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Review Article

Metabolic Considerations Regarding Age-related Macular Degeneration (AMD): A Focus on Current Knowledge Effects of Caloric Restriction (CR): A Review

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ABSTRACT

In Western countries, AMD (Age-Related Macular Degeneration) is the leading cause of blindness in individuals over the age of 55. AMD is one of the most severe pathologies affecting the eye; in fact it damages the macula causing a serious impairment of the central vision. There are two forms of AMD: early or dry AMD and advanced AMD, which can occur as an atrophic form (geographical atrophy) or as a wet or exudative (neovascular) form (10%-15% of cases), less frequent but more disabling. Many studies on mouse models have shown that caloric restriction (CR) decreases age-related decline of ocular functions by reducing oxidative stress. It is therefore potentially useful in modulating the endophenotype of individual AMD patients This type of intervention could also be effective in humans, but being not easily applicable, it has not yet been studied extensively in the clinical setting. However, it is now known that CR mimetics can have similar benefits as CR. To allow for the wide application of the benefits of CR in the clinical setting, mimetic compounds will be developed including the activators of sirtuins and adenosine monophosphate-activated protein kinase (AMPK). Even the ketogenic diet seems to have a protective role on retinal neurodegeneration, but the data supporting this notion in the literature are still few. Finally, the role of the low glycemic index diet should not be underestimated. Extensive studies on a large population of patients must be conducted to demonstrate the effectiveness of CR, CR mimetics, ketogenic diet or simply reduction of the glycemic index of the diet on the AMD prevention and/or progression.

Keywords: Age-related macular degeneration; Caloric restriction; Ketogenic diet; Glycemic index

INTRODUCTION

AMD Definition

According to the World Health Organization in Western countries, AMD (Age-Related Macular Degeneration) is the leading cause of blindness in individuals over the age of 65 and can significantly reduce the quality of life [1,2].

It is estimated that by 2020, more than 7.5 million people aged >65 years may experience vision loss [3].

Because of these alarming statistics, researchers are working to identify factors that could prevent and/or delay the progression of the disease and the consequent retinal damage.

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Age-related macular degeneration is one of the most severe diseases affecting the eye. It damages the macula, the central part of the retina containing the maximum concentration of cones, which are specialized photoreceptors for viewing details. The disease therefore causes a great impairment of central vision while preserving peripheral or lateral vision.

There are two forms of AMD: early or dry AMD and advanced AMD. The first can occur as an atrophic form (geographical atrophy) or as a wet or exudative (neovascular) form (10%-15% of cases), less frequent but more disabling. The dry form is the most frequent (80% of cases), is characterized by pigmentary anomalies and by the presence of drusen, yellowish deposits near the fovea and it occurs in multiple stages [4].

In the early stages the symptoms are modest and include difficulty in reading (some letters appear blurred), presence of dark or empty areas in the center of the visual field (scotomas), perception of straight lines as distorted or broken in some areas (metamorphopsias).

Advanced AMD can manifest as either an atrophic form (geographical atrophy) in which the retina undergoes a progressive thinning, with severe loss of the Retinal Pigment Epithelium (RPE) and choriocapillaris, or wet or exudative form (10%-15% of cases) less frequent but more disabling, also called neovascular AMD because it is characterized by newly formed blood vessels that develop from the choroid (the vascular membrane of the eye) and grow in the macular region. These blood vessels have a very fragile wall so they tend to break causing bleeding or exudations, causing lifting of the macula with irreversible damage and progressive loss of vision [5].

Exudative macular degeneration occurs acutely: the subject has an important reduction of his visual ability and perceives wavy or distorted images.

Prevalence

The AMD prevalence increases sharply with age, but despite the major geographic and lifestyle differences, it appears to be similar in the Caucasian populations of the United States, Australia and Europe [6,7].

In a meta-analysis performed in 2004 by Friedman and collaborators, the prevalence rates for late forms of the disease increase from 0.5% for subjects 50 to 60 years old to 12%-16% for subjects of 80 years or older [8].

With regard to the early AMD form, an increase from approximately 1.5% in Caucasians between 40 and 49 years old to more than 25% in individuals of 80 years and older was observed [8].

