December 30, 2020

PharmacologyOnLine

Special issue • 2020 • vol.3 • 93-101

OXIDATIVE STRESS AND SUPPLEMENTATION IN AGE- RELATED MACULAR DEGENERATION

Laurenziello Pasqualina[1], D'Elia Maria[1,2]

[1]Post Graduate University Course in "Diete e Terapie Nutrizionali Chetogeniche: Integratori e Nutraceutici (NutriKeto)" - Dipartimento di Farmacia, University of Salerno, Via Giovanni Paolo II – Fisciano (SA), Italy
[2]Nutriketo Lab, A.O.R.N. 'San Giuseppe Moscati', Contrada Amoretta, Avellino, Italy

Email address: alina.laurenziello@gmail.com; nutriketo@unisa.it

Abstract

Age-related macular degeneration (AMD) is the third leading cause of blindness worldwide. Globally, it accounts for 8.7% of the blind population. It is a complex disorder of the eye that is late onset with a multi-factorial etiology in the elderly. In fact AMD results in progressive and irreversible loss of central vision affecting the macula of the eye and involves the retinal pigment epithelium (RPE), Bruch's membrane (BM) and choriocapillaries.

Reduced contrast sensitivity, central visual field loss and spatiotemporal sensititvy are visual defects experienced by patients before the onset of AMD. These defects are the cause of difficulty with daily tasks.

It is estimated that by the year 2020, at least 80 million people will be affected by AMD globally [1]. If the aetiology of this multi-factorial disease isn't clear, age is the most consistent risk factor associated with AMD. Genetic factors, oxidative stress and inflammation are also significant contributors to AMD pathogenesis. Systemic oxidative stress, which is caused by cigarette smoking, is a significant risk factor for AMD. According to several clinical studies, the progression of AMD can be slowed by taking antioxidant supplements [2], which may reduce this oxidative damage.

Keywords: *AMD, antioxidant, oxidative stress, supplementation.*

Introduction

Worldwide, age-related macular degeneration, the complex progressive eye disease, is the main readon for legal blindness and elderly vision loss. The estimated global pooled prevalence of AMD in 2013 was about 17%. The amount of people affected by AMD is 196 million but projected to increase to 288 million people by 2040. The global costs of AMD are 101.1 million euros in the UK, 60.5 million euros in Italy, 91.4 million euros in Germany, and 51.3 million euros in France [4].

It is a degenerative disorder of the macula which is an area near the central retina and is responsible for the greatest visual acuity.

Chronologically, AMD can be categorized as early and late stage.

Early stage is associated with the pathological deposits (drusen) between the Bruch's membrane and the retinal pigment epithelium (RPE).

In the late stage, AMD can manifest in two forms: non-neovascular (known as 'dry') and neovascular (known as 'wet'). In neovascular AMD, new blood vessels often leak into the retina and cause hemorrhages, retinal detachment and disciform scars. Wet AMD can currently be treated with repeated intravitreous injections of anti-vascular endotheial growth factor A (VEGFA). Late stage non-neovascular AMD is also called geographic atrophy (GA) and is characterized by the degradation of RPE cells, overlying photoreceptors, and also the underlying choriocapillary. It accounts for 90% of AMD cases and at the moment is untreatable.

In the human body intensive oxygen metabolism, the retina is one the the highest oxygen-consuming tissues. The production of reactive oxygen species (ROS) is increased by continual exposure to light, high concentrations of polyunsaturated fatty acids, and the presence of photosensitizers. Overproduction by chronic oxidative stress can exceed the anti-oxidation capability of the retina and lead to modification and damage of carbohydrates, membrane lipids, proteins, and nucleic acids. In the aging of the retina, it has been observed an age-related increase in lipofuscin (potent generator of photoinducible ROS in RPE), 8-oxoguanine (a product of oxidative DNA damage), damage mitochondrial DNA, carboxyethylpyrol (an oxidation fragment of docosahexaenoic acid), and the presence of 4-Hydroxynonenal and malondialdehyde (products of lipid peroxidation). Being as photoreceptors (PR) in the retina, the cells are constantly exposed to light and oxygen, they are particularly susceptible to oxidative damage. RPE cells have many important functions such as phagocytosis of the PR outer segment membrane. This means they are vital for PR survival, function and renewal. Secondary PR cell death is usually caused by the degeneration of RPE, which in turn is caused by oxidative or other stresses. In AMD, oxidative stress collaborates with other risk factors which include aging, smoking, phototoxicity, and genetic factors. All of this leads to deposits of drusen on retinal pigment epithelium cells (RPE), death of RPE / PR cells, and the resulting inflammatory and immune responses. All these processes cause oxidative stress and inflammation which lead to the pathogenesis of AMD [2]

