

Degenerative Eye Diseases

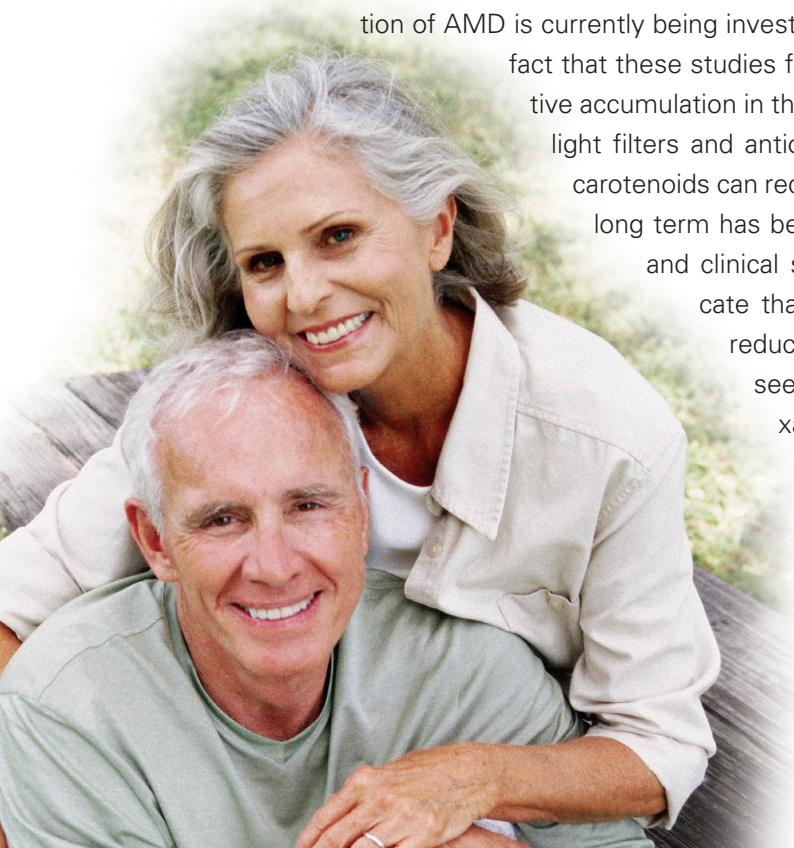
Increased Recognition of the Great Significance of Lutein and Zeaxanthin for Eye Health

With the increase in life expectancy, more and more people are at risk of developing degenerative eye diseases and suffering the consequences. The leading cause for serious vision impairment around the world is cataracts. However, because a defective lens is usually surgically replaced in western countries, this disease rarely leads to blindness there. Instead, in those countries, age-related macular degeneration (AMD) is now the main cause of serious vision impairment and irreversible blindness.

In Germany, AMD is the most common cause of legal blindness (loss of vision, visus < 1/50) in people over 65 years of age. According to the results of a recent cohort study in Denmark, the cumulative 14-year incidence for early AMD in at least one eye is 37.8% in Caucasians age group 60 to 80 years. For late forms of AMD, the cumulative 14-year incidence for this age group was 16.9%. A strongly age-dependent correlation in the incidence of AMD was also evident. People who were between 70 and 80 years of age at the beginning of the study had an 8.4 times higher risk of vision loss through advanced AMD and a 3.1 times higher risk for becoming blind than people who were between 60 and 64.¹ Based on their results the authors estimated 6,100 new cases of late AMD and 605 new cases of blindness annually per million residents for a typical northern European population. It is feared that these numbers will continue to increase in the future with the demographic changes, since, according to the World Health Organization, in the year 2025, 1.2 billion people around the world will be older than 60 years.²

Because there has been a lack of treatment options for AMD up to the present (for dry AMD) or a considerable limitation of options (for wet AMD), prevention of these diseases has top priority. In this regard, the effects of a healthy diet have received particular attention in recent years, whereby special attention is being paid to the dietary carotenoids lutein and zeaxanthin. The importance of these two carotenoids in the prevention of AMD is currently being investigated in a number of international research projects.

