Nutrition and the Eye

Lori Vollmer, O.D., M.S., F.A.A.O.
Associate Professor of Optometry
Masters' of Science Nutrition
Nova Southeastern University
Fort Lauderdale, FL USA

Disclosure

No financial interest in any of the products or research presented.

Is it my job?

- Overall health of the patient is a **team approach**
- Repetitive message
- **Preventative health care**
- **Prevention of vision loss**

Nutrition in the Optometric Practice

- Patient and case dependent
- Food Frequency Questionnaires
- 24 Hour Recall
- Food Diaries

Twenty-four hour diet recall interview is a quantitative research method used in nutritional assessment, and asks individuals to recall foods and beverage they consumed in the twenty-four hours prior to the interview.

Specifically:

- What food/drink was consumed?
- How much was consumed?
- Time it was consumed?
- How was it prepared?
- How was it served?
- Specifics of food (low fat, 1%, whole)

Food Diaries

- Get an idea of typical eating patterns
- How do they eat compared to RDA?
- Where can **small changes** be made that may have the biggest impact?
  - My Fitness Pal
  - My Plate (Livestrong)
  - My Daily Plate

Dietary Reference Intake (DRI)

- System of nutrition recommendations used in US and Canada made by the Food and Nutrition Board of Institute of Medicine of the National Academies.
- **Recommended Dietary Allowance (RDA):** average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals.
- **Adequate Intake (AI):** established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.

DRI's

- **Estimated Average Requirement (EAR):** average daily level of intake estimated to meet the requirements of 50% of healthy individuals. It is usually used to assess the adequacy of nutrient intakes in population groups but not individuals.
- **Tolerable Upper Intake Level (UL):** maximum daily intake unlikely to cause adverse health effects.

Macronutrients

- Required in relatively large amounts and provide calories
- Proteins
- Carbohydrates
- Lipids

Proteins

- Dietary proteins broken down into peptides and amino acids.
- Required for tissue maintenance, replacement, function, and growth.
- If the body is not getting enough calories from dietary sources or tissue stores (fat) protein may be used for energy.
- As the body uses dietary protein for tissue production (anabolic), there is a net gain of protein (positive nitrogen balance).
- During catabolic states (starvation, infections, burns), more protein may be used than absorbed, resulting in a net loss of protein (negative nitrogen balance).

Proteins…

- Enzymes: speed up chemical reactions (digest carbs or synthesis of cholesterol)
- Hormones: carry messages (insulin and glucagon which regulate blood sugar)
- Structural: collagen, bone, teeth, skin, keratin (hair and nails)
- Antibodies: immune system
- Fluid balancers: attract water and aid in maintaining fluid balance
- Transporters: hemoglobin transport of oxygen
- Acid-base balancers: buffers – negative charges pick up positive hydrogen ions when conditions are acidic, hydrogen ions released when conditions too alkaline
- Back up energy: starvation or low carb intake take protein from muscles to make new glucose (gluconeogenesis)

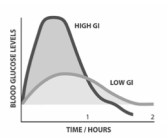
Proteins

- 1 gram of protein = 4 Calories
- Sources are legumes (beans), lentils, soy products, nuts, whole grains (quinoa, oats, brown rice), seeds, meat alternative product, some vegetable, animal sources.
- RDA for protein is 0.8 grams of protein per kg/BW

Carbohydrates

- Dietary carbohydrates are broken down into glucose/monosaccharides.
- Increase blood glucose levels and supply energy (increase insulin)
  - **Simple carbohydrates**: small molecules (monosaccharides or disaccharides) increase blood glucose levels rapidly.
  - **Complex carbohydrates**: larger molecules that are broken down into monosaccharides increase blood glucose levels more slowly.
- Glucose and sucrose are simple carbohydrates; starches and fiber are complex carbohydrates.

Carbohydrates and GI



- **Glycemic Index:** measures how rapidly consumption of a carbohydrate increases plasma glucose levels.
- Values range from 1 (slowest increase) to 100 (fastest increase, equivalent to pure glucose.
  - Incremental area under blood glucose curve after ingestion of 50 g carbohydrates compared to glucose (or white bread).

Glycemic Load

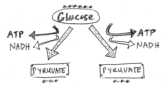
Considers both GI AND amount of carbohydrate consumed.

- GL = GI (decimal) x carbohydrate (grams)
- Useful for diabetics to determine how quickly sugar will rise
  - High GL≥20
  - Intermediate GL 11-19
  - Low GL≤10.

GI of watermelon is 76 and GI of a doughnut 76 BUT
One serving of watermelon 11 g of carbohydrate
One doughnut 23 g of available carbohydrate.

Food	GI	Serving Size	Net Carbs	GL
Peanuts	14	4 oz (113g)	15	2
Bean sprouts	25	1 cup (104g)	4	1
Grapefruit	25	1/2 large (166g)	11	3
Pizza	30	2 slices (260g)	42	13
Lowfat yogurt	33	1 cup (245g)	47	16
Apples	38	1 medium (138g)	16	6
Spaghetti	42	1 cup (140g)	38	16
Carrots	47	1 large (72g)	5	2
Oranges	48	1 medium (131g)	12	6
Bananas	52	1 large (136g)	27	14
Potato chips	54	4 oz (114g)	55	30
Snickers Bar	55	1 bar (113g)	64	35
Brown rice	55	1 cup (195g)	42	23
Honey	55	1 tbsp (21g)	17	9
Oatmeal	58	1 cup (234g)	21	12
Ice cream	61	1 cup (72g)	16	10
Macaroni and cheese	64	1 serving (166g)	47	30
Raisins	64	1 small box (43g)	32	20
White rice	64	1 cup (186g)	52	33
Sugar (sucrose)	68	1 tbsp (12g)	12	8
White bread	70	1 slice (30g)	14	10
Watermelon	72	1 cup (154g)	11	8
Popcorn	72	2 cups (16g)	10	7
Baked potato	85	1 medium (173g)	33	28
Glucose	100	(50g)	50	50

Carbohydrates are Fuel



- Glucose is the primary fuel for most cells and the **preferred energy** for the brain, nervous system and red blood cells.
- Glucose enters the cell, converted to carbon dioxide, water and ATP, the energy currency of the cell via **glycolysis**.
- More available glucose than your body needs for energy, **store glucose as glycogen via glycogenesis** in your liver and skeletal muscle.
- When glycogen stores are full, **extra glucose is stored as fat** and used as energy when needed.
- When blood glucose drops, **liver will break down glycogen via glycogenolysis** and release glucose into your blood.

Carbohydrates

- Carbohydrates spare protein
- Without eating or consume too little carbs - glycogen stores will quickly deplete.
- Body will acquire protein from diet (if available) OR skeletal muscles and organs and convert amino acids into glucose via **gluconeogenesis** for energy and maintain normal blood glucose levels.

Carbohydrates

- Carbohydrates prevent ketosis
- Even when fat is used for fuel, cells need some carbohydrate to completely break it down.
- The liver produces ketone bodies, which can eventually build up to unsafe levels in the blood causing a condition called ketosis.
- Ketoacidosis life threatening condition from dangerously high levels of ketones and blood sugar where the blood to become too acidic causing liver and kidney disfunction and the body to dehydrated.

Carbohydrates

- ROLE
  - Fuel during high intensity exercise
  - Spares protein and preserves muscle mass during exercise
  - Fuel for the CNS - brain
- RECOMMENDED ALLOWANCE
  - Sedentary: 40-50% of your total daily calories should be carbohydrates
  - Exercises: 60% of your total daily calories should be carbohydrates
  - Athletes: 70% of your total daily calories should be carbohydrates (3.5-4.5 grams per pound)

Lipids

- Key lipids in diet
  - Triglycerides (majority in human diet 95%)
  - Phospholipids
  - Cholesterol
- Fats broken down into glycerol (triacylglycerol) and fatty acids.
- Digestion: Fatty acids, monoglycerides, lysophospholipids and cholesterol - form droplets with micelles and bile acids for absorption.
- Absorbed tryglycerides, phopholipids and cholesterol esters reformed and transported to ER to be packaged with protein (apoprotein) as lipoproteins (in the chylomicrons)….

