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GRAU EN ÒPTICA I OPTOMETRIA

TREBALL FINAL DE GRAU

THE ROLE OF NUTRITION IN VISION

SARA FONT ARMADANS

MIREIA PACHECO CUTILLAS
DEPARTAMENT D'ÒPTICA I OPTOMETRIA

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La Sra. MIREIA PACHECO CUTILLAS, com a tutora i directora del treball,

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Que la Sra. SARA FONT ARMADANS ha realitzat sota la seva supervisió el treball "THE ROLE OF NUTRITION IN VISION" que es recull en aquesta memòria per optar al títol de grau en Òptica i Optometria.

I per a què consti, signo aquest certificat.

Sra MIREIA PACHECO CUTILLAS

Directora i Tutora del TFG

Terrassa, 16 de Juny del 2017

UNIVERSITAT POLITÈCNICA DE CATALUNYA
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DEGREE IN OPTICS AND OPTOMETRY

ROLE OF NUTRITION IN VISION

ABSTRACT

The main purpose of this project is to do a literature research on the role that nutrition has on the eye health, in order to improve the knowledge on this subject and analyse the results of the studies with the main goal of identifying the most appropriate nutritional components to protect of preventable ocular diseases.

The most important nutritional elements present in the eye, and their function in the visual process and ocular health are explained. Carotenoids, essential fatty acids and some types of vitamins are the most relevant nutritional components. This project also reports on the foods that contain these nutrients.

Carotenoids are pigments found in the retina having a protective role absorbing blue light and reducing retinal damage. This protective role is important in order to avoid the oxidative damage, the major risk factor for typical ocular pathologies like cataract or AMD. Carotenoids are mostly found on red and orange vegetables.

Omega – 3 fatty acids are necessary for the correct function of the rhodopsin, playing an important role in the vision process. DHA affects the membrane structure by altering its permeability, thickness and lipid-phase properties while increasing the rate of rhodopsin activation and hence the phototransduction cascade. These nutritional components are found basically on cold-water fish and seeds oils.

Some vitamins, such as A, C, and E, serve as antioxidants and protect cells against free radical damage, and they are found on vegetables and fruits.

Although not all nutrients have a beneficial role, the beneficial effect of supplementation on the delay of some pathologies is reported. Some relevant studies have reported the beneficial role that nutrition plays on our visual system, showing a delay of AMD progression with carotenoids and omega – 3, and an improvement of the tear film quality with omega – 3 supplementation or a delay on retinal damage with retinitis pigmentosa with lutein and vitamin A supplementation.

Nutritional supplementation still needs more studies to definitely prove its beneficial effect. It is important to remember that a varied and balanced diet is paramount and that other interventions such as the use of sun protection, healthy habits like to avoid smoking should be considered as much as nutritional supplementation.

GRAU EN OPTICA I OPTOMETRIA

EL PAPER DE LA NUTRICIÓ EN LA VISIÓ

RESUM

L'objectiu principal d'aquest projecte és realitzar una recerca bibliogràfica sobre el paper que té la nutrició en la salut ocular amb la finalitat de millorar els coneixements sobre aquest tema i analitzar els resultats dels estudis amb l'objectiu d'identificar els components nutricionals més adequats per protegir de malalties oculars prevenibles.

S'expliquen els elements nutricionals més importants presents a l'ull i la seva funció en el procés visual i de salut ocular. Els carotenoids, els àcids grassos essencials i algunes vitamines són els components nutricionals més rellevants. Aquest projecte també informa sobre els aliments que contenen aquests nutrients.

Els carotenoids són pigments que es troben a la retina desenvolupant un paper protector on absorbeix la llum blava i redueix el dany de la mateixa. Aquest paper protector és important per evitar el dany oxidatiu, el principal factor de risc per a patologies oculars típiques com la cataracta o la DMAE. Els carotenoides es troben sobretot en els aliments vermells i ataronjats.
Els àcids grassos omega-3 són necessaris per al correcte funcionament de la rodopsina, exercint un paper important en el procés de la visió. El DHA afecta l'estructura de la membrana alterant la seva permeabilitat, gruix i propietats de la fase lipídica, així com, augmentant la velocitat d'activació de la rodopsina i, per tant, la cascada de fototransducció. Aquests components nutricionals es troben bàsicament en peixos d'aigua freda i en l'oli de les llavors.
Algunes vitamines, com A, C i E, serveixen com a antioxidants i protegeixen a les cèl·lules contra el dany dels radicals lliures, i es troben principalment en verdures i fruites.

Encara que no tots els nutrients tenen un paper beneficiós, l'efecte beneficiós dels components nutricionals en el retard d'algunes patologies esta estudiat. Alguns estudis rellevants han informat del beneficiós paper que la nutrició juga en el nostre sistema visual, mostrant un retard en la progressió de la DMAE amb carotenoids i omega - 3, i una millora en la qualitat de la pel·lícula llagrimal amb suplements d'omega - 3 o un retard en el dany de la retina, amb la retinitis pigmentosa amb luteïna i suplements de vitamina A.

Els components nutricionals encara necessiten més estudis per provar definitivament el seu efecte beneficiós. És important recordar que una dieta variada i equilibrada és primordial i que altres intervencions com l'ús de protecció solar, hàbits saludables o evitar fumar s'han de considerar tant com el fet de pendre complements nutricionals.

GRADO EN ÓPTICA Y OPTOMETRÍA

EL PAPEL DE LA NUTRICIÓN EN LA VISIÓN

RESUMEN

El objetivo principal de este proyecto es realizar una investigación bibliográfica sobre el papel que tiene la nutrición en la salud ocular con la finalidad de mejorar los conocimientos sobre este tema y analizar los resultados de los estudios con el objetivo de identificar los componentes nutricionales más adecuados para proteger de enfermedades oculares prevenibles.
Se explican los elementos nutricionales más importantes presentes en el ojo y su función en el proceso visual y de salud ocular. Los carotenoides, los ácidos grasos esenciales y algunas vitaminas son los componentes nutricionales más relevantes. Este proyecto también informa sobre los alimentos que contienen estos nutrientes.

Los carotenoides son pigmentos que se encuentran en la retina desarrollando un papel protector donde absorbe la luz azul y reduce el daño de la misma. Este papel protector es importante para evitar el daño oxidativo, el principal factor de riesgo para patologías oculares típicas como catarata o la DMAE. Los carotenoides se encuentran sobre todo en los alimentos rojos y anaranjados.
Los ácidos grasos omega-3 son necesarios para el correcto funcionamiento de la rodopsina, desempeñando un papel importante en el proceso de la visión. El DHA afecta la estructura de la membrana alterando su permeabilidad, espesor y propiedades de la fase lipídica, así como, aumentando la velocidad de activación de la rodopsina y, por lo tanto, la cascada de fototransducción. Estos componentes nutricionales se encuentran básicamente en pescados de agua fría y en el aceite de las semillas.
Algunas vitaminas, como A, C y E, sirven como antioxidantes y protegen a las células contra el daño de los radicales libres, y se encuentran principalmente en verduras y frutas.

Aunque no todos los nutrientes tienen un papel beneficioso, el efecto beneficioso de los complementos nutricionales en el retraso de algunas patologías esta estudiado. Algunos estudios relevantes han informado del beneficioso papel que la nutrición juega en nuestro sistema visual, mostrando un retraso en la progresión de la DMAE con carotenoides y omega - 3, y una mejora en la calidad de la película lagrimal con suplementos omega - 3 o un retraso en el daño de la retina con la retinitis pigmentosa con luteína y vitamina A.

Los complementos nutricionales todavía necesitan más estudios para probar definitivamente su efecto beneficioso. Es importante recordar que una dieta variada y equilibrada es primordial y que otras intervenciones como el uso de protección solar, hábitos saludables o evitar fumar deben considerarse tanto como los complementos nutricionales.

ACKNOWLEDGEMENT

This project consumed huge amount of work, research and dedication. Still, the fulfillment would not have been possible if we did not have a support of many people. Therefore we would like to extend our sincere gratitude to all of them.

First of all I wish to express my sicere thanks to my supervisor Dr. Mieria Pacheco Cuntillas, for providing me with all the necessary facilities for the research and for sharing expertise, sincere and valuable guidance and encouragement extended to me.

I take this opportunity to express gratitude to my family, my mother Montse and my sister Judith, for the unceasin encouragement, support and attention. I am also grateful to my partner, Bernat, who supported me throught this venture.

At last, I would like to dedicate this project to my father, Carles, because I am sure that he would be proud of me.

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1. INTRODUCTION

I am a student of Optics and Optometry from UPC University, and one of the goals of optometrists is to protect the eyesight of patients so that they have good vision throughout their lifetime [1], and that is why in my final thesis I have decided to evaluate the role of nutrition in vision.

The main purpose of this project is to do a literature research about the role that nutrition has on the eye in order to improve the knowledge of this item and make a sum up of different articles and studies, writing a report where it encompasses all new and old relevant information, so finally, we will achieve a memory with all the update information.

In this final memory, it is analysed the different dietary components, nutrition-related with the eye protection and prevention, and finally, how nutrition could influence on eye health.

There are a lot of people with nutritional problems and it is important to know how is their life with these diseases and how to improve it. There is a growing interest in the role of nutritional factors in ocular diseases, because they are amenable to modification, by acting on food habits or by supplementation with specific nutrients.

That is why this memory talks about how supplementation works in our body, and how with nutrition we can improve our eye health or prevent/delay some eye diseases.

2. AIMS AND OBJECTIVES OF THE PROJECT

Before starting it is necessary a previous documentation and familiarisation with the subject in order to understand and organised the different information. A lot of articles, books, and reviews are going to be read to collect information for the final memory.

The main project initial ideas are provided by the supervisor Dr Mireia Pacheco Cutillas, from the department of Optics and Optometry (UPC).

The main goal is a literature review on the importance that diferent dietary components play in the eye health.

