Macular Degeneration

- Incurable, degenerative disease of the macula
- Leading cause of blindness in adults >55 years
- AMD is four times more common than Parkinson’s and Alzheimer’s disease combined

Normal retina
Early AMD
Late AMD retina
Neovascularisation
Atrophy

Age & Age-related Macular Degeneration

Risk of developing some form of AMD increases with age

40-54 55-64 65-74 75+
8.5% 14.4% 19.4% 36.8%
**Aging Canadian Population**

- 2.1 million: population with AMD
- 78,000 new cases of AMD per year
- Proportion of older adults is increasing more rapidly than all other age groups:
  - 2001: 1 in 8 was >65 (3.92 million)
  - 2026: 1 in 5 will be >65 (6.7 million)

**The Impact of AMD**

AMD leads to:
- Reduced central vision (acuity)
- Central blind spots (scotoma)
- Distortion of vision (metamorphopsia)
- Loss of contrast sensitivity
- Decreased colour vision, depth perception, stereovision
- Increased glare sensitivity

= Loss of Visual function

**Loss of Visual Function**

- Decreased mobility
- Increased risk of injury due to falls
- Loss of driving privilege
- Increased dependence on others/social services
- Depression

**Impact Of Age-related Macular Degeneration**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Utility Score (Patient-reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate stroke (requiring help)</td>
<td>0.69</td>
</tr>
<tr>
<td>Moderate AMD: 20/50 to 20/100</td>
<td>0.56</td>
</tr>
<tr>
<td>Ulcerative colitis requiring surgery</td>
<td>0.58</td>
</tr>
<tr>
<td>Permanent renal dialysis</td>
<td>0.56</td>
</tr>
<tr>
<td>Severe AMD: 20/200 or worse</td>
<td>0.47</td>
</tr>
<tr>
<td>Severe stroke (bedridden)</td>
<td>0.34</td>
</tr>
</tbody>
</table>


### AMD Risk Factors

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Non-modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Age</td>
</tr>
<tr>
<td>Diet</td>
<td>Gender</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>Family history</td>
</tr>
<tr>
<td>Excess weight/BMI</td>
<td>Iris colour</td>
</tr>
<tr>
<td>Ultraviolet exposure</td>
<td>Race</td>
</tr>
</tbody>
</table>

### Treatment Options - Dry

- **Lifestyle modifications:**
  - Quit smoking
  - Improve dietary intake
  - Weight loss
  - Manage hypertension
  - UV protection
- **Vitamin therapy (AREDS, LAST, Rotterdam, AREDS 2)**
- **Monitoring through regular visits to the Eye Doctor**
- **Amsler grid testing**

### The Role Of Oxidative Stress In Age-Related Macular Degeneration

Under normal conditions:

- Metabolic processes lead to the generation of highly reactive oxygen intermediates (ROIs)
- **ROIs:**
  - Negatively charged molecules
  - Interfere with cellular function & damage retina layers
  - Commonly called free radicals
- **ROIs and antioxidants are balanced:**
  - Antioxidants protect cells from potentially damaging effects of ROIs

### Metabolism Of The Healthy Eye
What Is Oxidative Stress?

- Disturbance in the ROI/antioxidant balance occurring because:
  - ROI production is increased, and/or
  - Availability of antioxidants is decreased
- Believed to play major role in development of AMD

Factors Contributing To Oxidative Stress

- Age
- Low intake of antioxidants and minerals
- Excessive exposure to blue light
- Smoking
- Pollution

Lutein & Zeaxanthin: Blocking Formation Of Excess ROIs

- Reduced lutein and zeaxanthin levels allow blue light to overwhelm and damage photoreceptors
- Damaged RPE with increased ROIs from excessive light damage

Antioxidants: Preventing Build-up Of Excess ROIs

- Antioxidants - molecules that interfere with cellular function and damage the retinal layers
- Antioxidant nutrients - blocks with ROIs in involved in their effect

Unhealthy Retina Healthy Retina
Cross Section of Macula with Dry AMD

- Less Oxygen in, Less waste out, Less fluid out
- Reduced RPE functioning, impaired phagocytosis with accumulation of lipofuscin = drusen