Lipoproteins

- Chylomicrons
  - Transport dietary triglycerides and cholesterol from intestines to liver and other tissues
- Very low density lipoproteins (VLDL)
  - Transport cholesterol and triglycerides synthesized by liver to the cells of body
- Low density lipoproteins (LDL)
  - Particles small enough to enter lining of arteries and form atherosclerotic plaques when oxidized
- High density lipoproteins (HDL)
  - Remove excess cholesterol from cells and transport it to liver for disposal as bile.

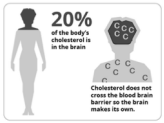
Lipids

- ROLE IN THE BODY
  - Energy reserve (can store a lot vs. glycogen)
  - Essential fatty acids (protects vital organs, insulation, cell membranes)
  - Transport fat soluble vitamins and carotenoids
  - Required for tissue growth and hormone production
  - Flavor to food
  - Satiating *
- RECOMMENDED ALLOWANCE
  - 20-35% of your total daily calories - less than 10% of total daily calories from saturated fat

Lipids

- 1 gram of fat = 9 Calories
- FOOD SOURCES: Oils, nuts, seeds, meat, fish, dairy

Cholesterol



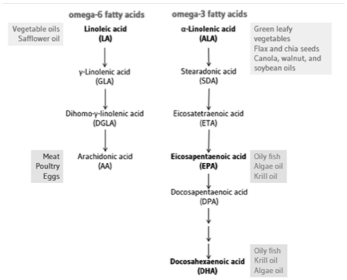
- Found only in animal products (meat, egg yolks, dairy)
- Body CAN produce cholesterol (NOT essential)
- Biological functions: bile, sex hormones, adrenal hormones, vitamin D
- Intake should be limited to <300 mg/day to prevent CVD
  - < 200 if already have CVD
  - No RDI for cholesterol *

EFA

- Essential fatty acids (EFAs)
  - Linoleic acid - omega-6 (n-6)
  - Linolenic acid - omega-3 (n-3)
- Long-chain omega 3 FA's, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can be synthesized from ALA (omega-6)
  - Low conversion efficiency, recommended to obtain EPA and DHA from additional sources.
- EFAs needed for formation of eicosanoids (biologically active lipids), including prostaglandins, thromboxanes, prostacyclins, leukotrienes.

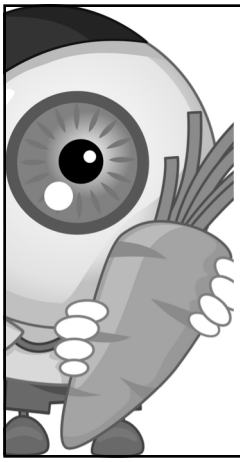
Omega Fatty Acids: Functions

- Cell membrane structure
- Brain development in infants
- Precursors for several important regulatory molecules
- Inflammation regulation
- Platelet aggregation
- Vasoconstriction and vasodilation
- Endocannabinoids (neuro-modulatory lipids)



Omega 3's

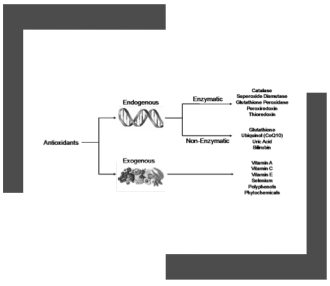
- EPA and DHA are what the human body requires for neurological health.
- ALA (plant based) has to be **converted to EPA and some DHA** to be of much use by the nervous system.
- Plant-based ALA is a less than ideal substitute for marine-sourced EPA and DHA, though all three are required.



Micronutrients

- Vitamins: A, B, C, D and E
- Minerals: iron, zinc, selenium, coQ10, copper
- Carotenoids: beta carotene, lutein, zeaxanthin

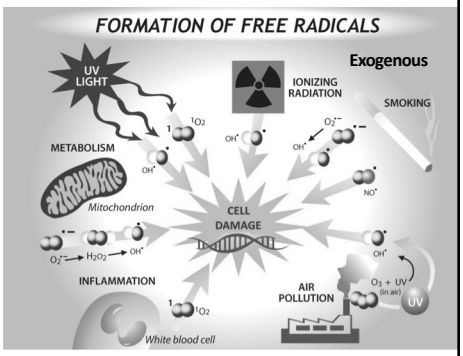
Antioxidants



- Vitamin C
- Vitamin E
- Selenium
- Vitamin A
- Coenzyme Q10
- Carotenoids
- Zinc

Free radicals normally formed every time oxygen is used to make energy

More are formed from UV, smoking, pollution, inflammation, exercise



Gives one of its electrons to the FR to reduce it from its excited state

We're cool like that!

Dry Eye

DEWS II

Definition and Classification Subcommittee

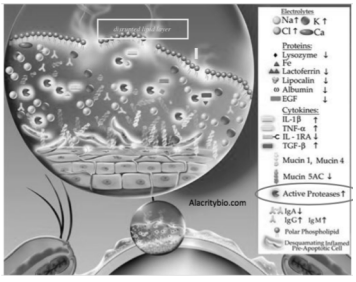
"Dry eye is a **multifactorial disease** of the ocular surface characterized by a **loss of homeostasis** of the tear film, and accompanied by ocular symptoms, in which tear film instability and **hyperosmolarity, ocular surface inflammation** and damage, and **neurosensory abnormalities** play etiological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

Types of Dry Eye

- **Sjogren's syndrome**: autoimmune process, lacrimal gland infiltration by activated T-cells, acinar and ductal damage = HYPOSECRETION
- **Non-Sjogren's syndrome:** not autoimmune related, most common
- Intrinsic: MGD, disorders of the lid, low blink rate
- Extrinsic:
  - Vitamin A deficiency
    - Deficient goblet cells and glycocalyx mucins
    - Lacrimal acinar damage
  - Topical meds, CL wear, allergies

Aqueous Deficiency

- Reduced aqueous volume
- Tear film hyperosmolarity
- Damaged ocular surface epithelial cells
- Cascade of inflammatory events
- MAP kinases, NFkB signaling, cytokines (IL's, TNF, MMP's)



Dry Eye and MMP 9

Matrix metalloproteinases are proteolytic enzymes produced by stressed epithelial cells on ocular surface

MMP-9 in Tears

- Non-specific inflammatory marker
- Normal range between 3-41 ng/ml
- More sensitive diagnostic marker than clinical signs
- Correlates with clinical findings

Ocular surface disease elevated levels of MMP-9 in tears

Fatty Acids and Inflammation

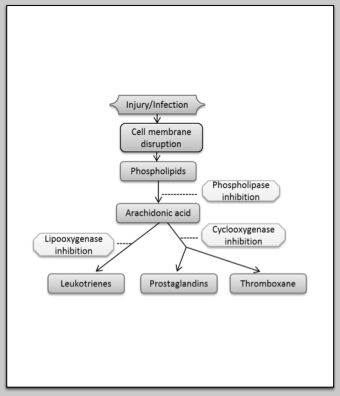
- Two major classes of polyunsaturated fatty acids (PUFAs) are the omega-3 (DHA and EPA) and omega-6 (ALA)
- DHA and EPA found in fish
- ALA found in plants/seeds
- EPA and DHA can be synthesized from ALA but has a low conversion efficiency.
- Essential: body cannot make them*

Omega 6

ALA (alpha-linoleic acid) converted to GLA (gamma-linolenic acid) for synthesis to AA (arachidonic acid)

Arachidonic acid (AA)

- Polyunsaturated fatty acid present in phospholipids
- Precursor to biologically important eicosanoids



Pinazo-Duran 2013 and Omega 3's

- Analyze formulation of antioxidants and long-chain EPUFA's.
- Prospective and randomized
- Non-severe DED (DED group [DEDG])
- Healthy controls (control group [CG]).
- Daily intake (+S) or not (-NS) of antioxidants and long-chain EPUFAs for 3 mos.
- Interview and ophthalmic examination, reflex tears and tear sample analysis.

Table 2

Composition of Brudysec 1.5[4]

Nutrient	Amount
DHA	350 mg
EPA	42.5 mg
Vitamin A	133.3 μg
Vitamin C	26.7 mg
Vitamin E	4 mg
Tyrosine	10.8 mg
Cysteine	5.83 mg
Glutathione	2 mg
Zinc	1.6 mg
Copper	0.16 mg
Manganese	0.33 mg
Selenium	9.17 μg
DPA	30 mg

Abbreviations: DHA, docosahexa

Pinazo-Duran 2013

- Significantly higher expressions of interleukin (IL)-1β, IL6, and IL10 in dry eye group.
- Difference in VEGF levels in the DEDG as compared to the CG.
- DEDG significant negative correlations between Schirmer and IL-1β, IL6, IL8 and vascular endothelial growth factor as well as between the fluorescein breakup time with IL6 and IL8 levels.
- Levels of IL-1β, IL6, and IL10 significantly lower in the DEDG+S versus the DEDG-NS and in the CG+S versus the CG-NS.
- Subjective symptoms significantly improved in the DEDG+S versus the DEDG-NS.

Olenik 2014 (Large Dry Eye Clinical Study Group)

Effectiveness and tolerability of omega-3 EFA's and antioxidants on dry eye symptoms.

905 patients - prospective, intervention study

Three capsules/day

Symptoms categorized as 0, none; 1, mild; 2, moderate; and 3, severe

Included scratchy and stinging sensation in the eyes, eye redness, grittiness, painful eyes, tired eyes, grating sensation, and blurry vision.

osition of Brudysec® 1.5 g

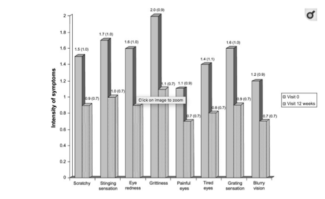
osition	Per capsule	% recommended daily amount	Per three capsules	% recom
ntrated oil in ω-3 fatty acids	500 mg		1500 mg	
:DHA 70%	350 mg	–	1050 mg	–
s 8.5%	42.5 mg	–	127.5 mg	–
s 6%	30 mg	–	90 mg	–
ins				
amin A (retinol)	133.33 μg RE	16.66	400 μg RE	50
amin C (ascorbic acid)	26.7 mg	33	80 mg	100
amin E (d-α-tocopherol)	4 mg TE	33	12 mg α-TE	100
ial trace elements				
e	1.6 mg	16.6	5 mg	50
per	0.16 mg	16.6	0.5 mg	50
ganese	0.33 mg	16.6	1 mg	50
nium	9.17 μg	16.6	27.5 μg	50
components				
ysine	10.8 mg	–	32.5 mg	
steine	5.83 mg	–	17.5 mg	
tathione	2 mg	–	6 mg	

Statistically significant improvement in symptoms after 3 months. (p<0.001)

68% reported better CL tolerance.

Number of instillation of AT during day decreased. (p<0.001)

30% reported fish-taste, nausea or digestive issues



Changes in individual symptoms of dry eye before and after 12 weeks of treatment with Brudysec® 1.5 g.

Note: Data expressed as mean and standard deviation ($P<0.001$ for all comparisons). Brudysec®; Brudy Laboratories, Barcelona, Spain.

Gatell-Tortajada 2016

- 1,419 patients DES and using AT
- 12 weeks
- 3 capsules/day Brudysec 1.5 g
- Results:
- Subjective: Symptoms improved ($p<0.001$), AT use decreased ($p<0.01$)
- Objective: **Schirmer's** and TBUT increased

Dry Eye Assessment and Management Study Research Group (DREAM)

- Multicenter, double blind
- Moderate to severe dry eyes
- 3,000 mg fish derived n-3 OR olive oil (placebo)
- Primary outcome based on Ocular Surface Disease Index Scores (0-100)
- Secondary outcome conjunctival staining score (0-6) and corneal staining score (0-15), TBUT (sec), Schirmer's

N Engl J Med 378;18 May 2018

DREAM

349 patients to supplement group

Not required to stop any current treatment

Meant to mimic "real world"

186 placebo

12 months

Results: No significant improvement to those in supplement group compared to control.

Recommendations

- Get adequate water intake
  - Half your body weight (pounds) in ounces of water
- Avoid fans/open windows
- Get adequate rest
- Blink often when reading/using computers & electronics
- Stop smoking
- Ensure adequate nutritional status for other nutrients

Recommendations

- **Balance O-6 and O-3 intake**
  - Determine current levels (Omega 3 Index)
  - FFQ
- **Food first approach with dietary modifications**
  - **Fatty fish twice a week (averages 250 mg/day)**
  - Add ALA sources in seeds and nuts for additional support in more than one way!
  - Eat less omega 6 in processed food
- **Nutritional supplements containing omega-3**
  - 1,000-3,000 mg/day of EPA+DHA combined

Why Oily Fish

- Oily fish: Sardines, herring, anchovies, salmon, trout, tuna, mackerel
  - **Oil in tissues AND belly cavity**
- White fish: grouper, flounder, haddock, pollock
  - **Oil only in liver**

Vitamin A

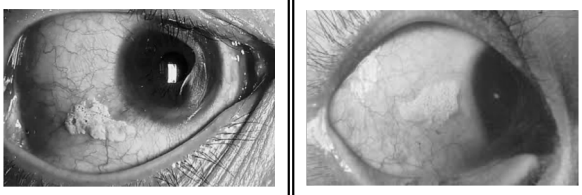
Important in dry eye syndrome

Included in almost all nutrient-based dry eye formulations.

Vital for the health of epithelial cells of the cornea and conjunctiva.

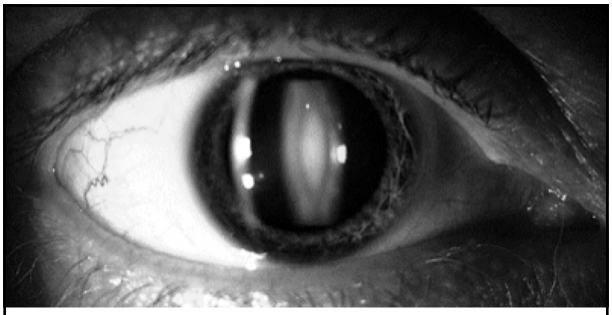
Necessary for **goblet cell and lacrimal gland** production of the large variety of mucins associated with the innermost layer of tear film.

Xerophthalmia



Vitamin A

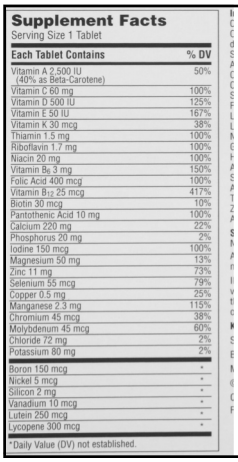
- Sweet potatoes
- Carrots
- Dark leafy greens
- Squash
- Dried apricots
- Yellow or red peppers
- Mango
- Tuna fish *



Cataracts and Nutrition

Physicians Health Study II

- Prevention of prostate cancer, CVD, cataract and macular degeneration.
- Alternate day beta-carotene 50 mg
- Alternate day vitamin E
- Daily vitamin C
- Daily multivitamin
- Long-term alternate-day use of 400 IU of vitamin E and daily use of 500 mg of vitamin C had no notable beneficial or harmful effect on the risk of cancer, CVD or cataract.



Supplement Facts
Serving Size 1 Tablet

Each Tablet Contains	% DV
Vitamin A 2,500 IU (40% as Beta-Carotene)	50%
Vitamin C 60 mg	100%
Vitamin D 500 IU	125%
Vitamin E 50 IU	167%
Vitamin K 30 mcg	38%
Thiamin 1.5 mg	100%
Riboflavin 1.7 mg	100%
Niacin 20 mg	100%
Vitamin B_6 3 mg	150%
Folic Acid 400 mcg	100%
Vitamin B_{12} 25 mcg	417%
Biotin 30 mcg	10%
Pantothenic Acid 10 mg	100%
Calcium 220 mg	22%
Phosphorus 20 mg	2%
Iodine 150 mcg	100%
Magnesium 50 mg	13%
Zinc 11 mg	73%
Selenium 55 mcg	79%
Copper 0.5 mg	25%
Manganese 2.3 mg	115%
Chromium 45 mcg	38%
Molybdenum 45 mcg	60%
Chloride 72 mg	2%
Potassium 80 mg	2%
Boron 150 mcg	*
Nickel 5 mcg	*
Silicon 2 mg	*
Vanadium 10 mcg	*
Lutein 250 mcg	*
Lycopene 300 mcg	*

*Daily Value (DV) not established.

PHS II

Multivitamin

- **Overall 9% reduction in cataract**
- **Subset**
  - **13% reduction in nuclear cataract**
  - **No significant effect on cortical or posterior subcapsular**
- No effect on AMD (actually increased, but not statistically significant)

Blue Mountains Eye Study

- Community based cross- sectional study
- New South Wales, Australia
- Self-reported MVM use at least 4 days per week
- **40% reduction in nuclear sclerotic cataracts**
- Longer duration associated with greater benefit

BMES Major Findings

NS cataract	• **Smoking and heavy alcohol intake** increase risk • High protein intake, vitamin A, thiamine, niacin, and riboflavin (B2) are protective
Cortical more frequent in women	• Vascular disease and DM increased risk • Alcohol (polyphenols), high PUFA intake, and post menopausal hormones protective
PSC cataract	• Inhaled steroids, dark iris, **smoking**, UV exposure, myopia, higher **dietary salt increase** risk

Vitamins and Cataract

Nurses Health Study

- 475 female nurses within NHS
- FFQ
- MVM used in 61.4% of women with NS
- MVM used in 70.2% without NS
- Not statistically significant
- **Longer duration of MVM use associated with lower incidence of nuclear sclerotic lens changes (43% reduction)**

AREDS – secondary analysis

- 67% of participants were taking Centrum
- **16% decrease in any lens opacity**
- **25% decrease in nuclear sclerotic cataract**
- Differences not sustained over 10 yrs. - ultimately deemed not effective.

Vitamins and Cataract

Linxian

- Two double blind, randomized, placebo- controlled studies in rural China
- **Significant** reduction in cataract with MVM
- Note: extremely poor area, monotonous diet with little variability in nutrients

AREDS 2

- Those with **lowest dietary intake** of lutein and zeaxanthin subjects, supplementation resulted in 32% reduction in cataract

Macular Degeneration

Risk Factors

- Non-modifiable
  - Age
  - Sex
  - Family History/Genes
- Modifiable
  - Nutrition
  - Lifestyle
  - Smoking
  - Obesity
  - UV protection
  - Others

Beaver Dam Eye Study

- **NEI funded** in 1987, last follow up done in 2010
- **5000 people** aged 43-84 at baseline 1900 final)
- 5, 10, 15, and 20 year follow-ups
- More than 300 publications arising from this study
- **Major Finding:**
  - **Cigarette smoking is a risk factor for both AMD and cataract**

Rotterdam Study

- **10,994** men and women 55 years and older in Rotterdam, Netherlands
- Investigate prevalence and incidence and **risk factors** for chronic diseases in the elderly
  - Eye (AMD and GLC)
  - Vascular, neurological, ambulatory
- **Risk factors are smoking, atherosclerosis, hyperopia, family history**

Rotterdam Study

Major Finding 2001:
- Most important predictors for progression were more than 10% of the macular area covered by drusen, presence of depigmentation or hyperpigmentation.

2001 — 2006

Major Finding 2006:
- Diet rich in antioxidants and zinc is protective
- Genetic risk with CFH and CRP genes is evident

Blue Mountains Eye Study (BMES-E)

Risk Factors for AMD:

- Age is major risk factor
- Smoking (4x higher risk)
  - Wet AMD appears 10 years earlier
- **Higher fish consumption is protective**
- Higher overall dietary fat INCREASES risk

LAST 2004

Stuart Richer, OD

Lutein Antioxidant Supplement Trial – Lutein (10 mg)

- Lutein + antioxidants/vitamins and minerals – placebo

90 patients VA based population

Several visual parameters measured

- Visual acuity, contrast sensitivity, amsler grid, MPOD, subjective data

Visual function (contrast sensitivity) is improved with lutein, with or without other nutrients

LAST II 2007

MPOD at baseline may be predictive of response to supplementation

Lower the MPOD the better the effect

CAREDS - 2006

Offshoot of the Women's Health Initiative 50-79 yrs. age

Carotenoids in Age Related Eye Disease Study

- Stable **intake of lutein and zeaxanthin rich foods** over time could reduce the risk of intermediate AMD by 43% (OR 0.57%) in healthy women under 75 years of age.
- MPOD can be measured reliably using heterochromatic flicker photometry

CARMIS 2008

Carotenoids and Antioxidants in Age-Related Maculopathy Italian Study

N=27 treatment vs. placebo

- Vitamin C, E, zinc/copper
- 10 mg lutein, 1 mg zeaxanthin, **4 mg astaxanthin**

Assessed with mfERG centrally up to 20 degrees

CARMIS Findings

1 year results: non-advanced AMD eyes increased ERG function centrally (0-5 degrees), but not peripherally with supplementation

2 year results: supplemented patients more likely to report clinically meaningful stabilization or improvements in VA, CS and visual function

LUTEGA Study

Determine long-term effect of supplementation with lutein, zeaxanthin, O-3-LCPUFA and antioxidants on MPOD in patients with non-exudative AMD

10 mg lutein, 1 mg zeaxanthin, O3 PUFAs (100 mg DHA, 30 mg EPA) and antioxidants with varying dosing (once or twice a day)

Major Finding: MPOD increased with supplementation and reached a saturation point beyond which no further MPOD increases were seen.

Graefes Arch Clin Exp Ophthalmol. 2013 Dec;251(12):2711-23. doi: 10.1007/s00417-013-2376-6. Epub 2013 May 22. **Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: the LUTEGA study.** Dawczynski J1, Jentsch S, Schweitzer D, Hammer M, Lang GE, Strobel J.

AREDS

- To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity
- Patients divided into 4 categories based on level of ARMD
- 25% decreased risk of progression from stage 3 to 4 AMD (intermediate to advanced)
- AREDS formula
  - 500 mg vitamin C
  - 400 IU vitamin E
  - 15 mg vitamin A (25,000 IU beta carotene)
  - 80 mg zinc
  - 2 mg copper

Questions from AREDS?

No apparent benefit in category 1 and 2 80% fall into this group

- Should they take supplements or not?

Beta carotene associated with increased risk of lung cancer in smokers

- How long a non-smoker is debatable?

DRI and RDA vs AREDS Dosing

Element	US RDA/RDI for adults (Men/women)	AREDS dose
Beta carotene	3000 /2333 (provitamin A)	15000 IU
Vitamin C* (nonsmokers)	90 / 75	500 mg
Vitamin E	22.5 IU	400 IU
Zinc	11/8	80 mg

Zinc

NIH

Life Stage	Recommended Amount
Birth to 6 months	2 mg
Infants 7-12 months	3 mg
Children 1-3 years	3 mg
Children 4-8 years	5 mg
Children 9-13 years	8 mg
Teens 14-18 years (boys)	11 mg
Teens 14-18 years (girls)	9 mg
Adults (men)	11 mg
Adults (women)	8 mg
Pregnant teens	12 mg
Pregnant women	11 mg
Breastfeeding teens	13 mg
Breastfeeding women	12 mg

- Marginal deficiency is common
- Important structural, catalytic, and regulatory roles in growth and development, immune response, neurological function and reproduction.
- Component of **retinol-binding protein**
- **Transports vitamin A** in the blood
  - **Required for conversion of retinol to retinal**
- Necessary for synthesis of rhodopsin
  - Absorbs light
  - Involved in dark adaptation
- Zinc deficiency reduces release of vitamin A from liver

Zinc

Bioavailability is higher in meat, eggs, and seafood

Less from whole grains and legumes due to inhibitory effects of phytic acid on absorption

Long term consumption of zinc >40 mg/day can result in copper deficiency

Zinc can be depleted by lisinopril

Role of Centrum Silver??

Supplement Facts

Serving Size: 1 Tablet

Amount Per Serving		% DV
Vitamin A (as Acetate & 40% as Beta Carotene)	2,500 I.U.	50%
Vitamin C (as Ascorbic Acid)	90 mg	150%
Vitamin D (as Cholecalciferol)	500 I.U.	125%
Vitamin E (as d-alpha Tocopheryl Acetate)	50 I.U.	167%
Vitamin K (as Phytonadione)	30 mcg	38%
Thiamin (Thiamin Mononitrate, B1)	1.5 mg	100%
Riboflavin (Vitamin B2)	1.7 mg	100%
Niacin (as Niacinamide)	20 mg	100%
Vitamin B6 (as Pyridoxine HCl)	3 mg	150%
Folic Acid	500 mcg	125%
Vitamin B12 (as Cyanocobalamin)	25 mcg	417%
Biotin	30 mcg	10%
Pantothenic Acid (as d-Calcium Pantothenate)	10 mg	100%
Calcium (as Calcium Phosphate & Carbonate)	220 mg	22%
Phosphorus (as Calcium Phosphate)	110 mg	11%
Iodine (as Potassium Iodide)	150 mcg	100%
Magnesium (as Magnesium Oxide)	50 mg	13%
Zinc (as Zinc Oxide)	11 mg	73%
Selenium (as Sodium Selenate)	55 mcg	79%
Copper (as Copper Sulfate)	0.9 mg	45%
Manganese (as Manganese Sulfate)	2.3 mg	115%
Chromium (as Chromium Picolinate)	45 mcg	38%
Molybdenum (as Sodium Molybdate)	45 mcg	60%
Chloride (as Potassium Chloride)	72 mg	2%
Potassium (as Potassium Chloride)	80 mg	2%
Boron (as Borates)	150 mcg	**
Nickel (as Nickelous Sulfate)	5 mcg	**
Silicon (as Silicon Dioxide)	2 mg	**
Vanadium (as Sodium Metavanadate)	10 mcg	**
Lycopene	300 mcg	**
Lutein	250 mcg	**

** Daily Value (DV) not established.

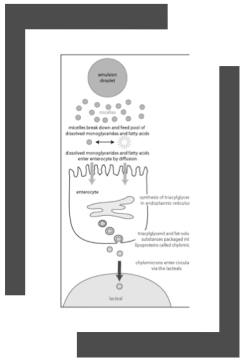
AREDS plus Centrum

67% of patients

Some taking as much as **91 mg zinc** a day!

Beta Carotene

- Pro-vitamin A carotenoid
- Converted by the body into retinol
- Lutein, zeaxanthin and lycopene have no vitamin A activity
- Unclear if beta carotene's primary role is as an anti- oxidant



Beta Carotene

- Fat soluble
- Carotenoids in food need fat to be absorbed
  - At least 3-5 grams in a meal
  - They have to be **released from food and made into mixed micelles**
- Carotenoids in supplements do NOT need to be released from food matrix

Conversion to Vitamin A

- Because the body converts dietary sources of vitamin A into retinol, 1 mcg of physiologically available retinol is equivalent to the following amounts:
  - From dietary sources: 1 mcg of retinol, 12 mcg of beta-carotene, and 24 mcg of alpha-carotene or beta-cryptoxanthin.
  - From supplements: body converts 2 mcg of beta-carotene to 1 mcg of retinol.

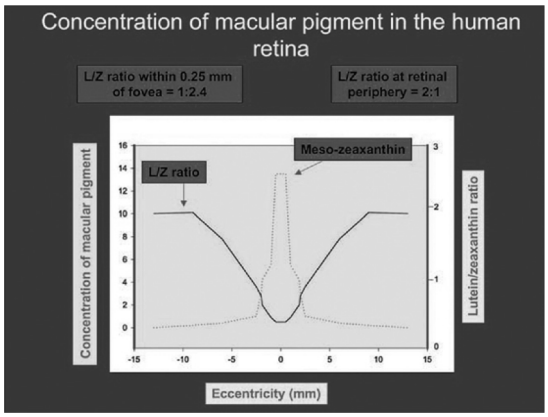
AREDS REPORT NUMBER 22

- The Relationship of Dietary Carotenoid and Vitamin A, E, and C Intake With Age-Related Macular Degeneration in a Case-Control Study: AREDS Report No. 22.
- Objective: To evaluate the relationship of dietary carotenoids, vitamin A, alpha- tocopherol, and vitamin C with prevalent AMD in AREDS
- Demographic, lifestyle, and medical characteristics of **4519** AREDS subjects at enrollment
- Categorized into 4 AMD severity groups and a control group
- Nutrients assessed by self-administered semi- quantitative FFQ

AREDS 22 Findings

- Dietary **lutein and zeaxanthin** intake inversely associated with:
- Neovascular AMD - OR 0.65, CI 95% (**35% reduction)**
- Geographic Atrophy – OR 0.45, CI 95% (**more than 50% reduction)**
- Large or intermediate drusen – OR 0.73, CI 95% **little higher than AREDS reduction**

Submitted July 2006
Accepted December 2006
AREDS 2 began recruitment in 2006
First report released May 5, 2013



AREDS 2

Whether adding **10 mg of lutein and 2 mg of zeaxanthin, 350 mg DHA/650 mg EPA** to the AREDS formulation was beneficial.

Study question: Will it reduced the risk of progression to advanced AMD by an **additional** 25% as compared to study subjects taking the original AREDS supplement, which was the study control arm?

AREDS 2: Set Up

- Primary study:
  - Assessed effect on cataracts, AMD and moderate vision loss
  - 10 mg lutein + 2mg zeaxanthin and/or
  - 650mg EPA + 350 mg DHA (ethyl ester form)
- Second randomization:
  - Original AREDS
  - AREDS minus beta carotene
  - AREDS with low dose zinc (25mg)
  - AREDS with no beta carotene and low dose zinc

AREDS 2 Demographics

- Patient were older
- 89% taking multivitamin (Centrum Silver)
- Most taking statin drugs (important for carotenoids)
- More diabetics
- Overall better nourished than original AREDS group

Addition of omega 3 fatty acid not harmful nor beneficial

- No evidence to support omega 3 fatty acids to the formula

Addition of **lutein and zeaxanthin added beneficial effect of 10% beyond original AREDS formula** in reducing risk of progressing to advanced AMD

When **beta carotene removed incremental benefit increased to 18%**

AREDS 2 Results

AREDS 2

- Comparison **low dose zinc (25mg)** to original dose (80mg) showed **no statistical difference**
- Cataract: overall dietary supplement with lutein and zeaxanthin **no statistically significant difference** overall.
- But… those with low intake L/Z there was 32% reduction *

AREDS 2

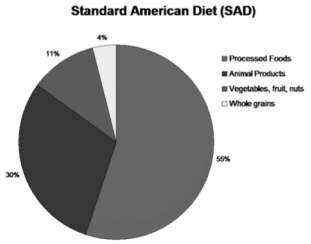
- "The addition of 10 mg lutein, 2 mg zeaxanthin, 350 mg DHA, and 650 mg EPA (ethyl esters) had no additional overall effect on the risk of developing advanced AMD".
- Lutein and zeaxanthin are **SIGNIFICANTLY MORE BENEFICIAL** than beta carotene for the typical American in preventing intermediate to advanced AMD progression as a part of a supplement containing zinc + vitamins C and E.

AREDS 2

- Lutein and zeaxanthin beneficial effect was most pronounced in patients with **low dietary L/Z**.
- Individuals consuming an average 0.7 mg per day or less showed a **26% additional reduced risk of progression to advanced AMD**.
- 18% risk reduction in legal blindness in patients with lowest L/Z intake (huge improvement in lower quintile)

AREDS 2

- **Most Americans consume about 1.5 L/Z in the diet daily**, as opposed to the AREDS 2 group which was much more well nourished than the general population.



AREDS 2

- Recommendation from AREDS2
  - Removal of beta-carotene from the supplement since it…
    - Did not contribute to efficacy
    - Increased the risk of lung cancer, especially in people who smoke or previously smoked
    - Led to a reduced absorption of lutein/zeaxanthin
- More patients taking supplement containing beta-carotene died of lung cancer during the study than those not taking beta carotene. Most that died were former smokers.
- Lowering zinc from 80 mg to 25 mg had no significant effect on the risk of advanced AMD.

Zeaxanthin & Lutein: How Much?

Supplement based on patient: measure in serum or MPOD or FFQ
10-20 mg lutein and 2-4 mg zeaxanthin are often recommended
What is their BMI and adiposity? Adipose tissue affects carotenoids.
Are they on statins?
Caution with warfarin (likely safe with coumadin)
Lutein can isomerize during storage.
Foods **dark green in color** tend to have relatively more lutein
Foods **orange-yellow** in color tend to have relatively more zeaxanthin

Nutrigenomics

Nutrigenomics is the **study of the interaction of nutrition and genes, especially with regard to the prevention or treatment of disease.**

Genes and SNP's

- More than 30 genes that affect the risk for AMD progression.
- **Compliment factor H (CFH) and age related maculopathy 2 (ARMS2) risk alleles** are most common.
- CFH **
  - rs412852, rs3766405, rs1048663, rs3766405, rs1061170
- ARMS2 **
  - 372815del443ins54, rs10490924

Klein 2008

- Examined CFH and ARMS2 relationship with AREDS formulation.
- The benefit of AREDS formulation was eliminated for subjects with high-risk CFH alleles.
- Postulated the response was due to high dose of zinc.
  - Interfere with ability to inactivate complement component
- Conclusion: "An individual's response to AREDS supplements may be related to CFH genotype".

Michael L. Klein, MD et al. *CFH* and *LOC387715/ARMS2* Genotypes and Treatment with Antioxidants and Zinc for Age-Related Macular Degeneration. Ophthalmology. 2008 Vol. 115, 6: 1019-25.

Awh et al 2013

Analyzed the response to AREDS supplement as influenced by CFH and ARMS2 genetic risk alleles.

Subjects with high CFH and low ARMS2 risk alleles had an increased progression to AMD if treated with zinc (alone or as a component of AREDS formulation).

Those with low CFH and high ARMS2 had a decrease in progression.

Chew et al. 2014

- Statistical analysis of 1,237 AREDS subjects.
- Found no influence of genetics on response to AREDS formulation.
- Analysis performed on 27 relatively small genetic risk treatment groups and possibly under-powered.

Chew E, et al. No clinically significant association between CFH and ARMS2 genotypes and response to nutritional supplement: AREDS report number 38. Ophthalmology 121:2173-2180.

Seddon et al. 2016

- Analyzed overall progression to advanced AMD and progression to Wet (NV) and Dry (GA).
- Subjects with low CFH and high ARMS2 had a reduction in overall advanced AMD
- Reduction due to decreased progression to NV with no significant effect on advanced GA.
- Conclusion: effectiveness of antioxidant and zinc supplementation appears to differ by genotype.

Seddon JM, et al. Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis. Br J Ophthalmol 100:1731-1737.

Vavvas et al 2018

- Evaluated effect of AO and zinc in AREDS formulation on progression to **NV AMD only** as a function of CFH and ARMS2 genotypes.
- Reduction in AREDS due to slowed progression of wet AMD not dry AMD.
- High CFH and no ARMS2 risk alleles and taking AREDS formulation had increased progression to NV compared to placebo.
- Low CFH and high ARMS2 genotype had decreased progression to NV AMD.
- Conclusion: AREDS formulation modifies risk of progression to NV based on individual genetics and use **should be based on patient-specific genotype.**
- Approx. 18% population may do WORSE with zinc.

Vavvas DG, et al. *CFH* and *ARMS2* genetic risk determines progression to neovascular age-related macular degeneration after antioxidant and zinc supplementation. Proc Natl Acad Sci USA. 2018 Jan 23;115(4):E696-E704.

Smoking

Smoking consistently been shown to be a risk factor for onset and progression of ARMD in several studies

Nurses Health Study

- 2.5 fold increase in ARMD among current smokers
- 2 fold increase for past smokers
- Former smokers did not show decreased risk for ARMD up to 15 years after cessation

29% of all ARMD associated with smoking

Smoking

POLA Study (Pahologies Ocularies Liees a l'Age)

- Greater than a **3 fold increased risk for late ARMD in current and former smokers**

Blue Mountain Eye Study

- **4 fold increase in late AMD among current smokers**
- Smokers developed AMD 5 years earlier than non- smokers

Smoking

Seddon Twin Study
- Current smokers 1.9 fold increased risk
- Past smokers 1.7x

2006

2011

Seddon Twin Study 2
- Twin with more advanced stage of AMD tends to be heavier smoker

Second Hand Smoke?

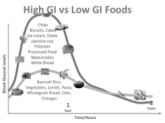
- Khan et al: BJO Jan 2006
- Study shows increased rate of ARMD, both GA and CNVM, with increasing amount of smoking
- Passive smoking increased risk
- Living with smoker > 5 yrs. had almost 2 x the risk!!

Smoking and Genetics

- More than additive!
- Former Smokers: 1.29x
- Current Smokers: 2.4X
- Non-Smoker and CFH,Y402H: 7.6X
- **Current smoker and CFH,Y420H: 34X**

Further support your patient education to STOP SMOKING

Glycemic Index, Glycemic Load and AMD



GI is the incremental area under the 2-hour blood glucose response curve of a 50g portion of test food compared to a standard (white bread or glucose)

Glycemic Load

- Considers GI AND amount consumed
- GL = GI x carb (grams)

Advanced Glycation End-Products (AGEs)

- Proteins or lipids that have become glycated and oxidized after contact with sugars
- AGEs can product ROS, bind to various cells, and form cross-links
- AGEs form during hyperglycemic conditions and during aging
- Contribute to many disease states

High dGI shown to be a risk factor in AMD
Blue Mountains Eye Study: Secondary analysis of AREDS patients

Chiu et al, Am J Clin Nutr Jul 2007

- Association between dGI and AMD in non-diabetic participants in AREDS
- 4099 participants enrolled in AREDS - age 55- 80
- **Significant positive relation between dGI and severity of AMD**
- **49% increased risk of advanced AMD (GA + SRNV) if dietary glycemic index (dGI) was above the sex median**
  - **women: 77.9 and men: 79.3**
- "20% of prevalent AMD cases would have been eliminated if dGI was < sex median"

Chiu C, et al. **Association between dietary glycemic index and age-related macular degeneration in nondiabetic participants in the Age-Related Eye Disease Study.** Am J Clin Nutr. 2007 Jul; 86(1):180-8.

Carbs and AMD

Poor dietary carbohydrate quality (dGI) is a modifiable risk factor which may increase the risk of AMD

- Diabetes, CVD, formation of AGE and increases in oxidative stress, inflammation and hyperlipidemia.

The **quality, not the quantity, of dietary carbohydrate influences the risk of AMD** in both the early and late stages of the disease.

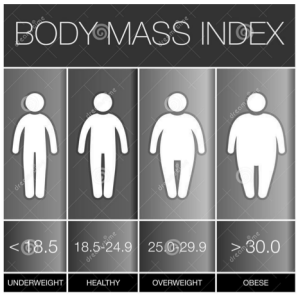
Body Mass Index

Many new studies indicate that increased BMI is a significant factor for both the onset and progression of AMD

Perhaps second only to smoking

BMI

- Body Mass Index is a measure of body fat based on height and weight
- Weight (kg) / height(m)2
  - <19: Underweight
  - 19-24: Normal
  - 25-29: Overweight
  - >30: Obese



BMI

- Progression of AMD Study Mass Eye and Ear Infirmary, Boston, MA
  - 261 patients with dry AMD in at least 1 eye
  - Mean age 72.8 years, followed 4.6 years
- Increased risk for AMD progression with higher BMI >25
- **Higher waist circumference** associated with an increased risk of progression
- Increased **physical activity** tended to decrease the risk for progression
  - Vigorous activity at least 3 times a week
- **Body fat percentage is inversely related to MPOD**

Diabetes…It's a Big Deal

- One of the leading causes of blindness in the United States (U.S.) for persons 20–74 years of age.
- Estimated 10 million adults in US over the age of 40 with Type 2 DM
  - 40% have been diagnosed with DR
  - 8% have vision-threatening retinopathy.
- Greater severity associated with lower general and vision-specific quality of life.
- Those with bilateral moderate NPDR had most substantial decrease in quality of life compared to those with less severe DR. (Los Angeles Latino Eye Study 2011).

Diabetes and Weight Loss

- Reducing energy intake while maintaining a healthful eating pattern
- Ten (10%) weight loss improvement in diabetic control
- Modest weight loss correlates with clinical benefits; improved glycemic control, blood pressure and lipid profiles
- May be able to remove or reduce medications

Diabetes and Macronutrients

- "Carbohydrate" intake has a direct effect on postprandial glucose levels and is the primary macronutrient of concern.
- GI and GL
- No ideal/prescriptive percentages, but on average:
  - Carbohydrates 45%
  - Protein 16%-18%
  - Fat 36%-40% (healthy fats)
- **Mediterranean eating pattern reported with largest improvement in A1C at 1 year**

Mediterranean Diet

Primarily plant-based foods, such as fruits and vegetables, whole grains, legumes and nuts

Replacing butter with healthy fats (olive oil and canola oil)

Using herbs and spices instead of salt to flavor

Limiting red meat to no more than a few times a month

Eating fish and poultry at least twice a week

Enjoying meals with family and friends

Drinking red wine in moderation (resveratrol)

Getting plenty of exercise

Mediterranean Diet

- Comparing the effects of a low-carbohydrate Mediterranean-style (<50% carb) OR a low-fat diet (<30%) on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes
- After 4 years, 44% of patients in the Mediterranean-style diet group and 70% in the low-fat diet group required treatment. (95% CI and P < 0.001).
- Participants on Mediterranean-style diet lost more weight and experienced greater improvements in some glycemic control and coronary risk measures than did those assigned to the low-fat diet.

Esposito K, et al. Ann Intern Med. 2009 Sep 1;151(5):306-14. **Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial.**

Intermittent Fasting

- Essentially a calorie restricting diet
- Effective at reducing fat and reducing significant health risks.
- Reduce cardiovascular risks, blood pressure, inflammation and body fat
- Impact insulin levels, increase the production of human growth hormone and gene function related to longevity of life.
- BUT…food needs to be nutritious and may not be ideal long term.

American Journal of Clinical Nutrition, 2018.

Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev. 2017 Oct; 39:46-58.

Longo V. Programmed Longevity, youthspan and juventology. Aging Cell. 2019 Feb;18(1):e12843.

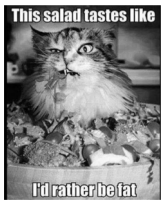
Dietary Restrictions and Nutrition in the Prevention and Treatment of Cardiovascular Disease. Brandhorst S, Longo V. Circulation Research. March 2019

AHEAD Study

LOOK AHEAD

- Action for Health in Diabetes (Look AHEAD): randomized trial comparing Intensive Lifestyle Intervention (ILI) focused on weight loss through healthy eating and increased physical activity VS. control condition of Diabetes Support and Education (DSE) in overweight and obese individuals with Type 2 DM.
- Primary aims: Long term effects of ILI relative to DSE on lifespan and reduced health care costs.
- Secondary aim: Long term effects of ILI relative to DSE on healthy aging, frailty, reduced diabetic microvascular complications and quality of life.
- Also compare long-term trajectories of weight, physical activity, fat and lean mass, and bone density.

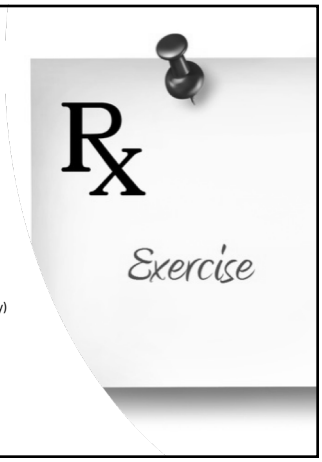
What Works?



- At 10 years mean weight loss from baseline was 6% in intervention group and 3.5% in control group.
- **Mediterranean-style eating pattern largest improvement in A1C at 1 year.**
- Look AHEAD study intensive intervention (healthy eating and physical activity) next largest improvement.

Exercise Works!

- Insulin action in muscle and liver can be modified by exercise
- Acute state: aerobic exercise increases muscle glucose uptake 5-fold
- After exercise:
  - Glucose uptake remains elevated up to 48 hours following prolonged bouts
  - Shorter bouts of exercise (high intensity) glucose uptake remains elevated for up to 24 hours
  - Low intensity 60 minutes enhances insulin action in obese, insulin resistant adults.



Recommendations

- Increase monounsaturated fats (Mediterranean diet)
- Increase EPA and DHA (fatty fish) and ALA for beneficial effects on lipoproteins, prevention of heart disease
- Decrease saturated (<10%) and trans fats (zero)
- Focus on quality of carbohydrate (GI/GL)
  - Replace sucrose (table sugar) for starch – both affect blood glucose but want food to be nutrient dense
- Fructose in fruit results in better glycemic control compared to sucrose and starch without affecting triglycerides
  - Obesity and diabetes rates were low when total fructose intake was in the range of 25–40 g/d.
- Add fiber and whole grain

Diabetes

- MPOD is lower in patients with diabetes and even lower in patients with diabetic retinopathy
- Higher serum zeaxanthin/lutein is associated with 2/3 lower risk of developing type 2 diabetes and early NPDR
- Should measure and optimize MPOD in patients with DM and at-risk for diabetes

Invest Ophthalmol Vis Sci. 2010 Nov;51(11):5840-5

Diabetes Visual Function Supplement Study (DiVFuSS)

6 month double-blind placebo-controlled, randomized, clinical trial of adults with T1DM or T2DM ≥ 5 years

No DR (2:1) and mild-moderate NPDR (1:1)

Daily use of a multi-component nutritional supplement (zeaxanthin, lutein, vitamins D/C/E including tocotrienols, curcumin, benfotiamine, Pycnogenol™, lipoic acid, NAC, resveratrol, green tea & grapeseed extracts, O-3 FAs, CoQ10, Zn)

Pre- and post- analysis of CSF, MPOD, color vision, macular perimetry, OCT, A1c, lipids, 25(OH) vitamin D3, hsCRP, TNF-a, NFL thickness and diabetic peripheral neuropathy symptom scores (DPNSS)

Br J Ophthalmol 2015 e-published June 18

(DiVFuSS)

- N=67 (28-79 yrs)
- 27 type 1 diabetes & 40 type 2 diabetes
- HbA1c range 5.85 to 10.3% (mean 7.2%)
- Diabetes duration 5-52 years (mean 16.1 yrs.)
- Both Placebo and Supplement Groups showed similar and significant deficits in contrast sensitivity, color vision and visual field at baseline

- Results:
- 31% increase in MPOD
- 19% improvement in contrast sensitivity
- 21% improvement in color vision
- 3 dB (12%) increase in 5-2 visual field

Diabetic Retinopathy and Vitamin D

Look at serology

Vitamin D status hypothesized to protect against development of diabetic retinopathy via its anti-inflammatory and anti-angiogenic properties.

Studies suggest vitamin D favorably influences blood pressure and blood glucose control.

Diabetes and Vitamin D

- Participants in the Atherosclerosis Risk in Communities (ARIC) study
- N = 1339 (906 Caucasians, 433 African Americans)
- Serum 25-hydroxyvitamin (25[OH]D) concentrations assessed and non-mydriatic retinal photographs taken to assess retinopathy.
- **Conclusion:**
  - 25(OH)D concentrations ≥75 nmol/L were associated with lower odds of any retinopathy assessed 3 years later.

Millen A, et al. Adequate vitamin D status is associated with the reduced odds of prevalent diabetic retinopathy in African Americans and Caucasians. Cardiovasc Diabetol 2016; 15:128

Diabetic Retinopathy & Vitamin D

- Two groups: N= 139 and 144 patients with and without retinopathy. (Advanced diabetic complications excluded)
- 25-Hydroxy-vitamin D_3 (25(OH)D) concentrations and vitamin D deficiency were associated with the presence of diabetic retinopathy.
- Patients with **more advanced stages of retinopathy had lower concentrations of 25(OH)D and were more frequently vitamin D deficient compared with patients without eye complication.**
- **Conclusion: Association of vitamin D deficiency with the presence and severity of diabetic retinopathy in type 2 diabetes.**

Alcubierre N, et al. Journal of Diabetes Research. Vol 2015 (2015) Vitamin D Deficiency Is Associated with the Presence and Severity of Diabetic Retinopathy in Type 2 Diabetes Mellitus.

Glaucoma and Research

- Need a better understanding of WHY people get glaucoma to perform effective nutritional research.
- Some individuals with high IOP do not develop glaucoma
- Some individuals with normal IOP do develop glaucoma
- Some progress with lower pressure and some do not progress at all
- Research is very challenging in nutrition: metabolism, genetics, environment, overall nutrient intake
- Future and non-IOP lowering treatment: Treatment for NTG or adjunctive?

Exercise and IOP

- IOP quantitatively linked under genetic control, though certain lifestyle activities increase risk of elevated IOP, such as wind instruments, tight neck ties, certain yoga positions (inversions), lifting weights and caffeine.
- Magnitude of reduction related to intensity of exercise performed.
- IOP reduction noted after 15 minutes of exercise at 40% heart rate of 0.9mmHg versus 4.7 mm Hg after 80% intensity.
- **Conclusion: Individuals more physically fit likely to have lower IOP**

Qureshi IA, et al. Magnitude of decrease in intraocular pressure depends upon intensity of ex Posso MS, et al 1991
Qureshi IA, et al 1997
Marcus DF, et al 1970
McDaniel DR, et al 1983 ercise. Korean J Ophthalmol. 1996; 10: 109-15.

Korea National Health and Nutrition Examination Survey

- Anthropometric measurements
  - BMI, waist circumference, total fat mass
- Positively associated with IOP
- In addition to BMI, WC and total fat mass, total and regional fat mass percentage in men and trunk fat percentage in women positively associated with IOP.
- Defined obesity BMI > 25, overweight BMI <25 (slightly different than in definition of obesity)

Jang, et al Relationship between IOP and parameters of obesity in Korean adults: The 2008-2010 Korea National Health and Nutrition Examination Survey. Current Eye Research. 2015: 40(10): 1008-1017.

Korea National Health and Nutrition Examination Survey

- Mechanisms: affect intraorbital adipose tissue, blood viscosity and episcleral venous pressure and impaired aqueous outflow.
- Obesity related conditions: diabetes, hypertension, dyslipidemia and insulin resistance are associated with elevated IOP

Korea National Health and Nutrition Examination Survey

- Pro-inflammatory adipokines secreted from fat promotes insulin resistance and induce catabolic effect on muscle; leading to further fat accumulation.
- Increased risk of cardiometabolic dysregulation, metabolic syndrome and cardiovascular risk, which are associated with high IOP, even in those with normal BMI.
- Men have more visceral fat and women have more subcutaneous fat: **visceral fat and fat in the abdominal area associated with higher IOP and greater cardiovascular risk**

BMI and IOP

- N=18,575
- Retrospective and cross-sectional
- Result: subjects with abnormal BMI compared to subjects with normal BMI had increased odds ratio of having IOP>18mm Hg.
- Conclusion: **obesity is an independent risk factor for increasing IOP in both men and women.**

Cohen, et al. Relationship between body mass index and intraocular pressure in men and women: A population-based study. J Glaucoma. Vol 25, N5, May 2016.

Which is better?

One or Two?

Blue Mountain Eye Study

- Modest elevation IOP in **smokers** (P=0.03) *mixed studies
- OAG which consumed **coffee r**egularly had higher IOP (P=0.03)
  - Other: consuming 5 or more cups/day associated with a 1.6 fold increased risk of POAG (Kang et al)
- **Hormones**: estrogen is protective to RGC.
  - Proposed that post-menopausal women have higher risk of POAG

Kang JH, et al. Caffeine consumption and the risk of primary open-angle glaucoma: a prospective cohort study. Invest Ophthalmol Vis Sci 2008; 49: 1924-31.

Hormones

Rotterdam and Nurse Health Study: postmenopausal age associated with risk of glaucoma.

Nurses Health Study: Hormone therapy may reduce risk high IOP glaucoma

Mirtogenol®

- Combination of standardized bilberry extract Mirtoselect® and Pycnogenol® French maritime pine bark extract
  - **Procyanidins – Nitric oxide and blood flow**
  - Anti-inflammatory
- Proposed mechanism: vascular response
- Pycnogenol® enhances endothelial function and Bilberry extract Mirtoselect® may improve ciliary function in animal testing

Mirtogenol®

- N=38
- 20 treated with Mirtogenol and 18 not treated
- Tablet 40 mg French maritime pine bark (Pycnogenol®) and 80 mg Mitroselect® standardized billberry extract
- VA, IOP and ocular blood flow (2, 3 and 6 months)

Steigerwalt R, et al. Effects of Mirtogenol® on ocular blood flow and intraocular hypertension in asymptomatic subjects. Molecular Vision 2008; 14: 1288-1291.

Mirtogenol®

- After 2 months, mean IOP in treated group lower from 25.2 mm Hg to 22.2 mm Hg.
- After 3 months, treated group significantly lower compared to untreated ($p<0.05$) 22 mm Hg
- After 6 months, no further improvement
- No side effects
- Increased ocular blood flow color Doppler imaging
  - After 3 months, ocular blood flow in treated group significant improvement (P=0.05)

Nitric Oxide

- Intracellular signaling molecule produced by endogenous NO synthase
- Role in vasodilation through action on smooth muscle cells
- Mediate IOP lowering through cell volume and contractility changes
- Increase conventional outflow through TM
  - Possibly some increase in uveo-scleral outflow (relaxation of ciliary muscle)?
- Neuroprotective through alterations in blood flow and reduction of apoptosis? Remains to be proven.

Cavet M, et al. Nitric oxide (NO): An emerging target for the treatment of glaucoma. 2014. Invest Ophthalmol Vis Sci. 55: 5005-15.

Dietary NO

- Dietary NO VS. inorganic nitrate from dietary sources is metabolized to various bioactive nitrogen oxides including NO.
- Dietary **nitrate** as a precursor to endogenous synthesis of NO from L-arginine.
- Certain leafy vegetables are high in nitrate: **spinach, lettuce, or beetroot**
- Large prospective study of 1483 POAG patients found greater intake of dietary nitrate and green-leafy vegetables was associated with **20% to 30% lower risk for POAG.**
- The relation was particularly strong—40% to 50% lower risk—for POAG with early paracentral visual field loss at diagnosis, wherein ocular vascular dysregulation has been implicated. (NTG)

Oxidative Stress

- Polyphenolic flavonoids: protect mitochondria from oxidative stress and protect retinal ganglion cells

Oxidative Stress

- Polyphenols are strong antioxidants due to free radical scavenging properties
  - Ginko biloba
  - Black and green tea: catechin, epicatechins, epigallocatechin (ECG)
  - Red wine, chocolate
  - Bilberry: anthocyanin (positively charged O2 atom)
  - Ubiquinone (CoQ10): co-enzyme for inner mitochondrial enzyme complex
  - **Prevention of lipid peroxidation and DNA damage**
  - Melatonin: Reduces elevation of cGMP by suppressing NOS activity and lowing levels of NO