The specyfic objectives are:

- To carry on the necessary literature review on the subject.
- To specify what function each component play.
- To evaluate the importance of nutrition in the health provision of the eye, and in maintaining ocular health.
- To value how some pathological problems could benefit from a good diet.
- And finally, to know different ocular nutritional supplements and which is their function.

3. IMPORTANCE OF DIETARY COMPONENTS IN THE VISUAL FUNCTION AND EYE HEALTH

Nutrition is the study of foods and nutrients vital to health that explain how the body uses these to promote and support growth, maintenance, and reproduction of cells.[2]

Good nutrition is essential for body and has three main functions [3]:

- Builds and repairs body tissues
- Regulates metabolism
- Supplies energy.

Each macronutrient has its micronutrients, such as vitamins, minerals, carotenoids, and enzymes [3,4] . All of this macronutrients have antioxidant properties and their function is to protect against free radicals. It is important to mention that they have to work synergistically, for example, beta-carotene needs zinc to form vitamin A.
As the body's antioxidants reduce with age, their deficiency can disable the normal antioxidant system and become a pathological problem, that is why any shortfall in the diet should be tackled with supplements.

3.1 ESSENTIAL FATTY ACID

There are different types of fatty acids, the ones which are necessary to be obtained from the diet because our body can't produce them are called essential fatty acids (EFAs). This EFAs are divided into two groups: Omega 3 (linolenic acid [LNA]), and Omega 6 (linoleic acid [LA]). [4,7]

Omega-3 fatty acids are important for good vision, learning ability and co-ordination, and it is converted into docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). [4] *(see section 6).* DHA is found in high concentrations in the retina, as highest body concentrations of DHA. [6] In the rods, there are 50% of DHA compared with the others EFAs. [5]

A study reported by Neuringer & Connor has demonstrated that a diet lacking EFAs show a modification in the composition of the fatty acids in the retina, with less renovation of visual cells and consequently an abnormal visual function. In the photoreceptors membrane, the EFAs are necessary for the correct function of the rhodopsin. [5]

Polyunsaturated fatty acids are abundant in the retina, predominantly found in photoreceptor outer membranes playing an important role in the vision process, are readily oxidised. These membranes have a short lifetime and are replaced every 9–14 days. However, the retina conserves its DHA by retrieving it from the phagosomal membranes within the RPE and recycling it for incorporation into newly forming disc membranes. [5,6]

DHA affects the membrane structure by altering its permeability, thickness and lipid-phase properties while increasing the rate of rhodopsin activation and hence the phototransduction cascade. This involves the activation of three proteins, with an amplification of the signal at each stage. When the capture of a photon is realised by the opsin, rhodopsin is activated leading to the formation of metarhodopsin II (MII). MII interacts with, and the second type of disc membrane protein, transducin, is activated. At that point, MII and transducin first dissociate, and then MII activates further transducin molecules leading to an amplification (or cascade) of the signal. The third type of membrane protein, phosphodiesterase (PDE), is activated by the transducin, and again these proteins dissociate and transducin activates further PDE proteins, it comes into contact with the disc membrane, leading to further amplification of the signal. [6]

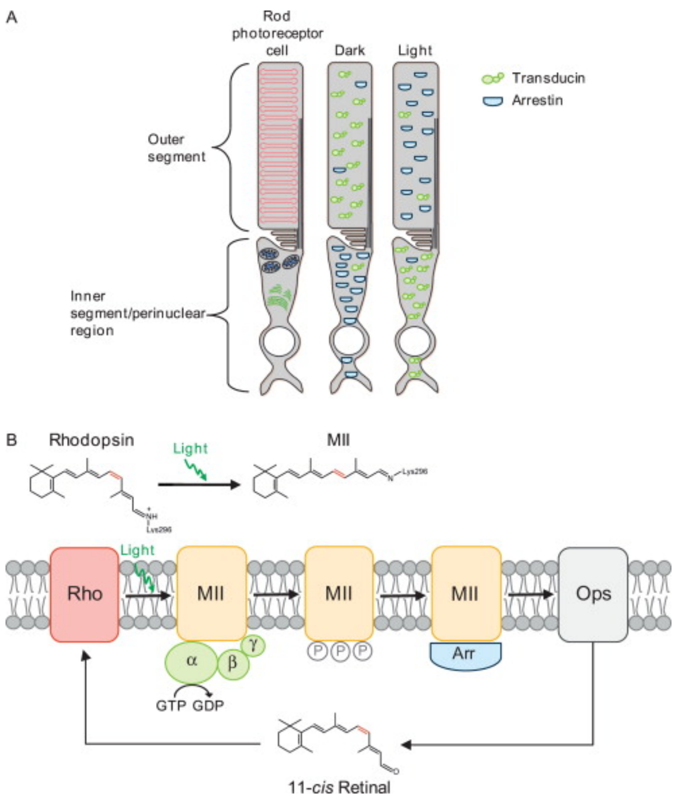

Illustration 1. Function of the photoreceptor disc membrane. [7] *Arrestins coordinate processes by recluting PDEs.* [8]

Studies have shown that disc membrane phospholipids containing DHA have higher MII formation, MII–transducin interaction and activation, and finally, PDE activation. Therefore, DHA confers properties on the disc membranes which maximise the efficiency and gain of the phototransduction cascade. [6] DHA also carry out an important paper in the rhodopsin regeneration. The 11-cis retinal required to form rhodopsin is synthesised in the pigment epithelium of the retina, but this does not appear correctly to the opsin of the rods if there is no DHA. In addition, DHA, as essential fatty acid, deletes the potential gradient L in the channels for Ca2+ and Na+ in the depolarization process of the photoreceptor in the called dark current. [5]

The retinal dysfunction occurs due to inadequate disc membrane DHA phospholipids to support rhodopsin in the light capture, and hence MII formation. Some effects of DHA deficiency appear to be transitionary, others are long-lasting and irreversible. [5,6]

Carlson SE, Werkman SHT et al. clinical studies have shown that omega-3 fatty acids are essential for normal infant vision development. In the maternal breast milk DHA and other Omega-3 have found. The deficiency of Omega-3 during pregnancy can cause learning difficulties and visual impairment, so regular intake is especially important. [4,5]

3.2 CAROTENOIDS

Carotenoids are essential micronutrients that provide many of the colours found in nature as a result of their light absorption characteristics. They are classified as carotenes if they are exclusively hydrocarbons, but if they contain oxygen as a result of oxidation or enzymatic addition, they are known as xanthophylls. [8], [9]

Xanthophylls are divided into two groups termed lutein (L) and zeaxanthin (Z) that have an important function in the eye. This carotenoid can only be obtained from the diet, they are synthesised in plants, and their major storage site is adipose tissue. The assumption that L and Z within the retina are of dietary origin, is supported by Malinow. M, Feeney-Burns L et al. fundus photographs of rhesus monkeys on carotenoid-depleted diets that demonstrate an absence of macular pigmentation.[9]

In addition to lutein and zeaxanthin, the only other carotenoid present in the macular pigment is Meso-zeaxanthin (MZ) which is formed via isomerization of L. [8–10]

Another classification of carotenoids that is the most familiar being the provitamin A carotenoid (those that can be converted to vitamin A in the human body) and the non-provitamin A carotenoid (those that cannot be converted to vitamin A in the human body). [4]

Lutein and zeaxanthin belong to the subclass of non-provitamin A carotenoids known as the xanthophylls. These two xanthophylls are accumulated at the macula as a macular pigment (MP), but the macular optical density (MPOD) is not uniformly distributed across the retina. The Zeaxanthin predominates in the central macula and that may be explained by the fact that L can be metabolised to Z. [9,11]

Zeaxanthin is reported to be a superior photoprotector during prolonged light exposure, the shorter time-scale of protective efficacy of L has been attributed to oxidative damage of the carotenoid itself. [9,11]

The human retina, and more specifically the macula, is the single richest site of carotenoid accumulation within the human body as Malinow. M, Feeney-Burns L et al. report. Post-mortem retinal analysis has shown that the total L and Z concentration at the macula is 100 times more than at the peripheral retina. Within the layer structure of the retina, the maximum concentration of carotenoids is found in the Henle fiber layer, the axons of the photoreceptors and the inner plexiform layer.[9]

The differences between Lutein and Zeaxanthin is that Lutein is orientated both parallel and perpendicular to the membrane surface and is reported to be a superior filter due to the fact of that orientation to the plane of the membrane. Zeaxanthin is orientated only perpendicular to the membrane and so may not be able to absorb the excitation beam from all directions. [11]

PROPERTY	LUTEIN	ZEAXANTHIN
MAXIMUM ABSORPTION SPECTRUM	Below 500nm	Above 500nm
ORIENTATION IN LIPID BILAYES MEMBRANE	Two types of orientation : perpendicular or parallel to membrane	Perpendicular to the membrane
SCAVENGING ACTION	As effective as beta-carotene in quenching single oxygen	As effective as beta-carotene in preventing auto-oxidation of lipids

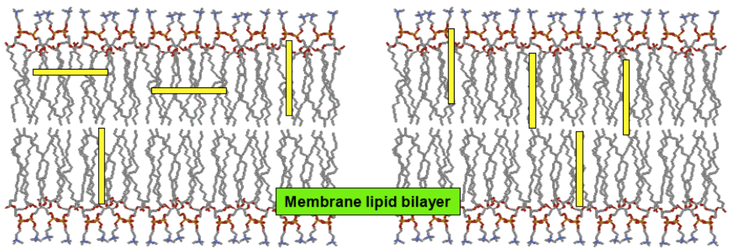

Illustration 2. Structure of macular pigment. [11]

Table 1. Differences between lutein and zeaxanthin. [8]

These two xanthophylls are believed to function in this area of the retina as antioxidants to protect the photoreceptor cells from the potential damage caused by free radicals that can be generated in these cells by the high oxygen tension and exposure to light. In addition to antioxidant activity, lutein and zeaxanthin are also believed to be responsible for filtering the high-energy wavelengths of blue light. These functions have prompted interest in their potential role in the prevention of disease. [3,4,8–10,12–14]

The blue light filter effect of L and Z may reduce longitudinal chromatic aberration. The acuity hypothesis states that these nutrients may improve visual acuity for images that are illuminated by white light by absorbing poorly focussed short wavelengths before this light is processed by the retina.

