Ophthalmol Vis Sci. 2005 Dec;46(12):4474-9

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OMEGA-6; GAMMA-LINOLENIC ACID(GLA)

- **Additional Studies**
  - Effect on Contact Lens Dryness/Irritation
    - Supplement: (~2000mg linoleic acid and 600mg gamma-linolenic acid/day) (180 days)
      - Significant improvements in "dryness" symptoms and lens comfort
      - Significant improvement in tear meniscus height
  - Effects on Sjögren's Syndrome
    - Supplement: (224 mg linoleic acid and 30mg gamma-linolenic acid) 30 days
      - Significant improvements in PGE1 levels in tears of patients with SS and improves ocular surface signs and symptoms of ocular discomfort.

- Pinna A, et al. Cornea. 2007 Apr;26(3):260-4.
- Macri A, et al. Graefes Arch Clin Exp Ophthalmol. 2003 Jul;241(7):561-566.
- Kokke KH, et al. Cont Lens Anterior Eye. 2008 Jun;31(3):141-6; quiz 170.
- Aragona P, et al. Invest Ophthalmol Vis Sci. 2005 Dec;46(12):4474-9

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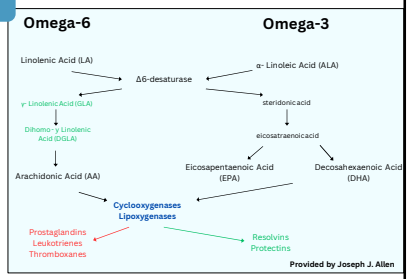
OMEGA-3 FATTY ACIDS (ALA, EPA, DHA)

- **Omega - 3s**
  - α-linolenic acid (ALA)
  - eicosapentaenoic acid (EPA)
  - docosahexaenoic acid (DHA)

Omega-6 (n-6) to omega-3 (n-3) PUFA ratio useful??



Rett BS, Whelan J. Increasing dietary linoleic acid does not increase tissue arachidonic acid content in adults consuming Western-type diets: a systematic review. Nutr Metab (Lond). 2011 Jun 10;8:36.
nnes JK, Calder PC. Omega-6 fatty acids and inflammation. Prostaglandins Leukot Essent Fatty Acids. 2018 May;132:41-48.
Jackson KH, Harris WS, Belury MA, Kris-Etherton PM, Calder PC. Beneficial effects of linoleic acid on cardiometabolic health: an update. Lipids Health Dis. 2024 Sep 12;23(1):296.
Retterstøl K, Rosqvist F. Fat and fatty acids - a scoping review for Nordic Nutrition Recommendations 2023. Food Nutr Res. 2024 Jan 12;68.

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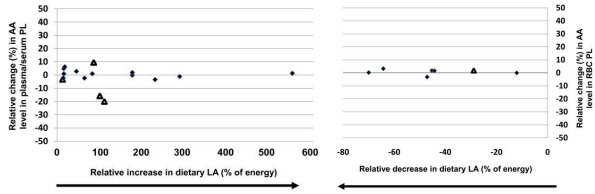

Rett BS, Whelan J. Nutr Metab (Lond). 2011 Jun 10;8:36.

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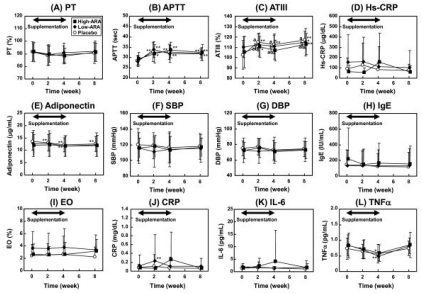
ARA Supplementation Raises Plasma AA but Does NOT Affect CHD, Allergy or Inflammation Markers



Kakutani S, et al. Lipids Health Disease. 2011 Dec 22;10:241.

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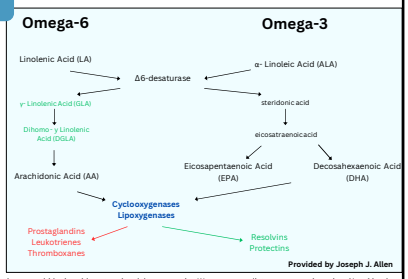
OMEGA-3 FATTY ACIDS (ALA, EPA, DHA)

- **Omega - 3s**
  - α-linolenic acid (ALA)
  - eicosapentaenoic acid (EPA)
  - docosahexaenoic acid (DHA)

Omega-6 (n-6) to omega-3 (n-3) PUFA ratio useful??