The fact that these studies focus on lutein and zeaxanthin is due to their highly selective accumulation in the *macula lutea* as well as to their biological effects as blue light filters and antioxidants. The biologically plausible assumption that both carotenoids can reduce the risk of degenerative diseases such as AMD in the long term has been bolstered in recent years by a series of experimental and clinical studies. When examined collectively, these studies indicate that sufficient intake of lutein and zeaxanthin considerably reduces the risk of developing AMD. A new prospective study seems to suggest that supplementation with lutein and zeaxanthin, in combination with antioxidants and micro-nutrients, significantly alleviates the symptoms of AMD in its early stages.²¹

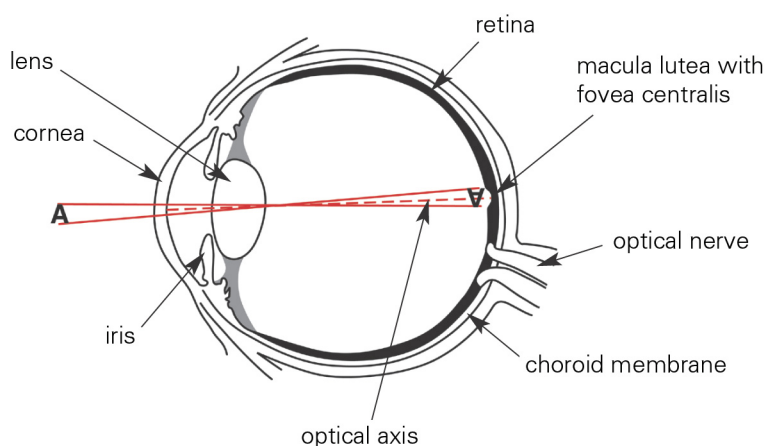


AMD and Cataracts

AMD is a disease of the central retina in which the photoreceptors in the region of the *macula lutea* become irreversibly damaged. It is characterized by blur or distortion in the center of the visual field, ultimately losing the ability to read or to recognize faces. Early signs of the disease can be detected by using the Amsler grid test. According to the current state of knowledge, the pathophysiological cause of the disease involves photooxidative damage of the retinal pigment epithelium (RPE), and disturbances of the functional unit composed of the photoreceptors, the retinal pigment epithelium (RPE) cell, Bruch's membrane, and the choroid. Histologically, the dry form of the disease is characterized by extracellular deposits of metabolic products between the RPE and Bruch's membrane (soft drusen), which are probably the result of a sustained overload. The disease progresses only slowly, so that people affected do not notice any symptoms for a long period of time. Generally, it takes years or even decades for a noticeable reduction in vision to become apparent. In the disease process, peripheral vision usually remains intact, while central vision is destroyed. The dry form of AMD, from which 85% of all AMD patients suffer, cannot, to date, be treated. Because this form of the disease can transform into the more aggressive – and treatable – wet variation, regular check-ups are necessary. The typical characteristic of wet (neovascular) AMD is the growth of new, fragile blood vessels in the subretinal region. Leakage of fluid from these vessels leads to edema development and exudative retinal detachment, scar formation and the loss of photoreceptors. Wet AMD, if left untreated, leads to loss of vision within an average of two years. Progression can be slowed down by treatments such as laser coagulation or photodynamic therapy (PDT). These therapies can, however, only be used for a small proportion of patients, and even for them, success is neither guaranteed nor permanent. Due to the very limited treatment options, prevention approaches are of great importance. Special attention is being paid to nutritional strategies, and especially to the carotenoids lutein and zeaxanthin.

Cataract Extraction Increases AMD Risk

Established risk factors for AMD include advanced age, genetic disposition and smoking. Low macular pigment density is being discussed as a risk factor.^{3,4} Also, cataract extraction appears to increase the risk for AMD: During life, photooxidative damage to proteins in the lens leads to their aggregation and precipitation.



The result is a clouding of the lens (cataract). These processes, primarily induced by UV light, also reduce the transmission of blue light through the lens – at an age when the light shielding properties of the retina via macular pigment decrease and the amounts of the photosensitizer lipofuscin deposited in the RPE increases. Here, one could speculate that the increased photoprotection by the lens may counteract diminishing light shield factors of the retina. If the lens is removed during cataract surgery, its photoprotective effect is also gone, so that the probability of photooxidative retina damage via blue light increases.