The fact that images are not degraded may be explained in part by the pre-retinal filtering effect of L and Z. The macula is specialized for high spatial resolution and also for color vision, and so it may be that L and Z play a part in these processes. [14]

3.3 VITAMINS

Vitamins are organic micronutrients, which protect cells and tissues from detrimental effect of physical, chemical and microbial agents.

Vitamins are an essential component of a balanced diet, as they cannot be synthesised by humans. The human body needs 13 different vitamins, of these, four are fat-soluble (A, D, E, and K) and nine are water-soluble vitamins (C and B-group).

Some vitamins, such as A, C, and E, serve as antioxidants and protect cells against free radical damage, acting synergistically with antioxidant enzymes in scavenging free radicals, and their site of action can be intracellular or extracellular.[3], [4], [15]

3.3.1 Vitamin A

Vitamin A is essential for the promotion of growth, embryonic development, and visual function, and it is performed for two main groups: vitamin A (retinoids) and provitamin A(carotenoids).

The major source of vitamin A for the human body provides from beta-Carotene, the principal carotenoid found in sources of plant origin where they are closely associated with chlorophyll. One molecule of b -carotene gives rise to two molecules of retinal. [15]

Vitamin A it is intimately involved in visual transduction and it is associated with specific proteins (opsins) in the form of visual pigments within the rods and cones. These opsins are different for each type of photoreceptor; the rods are especially sensitive to low-intensity light (black and white vision) and the cones are sensitive to high-intensity light (color vision).

The retinal form of vitamin A is an active component of the photosensitive pigment in both rods and cones. In the rods, the retinal form of vitamin A (11 cis-retinal) is found associated with opsin in the form of the visual pigment, rhodopsin. In cones, retinal is combined with other forms of opsin; the type of opsin determines the wavelength of light that can be absorbed by the retinal.

When exposed to light, the rhodopsin is broken down into retinal and opsin, a process known as bleaching. The reformation of rhodopsin requires a fresh supply of vitamin A. Incomplete reformation of rhodopsin, found in those who are vitamin A deficient, results in poor dark adaptation. This is also known as night blindness. It is a low sensibility of all photoreceptors. *(explained on section 6.6)* [3,4,7,15,16]

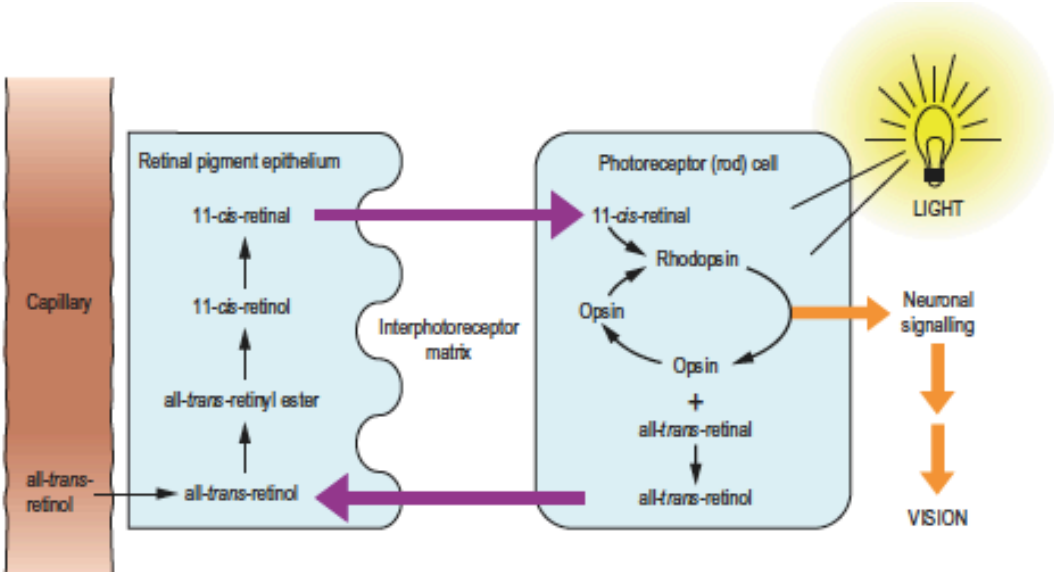

Illustration 3. Role of vitamin A in vision. [15] *Light enters the eye and strikes the retina, where it activates rhodopsin pigments in the membranes of photoreceptor outer segments (POSs). This induces the release of both the bleached pigment (opsin) and a molecule of all-trans-retinal, which is converted to vitamin A (all-trans-retinol) before forming the chromophore 11-cis-retinal in the adjacent retinal pigment epithelium (RPE) cells through the visual cycle. The binding of 11-cis-retinal to opsin restores the photoactivable pigment rhodopsin, which can react again with light and start the phototransduction cascade.*

It is believed that vitamin A may protect photoreceptor membranes against oxidative damage by breaking the chain reaction during lipid peroxidation. In addition, vitamin A is also involved in the repair of cells that have been injured by oxidation. [3], [4], [7], [15], [16]

3.3.2 Vitamin E

Vitamin E is recognised as one of the most important chain-breaking antioxidants of cellular membranes.

Research has shown that vitamin E, can protect cells of the eyes from oxidative damage, caused by unstable molecules called free radicals, which break down healthy eye tissue. When this happens, the risks for age-related macular degeneration (AMD) and cataract formation increase.

Vitamin E acts synergistically with carotenoids in their main function of scavenging free radicals. In the deficiency of vitamin E, various changes indicative of oxidative damage is seen in the rod outer segments and RPE, suggesting that this vitamin protects the retina against such injury.

It also has anti-inflammatory properties and plays a role in the maintenance of cell membrane integrity.

In addition, in the retina, vitamin E is believed to protect vitamin A from oxidative degeneration. [4,15]

And the major site of vitamin E storage is adipose tissue.

3.3.3 Vitamin C

Vitamin C (also known as ascorbic acid) is a powerful antioxidant and also helps the body form and maintain connective tissue, including collagen synthesis found in the cornea, hence, it is also required for wound-healing. This vitamin is required to be consumed in the diet because the body can not synthesize.

It is an ideal scavenger because of its water solubility, have stability and mobility, and because it can be transported, reabsorbed and recycled (The vitamin C radical is then converted back to vitamin C by glutathione). Compared to the plasma, all ocular tissues have very high concentrations of vitamin C.

Vitamins C and E are interrelated in their antioxidant capabilities hence vitamin C may regenerate the active form of vitamin E following scavenging of free radical.

An American study 1997, suggest long-term consumption of vitamin C also may reduce the risk of forming a cataract and vision loss from macular degeneration. [4,15]

3.4 PROTEINS

The proteins have an outstanding paper in vision, and it takes part in different parts in the eye and vision.

3.4.1 Retina

All visual pigments consist of an apoprotein, opsin, to which a chromophore is attached.

The rhodopsin, that are in the rods, contains the chromophore 11-cis-retinal, an aldehyde derivative of vitamin A with a peak sensitivity/absorption of 489 nm, and the cone opsins have the same 11-cis retinal as is found in rhodopsin, but they have different opsins.

Rhodopsin is located in the disc membranes of the rod outer segments (ROS) of the photoreceptor, where it comprises 80% of the total protein with the other proteins present all involved in the phototransduction cascade.

A chromophore 11-cis-retinal lies in an opsin, which is isomerized to all-trans-retinal when the light is absorbed. The isomerization of the chromophore in the internal pocket leads to a conformational change which is propagated to the cytoplasmic surface of the receptor, enabling binding and activation of visual G-protein (transducin). This initiates a cascade of reactions leading to a nerve impulse, which is transmitted to the brain by the optical nerve.[4,17]

3.4.2 Lens Crystalline

The lens is an avascular tissue, that provides part of the power on the eye. The concentration of proteins in that tissue is the highest of any organ and this high concentration is necessary in order that the tissue brings about their function.

The lens has a unique grown pattern where proteins are uniformly packed density within the fiber cells. That minimizes the light scattering and also contributes to the transparency of the lens.

These proteins that take part in the lens is classified into a, b and g.

In the nucleus of the lens, the older proteins begin to unfold and denature with age, and lens exposure. Once denatured, it is leading to the formation of insoluble aggregates. Such insoluble protein aggregates cause light-scattering which interferes with lens transparency and, hence, with vision. That is called cataract.

However, the a-crystallins appear to maintain lens transparency in a twofold manner: first, structurally, by packaging in symmetrical oligomeric assemblies, and secondly functionally preventing denatured lens proteins forming insoluble precipitated aggregates which would cause light-scattering.

However, a-, b - and g -crystallins themselves are subject to in vivo aggregation and precipitation, contributing to lens opacification. [4,17]

3.4.3 Vitreous

The vitreous is like a gel structure that contains two macromolecules which interact in a stabilizing manner providing, in one hand elastic collagen network by the crossed protein fibrils, and on the other hand viscosity by the hyaluronan carbohydrate.

The gel structure is maintained by a network of thin unbranched collagen fibrils with Glicoaminoglycans (GAGs - principally hyaluronan) filling the spaces of the network. This protein/carbohydrate structure excludes cells and large molecules from the central vitreous in order to maintain transparency. [4,17]

3.4.4 Cornea

The cornea consists of five layers, and the connective tissue, stroma, forms the 90% of the cornea and contain a 78% of water, 1% salts and 21% biological macromolecules composed of collagen fibers (proteins), ground substance, and stromal cells.

The transparency of the corneal stroma is associated with the organized structure of the collagen fibrils. The distance and the organization between them provides a consequential destructive interference, where light scattered by neighboring fibrils in predictable and opposing directions cancels each other out, except in the primary visual axis. However, it is now also believed that fibril size and interfibrillar space play important roles in maintaining transparency of this tissue.