In the past 10 years, close to 40 genetic variants have been discovered. They are all linked to AMD risk and are made up of genes that encode proteins involved in oxidative stress. It strengthens the theory that oxidative stress has an etiologic role. Mitochondira are an ample source of reactive oxygen species (ROS) formation, for example. The recognition of polymorphisms in mitochondrial MTND2*LHON4917G, NADH dehydrogenase subunits, and mitochondrial superoxide dismutase 2 (SOD2), which are correlated with AMD risk, proposes a pathogenic role for oxidative stress. In like manner, the LOC387715 locus polymorphism that is related to AMD risk is more elevated in smokers than either smoking or the polymorphism alone. This is more evidence of a pathogenic role of oxidative stress.

Since RPE are enhanced with mitochondria, the aftermath is a majot source of ROS in the RPE compared with young cells. Moreover, ageing mitochondria generate more ROS so ageing cells are increasingly prone to mitochondria derived ROS.

Physiologically, the ETC complex during the production of ATP, generates reactive oxygen species that escape from the mitochondrial membrane. in pathological conditions the generation of ROS is significantly increased,

principally at NADH complex and cytochrome complex.

Now it is clear that oxidative modifications of molecules inside the eye are pro-inflammatory and promote the progression of early AMD drusen to CNV or GA.

Oxidized molecules recruit T cells and monocytes into subretinal tissue, where monocytes differentiate into macrophages generating an inflammatory response and their conversion into foamy cells which leading to a potent inflammatory burden within the retina (8, 111).

It appears that oxidized lipids directly affect the growth, differentiation and survival of vascular cells. In fact, studies indicate that even early forms of oxidized lipoproteins cause changes in gene expression of vascular cells, leading to the initiation and maintenance of an inflammatory response that could contribute to conversion of early drusen into advanced CNV [5].

Methods

At the time, there are no prescription drugs available to prevent AMD. Recent studies have highlighted the role of the action of specific nutrients in the progression of the disease. Antioxidants seem to reduce oxidative damage.

Results

Carotenoids

Extensive research has been done regarding the health benefits of carotenoids. The appeal of this is because: 1) extremely high levels of carotenoids are present in the retina, 2) have salutary effects on the body and 3) for their antioxidant properties, in particular, in lipophilic environments.

The carotenoids, lutein and zeaxanthin, are found in considerable levels in the macula (from 30 to 10,000 times higher than in other tissues) [6]. Lutein and zeaxanthin protect the macula from damage caused by blue light. They also improve visual acuity and eliminate reactive oxygen species. Lutein and zeaxanthin combined with meso-zeaxanthin are commonly referred to as macular pigments (MP).[7]

In the fovea, the carotenoid concentration is 1 mM and the ratio of lutein to zeaxanthin and meso-zeaxanthin is 1: 1: 1.

The concentration of macular carotenoids decreases 100-fold a few millimeters from the foveal center. The compostion ratio nears 3: 1: 0 in the peripheral retina.

Many studies have been done and shot that lutein and zeaxanthin are significant carotenoids for the prevention and progression of AMD [8].

The POLANUT study showed that subjects that had the highest levels of zeaxanthin or a combination of lutein and zeaxanthin in their blood have a reduced risk for any stage of AMD [9].

The CARMIS study showed that subjects with AMD who had received a mix of 10 mg lutein, 1 mg zeaxanthin, 4 mg astaxanthin and an antioxidant supplement for 24 months, improved visual acuity and contrast sensitivity in comparison to the group that did not receive the integration. The LAST study evaluated that on 90year old subjects with geographic atrophy, after 12 months of taking a supplement of 10 mg of lutein or 10 mg of lutein plus an antioxidant, they improved MPOD, visual acuity and contrast sensitivity [10].

Both of the AREDS2 studies have evidence suggesting that levels of intake of L/Z are valid. L/Z intake levels much less than 6 mg are linked to a decreased probability of AMD. This indicates that lower levels of intake could be enough to provide some protection from the advancement of the disease. [9].

Evidence at the moment shows that higher dietary intakes of lutein and zeaxanthin will probably play an important role in safeguarding against AMD.

Zinc

Zinc is one of the most abundant elements within cells (about 95%), and plays an important role in a series of physiological processes including immunity, reproduction and neuronal development.

The main sites of zinc accumulation are in muscle, bone, skin, liver, kidney and plasma but very high concentration of zinc is also present in the retina.

In the Beaver Dam Eye study, a retrospective analysis of 1.968 participants, it was found that, compared to people with the lowest and highest dietary zinc intake, those with the highest intake of zinc had a reduced risk of developing early AMD.

Furthermore it was shown that zinc supplements reduce the risk of pigmentary abnormalities and risk for each type of AMD. [12] [13]
The Rotterdam study shows that in 4,170 participants a higher zinc intake is associated with a reduced risk for any stage of AMD. [14]
In a study of 90 subjects, Newsome and colleagues, observed a reduced vision loss with 100 mg of zinc taken twince a day for 2 years.

Vitamin E

Vitamin E is a lipophilic antioxidant and is presumably associated with AMD risk. Several studies show that vitamin E serum levels in patients with macular degeneration are significantly lower than in healthy subjects, and that it is also lower in patients with advanced AMD compared to those with early AMD.

In the POLA study an analysis was done on the 2,584 participants. It showed that after an adjustment was made in the plasma lipid levels, the participants who had the highest levels of plasma vitamin E were at less risk for signs of early AMD. These include pigment changes or soft drusen and late.

AREDS study did a baseline analysis of the 4,003 participants and it was shown that the participants who had consumed the highest amounts of vitamin E had a slightly lesser risk for late AMD in comparison to those who had consumed the smallest amounts.

The cross sectional data has been corroborated by a prospective study. In the Baltimore Longitudinal Study of ageing demonstrated that amid the 976 men and women in the study, the people with the highest plasma tocopherol levels were had a reduced risk for any stage of AMD.

Vitamine E intake was associated with an inconsequential reduction in risk for AMD (HR = 0.92; 95% CI: 0.84, 1.00) in the Rotterdam prospective cohort.

An indicator of early AMD is pigment abnormalities. In the NHS, 498 women who had increased amounts of vitamin E intake were related to a reduction of said pigment abnormalities.

There is also a relative amount of data suggesting that there is no relationship between vitamin E levels and AMD risk:

- Women's Health Study (WHS), gave 39,421 women 600 IU of vitamin E every other day or placebo for 10 years. At the end of the study they showed that vitamin E had no effect on the risk of visually significant AMD, late AMD or AMD with or without vision loss.
- ATBC study was conducted among 29,000 Finnish male smokers. Subjects received daily supplements of 50 mg of vitamin E, 20 mg of beta-carotene, both, or placebo. At the end of the study they observed that supplementation had no effect on the risk of AMD.
- a 10-year follow-up with over 2,000 subjects evaluated, conducted by the Blue Mountains Eye study, showed that higher intakes of vitamin E were associated with a greater risk for late-stage atrophic AMD compared to lower vitamin E intakes.[10]

Vitamin C

Many studies that were done have found that there is no association between vitamin C intake and AMD risk. These studies are the EDCC Study, the Beaver Dam Eye Study, the Rotterdam Study, the Baltimore Longitudinal Study of Ageing and the Blue Mountains Eye Study.

The Beaver Dam Eye and Blue Mountain Eye Studies remarkably suggest that the risk for the disease could be increased by taking a higher intake of vitamin C.

On the other hand the AREDS study made known that there is a positive association between vitamin C intake and AMD risk reduction. [19]

AREDS and AREDS2 study

Investigating the role of nutrients in AMD progression are the Age-Related Eye Disease Study (AREDS) and AREDS 2. These are the most relevant and biggest RCTs (randomized clinical trial).

Between 1995 and 2001, in the USA, the AREDS was a multicenter RCA that ran. 3,640 subjects between the ages of 55 and 80 were included in the analysis. There were 4 categories in the AMD grading according to increasing severity:

- category 1: no drusen or a few small drusen;
- category 2: pigment abnormalities, extensive small drusen or at least 1 intermediate size druse;

• category 3: geographic atrophy not involving the centre of the macula, extensive intermediate drusen or at least 1 large druse;

• category 4: advanced AMD or visual acuity less than 20/32 due to AMD in 1 eye.