Lutein and Zeaxanthin: Chemistry, Occurrence and Significance for Nutrition

Lutein and zeaxanthin are natural, fat-soluble pigments of the carotenoid group. Both substances belong to the oxygen containing carotenoids which are called xanthophylls, i.e., in contrast to lycopene and β -carotene – so-called hydrocarbons – lutein and zeaxanthin additionally carry hydroxyl groups. Carotenoids are exclusively produced by plants. Biosynthesis in higher plants takes place in photosynthetically active tissues as well as in petals, pollen and fruit. The xanthophylls lutein and zeaxanthin are easily recognized in nature due to their yellow and orange-red colors. Two examples: Lutein lends leaves their golden yellow color in autumn after chlorophyll is decomposed ("Indian Summer"); and lutein and zeaxanthin are the pigments responsible for the yellow color of corn.

One major biological function of carotenoids in plants is the optimization of the photosynthetic process. Xanthophylls accumulate to a great extent in the thylakoid membranes of the chloroplasts. There, they act as accessory pigments, making light available for photosynthesis which is not absorbed by the chlorophylls due to their absorption gap in the spectral range of 450 - 570 nm. Carotenoids are capable of absorbing light in this region and to transfer it to neighboring chlorophyll molecules, thereby increasing the efficiency of photosynthesis. The most important carotenoid in the plant's so-called light harvesting complexes is lutein, with its absorption maxima of 445 nm (main peak), 421 nm and 475 nm. The other important function of the carotenoids is to protect plants from oxidative damage: By capturing excess energy from excited chlorophyll molecules, they prevent the formation of highly reactive and damaging singlet oxygen, thus acting in a photoprotective manner.

A similar photoprotective effect is also assumed for lutein and zeaxanthin in human tissue. Lutein and zeaxanthin occur, along with other carotenoids, in all parts of the eye. In lens and retina, however, only lutein and zeaxanthin and their metabolites have been detected. They form the "macular pigment" in the central region of the retina (*macula lutea* and *fovea centralis*). Here, their accumulation in the macula is highly selective in quality and quantity, with their concentrations being by factor 1,000 higher than in blood.⁵ As studies have shown, zeaxanthin and its isomer trans-meso-zeaxanthin accumulate especially abundantly in the center of the fovea centralis, while the concentration of lutein in peripheral areas is two times higher. Even if the mechanisms of accumulation are yet unclear, it is currently considered certain that lutein and zeaxanthin perform specific biological functions. As with all other carotenoids, lutein and zeaxanthin cannot be synthesized by the human body. They thus must be introduced regularly through food.

Macular pigment: Protects photoreceptors from radiation damage...

In the region of the *macula lutea* and the fovea centralis, the retina is relatively thin, so that incoming light reaches the photoreceptors more directly. Thus, when exposed to high-energy blue light of 400 – 475 nm over long periods of time, the photoreceptors are at increased risk of irreversible damage ("*blue light hazard*"). Because lutein and zeaxanthin very effectively absorb in that wavelength region, their selective accumulation in the macula can reduce the risk of radiation damage. It is assumed that, because of this filtering effect, lutein and zeaxanthin serve as a form of protective shield ("internal sunglasses"). This hypothesis is supported by findings from experiments in which animals were exposed to a strong acute light source. In animals with a high carotenoid content in the retina, significantly less photoreceptors apoptosis was observed compared to animals with lower retinal carotenoid content, the effect was dose-dependent.⁶ The observed spatial distribution of the macular pigment – with the highest concentration in the *foveola*, diminishing towards the periphery – correlates with the distribution of cones within the retina, and may provide insight into the protective function of the macular pigment.

From animal experiments we also know that, when raising animals on a lutein and zeaxanthin-free diet, no macular pigment is formed⁷, while characteristic changes occur in the density and distribution of the cells in the pigment epithelium.⁸ This may be interpreted as compensatory mechanisms taking place in the retina. Due to the lack of macular pigment, there is presumably a higher exposure of the retina to blue light, which leads to more intense damage and, as a result, to the observed loss of RPE cells in the *macula lutea*.

It is also hypothesized that macular pigment reduces chromatic aberration in the short-wave range and thus improves visual acuity. This may result in improved contrast sensitivity and color perception as well as the reduction of glare effects.⁹ Such effects may be achieved through a preferred spatial orientation of the lutein and zeaxanthin molecules in the axons of the photoreceptors. This may lead to preferred absorption of polarized light at certain angles and thus contribute to reduced glare sensitivity.