The stromal collagen is composed of types I (~60%), V (~10%) and VI (~30%). Type III collagen may be present in low concentrations, but it is mainly associated with fetal cornea or post corneal injury. [4,17]

3.5 CARBOHYDRATES

GAGs are very important carbohydrates present in the ocular tissues. Glucose supplies the cornea, lens, and retina where metabolism produces ATP, an important cellular energy supply. [4,18]

3.5.1 Cornea

The cornea and vitreous contain a macromolecular structure which form fibers and interfibrillar spaces are filled with polysaccharides (known as GAGs and proteoglycans), at intervals which reduce the effects of diffraction. Both components appear to be functional in maintaining the structure and transparency of the cornea.

3.5.2 Vitreous

The gel structure is maintained by a network of thin unbranched collagen fibrils with GAGs (The major GAG of the vitreous is hyaluronic acid) filling the spaces of the elastic collagen network. This protein/carbohydrate structure excludes cells and large molecules from the central vitreous in order to maintain transparency and providing viscosity.

The vitreous glucose is utilized by the hyalocytes to form glucosamine, and ultimately hyaluronic acid; however, much of the glucose is utilized by the adjoining retina.

3.6 MINERALS

Minerals, also known as micronutrients, are needed in small quantities. It can be categorized into two following groups based on the daily requirement: macrominerals and microminerals.

As well as we explained in the sections before (*section 3.1 – 3.5*), there is a general decline in the antioxidant defenses on the eye, with aging, and oxidative stress has been proposed as the main mechanism for many age-related eye diseases. Thus, it is reasonable to hypothesize that a declining bioavailability of trace elements could exacerbate the overall age-related reduction in antioxidant capability, and contribute to the onset of various age-related eye diseases.

An important point to contemplate is that mineral and trace element deficiency is more common than vitamin deficiency. [3,19]

3.6.1 Zinc

Zinc is an essential trace element and is believed to play a role in maintaining the health of the eye by protecting ocular tissues from age-related problems. The maximum concentration of Zn is present in melanin-containing tissues of the eye, and other ocular tissues that contain Zn, in descending order of concentration, include RPE, iris, choroid, sclera, vitreous, lens, cornea and retina. [3,4,19]

It has many functions in the body, and is a constituent of numerous enzymes. One of the most important functions is the protection against free radical damage, playing a fundamental role in the antioxidant activity within cells. Though the specific role of zinc in visual function has not been established, it has been shown to have possible potential benefits in the prevention of AMD. [3, 4,19]

The other remarkable function of Zinc is the important role in the transport and metabolism of vitamin A. In the retina, the conversión of retinol to retinal is mediated by a Zinc. The conversion of beta-carotene to vitamin A is zinc-dependent. [13]

Although the existing knowledge of Zinc metabolism in the cornea is not extensive, experimental studies have shown that Zn may play a role in the corneal repair process. But, it is certainly known that Zinc protects against macular degeneration and night blindness (metabolism of vitamin A). [3,4,19]

3.6.2 Selenium

Selenium is another essential trace element with important antioxidant properties. It is the metal element of four glutathione peroxidase enzymes, which convert glutathione to an antioxidant in the lens.

This mineral helps your body to absorb vitamin E and acts in conjunction with it to protect cells against free radical damage by preventing lipid peroxidation.

The decreased levels of this mineral in the aqueous humour have been linked to cataract formation, macular degeneration and diabetic retinopathy. [3], [4], [19]

3.6.3 Manganese

Manganese is the other mineral trace with antioxidant function. Primarily, limits the damaging effects of the superoxide free radical from destroying eye cellular components. Therefore, may prevent cataract formation via its antioxidant properties, as a development of age-related cataract is ultimately related to oxidative damage. [3], [4], [19]

4. DIETARY COMPONENTS IN FOOD RELEVANT TO VISUAL FUNCTION AND EYE HEALTH

This section shown which type of food is more beneficial in each nutrient.

4.1 ESSENTIAL FATTY ACID

The most common fatty acid in the eye is DHA and the sole source of it is the diet. [4–6]

There are different sources of fatty acids, and of the best dietary sources of these are seeds and their oils: pumpkin, sunflower, sesame and hemp. As well as, soya beans and wheat germ oil.

Amongst the recommendations, that are well-regarded related to EFA, I would like to highlight that the cold-water fish contain beneficial omega-3 fatty acids, such as mackerel, salmon, sardines, trout, herring and tuna.

Other good sources of omega-3 fatty acids include flaxseeds, flaxseed oil, walnuts, dark green leafy vegetables and eggs. [4–6, 20,21]

4.2 CAROTENOIDS

As well as it is in the essential fatty acids, the diet is the sole source of Lutein and Zeaxanthin. These two nutrients are present in dark green leafy vegetables as spinach, collard greens, red pepper, corn, broccoli and kales, and also yellow-red or orange-red fruits and vegetables. Z is found in much smaller quantities than L.
Egg yolk and maize have the highest mole percentages of L and Z, although good sources are also preformed vitamin A from animal products such as milk, meat, and liver.[3, 4, 8, 9,11,13,14]

4.3 VITAMINS

4.3.1 Vitamin A

This vitamin is only found in animal resources. Common dietary sources of this vitamin include liver; dairy products like milk, butter or cheese; oily fish and fish oils. And the richest sources of vitamin A are beef and chicken liver. As we already know, carotenoids can be converted in the body to vitamin A. [3, 4, 9, 11, 13–15, 22]

Substances that adversely affect vitamin A availability include high doses of ferrous sulphate, tannic acid as black tea, aspirin and nitrates from processed meats. [15]

4.3.2 Vitamin C

In humans, vitamin C has to be obtained from the diet. Good sources of this vitamin include fruit, especially strawberries, blackberries, kiwis and citrus fruits; and vegetables like spinach, broccoli, potatoes, sweet red pepper and tomatoes. [3, 4, 15, 23]

4.3.3 Vitamin E

Good sources of vitamin E are found in egg yolk, nuts, seeds, vegetable unrefined oils, meat, animal fat, fruit ad fish. Dietary sources of vitamin E, except for fish, are largely limited to the food sources rich in fat. [3, 4, 15, 24,25]

4.4 PROTEINS

A protein food which contains all eight essential amino acids is considered a complete protein. Meat, fish, eggs and dairy products fall into this category. Plant foods are usually lacking in at least one essential amino acid, so vegetarians and vegans require a wide variety of foods to ensure that they are eating a full complement. Combining foods, such as beans and lentils, nuts and seeds, or grains and legumes, usually overcomes this. [4,17]

4.5 CARBOHYDRATE

Plants are our essential source of carbohydrate such as grains, rice, vegetables, potatoes, beans, lentils and fruit. [4,18]

4.6 MINERALS

4.6.1 Zinc

Zinc is found in a wide variety of foods, and a good source of it include oysters, which contain the highest mole concentration of Zinc, followed by shellfish, red meat, green leafy vegetables, nuts and pumpkin seeds. [4, 13, 19, 26–28]

Of note, vegetarians need 50% more Zn than nonvegetarians, as a diet rich in plant proteins has high concentrations of phytates, which decrease Zn absorption from the digestive tract. [3,4]

4.6.2 Selenium

The most concentrated food source for Selenium is the Brazil nut, followed by seafood, fish, meats, cereal grains, dairy products, fruit and vegetables. [4,19,29]

4.6.3 Manganese

A good sources of Manganese is found in tea, cereals, pulses, blackberries, raspberries, leafy vegetables and pineapples. [4, 19,29]

All seed foods are rich in zinc and manganese.[3]

5. NUTRITION AND EYE PROTECTION

5.1 ROLE OF EYE PIGMENTS IN THE EYE

Lutein and Zeaxanthin are pigments, found in the retina, also known as macular pigment (MP). MP absorb blue light reducing incidence on the fovea by approximately 40%, and consequently reducing retinal damage. [7,9,13,30,31]

The macular pigment has been located in the inner axons of the photoreceptors, on the rod outer segments. Within the rod outer segments, the concentration of L and Z is highest in the perifoveal region, where it is approximately 2.5 times higher than in the peripheral retina. The ratio of L to Z and MZ within 0.25mm of the fovea is approximately 1:2.4, but the situation reverses at the retinal periphery, where the ratio is 2:1 *(see illustration 4).* [9]

MZ reach their maximum level in the central macular, where L levels reach a mínimum. H.Bartlett and F. Eperjesi (2006) have shown that there are specific mechanisms or biological pathways for the conversion of L to MZ within the central macula. This difference in concentration may be due to the fact that MZ is more effective at some role within the central macula that L. [9]

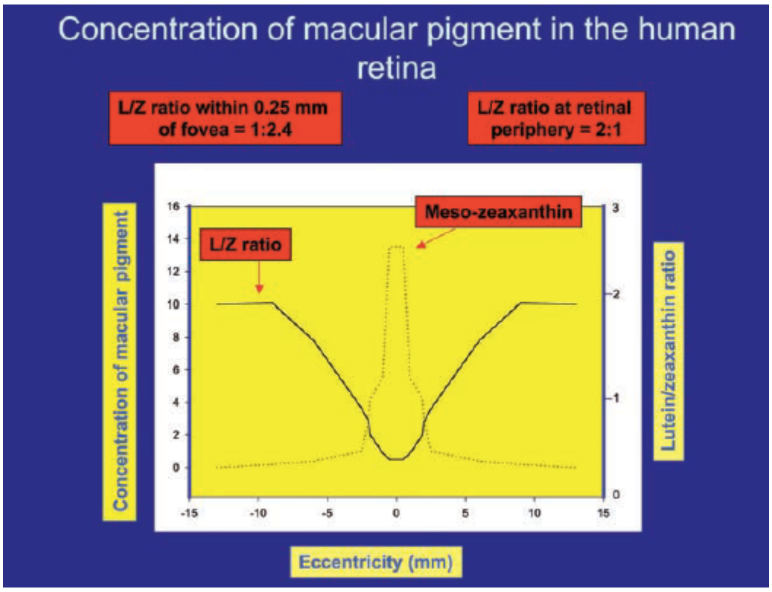

Illustration 4. Graph showing the spatial profile of xanthophylls. The density of the MP is greatest within the central fovea, 7mm2 of the central human retina, but the fovea also contains a high concentration of meso-zeaxanthin (MZ). [9]

On the other hand, there is a one hundred-fold drop in the concentration of MP in the peripheral retina compared with the fovea, although levels vary considerably between donors. The ratio of L to Z and MZ varies linearly with the ratio of rods to cones with increasing eccentricity up to approximately 6 degrees from the fovea.

When humans discovered that that squirrel monkey and macaque retinae have their highest concentration of L and Z in the central fovea, the hypothesis that Z was only found in the rods was refuted by the fact that the fovea contains predominantly cones. [9,13,14]

The functions of MP are different. At first, it was suggested that xanthophyll play a similar role in humans as in plants, as antioxidants and screeners of high-energy blue light.

Blue light is the highest energy form of visible light and is known to induce photo-oxidative damage by generation of Reactive oxygen species (ROS). The presence of MP in the inner retinal layers supports this photoprotective role of high blue light. The absorbance spectrum of MP peaks at 445nm and act as a broadband filter, reducing the sensitivity of the macular region to short wavelength light which is most damaging in the 430 to 470nm range.

The filtering function of MP is particularly important in young individuals (30–40 years), when the lens is virtually transparent to blue light, because they are at higher risk of macular exposure to blue light, and this may represent a risk for AMD.

As well as filtering the blue-light for photo-oxidation, MP may also reduce chromatic aberration, increase contrast, reduce glare and improve visual acuity.

MP absorbs the shortwavelength light, and it has been shown that a filter covering a similar spectral range to MP can reduce the radiance of the short-wavelength blur circle to a sub-threshold value, so MP might reduce longitudinal chromatic aberration. This hypothesis that the MP reduces shortwavelength chromatic blur and therefore enhances spatial vision has been termed the acuity hypothesis by *Wooten and Hammond (2002).* [14]

Wooten and Hammond (2002) also hypothesize that the contrast of the object is increased because MP may increase visibility by reducing the luminance of the background with respect to the object itself. [14]

5.2 ROLE OF ANTIOXIDANTS IN THE EYE

Oxidative damage is a major risk factor for degenerative eye diseases, like cataract or AMD. This metabolic process called oxidation occurs throughout the span of life, affecting and causing negative effects in the eye.

Is a natural process essential for providing energy to the cells for vital functions, however during this process, a type of free radicals are produced, which are capable of damaging membrane by an oxidative stress

Some natural antioxidant, like enzymes, acts against this oxidative stress, neutralising these free radicals.

The two most important antioxidants are Vitamin C and Zinc. So it is very important to include them in our diet. Also vitamins, minerals, enzymes or carotenoids should be included, since most of these nutrients are not synthesized by our body.

Free radicals are normal in our body as a natural metabolic process, but if this production overtakes the antioxidant capacity it becomes a problem. This instability starts with oxidative stress and ends up with cellular damage.[3,13]

On next section, a discussion follows on how specific nutrients may have a good influence on the prevention of some ocular pathologies, due to this antioxidant function.

6. ROLE OF NUTRITION IN PREVENTION OF SOME EYE DISEASES

In this section, the role of some nutritional elements or supplementation in the diet will be discussed in relation to the prevention and/or delay of different common eye pathologies.

First of all, it is necessary to explain some important concepts used in the studies that we accepted to elaborate this thesis. These concepts are statistical parameters which help to understand the efficiency of the study and the reliability, and they are the odds ratio [OR], the relative risk [RR], and the confidence interval [CI].

- [OR]: It is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. And it is evaluated like follows:
  - [OR] = 1 The probability is the same in both groups
  - [OR] > 1 The probability is without exposure
  - [OR] < 1 The probability is with exposure

In our case, it is interesting the exposure with nutritional supplementation give us [OR] < 1 because of that demonstrates that nutritional supplementation has some beneficial effect on the pathology.

And if with supplementation we achieve this ratio [OR] > 1 means that the supplementation is a risk factor for the disease.[32]

- [RR]: The relative risk (or risk ratio) is an intuitive way to compare the risks for the two groups. Simply divide the cumulative incidence in exposed group by the cumulative incidence in the unexposed group.
  - [RR] = 1 It suggests the same incidence on both groups
  - [RR] > 1 It suggests an increased risk of that outcome in the exposed group.
  - [RR] < 1 It suggests a reduced risk in the exposed group.

So we are interested in achieving a [RR] < 1 value which means that our supplementation reduces the risks. [33]

- [CI]: gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data. [34]

This parameter is given as a certain percentage, and a higher parameter means better confidence. But is also associated with an interval of numbers which means the interval that we are talking about, and also a parameter p which is defined as the probability under the assumption of no effect or no difference (null hypothesis), of obtaining a result equal to or more extreme than what was actually observed. This value p can take any value between 0 and 1. Values close to 0 indicate that the observed difference is unlikely to be due to chance, whereas a P value close to 1 suggests no difference between the groups other than due to chance.

So we, in this case, we are interested in achieving a high a certain percentage, and a small p-value. [35]

6.1 CATARACT

Cataracts have different etiological factors. Damaging of the lipids and proteins in the lens, and also metabolic and ion changes are some of them. There are different classifications of cataract, but only the location classification: nuclear, cortical and posterior subcapsular cataract (PSC) will be used here.

Oxidation is the major risk factor of cataracts. This process inside the lent affects lipoproteins, important for the cell membrane, and proteins, important in the cytoplasm within the fibers. The coming studies have been suggested that antioxidant vitamins are very important for helping our lens preventing cataractogenesis. [3,7,11,14,26,30]

Study	**Participants**		**Nutrients Evaluated**		**Parameters Evaluated**	**Study Results**
Sperduto RD, Hu TS, Milton RC, et al. (1993)	Trial 1	2141	Placebo		Prevalence of cataractogenesis in different types of cataract	Beneficial effects delaying the cataractogenesis, mostly on nuclear cataract
			Multivitamin + mineral			
	Trial 2	3249	Placebo			
			Vitamin + mineral	retinol/zinc		
				Riboflavin / niacin		
				ascorbic acid/molybdenum		
				Selenium/alpha-tocopherol/beta carotene		
Age-Related Eye Disease Study Research Group (AREDS) Report No. 9 (2001)	4629		Carotenoids + zinc		Photographic quality – slit lamp	≡
			Carotenoids			
			Zinc			
			Placebo			
REACT Group (2002)	445		Vitamin C		"increase % opaque pixels" (IPO)	IPO improves after 3 years of supplementation
			Vitamin E			
			Beta - carotene			

Table 2. Comparation of Cataract studies

During the Sperduto RD, Hu TS, Milton RC, et al. (1993) study there was two trials. On the first one the supplement was multivitamin + mineral, and then a placebo, and on the second one was vitamin + mineral in different combinations (etinol/zinc, riboflavin/niacin, ascorbic acid/molybdenum, and selenium/alpha-tocopherol/beta carotene), and placebo as well.

In the first trial, there was a statistically significant 36% reduction in the prevalence of nuclear cataract for persons who received the supplements.

In the second trial, the combination of riboflavin/niacin showed a significantly lower prevalence of nuclear cataract, up to a 44% reduction, in contrast with the others combinations.

The maximum level of reduction was achieved for the older group (65 – 74 years of age).

The treatment with riboflavin/niacin, also shows a deleterious effect on the posterior subcapsular cataracts, although the number of it was very small.

So, these findings suggest that supplementation with vitamins + minerals can decrease the risk of cataract, mainly nuclear cataract. [36]

On the AREDS report No.9 study (2001), which investigated cataracts and AMD cases, found no improvement with supplementation.

The study was divided into:

- Non carotenoids
    - With zinc + copper
    - Without zinc
- Carotenoids
    - With zinc + copper
    - Without zinc

The result did not show any reduction in the development of cataract. [27]

On the REACT group (2002) the percentage of opaque pixels in different stages of cataract formation was assessed during a maximum of four years. The results show us how the percentage of opaque pixels is reduced with years of supplementation. This study is done with people at the beginning of the pathology.

The beneficial effect of supplementation and how this effect increases with the number of years of supplementation. It is important to mention that this study was performed in UK and US, and although there was an overall beneficial effect, only had beneficial effects in the US, which is may be caused by a better nutritional status in the US group.

The results demonstrate some type of efficacy of daily oral antioxidant micronutrients, and after three years there was a small deceleration in the progress of cataractogenesis. [37]

Although there is not a huge difference in supplementation with cataracts in different studies, the more relevant and the ones with best results have been mentioned here.

In my opinion and although the benefits of supplementation do not seem to be clearly proven, some minimal improvement effects can be achieved it may be important for the eye's health. However, is important to remember that this supplementation has to start at the beginning of cataractogenesis.

6.2 AGE-MACULAR DEGENERATION (AMD)

Age-Macular degeneration affects basically the foveal area on the retina. An early sign of AMD is associated with drusen, an accumulation of extracellular material located between retinal pigment epithelium and Bruch's membrane, and also pigment changes.
There are two types of AMD, dry and wet, but the most common are the first one, dry form, which involves the 85% - 90% of the cases of AMD. Although, the wet form is less common but more virulent.

The common symptoms are blurring, distortion or scotoma on the central visual field (VF), and worst vision acuity (VA).

