

Age-Related Macular Degeneration and Supplements

What is the evidence?

Quick facts:

- No evidence that supplements prevent AMD
- Anti-oxidant supplements, such as Vitalux-AREDS[®], have modest benefit in slowing the progression from intermediate to advanced stages of AMD
- Potential safety issues exist with anti-oxidant and zinc supplements; zinc may increase risk of anemia and hospitalizations due to genitourinary problems, and antioxidants caused yellowing of skin and an increase in all-cause mortality
- Increasing **dietary** lutein and omega-3 may protect against the early stages of AMD and slow progression, though evidence is limited; lutein and omega-3 **supplements** have not shown benefit

Many consumers ask about taking ocular vitamins or other supplements to help their eye health or prevent age-related macular degeneration (AMD). Some healthcare providers are also recommending supplements to their AMD patients¹ — but is there any proof ocular vitamins or supplements can benefit eye health or AMD?

AMD is a leading cause of blindness and visual loss in adults. There are two types of AMD—wet and dry—which influences what intervention may be effective. Dry AMD is more common than wet AMD. Dry AMD causes vision loss slowly and gradually, and progresses in three-stages: early, intermediate and advanced. In contrast, wet AMD causes rapid distortion and severe loss of vision. Dry AMD can progress into wet AMD^{2,3}.

So where do supplements fit in? Currently, ocular vitamins (eg. Vitalux[®] and Ocuville[®]), zinc, lutein and omega-3 are marketed for helping AMD. The following table is a review of the available evidence for supplements marketed for AMD.

		Benefits	Harms	Comments
AREDS Study formula: Anti-oxidants - Vitamin C 500mg - Vitamin E 400 IU - Beta-carotene 25,000 IU - Copper 2mg Zinc 80mg		<ul style="list-style-type: none"> Intermediate and advanced AMD patients had a reduced rate of 15 letter visual acuity loss vs. placebo (NNT 17 over 6.3 years⁴; OR 0.73, 99% CI, 0.54 – 0.99⁷) Fewer patients progressed to advanced AMD or wet AMD vs. placebo (NNT 13 over 6.3 years⁴; OR 0.72, 99% CI, 0.52-0.98⁷) 	<ul style="list-style-type: none"> Yellowing of skin with anti-oxidants (Absolute risk increase (ARI) of 2.3% vs. placebo; NNH 43 over 6.3 years^{7,8}) Increased risk of lung cancer in smokers^{17,25} with beta-carotene (RR 1.21, 95% CI, 1.09 – 1.34), but evidence conflicting in other analyses^{12,18} Higher beta-carotene intake associated with increased incidence of wet AMD (ARI 2.01% vs. lower intake; NNH 50 over 5 years)¹⁰ Increase in all-cause mortality from a meta-analysis with similar doses to the AREDS trial (RR 1.10, 95% CI, 1.05 to 1.15; ARI = 1.0% vs. placebo; NNH 100 over 3 years)⁶ 	<ul style="list-style-type: none"> Does not prevent or delay onset of AMD⁹ Increase in all-cause mortality also seen when beta-carotene and vitamin E given separately; (ARI of 2.7% and 1.7% over 3 years, respectively)⁶
Zinc 80mg		<ul style="list-style-type: none"> Reduced progression to advanced or wet AMD (NNT 13 over 6.3 years⁴; OR 0.75, 99% CI, 0.55 – 1.03⁷) 	<ul style="list-style-type: none"> Increased risk of anemia (ARI 2.3% vs. placebo; NNH 33 over 6.3 years)^{7,8} Increased risk of genito-urinary problems (unspecified UTI, stress incontinence, prostatic hyperplasia) leading to hospital admission (ARI 3% vs. placebo; NNH 29 over 6.3 years)^{7,8} 	<ul style="list-style-type: none"> Harms with zinc also apply to anti-oxidants + zinc group above Did not slow 15 letter visual acuity loss (unlike anti-oxidants + zinc)
Lutein and zeaxanthin	Dietary	<ul style="list-style-type: none"> Consuming >942ug per day of lutein, compared to lower intake, led to lower rates of advanced or wet AMD (RR 0.35, 95% CI, 0.13–0.92; <i>P</i> = 0.033)¹⁰ Consuming >743ug per day of lutein, compared to lower intake, had lower rates of the development of AMD (RR 0.66, 95% CI, 0.48–0.92; <i>P</i> = 0.013)¹⁰ 	<ul style="list-style-type: none"> No harms identified with dietary lutein⁵ 	<ul style="list-style-type: none"> The dietary study¹⁰ was done on an Australian population. Average intake of lutein and zeaxanthin for elderly Australian people is 914ug²¹ Average intake of lutein and zeaxanthin in North America appears to be 1000-2000ug^{22,23}; results may not apply to this population
	Supplement	<ul style="list-style-type: none"> AREDS II trial demonstrated no difference in progression to advanced AMD with the addition of lutein 10mg and zeaxanthin 2mg to the AREDS formula²⁵ Only two small, short-duration studies (N=25, 10mg dose, 12 month follow-up; and N=84, 20mg dose, 6 months follow-up) with lutein published; neither showed any difference versus placebo^{19,20} 	<ul style="list-style-type: none"> No harms found with supplementary lutein in three studies^{19,20,25}; some evidence of safety for long-term supplementation (4.9 years with no adverse effects)²⁵ 	<ul style="list-style-type: none"> AREDS II trial did not have a placebo comparator—only compared to the AREDS formula without addition of lutein or zeaxanthin²⁵
Omega-3	Dietary	<ul style="list-style-type: none"> Higher dietary intake of EPA and DHA was associated with lower chance of AMD progression to advanced stages, but not wet AMD (OR 0.44, 95% CI 0.23 – 0.87)¹¹ 	<ul style="list-style-type: none"> No harms expected with dietary intake of fish⁵ Mercury intake concern for pregnant women⁵ 	<ul style="list-style-type: none"> When just higher intake of servings of fish measured, it was not associated with any benefit; possible benefit only apparent if fish high in EPA and DHA are consumed¹¹
	Supplement	<ul style="list-style-type: none"> AREDS II trial demonstrated no difference in progression to advanced AMD with the addition of DHA 350mg and EPA 650mg to the AREDS formula²⁵ 	<ul style="list-style-type: none"> Under 2-3 grams per day of fish oil is safe⁵ Fishy aftertaste or burp, nausea or heartburn possible⁵ 	<ul style="list-style-type: none"> AREDS II trial did not have a placebo comparator—only compared to the AREDS formula without addition of EPA or DHA²⁵

1) Ocular vitamins (eg. Vitalux-AREDS®, Ocuville®)

Vitalux-AREDS® is the most commonly used supplement to treat AMD, but the available evidence supporting its efficacy weak. The largest study (the AREDS trial) compared anti-oxidants vs. anti-oxidants plus zinc vs. zinc alone vs. placebo in a randomized controlled trial of 3640 participants aged 55-80. The trial included patients with dry AMD at early, intermediate and advanced stages; patients with no AMD were excluded⁷.

The available evidence suggests the use of the AREDS-formula supplement should be restricted to patients with intermediate or advanced dry AMD; it appears there is no protective effect in patients without AMD and the effect on early disease is unknown, but likely insignificant⁷. Also, the safety profile of anti-oxidants in supplements is not yet determined, so they should not be used unless benefit is expected. There have been harms associated with anti-oxidants, such as yellowing of skin, genito-urinary problems, and an increase in all-cause mortality.

The ocular supplements currently available in Canada do not match the AREDS trial formula.

	Beta-carotene	Vitamin C	Vitamin E	Zinc	Copper	Other
AREDS trial	25,000 IU	500mg	400 IU	80mg	2mg	--
Vitalux-AREDS¹⁵	19,000 IU	500mg	400 IU	80mg	2mg	• Lutein 10mg
Ocuville Adult 50+¹⁶	--	150mg	30 IU	9mg	1mg	• Zeaxanthin 1mg • Lutein 6mg • EPA 160mg • DHA 90mg
Icaps Time Release Formula With Lutein & Zeaxanthin¹⁶	--	400mg	150 IU	50mg	4mg	• Vitamin A 6600 IU • Manganese 10mg • Riboflavin 10mg • Selenium 40mcg
Preservision AREDS 2 formula¹⁶	--	452 mg	400 IU	69.6mg	1.6mg	• Lutein 10mg • EPA 650mg • DHA 350mg
Eye Care Multivitamins and Minerals with Lutein – AREDS¹⁶	19,000 IU	500mg	268 IU	50mg	2mg	• Lutein 10mg
I-Care Formula¹⁶	5000 IU	300mg	100 IU	40mg	2mg	• Lutein 10mg • Zeaxanthin 1mg

*Doses are the daily amounts taken per manufacturer recommendation

2) Lutein and zeaxanthin

Lutein and zeaxanthin has been examined for use in AMD. Lutein is a carotenoid with antioxidant properties; zeaxanthin is the stereoisomer of lutein.

The available evidence shows possible benefit for normal dietary intake of lutein and zeaxanthin¹⁰—approximately 1000 ug per day, found in green, leafy vegetables such as kale, spinach, swiss chard and romaine lettuce—which most North Americans already meet^{22,23}. Lutein and zeaxanthin supplements have been evaluated in the AREDS II trial, and were found to have no additional benefit over placebo (which was the AREDS formula). However, no harms were found with supplementary lutein over 4.9 years in this study²⁵.

3) Omega-3 fatty acids

Omega-3 continues to be investigated for many uses, but few quality studies exist for its use in AMD. As with lutein, higher dietary intake of omega-3 was associated with a lower chance of AMD progression, though evidence is limited¹¹. There is only one quality study available that investigated EPA and DHA supplementation for AMD—the AREDS II trial—which did not demonstrate a different versus placebo (the AREDS formula) in reducing the progression of AMD²⁵.

Advise patients that increasing fish intake to at least two servings of fish per week, as per the Health Canada Food Guide, may be beneficial for AMD, but it appears omega-3 supplements do not treat or prevent AMD.

Summary

Although patients may want to try supplements to help their AMD, evidence is still fairly weak. The recently completed AREDS II trial suggests lutein, zeaxanthin or EPA and DHA supplementation have no role in the treatment or prevention of AMD. With the available evidence, consider recommending Vitalux-AREDS or similar supplements only for patients with intermediate or advanced AMD^{13,14}. Also, increasing fish and green-leafy vegetable intake to normal levels may be beneficial; however, all other interventions and supplements have limited evidence, or evidence they have no effect, and there are possible safety issues associated with the use of anti-oxidants and zinc supplements.

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