Subjects were randomised to the intervention arms listed below:

• antioxidants: vitamin C (500 mg) + vitamin E (400 IU) + β-carotene (15 mg);
• zinc (80 mg) + copper (2 mg) to prevent anaemia;
• antioxidants + zinc and copper;
• placebo.

In categories 3 and 4, the group randomized to antioxidants + zinc and copper was 25% less likely to progress to advanced AMD than placebo. No effect was found in categories 1 and 2 (early AMD).

So the authors concluded that antioxidants plus zinc should be taken in patients in categories 3 and 4 that are older than 55 and who do not smoke.

However, different studies have found a higher risk of developing lung cancer in smokers, using the dose of B-carotene proposed by the AREDS study. Moreover, the recommended dose of zinc was considered excessive by many researchers because it leads to an increased in hospital admission secondary to urinary tract infections.

To examine the role of these nutrients in preventing AMD progression a new study was authorized. It was the AREDS2 study and it was published in May of 2013. This study was made up of 4,203 participants running from 2006 until 2012 and was a considerable multicenter RCT located in the USA. The participants ranged in age from 50 to 85 years old and complied with the criteria of categories 3 and 4 from AREDS.

Individuals were randomized and treated using: 1) AREDS formula, 2) AREDS formula + lutein (10 mg / day) + zeaxanthin (2 mg / day), 3) AREDS formula + DHA (350 mg) + EPA (650 mg), 4) AREDS formula + lutein (10 mg / day) + zeaxanthin (2 mg / day) and DHA (350 mg) + EPA (650 mg)

To investigate the effects of eliminating β-carotene and the diminution of the dose of zinc to 25/mg per day in the AREDS formula the participants went through secondary randomization.

The first phase of randomization showed that the carotenoid and PUFA supplements stated above had no statistical significance on the effect on AMD progression. There was no effect shown regarding the use of PUFAs in a subgroup investigation. Participants taking lutein and zeaxanthin compared to the participants in the lowest quintile of their dietary intake had a protective effect. Post hoc analysis showed that a reduction of 10% in the progression to advanced AMD patients who were taking the AREDS formula of lutein and zeaxanthin in comparison to who had the AREDS nutrients without β-carotene.

Lower zinc dosage or the exclusion of β-carotene caused no decreased efficacy or reduction in vision from the AREDS formula. In the end, there was a significant increase [15] in the group that was randomized to β-carotene and the incidence of lung cancer (2%).

Polyphenols

The many heterogeneous groups of chemicals found in plants and beverages are called dietary polyphenols (phenolics).

They can be categorized based on their chemical structure, origin, potential or actual biological function. Dietary polyphenols can be separated chemically into the following groups: phenolic acids (benzoic acid and cinnamic acid), flavonoids (isoflavones, neoflavonoids, chalcones, flavones, flavonols, flavanones, flavanonols, flavanols, proanthocyanidins, and anthocyanidins), and polyphenolic amides. Possibly important for human health are the following other bioactive polyphenols: curcumin, resveratrol, ellagic acids and their derivatives, lignans, rosmarinic acid.

Dietary polyphenols are significant for the reduction of oxidative stress in the retina and we have seen this through different reports of studies.

Quercetin and chlorogenic acid, that are abundant dietary polyphenols, reduced the levels of inflammatory cytokines including interleukins IL-8 and IL-β, TNFα, COX-2, and inducible nitric oxide synthase, decreased the levels of proapoptotic proteins and increased the levels of antiapoptotic proteins. Furthermore, the polyphenols reduced the expression of the angiogenic factors VEGF and HIF-1α (hypoxia-inducible factor 1α).

In addition, studies conducted on rabbits have shown that quercetin inhibits choroidal neovascularization (CNV).
Resveratrol was reported to protect against H2O2-induced oxidation.

Resveratrol inhibited cell proliferation related to the inhibition of the MAPK/ERK1/2 pathway when acting in a nonstress condition. Inhibition of RPE cell proliferation can be translated into the protective action of resveratrol against proliferative vitreoretinopathy (PVR), associated with hyperproliferation of RPE cells.

Stress induced by UVB irradiation in a human RPE cell line were said to have a strong protective effect by a mixture of 8 polyphenol (catechins) extracts from green tea (GTP). This was reported by Xu et al.

The viability of UVB-irradiated cells was increased by GTP by way of means of a dose-dependent manner all the way up to a concentration of 140 mg/l.