Risk factors

There are non-modifiable and modifiable risk factors.

Among the non-modifiable risk factors in addition to genetic polymorphism and a family history of AMD, aging is associated with the exponential increase in the incidence and prevalence of the disease [9-12].

Other unchangeable factors are light skin colour, light iris colour and probably the female gender [13-16].

Among the modifiable risk factors, smoking is the most recognized environmental risk factor for AMD and a dose-dependent association has been found for the risk of late AMD that appears to be cumulative over time [17,18]. In fact, AMD correlates with the number of years the subject smoked and the number of cigarettes smoked per year. Smokers develop the disease 5-10 years earlier than non-smokers and have double the risk of experiencing the neovascular form [17-19].

Other modifiable risk factors include high blood pressure, cardiovascular disorders, dyslipidemia, a sedentary lifestyle, obesity, an unbalanced diet low in vitamins and fatty acids, excessive alcohol consumption [17-19].

These risk factors guide the development of new therapies and new treatment strategies, but the current situation requires efforts to identify and eliminate some of the modifiable risk factors.

Since there are no other effective means of primary prevention other than smoking cessation, lifestyle changes, including diet acquires enormous importance.

Concerning the current state of knowledge the oxidative stress is the most mechanism studied in the link between AMD and CR, although should not be considered the only mechanism at all.

AMD and oxidative stress

Numerous studies have revealed oxidative stress as one of the mechanisms implicated in the AMD pathogenesis and diet is generally the main source of antioxidants [5,20]. Regarding ocular tissues, their biological integrity depends on the balance between the production of free radicals and their catabolism [21,22].

The production of free radicals increases with age, but some of the endogenous defence mechanisms decrease, creating an imbalance that leads to progressive damage to cellular structures [22]. The extensive antioxidant network includes vitamins (C, D and E), enzymes (superoxide dismutase, catalase and glutathione peroxidase), carotenoids (alpha and beta carotene, lycopene, lutein and zeaxanthin) and many other compounds (flavonoids, lipoic acid, acid uric, selenium and coenzyme Q10) [23]. Antioxidants act as a protective chain and several of them have a synergistic effect.

Therapies for neovascular AMD exist, but there is no effective treatment for early AMD and geographic atrophy, a dramatic public health event over the next two decades [9].

The first available treatment included the use of VEGF inhibitors, effective in wet end-stage AMD [2-5]. The study on age-related eye diseases (AREDS) has shown that integration of high levels of antioxidants and zinc can delay advanced AMD [6,7].

However, the ideal therapy would be the one that prevents the onset or delays the progression of early dry AMD.

Many studies have shown that elevated levels of oxidative stress increased mutations in mitochondrial DNA and accumulation of lipids and lipofuscin can be associated with dry AMD, suggesting that in this setting the metabolism of photoreceptors and RPE is compromised [10-17].

The accumulation of lipofuscin in lysosomes is a sign of high cell metabolic activity. Lipofuscin is a complex fluorescent mixture composed of macromolecules (proteins, carbohydrates, lipids, metals), arranged in a reticular way, which have undergone an oxidation process, and which originate from different metabolisms.

The nature and structure of the lipofuscin complexes seem to vary in the different tissues and shows heterogeneous composition: 20%-70% proteins, 20%-50% lipids, glucidic residues, presence of cations (iron, copper, zinc, aluminium, manganese, calcium) [24].

Due to its highly cross-linked structure, lipofuscin cannot be easily degraded or removed *via* exocytosis, it is therefore accumulated in lysosomes or in the cytoplasm.

In the human RPE, lipofuscin accumulates progressively during the first six decades of life occupying a space equal to 19% of the cytoplasmic volume, but over time, the levels tend to reach the plateau [25].

Excessive accumulation of lipofuscin has been associated with several retinal disorders including AMD, retinitis pigmentosa, Stargardt's disease, Best's disease. Lipofuscin genesis in RPE is still an area of discussion: it has been hypothesized that lipofuscin derives from the incomplete degradation of the photoceptors subjected to the phagocytosis process by external segments, organelles and proteic aggregates [25].