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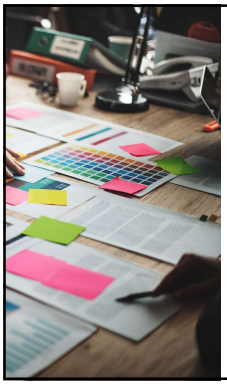

Effect of Dietary Linoleic Acid on Markers of Inflammation in Healthy Persons: A Systematic Review of Randomized Controlled Trials

Guy H. Johnson, PhD · Kevin Fritsche, PhD

After reviewing 15 RCTs, "We conclude that virtually no evidence is available from randomized, controlled intervention studies among healthy, noninfant human beings to show that addition of LA to the diet increases the concentration of inflammatory markers."

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Association between Fatty Acids and Markers of lipid oxidation and inflammation.

Finnish Populaton
N= 2196
Mean age 32

Table III. Linear regression models between fatty acid variables and the markers of *in vivo* LDL oxidation or inflammation.

		oxLDLprot*		oxLDLlipids: LDL dienes/ApoB*		Serum C-reactive protein*	
Serum FA%s	Step	*B*	*P*	*B*	*P*	*B*	*P*
PUFA	1	−5.4	<0.001	−9.4	<0.001	−33.3	<0.001
	2	−5.8	<0.001	−9.9	<0.001	−14.8	<0.001
n3	1	6.1	0.007	−6.9	<0.001	−35.7	<0.001
	2	0.5	0.79	−4.5	0.014	−23.8	0.004
n6	1	−6.4	<0.001	−9.6	<0.001	−33.2	<0.001
	2	−6.1	<0.001	−10.1	<0.001	−13.4	<0.001

Adjustments: model 1, age; model 2, age, PA, oral CA, vitamin E intake, smoking BMI, alcohol, glucose insulin, SBP, LDL-C. B coefficients x 10^3

Kaikkonen JE, et al. Free Radic Res. 2014 Apr;48(4):420-6.
Bill Harris, Rethinking Omega 6. OmegaQuant Nutrition Talks 2025

92

Omega 6 VS Omega 3 – the Great Debate

Jackson, K.H., Harris, W.S., Belury, M.A. *et al.* Beneficial effects of linoleic acid on cardiometabolic health: an update. *Lipids Health Dis* **23**, 296 (2024). https://doi.org/10.1186/s12944-024-02246-2
Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, Willett WC, Hu FB. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. Circulation. 2014;130:1568–78
Marklund M, Wu JHY, Imamura F, Del Gobbo LC, Fretts A, de Goede J, Shi P, Tintle N, Wennberg M, Aslibekyan S, et al. Biomarkers of Dietary Omega-6 fatty acids and Incident Cardiovascular Disease and Mortality. Circulation. 2019;139:2422–36.

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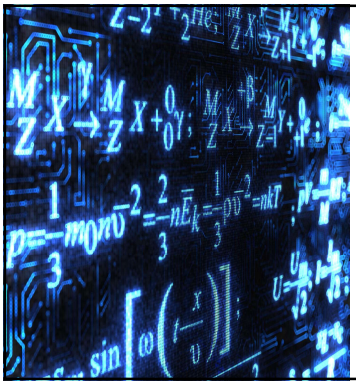

Is the Omega 6:Omega 3 Ratio Still Relevant?

- Relevancy of omega6:omega3 ratio is debated
- The "ratio" lacks official recommendations because it oversimplifies the complex functions of these fatty acids.
  - Assumes all n-6 PUFAs are harmful, all n-3 PUFAs are beneficial, or that they act in direct opposition.
  - Not all PUFAs within each category are the same, meaning the ratio does not accurately reflect their individual effects on health.
  - Studies show that similar ratios can have very different effects on tissue fatty acid levels, proving that absolute intake of specific fatty acids matters more than the ratio.

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What about other vitamins and supplements?

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Others Supplements?

Lutein	Omega-7
Curcumin	Omega-9
Astaxanthin	L-Carnitine
Vitamin A	Lactoferrin
Vitamin C	Coenzyme Q10
Vitamin D	Spermidine
Vitamin E	Royal Jelly
Selenium	Polyphenols

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Lutein & Zeaxanthin for Dry Eye?

A 6-month lutein and zeaxanthin supplementation
10mg lutein & 2mg zeaxanthin isomers
- improved Schirmer Test
- Tear Break-Up Time

- Lutein and zeaxanthin, may exert benefits through antioxidant and anti-inflammatory mechanisms.
- Lutein has been shown to inhibit pro-inflammatory cytokines and NF-κB signaling
  - reduce oxidative stress and nitric oxide synthase expression

Lopresti AL, Smith SJ. The effects of lutein/ zeaxanthin (Lute-gen®) on eye health, eye strain, sleep quality, and attention in high electronic screen users: a randomized, double-blind, placebo-controlled study. Front Nutr. 2025 Feb 3;12:1522302.

97

Ophthalmol Ther. 2021 Sep;10(3):581-599. doi: 10.1007/s40123-021-00357-y. Epub 2021 Jun 15.

A Novel Multi-Ingredient Supplement Reduces Inflammation of the Eye and Improves Production and Quality of Tears in Humans

Pranav Radkar [1], Prabhu Shankar Lakshmanan [2], Jenet Jemila Mary [2], Sunil Chaudhary [1], Sathish Kumar Durairaj [3]

Supplement
- lutein 20 mg
- zeaxanthin 4 mg
- curcumin** 200mg
- vitamin D3 600 IU

60 Subjects with moderate dry eye - given supplement or placebo (soybean oil) for 8 weeks

Findings at day 56

Significant improvements in
- Schirmer's test (P = < 0.0001)
- OSDI (P = < 0.0001)
- TBUT (P = < 0.0001)
- SPEED (P = < 0.0001)
- ocular staining scores (cornea & conj) (P = < 0.0001)
- tear osmolarity (P = 0.0005)
- MMP-9 (P = 0.0017)
- reduced artificial tear use (P = 0.0004)
- reduced tear frequency of use (P < 0.0001)

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- vitamin D3 600 IU

Front Ophthalmol (Lausanne). 2024 Apr 24;4:1362113. doi: 10.3389/fopht.2024.1362113. eCollection 2024.

A novel multi-ingredient supplement significantly improves ocular symptom severity and tear production in patients with dry eye disease: results from a randomized, placebo-controlled clinical trial

Neda Gioia [1], Jeffry Gerson [2], Robert Ryan [3], Krista Barbour [3], Julie Poteet [4], Brooke Jennings [3], Matthew Sharp [5], Ryan Lowery [5], Jacob Wilson [5], Abhijeet Morde [6], Deshanie Rai [6], Muralidhara Padigaru [6], Laura M Periman [7]

155 Subjects with dry eye - given supplement or placebo (soybean oil) for 8 weeks

Findings at day 56

Significant improvements in
- Schirmer's test (P = < 0.001)
- OSDI (P<0.001)
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- tear osmolarity(P = < 0.001)
- MMP-9 (P = < 0.001)

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Curcumin

- anti-inflammatory
- anti-oxidant
- anti-diabetic
- anti-atherosclerotic

May help with
- polycystic ovarian syndrome
- metabolic syndrome
- fatty liver
- cardiovascular disease
- digestion

Qiu Let al. Effects of dietary polyphenol curcumin supplementation on metabolic, inflammatory, and oxidative stress indices in patients with metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne). 2023 Jul 14;14:1216708.

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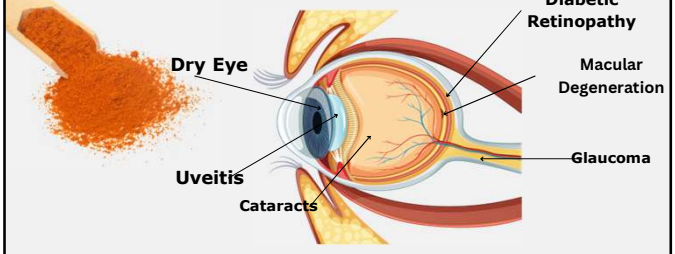
Curcumin



Franzone F, et al. Exp Ther Med. 2021 Jul;22(1):790
Radomska-Leśniewska DM, et al. Cent Eur J Immunol. 2019;44(2):181-189.

101

Curcumin

Dosage?

Curcumin 500–1500 mg/day

Black Pepper/Piperine 5-15 mg/day

Armin Ebrahimzadeh, et al, Complementary Therapies in Medicine, Volume 61, 2021, 102773,
Tagde P, et al. Molecules. 2021 Nov 24;26(23):7109

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- SPEED (P = < 0.001)
- ocular staining scores (cornea & conj) (P = < 0.001)
- tear osmolarity(P = < 0.001)
- MMP-9 (P = < 0.001)

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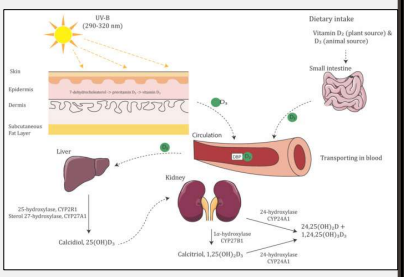
"steroid hormone"

- diverse functions
  - calcium homeostasis
  - regulating gene expression
  - immune system
  - inflammation
  - cell proliferation and differentiation
  - apoptosis
  - angiogenesis
- Low vitamin D levels associated with
  - cardiovascular diseases
  - hypertension
  - diabetes mellitus
  - cancers



Chan HN, Zhang XJ, Ling XT, Bui CH, Wang YM, Ip P, Chu WK, Chen LJ, Tham CC, Yam JC, Pang CP. Vitamin D and Ocular Diseases: A Systematic Review. Int J Mol Sci. 2022 Apr 11;23(8):4226.