Using GTP, the protective effect was only stronger when the cells were preincubated and and not when they were postincubated. Quite a few abnormalities in the microstructure or RPE cells were induced by UVB irradiation. An example of an abnormality is deformation to mitochondria. UVB exposure eased these changes with GTP both before and after the exposure. A nonspecific DNA fragmentation by UVB and protective influence of the GTP on this effect [16] was shown from DNA damage analysis that was simply made from agarose gel electrophoresis.

At the University of Oklahoma Health Sciences Center, a study was published by the Department of Ophthalmology. The study showed significant retinal neuroprotection in rats that were fed diets with curcumin supplementation (0.2%) for 2 weeks. Curcumin seems to modulate the expression and activation of numerous cellular regulatory proteins such as NF-κB, AKT, NRF2 and growth factors, then inhibiting cellular inflammatory responses and protect cells. For preventive and augmentative AMD therapy [17], it has been suggested that curcumin would be an effective nutraceutical compound.

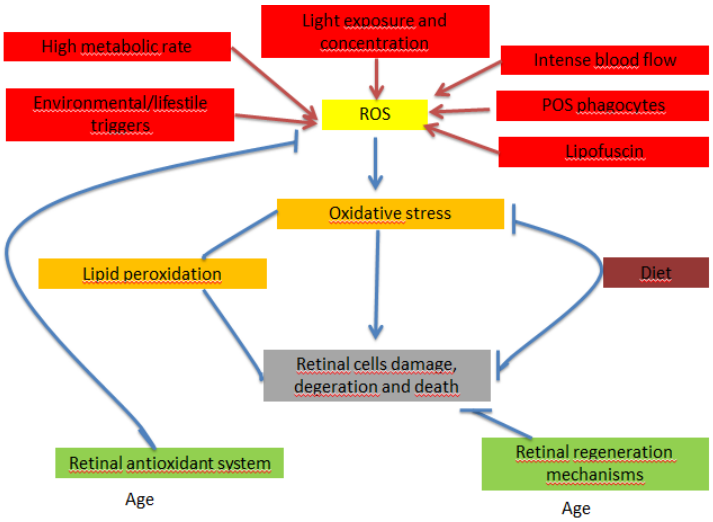

Fig.1 A vital feature of age-related macular degeneration is the oxidative events that occur in the retina and their taking part in the degeneration and death of retinal cells. Physiological sources of reactive oxygen species (ROS) are a high metabolic rate, intense blood flow in the retina and also its massive light exposure.

The further ROS production is led by phagocytosis of photoreceptor outer segments (POS) and accumulation of lipofuscin, a protein/lipid mixture, lead to further ROS production. Additional exposure to blue light, smoking and diet are environmental and lifestyle factors that can potentiate ROS production.

ROS overproduction and ameliorate retinal damage can be associated with some nutritional compounds that can inhibit oxidative stress. Retinal antioxidant defense can directly inhibit oxidative stress and its intermediates which include lipid peroxidation, but it decreases with age. Limited regenerative and renewal mechanisms in the retina also decline with age. [16]

Carbohydrates

Epidemiologic studies indicate that a low-GI diet is associated with reduced risk for AMD. After consuming a food that contains carbohydrates, the glycemic index (GI) indicates how fast blood glucose is elevated. Human metabolic studies show that GI is correlated to patho-physiological reactions after meals. In comparison to a low-GI meal, a high-GI meal is characterized by hyperglycemia during the initial postprandial stage and a hyperlipidemia which is associated with hormone responses during late postprandial stage. There are positive links between

GI and the risk for age-related macular degeneration (AMD) in people without diabetes. We see this from ample epidemiological evidence. There are molecular theories that illustrate hyperglycemic pathogenesis. It involves a mitochondria linked pathway and also 4 glycolysis linked pathways. These include advanced glycation end products formation, polyol pathway, hexosamine pathway and protein kinase C activation. Some evidence shows us that when hypoxia coincides with hyperglycemia the retina is notably vulnerable. In addition, it has been observed that a high glycemic index diet determines the expression of inducible HIF genes, such as endothelial growth factor (VEGF) which leads to angiogenesis.