Basis for Vitamin Therapy:
1. AREDS
2. LAST
3. Rotterdam Study
4. AREDS II

Age Related Eye Disease Study (AREDS)

- Effect of high doses of vitamins and minerals on AMD progression and visual acuity
- Randomized prospective controlled, 3640 patients, 55 – 80 years old, followed for a mean of 6.3 years

Age Related Eye Disease Study (AREDS)

Results:
- The AREDS formulation of antioxidants plus zinc was shown to delay the progression of advanced AMD and help preserve vision (approximately 25% risk reduction)

Age Related Eye Disease Study (AREDS)

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-carotene (Provitamin A)</td>
<td>15 mg</td>
</tr>
<tr>
<td>Vitamin C (Ascorbic acid)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Vitamin E (d-alpha tocopheryl acetate)</td>
<td>400 IU</td>
</tr>
<tr>
<td>Zinc (oxide)</td>
<td>80 mg</td>
</tr>
<tr>
<td>Copper (hydrolyzed vegetable protein chelate)</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

Ocular Vitamins

- Vitalux (contains Lutein and Zeaxanthin)
- B & L Preservision
- Ocuvite
- I-Caps (4x daily)

Lutein & Zeaxanthin

- High concentration of lutein in the macula – (macula lutea)
- Available only through diet
- AMD patients shown to have 32% lower levels of macular lutein
- AMD patients consuming diet high in lutein had 57% lower chance of developing wet AMD
- Not commercially available at time of AREDS

References:
Lutein Antioxidant Supplementation Trial (LAST)

- 10 mg of lutein supplementation daily increased Macular Pigment Optical Density (MPOD) by 36% in AREDS category 2, 3 and 4 patients.
- 10 mg of lutein supplementation daily increased visual acuity by 5.4 letters. (p=0.01)
- Lutein supplementation led to improved overall visual function


Rotterdam Study: Dietary Intake Of Antioxidants & Risk Of Age-Related Macular Degeneration

van Leeuwen R et al, Dietary Intake of Antioxidants and Risk of Age-related Macular Degeneration. JAMA. 2005; 294: 3101-3107

Study Overview

- Objective:
  - To investigate whether regular dietary intake of antioxidants is associated with a lower risk of incident AMD
- Design:
  - Prospective, population-based cohort, observational study
  - Dietary intake assessed at baseline in the Rotterdam Study (1990-1993) using food frequency questionnaire divided into 3 intake groups
- Study Population:
  - 4170 adults >55 years of age
  - Mean follow-up of 8.0 years
Study Overview

- **Primary Outcome:**
  - Incident AMD
  - Measured people who had no AMD at baseline to the progression to incident AMD in at least one eye

- **Data Analysis:**
  - Adjusted out risk factors to determine pure nutrition effect
  - Controlled approach to determining role of nutrition alone in reducing the incidence of AMD

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Results

- An above median intake of all 4 nutrients, beta carotene, vitamin C, vitamin E, and zinc was associated with a 35% reduced risk of AMD.

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Antioxidants:
Demonstrated Risk Reduction Of AMD

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Minimum Dose</th>
<th>Considered Above-Median Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C</td>
<td>114 mg</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>20 IU</td>
<td></td>
</tr>
<tr>
<td>Beta carotene</td>
<td>6,000 IU</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>10 mg</td>
<td></td>
</tr>
</tbody>
</table>

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van Leeuwen R et al, Dietary Intake of Antioxidants and Risk of Age-related Macular Degeneration. JAMA. 2005; 294: 3101-3107
Healthy Eyes

- Ocular vitamin specially formulated to reduce the risk of developing AMD:
  - Formulated with key ingredients from van Leeuwen Study (JAMA 2005) plus 10 mg lutein for added protective effect

<table>
<thead>
<tr>
<th>VitaminAREDS I</th>
<th>Vitamin Healthy Eye</th>
<th>Leading Multivitamin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Carotene</td>
<td>25,000 IU</td>
<td>10,000 IU</td>
</tr>
<tr>
<td>(not contained in Vitamin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>500 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
<td>110 IU</td>
</tr>
<tr>
<td>Zn</td>
<td>80 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Copper</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Lutein</td>
<td>6 mg</td>
<td>3 mg</td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