Some studies show that CR reduces the accumulation of lipofuscin in RPE of Wistar rats [25].

A 2010 study suggests the possibility that the accumulation of lipofuscin could be prevented or delayed by antioxidants: vitamin E, zeaxanthin, lutein, lycopene (Lipofuscin-formation in retinal pigment epithelial cells is reduced by antioxidants [25]. While, a study shows that the accumulation of lipofuscin is linked to a lower endogenous antioxidant activity: decreased activity of Catalase and SOD (superoxydismutase) up to 60% and in glutathione levels up to 28% (Inhibition of RPE lysosomal and antioxidant activity by the age pigment lipofuscin) [26].

AMD AND CR

In a more recent study on mouse models, CR shows neuroprotective effects in aged retinas by reducing age-related photoreceptor cell death [24,27].

Oxidative stress was reduced thanks to a pool of protective factors such as retinal thiol, glutathione, ascorbic acid and taurine [28].

However, another study in CR mice showed conflicting results demonstrating photoreceptor cell loss [24,27].

The ganglion cells of the retina decrease in number with increasing age and CR diminishes age-related loss of these cells [29].

Therefore, these studies suggest that CR protects against the loss of these cells.

There are numerous theories that attempt to explain the effects of CR.

Cava and Fontana hypothesize that to trigger a powerful anti-aging response, the body must perceive a low energy availability as in the case of CR, which translates into important simultaneous metabolic adaptations (i.e. low circulating levels of leptin, insulin, IGF-1, testosterone, estradiol, triiodothyronine and inflammatory cytokines coupled with increased serum concentrations of adiponectin, ghrelin and cortisol) aimed at cell conservation and repair [30]. Data from experimental murine studies have shown that CR delays aging and prolongs the average and maximum duration of life, compared to life-long exercise, which only extends the average lifespan (Figure 1) [31].

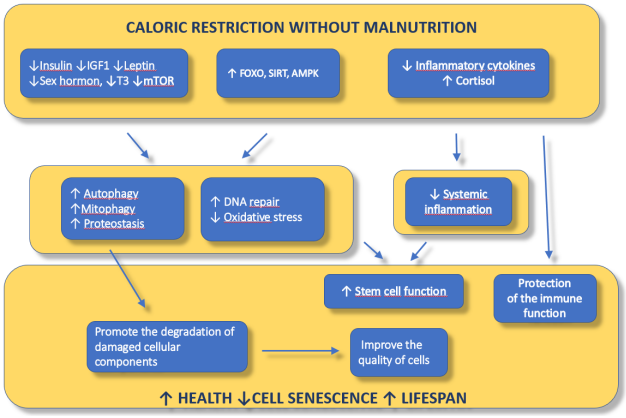

Figure 1: Caloric restriction without malnutrition.

CR with an adequate supply of nutrients represents the most powerful non-genetic intervention to improve health and lengthen lifespan in multiple animal models including yeast, fruit flies, worms and rodents [32]. In most mouse model strains, a 20 to 50% reduction in calories results in a substantial extension of the average and maximum lifespan, although mice with different genotypes respond differently to the same degree of restriction [33]. In humans, CR with an adequate supply of vitamins and minerals causes many of the same physiological, metabolic and molecular adaptations observed in animals subjected to CR.

The mechanisms mediating the benefits of CR are not fully understood.

CR, without malnutrition, leads to a significant improvement in insulin sensitivity and reduces protein glycation, oxidative stress and cell damage induced by free radicals (Figure 1).

CR reduces the anabolic hormones and growth factors that cause a down regulation of the nutrient-sensitive insulin/IGF signalling network and determines an activation of FOXO, a powerful cyclin D inhibitor, regulator of cycle progression and cell proliferation, which modifies several longevity genes including endogenous antioxidant enzymes, DNA repair genes

and autophagy. Autophagy and mitophagy promote the degradation of damaged cellular components by setting the ground for replacement with new and well-functioning components, thus helping to improve the quality of cells and tissues by accelerating cell turnover and preventing the accumulation of damage in the cells [34]. