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DIETARY NUTRIENTS AGAINST AGE RELATED MACULAR DEGENERATION AND DIABETIC RETINOPATHY

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Abstract

The human retina is susceptible to pathological changes such as oxidative stress and inflammation due to a high oxygen consumption, prolonged exposure to light and an abundant amount of polyunsaturated fatty acids in the photoreceptor cell membrane. Additionally, ageing and hyperglycemia further promote a lot of pathological mechanisms leading to retinal damage and vision loss. Due to their benefic effects not only into the whole body, but especially for the eyes, dietary carotenoids, vitamins, omega-3 fatty acids, zinc and polyphenols are seen as a therapy that could prevent damage to the retinal pigment epithelium and photoreceptor layer as well as visual impairment, characteristic to age related macular degeneration (AMD) and diabetic retinopathy (DR). The purpose of this article is to review the main dietary nutrients and their proposed mechanism of action into the body and to the eyes.

Key words: AMD, DR, carotenoids, vitamins, omega-3 fatty acids, zinc, polyphenols, oxidative stress, inflammation

INTRODUCTION

Nutrition plays a major role in human health as it can improve and maintain it. Good dietary habits and an active lifestyle have been associated over the years with the prevention of certain diseases. Age related-macular degeneration and diabetic retinopathy make no exception and studies show that certain dietary nutrients can prevent the onset and later progression to more severe stages. The nutrients that have been shown to exert benefic effects are carotenoids (lutein, zeaxanthin, meso-zeaxanthin, beta-carotene), omega-3 fatty acids, vitamins (A, C and E), minerals (zinc) and polyphenols.

AGE RELATED MACULAR DEGENERATION AND DIABETIC RETINOPATHY

Age related-macular degeneration is a complex and multifactorial disease that affects individuals over the age of 60 resulting in irreversible vision loss. Literature describes 2 types of AMD: the atrophic or dry form and the exudative or wet form [1] [2]. Between these 2, the wet one is characterized by a severe retinal damage. The pathological mechanism is

still uncertain and warrants more research, but previous studies identified several processes that may contribute in a major way to the onset of AMD and its progression to later stages. Oxidative stress and inflammation are the main processes involved [3] [4]. Oxidative stress results from an imbalance between the antioxidant systems and the reactive oxygen species/ROS generated in higher amount due to factors such as high content of PUFAs, high O_2 consumption, prolonged exposure to light and ageing [5][6]. Besides the above mentioned ways of inducing damage to the macular RPE layer and photoreceptors, the presence of lipofuscin and drusens is also important since lipofuscin promotes photooxidation through photosensitizing substances[1] [7], whereas drusens, the hallmark of AMD produce RPE detachment[1] [8]. Inflammation occurs as a result of cellular damage, lipofuscin-induced lysosome dysfunction, and the presence of drusens between the RPE layer and Bruch's membrane [8] [9][4].
Diabetic retinopathy is a chronic disease that leads to blindness inpopulation aged between 30 and 60 years old. Similar to AMD, there are 2 stages in the progression of DR: the nonproliferative stage and the proliferative one [10] [11] [12]. Fluid accumulation in the macular region due to increased vascular permeability leads to thickening and vision loss. This form of edema is known as diabetic macular edema and it can occur in any stage of DR [12].

The pathological pathway is triggered by hyperglycemia that induces oxidative stress. Furthermore, oxidative stress leads to increased cellular damage and the activation of the polyol pathway, the advanced glycation end product (AGE) pathway, protein kinase C (PKC) pathway, the hexosamine biosynthesis pathway, activation of NF-kB, increased caspase-3 activity, and promotes inflammation [10][13] [14]. Inflammation and hyperglycemia-induced VEGF upregulation are additional major processes that contribute to DR. Hyperglycemia, oxidative stress, inflammation, VEGF and the metabolical pathways mentioned above are interrelated and lead in the end to: pericyte apoptosis, endothelial cells apoptosis, capillary damage, ischemia, and retinal degeneration [12].

DIETARY NUTRIENTS

1. CAROTENOIDS.

Carotenoids are phytochemicals found in green leafy vegetables, corn, yellow pepper, eggs, carrots, tomatoes, zucchini, watermelon, red grapes, pink grapefruit, papaya, apricots, sweet potatoes, and cantaloupe [15]. Diet is the only source of nutrients due to the inability of the human

body to synthesize them. The main 2 classes of carotenoids are carotenes and xantophylls [16][17] .

Lutein and zeaxanthin are xanthophyll carotenoids that accumulate in high quantities in the macular region of the retina, and along with meso-zeaxanthin are known as macular pigments or MP [19] [20]. The benefic effects of carotenoids exert from their ability to neutralize ROS, reduce inflammation, protect against blue light, improve visual acuity, contrast sensitivity and maintain the integrity of the retinal membranes [22] [18][23] [24]. Between lutein and zeaxanthin, the last one is a more potent antioxidant and it is more abundant in the foveal region of the macula [16] [20]. Other carotenoids such as beta-carotene and lycopene have the same antioxidant, anti-inflammatory and anti-angiogenic properties [13].
Synergistic interactions that result in an increased antioxidant capacity are seen between carotenoids and also in combination with other classes of nutrients such as vitamins and omega-3 fatty acids [21].

2. VITAMINS A, C AND E

Vitamin A and C are essential nutrients since the human body cannot synthesize them. Vitamin A is obtained from cheese, milk, dairy products, eggs and liver as well as from carrots, spinach, kale as provitamin A or beta-carotene [25]. The main benefits of vitamin A are: improving vision in low-light, preserving the immunity, and cell growth [13]. Vitamin C is found in oranges, lemon, lime, pineapple, cabbage and tomatoes and possesses antioxidant properties as well as the capacity to regenerate vitamin E [26] [13] [27]. Vitamin E is obtained from dietary products like almonds, peanuts, hazelnuts, sunflower oil, corn oil and soybean oil [13], and it shares the antioxidant ability as the above-mentioned nutrients [28]. The human tissues and blood contain abundant amounts of α-tocopherol in comparison with the other forms of vitamin E: tocopherol, δ-tocopherol, and γ-tocopherol [28][29]. It is important to highlight that lipofuscin granules and oxidative stress can result due to the lack of vitamin E [28].

3. OMEGA-3- FATTY ACIDS

Omega-3 fatty acids are essential nutrients found mainly in fish, fish oil, chia seeds, flax oil and algae. The main omega-3 fatty acids located in the photoreceptor cell membrane that provide protection against inflammation, angiogenesis, and retinal degeneration are docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA) [30] [31]. The mechanism of action consist of inhibition of Nf-kb (nuclear factor kappa-light-chain-enhancer of activated B cells), VEGF, and TNF-α

and IL-1β [26]. Besides omega-3 fatty acids, diet is also a source of omega-6 fatty acids that exert opposite effects.

4. ZINC

Zinc is mineral abundant in the RPE and photoreceptor layer, where it acts as a cofactor for antioxidant enzymes such as superoxide dismutase and metallothioneins, participates in POS phagocytosis, regulation of retinol dehydrogenase activity, and rhodopsin regeneration [5][34][35]. The main dietary sources of zinc are red meat, poultry, oysters, whole grains, beans, mushrooms and eggs. In addition, cytotoxicity can occur after ingestion of a higher dose of zinc than recommended [32][33].

5. POLYPHENOLS

Besides carotenoids, polyphenols are another group of phytochemicals that exert benefic effects against oxidative stress, inflammation, and angiogenesis. The main mechanism of action consist of increasing the intracellular production of antioxidants, inhibition of further ROS synthesis, and inactivation of pro-inflammatory cytokine production[37] [36]. Polyphenols are divided into 4 classes: phenolic acids, stilbenes (resveratrol), flavonoids (anthocyanins, quercetin, epigallocatechin gallate), and isoflavone and lignans [37]. Dietary sources that contain polyphenols are red wine, coffee, broccoli, blueberries, onions, kale, wheat, oranges, apples, cherries, soybeans, and linseeds. Additionally to the before mentioned properties, polyphenols exert antimicrobial and antiviral properties as well as improving ocular blood flow and vision [37].