Healthy Body

- The added benefit of a multivitamin to promote overall general health

Age Related Eye Disease Study II (AREDS II)

- Effect of high dose macular xanthophylls and omega-3 LCPUFAs (long-chain poly-unsaturated fatty acids) on advanced AMD progression (and cataract)
- Effect of eliminating beta-carotene and reducing zinc in the original AREDS formulation on development and progression of AMD
- Randomized prospective controlled, 4000 patients, 50 – 85 years old, followed for a minimum of 5 years
### Primary Randomization Agents

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Lutein/Zeaxanthin</th>
<th>DHA/EPA</th>
<th>Lutein/Zeaxanthin + DHA/EPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10mg/2mg</td>
<td>350mg/650mg</td>
<td>10mg/2mg + 350mg/650mg</td>
</tr>
</tbody>
</table>

### Secondary Randomization Agents

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Vitamin C</th>
<th>Vitamin E</th>
<th>Beta Carotene</th>
<th>Zinc Oxide</th>
<th>Cupric Oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500 mg</td>
<td>400 IU</td>
<td>15 mg</td>
<td>80 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>2</td>
<td>500 mg</td>
<td>400 IU</td>
<td>0 mg</td>
<td>80 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>3</td>
<td>500 mg</td>
<td>400 IU</td>
<td>0 mg</td>
<td>25 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>4</td>
<td>500 mg</td>
<td>400 IU</td>
<td>15 mg</td>
<td>25 mg</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

### Conclusions

- Level 1 and Level 2 evidence that vitamin therapy is beneficial
- 50+ with minimal risk factors and no family Hx: Patients and Drs. discretion
- 50+ with risk factors and family Hx: Vitalux Healthy Eyes 2x daily
- 50+ with Category 1 and 2 AMD: Vitalux Healthy Eyes 2x daily
- 50+ with Category 3 or 4 AMD present: Vitalux 2x daily

- Category 1: No AMD
- Category 2: Mild AMD
  - Vitalux Healthy Eyes 2x Daily
Category 3: Intermediate AMD
- Large drusen >125um, extensive intermediate drusen, extrafoveal geographic RPE atrophy
  - Vitalux 2x Daily

Category 4: Advanced AMD
- Choroidal NV, geographic RPE atrophy involving macular center
  - Vitalux 2x Daily

AMD frustrations:

Macular Degeneration

- 'DRY' ~90% of visual loss
- 'WET' ~10% of visual loss

Treatment Options - Dry

- Lifestyle modifications:
  - Quit smoking
  - Improve dietary intake
  - Weight loss
  - Manage hypertension
  - UV protection
- Vitamin therapy (AREDS, LAST, Rotterdam, AREDS 2)
- Monitoring through regular visits to the Eye Doctor
- Amsler grid testing
Screening for AMD

- Early detection may be possible using an Amsler grid
  - High-risk patients should be encouraged to monitor their vision
  - Patients should perform daily checks on each eye

Cross Section of Macula with Dry AMD

- Less Oxygen in, Less waste out, Less fluid out
- Reduced RPE functioning, impaired phagocytosis with accumulation of lipofuschin = drusen

Development of Wet/Exudative AMD

AGE & DIET & GENETICS & UNKNOWN > ISCHEMIA > VEGF > Growth of abnormal choroidal vessels = WET AMD

Wet AMD - Subfoveal Occult CNV

- Exudation breaks into sub-retinal space through RPE
Type II CNV develops which typically shows classic components or remains occult to FA depending on activity of RPE cells.

VISION secondary outcome
Mean change in vision

Secondary Endpoint:
Mean Change in Visual Acuity Over Time

P < 0.0001 vs. sham at all visits for both doses

17.7 letter benefit for 0.5 mg
17.0 letter benefit for 0.3 mg
Thank You!

Lutein Supplementation

- Increases macular pigment optical density (MPOD)
- Filters blue light
- Provides protective effect