The etiology of this pathology is also unknown, but what we are aware of it is the risk factors associated with AMD, amongst the most important risk factors related to AMD are ageing, smoking, and diet is one well recognised nowadays. [1,3,13,16,26,30,37]

Caffery, B (2003) theory relates to the vascular system reporting that the blood flow could be reduced near to the macula due to the narrowing of the arterial duct and the common breakdown of the photoreceptors could not be removed in the correct way. The retinal pigment epithelium (RPE) has the role of digesting the membranes of the photoreceptors daily, when this process is not performed debris accumulation appears, causing lipofuscin which results in the development of drusen. And consequently, the normal macular function deteriorates. Another theory, macrophages with AMD have been observed at the level of Bruch's membrane, but this process is not well understood. The final theory suggests that constant interaction of light in our retina and the pigment breakdown produce a number of lipofuscin and free radicals, which cause oxidative stress and are harmful to the healthy retina, destroying the macular area. In order to avoid this process, our body has some antioxidant properties, that protect our RPE for this process, and the antioxidants are vitamins A, C, E and Zinc. [1]

<table>
<tr><th>Study</th><th>Participants</th><th>Nutrients Evaluated</th><th>Parameters Evaluated</th><th>Study Results</th></tr>
<tr><td rowspan="4">Age-Related Eye Disease Study Research Group (AREDS) Report No. 8 (2001)</td><td rowspan="4">3.640 participants 55-80 years old</td><td>Vitamin C, E, and beta-carotene</td><td rowspan="2">Probability of AMD</td><td rowspan="4">The best results were obtained from the supplementation antioxidants + zinc</td></tr>
<tr><td>Zinc</td></tr>
<tr><td>Vitamin C, E, and beta-carotene + zinc and cooper</td><td rowspan="2">Visual acuity</td></tr>
<tr><td>Placebo</td></tr>
<tr><td>Age-Related Eye Disease Study Research Group (AREDS) Report No. 20 (2007)</td><td>4519 participants</td><td>Omega-3 long-chain polyunsaturated fatty acids (LCPUFA)</td><td>Progres of AMD</td><td>A decrease likelihood of having NV AMD</td></tr>
<tr><td rowspan="5">Richer, S. Et al (2004)</td><td rowspan="5">90 participants (86 men and 4 women)</td><td>Lutein</td><td>MPOD</td><td rowspan="5">We can see an improvement in all parameters, and better improvement on the early state of pathology</td></tr>
<tr><td>Lutein + antioxidants + vitamins + minerals</td><td>Contrast sensivity</td></tr>
<tr><td rowspan="3">Placebo</td><td>Visual acuity</td></tr>
<tr><td>Amsler</td></tr>
<tr><td>Glare recovery</td></tr>
</table>

Table 3. . Comparation of AMD studies

There are basically three different nutritional elements that have demonstrated their efficiency in protecting against AMD: the antioxidants, the carotenoids (lutein and zeaxanthin) and the omega 3 polyunsaturated fatty acids (PUFA). It is important to recall that studies only show a delay of AMD what supplementation is used at the beginning of the pathology, not to stop or revert the pathology.

The AREDS Report No.9 (2001) study demonstrates that people with advanced AMD in one eye, but the opposite eye healthy, reduce the risk of several visual loss a 25% with the combination of vitamins C, E, beta-carotene, zinc and copper. With this combination, we can delay the process, but never reverse the visual loss, and the pathology.

The participants enrolled in this study have to have at least one eye that the visual acuity achieved 20/32 or better results with the best correction. The both eyes can have extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, pigment abnormalities, but only one eye can have advanced AMD.

On this study was evaluated the outcomes of the odds ratio [OR] in the two parameters evaluated (probability of AMD, and visual acuity) in the differents four groups of supplementation which was; placebo; Vitamin C, E and beta-carotene; Zinc; and Vitamin C, E, beta-carotene and Zinc.

This outcome, have shown how the best supplementation is with antioxidants (Vitamin C, E, beta-carotene) + zinc. This supplementation is the one who offers better delay of AMD probability, regarding a range of [0,098] on the first year, and [0,276] on the 7th year with antioxidants + zinc, and [0,142] on the first year and [0,375] on the 7th year with placebo. The same happens with the deterioration of visual acuity which with supplementation the range is [0.033] on the first year, and [0.314] on the 7th year, and with placebo, [0.044] on the first year and, [0.385] on the 7th year.

So, according to the results of this study, it is a good option to take supplementation of antioxidants+ zinc in order to delay the process of macular degeneration.

Richer, S. Et al (2004) have shown on their Lutein Antioxidant Supplementation Trial (LAST study) that a high intake of lutein increases macular pigment optical density (MPOD), and consequently it may play a preventive role.
On this point, we think it is important to mention that investigators used the concentration of MPOD as an indicator since Landrum J. And Bone R. accepted the MPOD as a marker protecting against AMD on their study.

The objective of this project was to evaluate the efficiency of lutein, and lutein with additional supplements (carotenoids, antioxidants, vitamins and minerals). The parameters evaluated were MOPD, contrast sensitivity, visual acuity, Amsler, and Glare recovery.
The study was divided into 3 groups, the first one was Group L, supplemented with 10mg Lutein (FloraGlo), the second one was Group L/A supplemented with 10mg Lutein + carotenoids + antioxidants + vitamins + minerals (OcuPower) and the last one was Group P with Placebo (maltodextrin).

The results obtained in this trial demonstrates us again how nutritional supplementation is beneficial for AMD, because, the CSF improve (decreases log value) on both L and L/A groups, but again MPOD increased in L group an average of 36% and an average of 43% in the L/A groups whereas the placebo group showed a reduction. That means that the best results were obtained from the L/A group in this two parameters.

Something similar happens with visual acuity where increased more on the L group than on L/A group, in contrast with the decrease in placebo.
On the Amsler grid, which is a test that assesses the visual field on the central part of the retina, there are represented by the net effect (the number of eyes that get better), which is also better on L group and then L/A group secondly. So on this two parameters, the better results are obtained from the L group.

Finally, glare recovery was faster on the L/A group.

The results above demonstrate that the progression of AMD may be slowed with this two groups of supplementation, but the effect is larger when nutritional supplementation is started in the early stages of the pathology. [38,39]

The AREDS report No.20 (2007) study have shown the beneficial effect of omega-3 intake with baseline severity of age-related macular degeneration (AMD).

This study is divided into 4 categories, depending on the severity group. The group 2 is determined by extensive small drusen (ESD) and nonextensive intermediate drusen (NEID), the group 3 by extensive intermediate drusen (EID) and large drusen (LD), the group 4 by geographic atrophy (GA), and finally group 5 by neovascular (NV) AMD.

The [OR] outcomes from that trial have shown that the group which shows better improvement/less delay of the pathology is the neovascular AMD. The better [OR] outcomes of total omega-3 LCPUFA come from group 5 with NV AMD with the [OR] = 0,63 (0.45-0.89) CI 95%. The worst outcomes come from the group 4 with (GA) with the [OR] = 1,27 (0.50-3.22) CI 95%. The other groups in the middle of this two achieves the following results, group 2 with (ESD and NEID) with the [OR] = 1,05 (0.80-1.37) CI 95%, and finally the group 3 with (EID and LD) with the [OR] = 0,84 (0.73-1.23) CI 95%.

Apart from that, this trial demonstrates how a higher fish intake delays the process of NV AMD.
This are the outcomes depending on the fish intake:

- The [OR] = 0,83 (0.50-1.40) CI 95% when the fish intake is 1-3 medium servings/ month
- [OR] = 0,61 (0.37-1.00) CI 95% when the fish intake is >2 medium servings/ week.

So, a higher intake of omega-3 LCPUFAs and fish is associated with a decreasing likelihood of having NV AMD.[37]

6.3 DRY EYE

Dry eye is one of the most common multifactorial eye disorders, which can be due to reduction lacrimal secretion. It could be caused by lacrimal gland disease or meibomian gland dysfuction, and the signs and sympthoms are decrease of corneal sensation, increase of palpebral fissure. An increase of tear film evaporation causes an increase of tear film osmolarity, overtaking the normal lomit of 311mOsm/L^4. [26], [38], [39]

Omega – 3 fatty acids have been shown how could imprrove the results of tear film. The effectiveness of anti-inflammatory omega-3 polyunsaturated fatty acids in the treatment of dry eye síndrome has been shown in multiple studies. [40]

Study	Participants	Nutrients Evaluated	Parameters Evaluated	Study Results
J. C. Wojtowicz et al (2010)	36 participants (21 treatment group and 15 placebo group)	Omega – 3 fatty acids	OSDI Slit-lamp TBUT Corneal Staining Schirmer test Tear flow Evaporometry	An ingreasing of the tear production and volumen
M. Mohammadpour, S. Mehrabi, N.Hassanpoor, R. Mirshahi (2016)	48 participants	Omega – 3 fatty acids	OSDI Schirmer TBUT Tear osmolarity	Improvments of the outcomes with omega -3 supplementation in all the parameters

*Table 4. . Comparation of Dry eye studies. *OSDI : Ocular surface disease index / TBUT : Tear break up time*

J. C. Wojtowicz et al. (2010) study wants to demonstrate how omega-3 supplementation could improve the lipid composition of meibum, aqueous evaporation and tear volume, in patients with dry eye. But the studies have shown that this improvement is only achieved on the tear production and volume.

And this is demonstrated with the Schirmer and Fluorophotometry outcomes. The tear production increase with omega-3 achieving a Schirmer from 8.13 ± 5.07 to 12.33 ± 9.86mm, in contrast with placebo 8.00 ± 6.05 to 10.52 ± 9.35mm. Something similar happens with tear volume, achieving a Fluorophotometry 0.86 ± 0.55μL at baseline to 0.98 ± 0.48μL whereas in placebo decrease from 1.44 ± 1.13μL to 0.62 ± 0.22μ.

So, the average tear production and volume increased adding a supplementation with omega-3 in diet, as Schirmer and fluorophotometry indicate.[41]

M. Mohammadpour, S. Mehrabi, N.Hassanpoor, R. Mirshahi (2016) have shown an interesting recent study with interesting outcomes, and it could be beneficial for all people, not only this group of people, although we know that a surgery cataract factor in taking an important part on it.

On this trial, there were two main groups, the control group and the treatment group (it is important to mention that in the both groups there was a normal treatment for dry eye syndrome). The treatment group is the one supplemented with omega-3.

On the four parameters evaluated have seen an improvement of the outcomes with omega -3 supplementations.

On the post-treatment, TBUT has a control group with 6.03 ± 2.26 s and a treatment group higher with 7.65 ± 3.26 s (p =0.0388).
Schirmer test control group have 3.85 ± 2.88mm and a treatment group value increases to 4.96 ± 2.84mm (p=0.155).