THE AREDS 1 AND 2

In order to demonstrate the benefic effects of dietary nutrients against AMD and also the optimal dosages, trials, observational studies and experiments on rodents and cell cultures were warranted. The most relevant trials so far are the AREDS 1 and 2 due to the big cohort of subjects (4757 subjects in the first study, and 4203 in the second one) that were observed over a time span of 5 years. The first AREDS (Age-Related Eye Disease Study) trial assigned the 4757 participants aged between 55 and 80 years old with at least one eye being affected by AMD to 4 study arms, each receiving one of the following formulations : zinc (80 mg + 2 mg cooper) supplements, antioxidant (vitamin C: 500 mg, vitamin E: 400UI, and beta-carotene: 15 mg) supplements, formulation containing both zinc and antioxidants, or placebo. The results showed that the formulation containing

both zinc and antioxidants had an efficiency in reducing the risk of progression from intermediate to advanced stage of AMD by 25%[9].

The second trial improved the initial formulation by removing beta-carotene, because of the higher incidence of lung cancer among smokers, and by adding lutein, zeaxanthin and omega-3 fatty acids. Following the same pattern, subjects where divided into 4 group and received 10 mg lutein+2 mg zeaxanthin, 350 mg DHA +650 mg EPA, lutein+zeaxanthin and DHA+EPA, or placebo. When compared with the first trial, the most significant results where that lutein and zeaxanthin are safer than beta-carotene and that they have proven to reduce the progression to later stages of AMD in opposition to the placebo arm. A second randomization took place using the initial AREDS formulation or a modified version that had a lower dosage of zinc, or didn't contain either beta-carotene or beta-carotene and zinc [37]. In opposition to lutein and zeaxanthin, omega-3 fatty acids didn't exert any benefic effects [9] [6].

CONCLUSIONS

In conclusion, oxidative stress and inflammation seen as the major pathological mechanism involved in AMD and DR lead to the hypothesis that nutrients with antioxidant and anti-inflammatory could help fight against retinal degeneration and vision loss. The main nutrients that were associated with the property to scavenge ROS, enhance the intracellular defense mechanism, reduce pro-inflammatory cytokine synthesis, and prevent cell apoptosis are in carotenoids, vitamins, omega-3 fatty acids, zinc and polyphenols. In addition, the existing therapies on the market are expensive and they target mostly the neovascularization. Thus, nutrients are seen an additional low cost therapy that could aid the fight against vision loss.

REFERENCES

1. Nowak JZ (2006) Age-related macular degeneration (AMD): pathogenesis and therapy. Pharmacol Rep 58, 353- 363.
2. Ranganathan Arunkumar, Charles M. Calvo, Christopher D. Conrady, Paul S. Bernstein. What do we know about the macular pigment in AMD: the past, the present, and the future. Eye (Lond). 2018 ; 32(5): 992–1004. doi: 10.1038/s41433-018-0044-0
3. Anu Kauppinen, Jussi J. Paterno, Janusz Blasiak, Antero Salminen, and Kai Kaarniranta. Inflammation and its role in age-related macular degeneration. Cell Mol Life Sci. 2016; 73: 1765–1786. doi: 10.1007/s00018-016-2147-8
4. Barry S. Winkler, Michael E. Boulton, John D. Gottsch, and Paul Sternberg. Oxidative damage and age-related macular degeneration.Mol Vis. 1999 Nov 3; 5: 32.

5. Ângela Carneiro , José Paulo Andrade. Nutritional and Lifestyle Interventions for Age-Related Macular Degeneration: A Review. Oxid Med Cell Longev. 2017; 2017: 6469138. doi: 10.1155/2017/6469138
6. Aruna Gorusupudi, Kelly Nelson, and Paul S Bernstein. The Age-Related Eye Disease 2 Study: Micronutrients in the Treatment of Macular Degeneration. Adv Nutr. 2017 Jan; 8(1): 40–53. doi: 10.3945/an.116.013177
7. Alexandra Moreno-García, Alejandra Kun, Olga Calero, Miguel Medina, and Miguel Calero. An Overview of the Role of Lipofuscin in Age-Related Neurodegeneration. Front Neurosci. 2018; 12: 464. doi: 10.3389/fnins.2018.00464
8. Long Hin Li, Jetty Chung-Yung Lee, Ho Hang Leung, Wai Ching Lam, Zhongjie Fu, Amy Cheuk Yin Lo. Lutein Supplementation for Eye Diseases. Nutrients. 2020 ; 12(6): 1721. doi: 10.3390/nu12061721.
9. Bernstein P.S., Li B., Vachali P.P., Gorusupudi A., Shyam R., Henriksen B.S., Nolan J.M. Lutein, zeaxanthin, and meso-zeaxanthin: The basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. Prog. Retin. Eye Res. 2016;50:34–66. doi: 10.1016/j.preteyeres.2015.10.003.
10. Renu A. Kowluru, Anjan Kowluru, Manish Mishra, and Binit Kumara. Oxidative stress and epigenetic modifications in the pathogenesis of diabetic retinopathy. Prog Retin Eye Res. 2015 ; 48: 40–61. doi: 10.1016/j.preteyeres.2015.05.001
11. Aruna Gorusupudi, Fu-Yen Chang, Kelly Nelson, Gregory S. Hageman, and Paul S. Bernstein. n-3 PUFA Supplementation Alters Retinal Very-Long-Chain-PUFA Levels and Ratios in Diabetic Animal Models. Mol Nutr Food Res. 2019 ; 63(15): e1801058. doi: 10.1002/mnfr.201801058
12. Wei Wang and Amy C. Y. Lo. Diabetic Retinopathy: Pathophysiology and Treatments. Int J Mol Sci. 2018 ; 19(6): 1816. doi: 10.3390/ijms19061816
13. Eleazar Uchenna Ikonne, Victor Okezie Ikpeazu, Eziuche Amadike Ugbogub. The potential health benefits of dietary natural plant products in age related eye diseases. Heliyon. 2020; 6(7): e04408.doi: 10.1016/j.heliyon.2020.e04408.
14. Renu A. Kowluru and Pooi-See Chan. Oxidative Stress and Diabetic Retinopathy. Exp Diabetes Res. 2007; 2007: 43603. doi: 10.1155/2007/43603
15. Barbara Demmig-Adams, Marina López-Pozo, Jared J. Stewart, William W. Adams, III. Zeaxanthin and Lutein: Photoprotectors, Anti-Inflammatories, and Brain Food. Molecules. 2020; 25(16): 3607.. doi: 10.3390/molecules25163607.
16. Barbara Demmig-Adams and Robert B. Adams. Eye Nutrition in Context: Mechanisms, Implementation, and Future Directions. Nutrients. 2013 ; 5(7): 2483–2501. doi: 10.3390/nu5072483
17. El-Sayed M. Abdel-Aal, Humayoun Akhtar, Khalid Zaheer, and Rashida Ali. Dietary Sources of Lutein and Zeaxanthin Carotenoids and Their Role in Eye Health. Nutrients. 2013 ; 5(4): 1169–1185. doi: 10.3390/nu5041169
18. Larisa-Bianca HOLHOS, Mihaela Cristiana COROI, Gineta HOLT, Claudia PUSTA, Cosmin VESA, Razvan PIRVAN, Daniela RAHOTA, Ioana DAMIAN, Corina BEIUSANU, Liviu LAZAR. The Burden of Assessing Ocular Status of Children – Causes and Control MAEDICA – a Journal of Clinical Medicine. https://doi.org/10.26574/maedica.2020.15.3.391
19. Bronwyn Eisenhauer, Sharon Natoli, Gerald Liew, and Victoria M. Flood. Lutein and Zeaxanthin—Food Sources, Bioavailability and Dietary Variety in Age-Related Macular Degeneration Protection. Nutrients. 2017 ; 9(2): 120. doi: 10.3390/nu9020120

20. Julie Mares. Lutein and Zeaxanthin Isomers in Eye Health and Disease. Annu Rev Nutr. 2016 17; 36: 571–602. doi: 10.1146/annurev-nutr-071715-051110
21. Coroi MC, Bakraoui A, Sala C, Ţica O, Ţica OA, Jurcă MC, Jurcă AD, Holhoş LB, Bălăşoiu AT, Todor L. Choroidal melanoma, unfavorable prognostic factors. Case report and review of literature. Rom J Morphol Embryol, 2019, 60(2): 673–678.
22. John M. Nolan, Katherine A. Meagher, Alan N. Howard, Rachel Moran, David I. Thurnham, and Stephen Beatty.Lutein, zeaxanthin and meso-zeaxanthin content of eggs laid by hens supplemented with free and esterified xanthophylls. J Nutr Sci. 2016; 5: e1 . doi: 10.1017/jns.2015.35.
23. John M Nolan, Stephen Beatty, Katie A Meagher, Alan N Howard, David Kelly, and David I Thurnham.Verification of Meso-Zeaxanthin in Fish. J Food Process Technol. 2014 1; 5(6): 335. doi: 10.4172/2157-7110.1000335
24. Alice S. Green and Andrea J. Fascetti. Meeting the Vitamin A Requirement: The Efficacy and Importance of β-Carotene in Animal Species. ScientificWorldJournal. 2016; 2016: 7393620. doi: 10.1155/2016/7393620
25. Ricardo Raúl Robles-Rivera, José Alberto Castellanos-González, Cecilia Olvera-Montaño, Raúl Alonso Flores-Martin, Ana Karen López-Contreras, Diana Esperanza Arevalo-Simental, Ernesto Germán Cardona-Muñoz, Luis Miguel Roman-Pintos, and Adolfo Daniel Rodríguez-Carrizalez. Adjuvant Therapies in Diabetic Retinopathy as an Early Approach to Delay Its Progression: The Importance of Oxidative Stress and Inflammation. Oxid Med Cell Longev. 2020; 2020: 3096470. doi: 10.1155/2020/3096470
26. https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/#en3
27. Hock Eng et al.. Nutrients for Prevention of Macular Degeneration and Eye-Related Diseases. Antioxidants (Basel). 2019 ; 8(4): 85. doi: 10.3390/antiox8040085
28. Yan Gong et al. Smith. ω-3 and ω-6 long-chain PUFAs and their enzymatic metabolites in neovascular eye diseases. Am J Clin Nutr. 2017 ; 106(1): 16–26. doi: 10.3945/ajcn.117.153825
29. Giuseppe Querques, Raimondo Forte, and Eric H. Souied. Retina and Omega-3. 2011 Oct .https://doi.org/10.1155/2011/748361
30. Mateusz Cholewski, Monika Tomczykowa, and Michał Tomczyk. A Comprehensive Review of Chemistry, Sources and Bioavailability of Omega-3 Fatty Acids. Nutrients. 2018 Nov; 10(11): 1662. doi: 10.3390/nu10111662
31. Ryo Terao, and Hiroki Kaneko. Lipid Signaling in Ocular Neovascularization. Int J Mol Sci. 2020 ; 21(13): 4758. doi: 10.3390/ijms21134758
32. Dinusha Rajapakse, Tim Curtis, Mei Chen, and Heping Xu. Zinc Protects Oxidative Stress-Induced RPE Death by Reducing Mitochondrial Damage and Preventing Lysosome Rupture. Oxid Med Cell Longev. 2017; 2017: 6926485. doi: 10.1155/2017/6926485
33. Magdalena Jarosz, Magdalena Olbert, Gabriela Wyszogrodzka, Katarzyna Młyniec, and Tadeusz Librowski. Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. Inflammopharmacology. 2017; 25(1): 11–24.doi: 10.1007/s10787-017-0309-4
34. Nour Yahfoufi, Nawal Alsadi, Majed Jambi, and Chantal Matar. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. Nutrients. 2018 ; 10(11): 1618. doi: 10.3390/nu10111618
35. Elzbieta Pawlowska, Joanna Szczepanska, Ali Koskela,, Kai Kaarniranta, and Janusz Blasiak. Dietary Polyphenols in Age-Related Macular Degeneration: Protection against Oxidative Stress and Beyond. Oxid Med Cell Longev. 2019; 2019: 9682318.. doi: 10.1155/2019/9682318

36. Simona Bungau et al. Health Benefits of Polyphenols and Carotenoids in Age-Related Eye Diseases. Oxid Med Cell Longev. 2019; 2019: 9783429. doi: 10.1155/2019/9783429
37. Hasna El Gharras. Polyphenols: food sources, properties and applications – a review. 2009; https://doi.org/10.1111/j.1365-2621.2009.02077.x