High concentrations of glucose transporters are expressed at the level of retinal blood vessels, which facilitates the formation and accumulation of AGE (end products of advanced glycation). AGEs can have a detrimental effects on the activity of degradative enzymes, on the function of RPE, and on the integrity of the choriocapillary and Brunch membrane. Foods that have high glycemic indexes that further compromise these processes, as they induce a sharp increase in blood glucose concentrations by providing an excess amount of glucose compared to the actual demand.[18]

Ketogenic Diet and treatment of Age-Related macular degeneration

Dr. Russell Wilder, in the 1923, at the Mayo Clinic proposed the ketogenic diets for the treatment of childhood refractory epilepsy. in ketogenic diets macronutrient ratio of fat to protein plus carbs equal to 3–4:1 (4 grams of fat to 1 gram of protein and carbohydrate combined).

The slight reduction of blood glucose concentration with increasing KBs is the resulting metabolic profile.

All KDs are a variation of the classic KD with a difference the macronutrient ratio: the Modified Ketogenic Diet (2:1–1:1), the Modified Atkins Diet (MAD; 1:1), and the more recent, Medium-Chain Triglyceride (MCT) oil diet (1.9:1)

When compared to glycolysis, KBs metabolism reduces oxidative stress, more precisely B-hydroxybutyrate reduce the production of ROS improving mitochondrial respiration. The ketogenic diet stimulates the cellular endogenous antioxidant system with the activation of nuclear factor erythroid-derived 2 (NF-E2)-related factor 2 (Nrf2), the major inducer of detoxification genes.

Fundamental enzymes such as glutathione reductase, thioredoxin and peroxiredoxin, are induced by Nrf2 and then implicated in the regeneration of the active form of endogenous antioxidants.

In conclusion on the basis of what was mentioned above, KD could be used to reduce oxidative stress in macular degeneration.

Lipid and macular degeneration

In humans, DHA comprises 40% of the polyunsaturated fatty acids (PUFA) in the brain and 60% of the lipid constituents of the retinal photoreceptor membrane. The beneficial effects of DHA and EPA for health come from the ability to reduce the production of inflammatory eicosanoids, cytokines, reactive oxygen species. Also to modulate the expression of numerous genes involved in the inflammatory pathways.

Several studies show that a higher intake of omega-3 fatty acids, DHA and EPA is associated with the improvement of a number of chronic diseases which include AMD.

High intakes of DHA + EPA (especially DHA) and fatty fish appear to be associated with a 17 to 40% lower risk of visually significant intermediate AMD, but with no reduction in the risk of advanced AMD.[21]

There are a large number of epidemiological studies examining the effects of diets rich in omega-3 on the progression of AMD. Of the studies estimating fish consumption, they all show that higher fish or oily fish consumption is associated with a lower risk of AMD.[22]

Discussion

Age-related macular degeneration is a very serious condition that can lead to vision loss or blindness.

The disease affects the central part of the retina known as the central macula. This is the most

sensitive area of the retina that is responsible for sharp and detailed vision.
AMD patients often experience severe depression because the disease creates significant difficulties in carrying out daily activities such as writing, reading, driving, and recognizing faces.
There are various medical therapies for wet maculopathy. However, they do not cure the disease but aim to stabilize and preserve the best possible vision.
For dry maculopathy, no treatment is effective in slowing or stopping the progression of the disease. Several studies have shown that disease progression can be slowed by taking supplements to reduce oxidative stress such as lutein, zeaxanthin, zinc and vitamin E supplements.
Furthermore, it would appear that a KD could be useful for combating oxidative stress in several neurological conditions, so it might be reasonable to use KD to slow the progression of AMD.

References

1. Katta, S., Kaur, I., & Chakrabarti, S. (2009). The molecular genetic basis of age-related macular degeneration: an overview. Journal of genetics, 88(4), 425-449.
2. 2.Jakub Hanus, Chastain Anderson, and Shusheng Wang (2015) RPE Necroptosis in Response to Oxidative Stress and in AMD. Ageing Res Rev.;24(Pt B):286-98
3. Sayantan Datta, Marisol Cano, Katayoon Ebrahimi Lei Wang, and James T. Handa (2017) The Impact of Oxidative Stress and Inflammation on RPE Degeneration in Non-neovascular AMD. Prog Retin Eye Res.; 60:201-218.
4. Kaarniranta, K., Pawlowska, E., Szczepanska, J., Jablkowska, A., & Blasiak, J. (2019). Role of mitochondrial DNA damage in ROS-mediated pathogenesis of age-related macular degeneration (AMD). International journal of molecular sciences, 20(10), 2374.
5. Shaw, P. X., Stiles, T., Douglas, C., Ho, D., Fan, W., Du, H., & Xiao, X. (2016). Oxidative stress, innate immunity, and age-related macular degeneration. AIMS molecular science, 3(2), 196.
6. Weikel, K. A., Chiu, C. J., & Taylor, A. (2012). Nutritional modulation of age-related macular degeneration. Molecular aspects of medicine, 33(4), 318-375.
7. Eisenhauer, B., Natoli, S., Liew, G., & Flood, V. M. (2017). Lutein and zeaxanthin—food sources, bioavailability and dietary variety in age-related macular degeneration protection. Nutrients, 9(2), 120.
8. Abdel-Aal, E. S. M., Akhtar, H., Zaheer, K., & Ali, R. (2013). Dietary sources of lutein and zeaxanthin carotenoids and their role in eye health. Nutrients, 5(4), 1169-1185.
9. Eisenhauer, B., Natoli, S., Liew, G., & Flood, V. M. (2017). Lutein and zeaxanthin—food sources, bioavailability and dietary variety in age-related macular degeneration protection. Nutrients, 9(2), 120.
10. 10 Weikel, K. A., Chiu, C. J., & Taylor, A. (2012). Nutritional modulation of age-related macular degeneration. Molecular aspects of medicine, 33(4), 318-375.
11. King, J. C. (2011). Zinc: an essential but elusive nutrient. The American journal of clinical nutrition, 94(2), 679S-684S.
12. Mares-Perlman, J. A., Klein, R., Klein, B. E., Greger, J. L., Brady, W. E., Palta, M., & Ritter, L. L. (1996). Association of zinc and antioxidant nutrients with age-related maculopathy. Archives of ophthalmology, 114(8), 991-997.
13. VandenLangenberg, G. M., Mares-Perlman, J. A., Klein, R., Klein, B. E., Brady, W. E., & Palta, M. (1998). Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. American journal of epidemiology, 148(2), 204-214.
14. Van Leeuwen, R., Boekhoorn, S., Vingerling, J. R., Witteman, J. C., Klaver, C. C., Hofman, A., & de Jong, P. T. (2005). Dietary intake of antioxidants and risk of age-related macular degeneration. Jama, 294(24), 3101-3107.
15. Andreatta, W., & El-Sherbiny, S. (2014). Evidence-based nutritional advice for patients affected by age-related macular degeneration. Ophthalmologica, 231(4), 185-190.

16. Pawlowska, E., Szczepanska, J., Koskela, A., Kaarniranta, K., & Blasiak, J. (2019). Dietary polyphenols in age-related macular degeneration: Protection against oxidative stress and beyond. Oxidative medicine and cellular longevity, 2019.
17. Md Nawajes A. Mandala, Jagan M.R. Patlollac, Lixin Zhenga, Martin-Paul Agbagaa, , Julie-Thu A. Trana, Lea Wickera, Anne Kasus-Jacobia, Michael H. Elliotta, Chinthalapally V. Raoc, and Robert E. Anderson. (2009) Curcumin Protects Retinal Cells from Light- and Oxidant Stress induced Cell Death. Free Radic Biol Med.;46(5):672-9.
18. Chiu, C. J., & Taylor, A. (2011). Dietary hyperglycemia, glycemic index and metabolic retinal diseases. Progress in retinal and eye research, 30(1), 18-53.
19. Weikel, K. A., Chiu, C. J., & Taylor, A. (2012). Nutritional modulation of age-related macular degeneration. Molecular aspects of medicine, 33(4), 318-375.
20. Pinto, A., Bonucci, A., Maggi, E., Corsi, M., & Businaro, R. (2018). Anti-oxidant and anti-inflammatory activity of ketogenic diet: new perspectives for neuroprotection in Alzheimer's disease. Antioxidants, 7(5), 63.
21. Wu, J., Cho, E., Giovannucci, E. L., Rosner, B. A., Sastry, S. M., Willett, W. C., & Schaumberg, D. A. (2017). Dietary intakes of eicosapentaenoic acid and docosahexaenoic acid and risk of age-related macular degeneration. Ophthalmology, 124(5), 634-643.
22. 22. Souied, E. H., Aslam, T., Garcia-Layana, A., Holz, F. G., Leys, A., Silva, R., & Delcourt, C. (2016). Omega-3 fatty acids and age-related macular degeneration. Ophthalmic research, 55(2), 62-69.