Osmolarity has a control group with 311.33 ± 6.35 osmol/L and a treatment group with low values 296.9 ± 14.39 osmol/L (p =0.01).

The last parameter was OSDI, the only subjective parameter which also shows an improvement with a control group 25.43 ± 14.49 and a treatment group value decreases to 16.31 ± 13.72mm (p=0.026).

So, Omega-3 supplementation has a positive effect on the tear film. We already mention that this trial was specifically for people that become with this syndrome after a cataract surgery, but we think that it could be beneficial as well for other people. [40]

6.4 GLAUCOMA

Glaucoma is characterized by the progressive loss of retinal ganglion cells. The etiology is multifactorial, but the most common is the rise of pressure inside the eye.
This pathology could end up with blindness, that is why is very important to control the pressure and also the affectation on the macula, because how we already know the damage in the retina is irreversible. [42,43]

On this point, we want to know how we can delay the process or improve the aqueous outflow with a nutritional diet.

Study	Participants	Nutrients Evaluated	Parameters Evaluated	Study Results
J.J. Garcia-Medina, M. Garcia-Medina, et al. (2014)	117 participants	Oral antioxidants supplementation	VF OCT MD PSD RNFL GCC	Non beneficial effect
C.T.O. Nguyen, B.V. Bui, A.J. Sinclair, A.J. Vingrys (2007)	87 rats	Omega – 3 fatty acids	IOP Aqueous outflow facility Ciliary body tissue fatty acid analysis	Beneficial reducion of IOP

*Table 5. Comparation of Glaucoma studies. *VF : Visual field // OCT : Optical coherence tomography // MD : Mean derivation // PSD: Standard pattern derivation // RNFL: Peripapillary retinal nerve fibre layer // GCC : Ganglion cell complex*

C.T.O. Nguyen et al. (2007) have shown that omega-3 improves the aqueous outflow, reducing the IOP.

This trial was carried out by rats, and compare the IOP and outflow on two groups: -3+ and -3-.

The IOP have an important reduction with -3+ diet from 15.46 0.29 mmHg to 13.48 0.32 mmHg ($p < 0.01$), and that is caused because of the aqueous outflow increase 56%.[44]

So, Omega-3 fatty acids have shown to be beneficial reducing the IOP and improving the aqueous outflow, in order to avoid the optic neuropathy.

J.J. Garcia-Medina, M. Garcia-Medina, et al. (2014) study demonstrates that oral antioxidant supplementation (OAS) have a beneficial effect in primary open-angle glaucoma.

This trial was divided into three different group, the group 1 OAS with -3 fatty acids (ICAPS R – Alcon Lab), the group 2 with OAS and without -3 fatty acids (OFTAN MACULA – Labortorios Esteve), and the last group, group 3 placebo.

The outcomes showed non-relevant differences after 2 years trial. [45]

So, Omega-3 fatty acids are reported to be beneficial in contrast with antioxidants supplementation which outcomes did not show any beneficial effect.

6.5 RETINITIS PIGMENTOSA

Retinitis pigmentosa (RP) is a group of hereditary retinal disorders characterised by progressive visual field loss, night blindness and abnormal electroretinogram (ERG).

It is known that some vitamins are beneficial delaying the progress of cones and rods degeneration, and the following studies show that. [46], [47]

Study	Participants	Nutrients Evaluated	Parameters Evaluated	Study Results
E.L. Berson, B. Rosner et al. (1993)	601 participants	Vitamin A Vitamin E	Cone electroretinogram amplitude	Vitamin A have beneficial effects, but vitamin E have adverse effects.
E.L. Berson, B. Rosner et al. (2011)	225 participants	lutein	MOPD	Slowed loss of midperipheral visual field
E. Berson, B. Rosner, et al. (2012)	357 participants	Omega -2 fatty acids	Visual acuity	Reduce the declines of VA

Table 6. Comparation of Retinitis Pigmentosa studies.

E.L. Berson, B. Rosner et al. (1993) on their trial was four groups of treatment, the group 1 receiving 15 000 IU/d of vitamin A, the group 2 receiving 15 000 IU/d of vitamin A plus 400 IU/d of vitamin E, group 3 receiving trace amounts of both vitamins and the last group, group 4 receiving 400 IU/d of vitamin E.

The two groups receiving 15 000 IU/d of vitamin A showed a delaying of the degenerative retinal function (P=.01). Apart from that, this two groups with vitamin A supplementation has a 32% less likely to have a decline in amplitude, while the two groups receiving vitamin E were 42% more likely to have a decline in amplitude.

So, like the outcomes show, vitamin A have beneficial effects against retinitis pigmentosa, but in contrast, it seems that vitamin E have an adverse effect. [48]

E.L. Berson, B. Rosner et al. (2011) realised a clinical trial in order to know if lutein is beneficial reducing the retinitis pigmentosa process. It was divided into two groups, the first one with Lutein (12 mg) + vitamin A (palmitate 15,000 IU/day), and the second one, the control group only with vitamin A(palmitate 15,000 IU/day).

But, although the not significant difference was found between the groups, it was shown that Lutein supplementation slowed the loss of mid-peripheral visual field on retinitis pigmentosa taking vitamin A. [49]

E.L. Berson, B. Rosner, et al. (2012) design a trial of ω-3 Intake and Visual Acuity in Patients With Retinitis Pigmentosa Receiving Vitamin A.

How we already mention in the 3.1 section, EFAs are necessary for the correct function of the rhodopsin, so it seems evident that ω-3 fatty acid could be a beneficial supplement on the delaying of Retinitis Pigmentosa, and this trial tries that.
This trial was divided basically into two groups, from high consumption of ω-3 to the low conception of ω-3. And the outcomes show a decline of VA from 0.59 per year on high consumption of ω-3 to 1.00 per year on low consumption of ω-3.

So, it demonstrates that high consumption of ω-3 reduces the declines of VA, so it is beneficial for this pathology. [50]

6.6 VITAMIN A DEFICIENCY

Vitamin A deficiency (VAD), also called as the term of xerophthalmia. It can be caused by the laking intake of carotenes, inadequate conversion of carotene to Vitamin A, interference with absorption, transport or storage of vitamin A.

This vitamin is essential for maintaining the integrity of epithelial tissues and is also associated in the form of visual pigments

The earliest symptom, and most common, is the night blindness, characterised by an increase in visual threshold, making it difficult to see in dim light. The administration of vitamin A could improve this situation between 24-48 hours, but only if this problem is not associated with digestion, absorption transport or storage. The effect on visual adaptation may be magnified when associated with Zinc deficiency, that is because this deficiency reduces the levels of retinol plasma, resulting with low levels of vitamin A in the retina, and and that can be reversed by supplementation of Zn. [4,14,47]

7. OCULAR NUTRITIONAL SUPPLEMENTS

Since now we talk about the role of nutrition in vision, and studies showed us the beneficial effect of supplementation on some pathological process, so now it is time to talk about this ocular nutritional supplements.

There are a lot of different ocular nutritional supplements, but we only are going to mention a selection of the most relevant ones, the ones which we talked since now on the different pathologies, and some interesting one, to my best knowledge.

As West et al. (2005) said in their article, a significant portion of patients presenting for eye care to a comprehensive general ophthalmology clinic use vitamin and/or herbal therapies. It is reported that the majority of patients use complementary and alternative medicine (CAM) supplements, above 46%.[51,52]

7.1 SUPPLEMENTATION FROM EACH NUTRITIONAL COMPONENT

7.1.1 Essential Fatty Acids

DHA supplementation is used to combat dietary deficiency, especially in premature human infants with formula milk, enriched with Omega 6 and Omega 3 fatty acids, which has been shown to improve visual function according to an analysis of several studies conducted by researchers at Harvard School of Public Health and published in the journal Pediatrics. [5,6,53]

We mention on section 6 the beneficial effect of omega-3 fatty protecting adult eyes from macular degeneration and dry eye syndrome, as well as reducing the IOP increasing the aqueous outflow.

7.1.2 Carotenoids

Landrum et al 1997 study have shown how daily supplementation for 140 days with 30 mg lutein esters produced a seven-fold increase in serum levels and a 20- 40% increase in MPOD. And something similar said the Berendschot et al 2000 study which supplementation with 10 mg/d lutein esters for 12 weeks increased serum levels by five-time and MPOD by 20 %. [11,53,54]

So like we already see on previous pathologies, carotenoids are beneficial for retinal pathologies.

7.1.3 Vitamins

Supplementation with vitamins does prevent retinal damage in several species, but it is also beneficial on cataracts and vitamin A deficiency, and important pathology which we already talk about and administration of vitamin A could reverse this situation between 24-48 hours.[15,28,53]

It is important to mention some interesting points of each important vitamin essential for the eye: [15]

- The principal forms vitamin A in supplements are retinyl palmitate and retinyl acetate. And, b-Carotene is also a common source of vitamin A in supplements, which we could find it alone or in combination with retinol.
- It is advisable to take vitamin E supplements rather than increase high-fat foods in the diet.
- Past studies have shown that the bioavailability of vitamin C from vegetables is similar to that from a supplement.

7.1.4 Minerals

A number of Zinc supplements are commercially available, including different Zn forms.

Vitamins and minerals supplements may be contraindicated for people with some illnesses, for example, insulin-dependent diabetes.[19,55]

7.2 COMMON SUPPLEMENTATION FOR THE EYE

7.2.1 EyeVit® PLUS

Omega – 3 is a beneficial supplement useful in the major of pathologies we talked. The most important are for patients with starting signs of dye eye, but it also includes retinitis pigmentosa reducing the declines of VA, glaucoma reducing the IOP and on AMD decreasing the likelihood of having NV AMD.

TECHNICAL DATA

Components
Omega – 3 In the form of natural triglycerides

Lab
Health Aid

Illustration 5. EyeVit Plus [56]

7.2.2 Eyegum

This innovation nutritional supplementation is a gum created exceptionally for improving the eye tissues nutrition.
It has the ability to increase the antioxidant capability, having a beneficial effect on the macula, and also on the tear production, achieving an ocular surface more hydrated and stable.