...and stops the formation of reactive oxygen species

Lutein and zeaxanthin have also been detected within the photoreceptors. Here, it is important to realize that the high oxygen supply to the retina and the high exposure to light facilitate the formation of reactive, potentially damaging oxygen species. This is especially true in the membranes of the outer photoreceptor segments, which have the highest content of oxidation-prone polyunsaturated fatty acids (such as DHA) in the human body.¹⁰ Since antioxidative effects have been described for lutein and zeaxanthin,^{11,12} it is obvious that a high concentration of these xanthophylls in this tissue is central for protection from lipid peroxidation. Due to its highly selective accumulation in the macula and its documented biological effects, it seems plausible that lutein and zeaxanthin contribute to the prevention of age-related degenerative eye diseases. In order to optimize the light protection of the photoreceptors, high lutein and zeaxanthin concentrations would be desirable in the region of the macula.

Nutrition and Eye Health

Because carotenoids cannot be synthesized by the human body, they must be regularly taken up from the diet. This is also true for lutein and zeaxanthin. In Germany, the mean dietary intake of lutein is about 1.9 mg/day, while the daily intake of zeaxanthin is around 0.1 to 0.2 mg.^{13,14} Depending on individual nutritional habits, a very high variation of intakes can be assumed. The main sources of lutein and zeaxanthin are yellow-red and green vegetables, yellow to red fruits, and eggs. One must take into consideration that the amount of the xanthophylls contained in the plants depends on where the plant has been grown, on the climatic conditions, and its stage of maturity. Depending on the type of plant, lutein and zeaxanthin are either present in free or esterified forms: Green vegetables (e.g. kale, lettuce, broccoli, spinach), as well as corn and eggs contain the free form; the esterified form (lutein ester) is formed in yellow-red fruits and vegetables (e.g. peppers, peaches and citrus fruits).



The association between carotenoid levels in the retina and ocular health has been investigated in several epidemiological studies. Two important studies in this respect are the Eye Disease Case Control Study¹⁵, in which a higher intake of lutein and zeaxanthin through food correlated with a lower incidence of neovascular AMD, and the Beaver Dam Eye Study¹⁶, in which no such association was observed. The discussion about the potential reasons for this

discrepancy focused on the fact that the participants in the Beaver Dam Eye Study had considerably lower carotenoids intakes, so that the resulting macular pigment levels may have been too low to exert protective effects. It must be kept in mind that epidemiological studies on nutritional status generally pose a methodological problem, since carotenoid levels in the blood are only partially determined by carotenoid intakes. In the general population, a number of additional environmental influences must also be taken into consideration which can potentially influence the blood levels achieved with a given dose in a positive or negative manner. Individual differences in carotenoid blood levels after supplementation have been related to factors such as smoking, physical activity, serum cholesterol levels and inflammatory processes (C-reactive protein)¹⁷. Currently, studies are under way to attempt to determine recommendations on optimal doses of lutein and zeaxanthin.

Dietetic Influence on Macular Pigment Density

Despite individually varying effects of supplementation, several studies have demonstrated that, upon increasing the intakes of free lutein or lutein esters, a significant rise in the lutein level in the blood can be expected. In one recent study, the serum levels increased upon after supplementation to six to seven times of the pre-supplementation levels. As a result, the macular pigment density was significantly increased in both healthy persons and patients with early forms of AMD.¹⁸ These results confirm findings of earlier studies in which supplementation with lutein resulted in significant increases in serum levels within one to two weeks. The macular pigment density increased in these studies after about four weeks. However, this effect lasted longer than in the increases in blood and, and the macular pigment density remained elevated even after the intake of lutein and zeaxanthin had been reduced to its initial levels.¹⁹ Further studies in which lutein was supplemented in doses of between 2.4 and 30 mg daily showed that the extent of macular pigment enhancement was dependent upon the lutein and zeaxanthin plasma level achieved. The macular pigment density before supplementation had no effect on this result.²⁰

The results of previous studies are presently being confirmed by an ongoing study: 108 subjects with and without AMD are being supplemented with 12 mg of lutein and 1 mg of zeaxanthin daily for a period of six months. The control group consists of 28 persons who are not receiving supplements. In the active treatment group, serum concentrations of lutein and zeaxanthin, as well as the macular pigment density, are measured every six weeks using an objective measurement technique: autofluorescence spectroscopy with a scanning laser ophthalmoscope (SLO). After supplementation has been discontinued, the macular pigment density is measured two more times at intervals of three months, in order to obtain further data on the biokinetics of both carotenoids in the retina. Already after three months of supplementation, an increase in macular pigment density was observed in the majority of the subjects, with apparently larger and faster increases when initial values were lower. *²¹

Lutein, Zeaxanthin and β-Carotene Content in Selected Foods (mg/100g), various Sources

	Lutein*	Zeaxanthin	β-Carotene
Kale	14.7 – 39.6	n.a.	2.8 – 14.6
Spinach	4.5 – 15.9	0.2 – 0.3	3.0 – 6.7
Broccoli	0.8 – 2.4	n.a.	0.3 – 1.1
Peas	1.1 – 2.4	n.a.	0.1 – 1.3
Corn	0.4 – 1.9	0.3 – 0.9	< 0.1
Carrots	0.2 – 0.3	n.a.	8.5 – 10.8
Peppers (yellow/red)	< 0.1 – 8.2	1.5 – 16.8	1.9 – 2.9
Oranges	0.1 – 0.2	0.07	< 0.1
Peaches	< 0.1	< 0.01	≈ 0.1
Apples	< 0.1	< 0.01	< 0.1
Eggs	0.1 – 2.1	0.1 – 1.6	n.a.
Potatoes	0.02 – 0.05	< 0.01 – 0.11	< 0.01
Grains	0.02 – 0.14	< 0.01 – 0.03	n.a.

*For analytical reasons, data in the literature is often represented as lutein plus zeaxanthin; n.a.: not available

* Product used: Ocuville Lutein (2 x 2 tablets/day), composition (per 2 tablets): 6 mg lutein, 0.5 mg zeaxanthin, 60 mg vitamin C, 8.8 mg vitamin E, 20 µg selenium, 5 mg zinc.

The bioavailability of lutein from various sources, which is important with regard to the plasma levels which can be achieved with a given dose, has also been studied extensively. As was reported in the renowned American Journal of Clinical Nutrition, in a clinical study the bioavailability of this carotenoid was highest from eggs. The bioavailability from the other three sources investigated – spinach, supplements containing free lutein and supplements containing esterified lutein – was comparable.²² Good bioavailability from both sources (free lutein and lutein esters, resp.) was also demonstrated in other studies, in which lutein was supplemented through food. There, there were some indications that the availability from the esterified form was higher as from the free form.²³ Overall, the available evidence demonstrates the lutein esters from dietary supplements represent an excellent source of lutein for the human body.

LAST Study

A recent study indicated that the importance of lutein may extend beyond the prevention of AMD. According to a trial known by the acronym LAST (Lutein Antioxidant Supplementation Trial),²⁴ a dietary supplement containing lutein can also improve symptoms of existing AMD. In the prospective, randomized trial, 90 patients with dry AMD received either placebo or lutein, either alone or in combination with vitamins and trace elements (such as vitamin C, vitamin E, β -carotene, zinc and selenium). After the supplementation period, macular pigment density had increased by approximately one third in both active treatment groups compared to placebo. Improvements in several parameters of vision, such as visual acuity, contrast sensitivity and glare

recovery were observed as well. These effects may be partly due to a decrease in chromatic aberration. However, the improvements in optical distortion effects and blind spots, which are conceived as distinct visual phenomena, may even suggest effects on ameliorating or revising disease progression. The authors hypothesize that the observed effects are due to free radical scavenging and prevention of apoptotic processes.

Expert Committee Confirms the Safety of High Lutein Dosages

Use of lutein and zeaxanthin for extended periods is safe. This is the conclusion of the Joint Expert Committee for Food Additives (JECFA) of the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) at their routine meeting in June of 2004. It is based on the formal safety evaluation for lutein (together with zeaxanthin) from *Tagetes erecta* (www.who.int/ipcs/publications/jecfa/en/summary_final.pdf). According to the committee, the acceptable daily intake (ADI) is 2 mg per kg body weight per day, equivalent to 120 mg of lutein (plus zeaxanthin) for a 60 kg (132 lbs) adult. The ADI is defined as the amount of a substance that can be ingested on a daily basis and over a lifetime without appreciable health risks.³⁰ The ADI only refers to the safety of a substance, and should not be confused with recommendations for optimal intakes for health benefits. Health benefits may be observed with much lower dosages: In clinical trials, supplementation with 2.4 mg lutein per day already resulted in increased lutein levels in the blood as well as increased macular pigment density.³¹

The results of the LAST study were not very surprising to experts, since the supplementation with antioxidants and trace elements had also resulted in a slowing down of disease progression in the previously published AREDS study (AREDS: Age-Related Eye Disease Study).²⁵ In this large-scale intervention study conducted by the U.S. National Eye Institute, 3,640 patients with varying stages of AMD (AREDS categories 2 to 4) were supplemented for an average of 6.3 years with either antioxidants (500 mg of vitamin C, 400 I. E. of vitamin E and 15 mg of β -carotene daily), high doses of zinc (80 mg daily), a combination of these substances or a placebo. The results: in patients with several medium or large drusen in both eyes and/or geographic atrophy or neovascularization in one eye, supplementation with vitamins and trace elements reduced the risk of disease progression by 28% compared to the placebo group.

If only zinc was supplemented, the risk of disease progression was reduced by 20%. The authors extrapolated their findings to all AMD patients in the USA and concluded that the intervention with vitamins and trace elements as given in AREDS could prevent a deterioration of vision in 300,000 of the eight million patients over a five-year period. Because lutein and zeaxanthin were not commercially available when AREDS was planned and started, the carotenoids were not part of the supplementation regimes. Whether or not their

not part of the supplementation regimes. Whether or not their regular administration would have improved the treatment success even more is now being examined in a new intervention study in which β -carotene is replaced by lutein.

Techniques for Measuring Macular Pigment Density

For some time now, scientists have been working on techniques to measure macular pigment density. Such techniques may provide insight into potential risk factors for AMD or even document the treatment success of supplementation strategies. Currently there is no standard procedure. One method widely used is the so-called heterochromatic flicker photometry (HFP). In this psychophysical procedure, test subjects look at a spot of light that rapidly switches between blue (460 nm) and green light (540 nm). The brightness of the blue stimulus is adjusted by the subjects until the stimulus appears constant. With higher macular pigment density more blue light is required to reach a non-flickering state due to increased absorption. Therefore, the macular pigment density can be estimated fairly accurately using this technique. However, there are limitations to HFP, in that the results are primarily determined by the subjective reaction of the subjects. In addition, HFP assumes an equal sensitivity of the photoreceptors to blue and green light. Under controlled laboratory conditions, HFP has produced good results. Its applicability in daily clinical work, however, may be limited for several reasons, for example because subjects require a certain amount of practice in this method. In addition, people with impaired vision may not, or only partially, be able to perform the test. Nonetheless, HFP is the most widespread method for measuring macular pigment density, and has been used in most studies.²⁶

Direct and objective procedures for the measurement of macular pigment density include reflection spectroscopy²⁷, autofluorescence spectroscopy²⁸ and Raman spectroscopy²⁹. The latter uses a specific physical property of carotenoids: their Raman spectra. When illuminating carotenoids with monochromatic light, part of this light is scattered with characteristic wavelength shifts due to the vibrational modes determined by the molecular structure of the carotenoid. The intensity of these characteristic Raman signals is determined by the amount of existing pigment, and can therefore be quantified. Fundus autofluorescence spectroscopy makes use of the fact that blue light is absorbed by the lipofuscin in the macula and is reflected as green autofluorescence. Because retinal areas with higher macular pigment density absorb more blue light than areas with a lower density, such regions can be easily differentiated.²⁸

These three so-called "objective" methods are technically complex and, due to a lack of commercially available equipment, can currently only be employed by specialized centers.



Conclusion

- Age-related macular degeneration is the most common cause of legal blindness in people over the age of 65.
- Established risk factors for AMD are advanced age, genetic disposition and smoking. Current research implies that a relative deficiency of the macular carotenoids lutein and zeaxanthin may be a further risk factor.
- Due to limited treatment options, strategies aiming at disease prevention have a high priority.
- Lutein and zeaxanthin are highly selectively accumulated in the macular region of the retina. The macular pigment is essential for the development and preservation of a normal RPE profile in the center of the retina.
- Both carotenoids may contribute to optimal light protection of the photoreceptors and thus to the prevention of age-related degenerative eye diseases.
- Favorable effects of supplementation on macular pigment density have been documented in healthy people as well in patients with early AMD.
- In the LAST study, AMD patients benefited from lutein supplementation through an improvement in vision, including visual acuity and contrast sensitivity.
- Lutein esters from dietary supplements represent an excellent lutein source for the human body.
- Even higher lutein and zeaxanthin intakes are safe for extended periods of time.

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