104

~15 minutes of sunlight exposure with 25% of skin exposure =1000IU (face, hands, arms)

Diverse therapeutic dosage of vitamin D recommended by scientific societies and international agencies.

25(OH)D ng/mL	NAM/NIH	ES	NOS	SACN-PHE	AGS [4]
		Initial Dose [3]— Maintenance [2]	Initial Dose [3]— Maintenance [2]		
<10	600 IU [5]	400,000 IU 1500–2000 IU [6,7]	300,000 IU 800–2000 IU	–	4000 IU [11]
10–20	600 IU [5]	400,000 IU 1500–2000 IU [6,7]	400 IU	400 IU [10]	4000 IU [11]
20–30	600 IU [5]	1500–2000 IU [6,8,9]	400 IU	400 IU [10]	4000 IU [11]
30–50	600 IU [5]	1500–2000 IU [8,9]	400 IU	400 IU [10]	4000 IU [11]
50–100	–	1500–2000 IU [8,9]	–	–	–
>100	–	–	–	–	–

Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. Metabolites. 2021 Apr 20;11(4):255.
Young AR, et al.. Optimal sunscreen use, during a sun holiday with a very high ultraviolet index, allows vitamin D synthesis without sunburn. Br J Dermatol. 2019 Nov;181(5):1052-1062.
van Ballegooijen AJ, et al. The Synergistic Interplay between Vitamins D and K for Bone and Cardiovascular Health: A Narrative Review. Int J Endocrinol. 2017;2017:7454376.

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often recommended to help calcium get into bones (not blood vessels)

Diverse therapeutic dosage of vitamin D recommended by scientific societies and international agencies.

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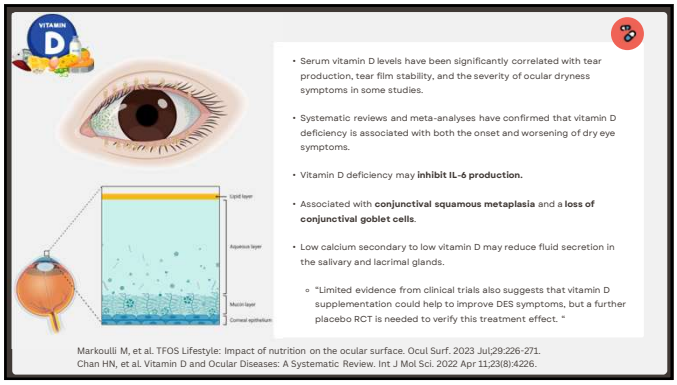
108



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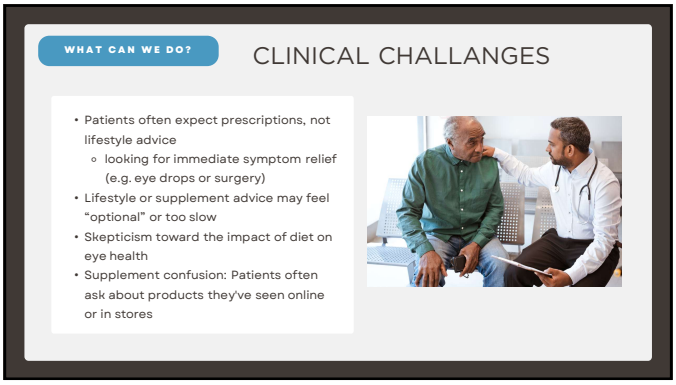

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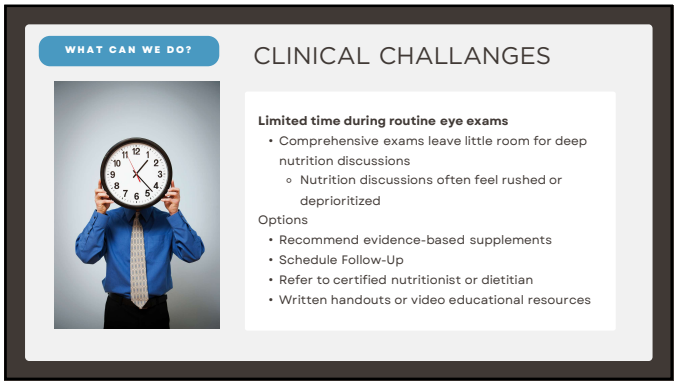

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