TECHNICAL DATA

Components
Lutein, Zeaxanthin, Vitamins A-C-E and Zinc

Lab
Oftalcare Nutravision

Illustration 6. Eyegum [57]

7.2.3 FloraGlo

High intake of lutein and zeaxanthin may play a role in lowering the risk of AMD, and that is the role of this supplement.
It was used in some trials which we talked previously.

But it is also beneficial for early stages retinitis pigmentosa.

TECHNICAL DATA

Components
10-mg lutein

Lab
Kemin

Illustration 7. FloraGLO [58]

7.2.4 I-Caps

It could be useful to a person with early AMD and also for those deemed at risk of developing AMD.
But their composition could be also beneficial for people with cataract because of the vitamins and minerals.

I have never would recommend it for retinitis pigmentosa because it contains vitamin E and studies have shown adverse effects on this pathology (section 6.5) [56]

TECHNICAL DATA

Components
Vitamin A-E-C, Riboflavin, Zinc, Selenium, Copper, Manganese, Lutein and Zeaxanthin.

Lab
Alcon Laboratories

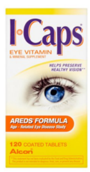

Illustration 8. I-Caps [60]

7.2.5 MacuShield

It is a formula which combines all three macular carotenoids. Like we already mentioned, these three nutrients are found at the back of the eye, at the macula, where they form the macula pigment. Meso-zeaxanthin is particularly concentrated at the centre of this pigment.
So this supplementation could be so beneficial for early stages of retinal pathologies whom AMD or retinitis pigmentosa.

TECHNICAL DATA

Components
Meso-Zeaxanthin, Lutein and Zeaxanthin

Lab
Macuvision

Illustration 9. MacuShield [61]

7.2.6 OcuPower

This supplementation is based on antioxidants and zinc, so it could be beneficial for people with AMD, but not for retinitis pigmentosa because of the vitamin E.

TECHNICAL DATA

Components
10-mg lutein
vitamin A – C – D3 – E - B1 - B2 - B3 - B5 - B6 - B12 - , beta carotene, calcium, magnesium, iodine zinc, copper, manganese, selenium chromium, molybdenum, lycopene, bilberry extract, alpha lipoic acid, N-acetyl cysteine, quercetin, rutin, citrus bioflavonoids, plant enzymes, black pepper extract, malic acid, taurine, L-glycine, L-glutathione and boron.

Lab
Alcon Laboratories

Illustration 10. OcuPower [62]

7.2.7 Ocuvite

There are two types of Ocuvite and depends on the components, there are the Ocuvite® PreserVisionTM and Ocuvite Lutein.
It has been shown to reduce the progression of AMD, and it is useful to a person with early AMD or at risk of developing AMD – especially if they have a low lutein diet.

But it is contraindicated for smokers. [56]

TECHNICAL DATA

Components
Beta-carotene, Vitamin A-C-E, Zinc and Copper

Lab
Bausch and Lomb

Illustration 11. Ocuvite [63]

7.2.8 Quest Eye Nutrient Complex

Their composition shows us that it could be useful to a person with early AMD or at risk of developing it. [56]

TECHNICAL DATA

Components
Vitamin A-E-C, Zinc, Copper and Lutein.

Illustration 12. Quest Eye Nutrient Complex [64]

7.2.9 Retinex Eye Nutrient

This supplement is very likely to be suitable for this type of person with early signs of retinal pathologies such AMD or retinitis pigmentosa. [56]

TECHNICAL DATA

Components
Lutein and Zeaxanthin.

Lab
Healthspan

Illustration 13. Retinex Eye Nutrient [65]

7.2.10 Visionace

It may be useful for those people who are at risk of ocular disease and who have a poor diet, because have a high doses of vitamins, minerals and antioxidants.

So it might be beneficial on AMD cases. [56]

TECHNICAL DATA

Components
Vitamin A - D – E – C – B2 – B3 – B6 – B12, Folacin, Pantothenic, Zinc, Copper, Magnesium, Iron, Iodine, Manganese, Selenium, Chromium, Natural mixed carotenoids, Citrus bioflavonoids, Bilberry extract equivalent to and Lutein esters.

Lab
Vitabiotics

Illustration 14. Visionace [66]

7.2.11 Vitalux Plus

It is a supplement of vitamins and mineral salts with antioxidant effect since they intervene in the cellular protection against the degenerative action of free radicals, and necessary for vision and the eye.

It related to the reduction of the risk of AMD, protect the eye from cataracts, is adjuvants against alterations of corneal epithelium with corneal opacity.

TECHNICAL DATA

Components

Ascorbic acid, zinc, vitamin E, beta carotene, selenium, Riboflavin, copper, lutein, microcrystalline cellulose, calcium silicate, hydroxypropylmethylcellulose, purified stearic acid, magnesium stearate, silicon dioxide.

Illustration 15. Vitalux Plus [67]

8. OUTCOMES

The analysis of the outcome is explained comparing what we expected and the final data. We will explain on every pathology the best nutritional supplements reported in studies and which supplement should be used in each case.

The first one is Cataract, and even though this pathology is the one where a huge benefit is not reported, benefits of supplementation are controversial although there is a consentment, and for example Vitamin C in general is necessary. The studies that have shown more improvement were supplemented with vitamins and minerals, so at early stages of the cataractogenesis with OcuPower which has a huge concentration of minerals and vitamins could be beneficial.

Another one is AMD, where more beneficial effects have been found in contrast with cataract. The studies reported that L + Z + Zinc are the best type of supplementation for this pathology. These nutrients are found at the macula, where they contribute to the health of macular pigment, delaying retinal damage. Also, Omega - 3 supplementation has been reported to be beneficial at decreasing the likelihood of having NV AMD. A good option of supplementation on this case could be I-Caps or Vitalux Plus + EyeVit® PLUS. The first two have high levels of antioxidants and minerals. And EyeVit® PLUS give the Omega -3 component on the supplementation.

In Dry Eye, the only benefit that has been shown come to Omega -3 fatty acids which helps to increase the tear production and volume. Glaucoma has also shown an improvement with Omega - 3 fatty acids in reducing of the IOP.

So the type of supplementation for both Dry Eye and Glucoma is with EyeVit® PLUS, which containg high levels of Omega-3.

A beneficial effect with Lutein supplementation has been reported on Retinitis Pigmentosa, showing a less loss of mid-peripheral visual field. Also Omega-3 supplementation reduce the decline of VA, and vitamin A supplementation resuts as a less loss of cone electroretinogram amplitude. In contrast, and adverse effect with vitamin E have been shown. So, Retinex Eye Nutrient + EyeVit® PLUS, which contains Omega – 3 and vitamins, could be a good provides of supplementation for Retinitis pigmentosa.

A Vitamin A deficiency (VAD) could be reverted using vitamin A supplementation for 24-48 hours. Since Zinc could play a role in the cause of Vitamin A deficiency a Zinc supplementation could be a good option in this case of VAD.

Most likely other actions than supplementation may be as effective as sun protection, healthy habits and also to avoid smoking.

9. RECOMENDATIONS AND IMPROVMENTS

In this project, I have had some difficulties searching the original articles and studies because most of them have not free access.

Another difficulty was how to limit the project and selected the correct studies for each pathology. Of course, there are a lot more studies apart from I mentioned but it is impossible to talk about all of them, so to be honest, I selected the studies depending on their beneficial results, but I also select some negative studies in order to compare the different pathologies and their different interaction with supplementation.

Another handicap was the language because although I was on the international program and practice English there, my spelling and grammar in not as fluent as I would like and to do this project it has been a challenge for me.

10. CONCLUSIONS

In general, we obtained what we thought, observing the studies we can see the beneficial role that nutrition has on our visual system.
Despite this, not all nutrients have this beneficial role in the whole eye or in all pathologies. And not all the nutrients are beneficially equally on the different eye tissues.

Accordingly, to our outcomes, supplementation is most of the time the best option in order to delay a pathological process, but it is important to start with it always on an early stage, following a good diet and avoiding other risk factors like smoking for example.

So I would recommend to all these patients with eye pathologies to follow a supplementation apart from the medicines, and for all this people with a healthy visual system follow a diet rich on Lutein, Zeaxanthin and Meso-zeaxanthin for the healthy retina, and rich in minerals, EFA and vitamins very important for most of the visual tissues.

11. GLOSSARY

- ALA : Alpha-linolenic acid
- AMD : Age macular degeneration
- AREDS : Age-Related Eye Disease Study Research Group
- CAM : complemenatry and alternative medicine
- DHA : docosahexaenoic acid
- DMAE : Degeneración ocular associada a la edad
- EFAs : Essential Fatty Acids
- EID : Extensive intermediate drusen
- EPA : eicosapentaenoic acid
- ERG : electroretinogram
- ESD : Extensive small drusen
- GA : Geographic atrophy
- GAGs : Glycosaminoglycans
- GCC : Ganglion cell complex
- IOP : Intra ocular presure
- L : Lutein
- LA : linoleic acid - Omega 6
- LD : Large drusen
- LNA : linolenic acid - Omega 3
- MII : Metarhodopsin II
- MD : Mean derivation
- MP : macular pigment
- MPOD : macular optical density
- MZ : Meso-zeaxanthin
- NEID : Nonextensive intermediate drusen
- NV : neovascular
- OCT : Optical coherence tomography
- OSDI : Ocular surface disease index
- PDE : phosphodiesterase
- POSs : Photoreceptor outer segments
- PSC : posterior subcapsular cataract

- PSD : Standard pattern derivation
- PUFA : Polyunsaturated fatty acids
- RNFL : Peripapillary retinal nerve fibrle layer
- ROS : Reactive oxygen species – therm to describe some types of free radicals, which all are capable of damaging membrane.
- ROS : Rod outer segments
- RP : Retinitis pigmentosa
- RPE : Retinal pigment epithelium
- TBUT : Tear break up time
- VA : Vision Acuity
- VAD : Vitamin A deficiency
- VF : Visual Field
- Z : Zeaxanthin

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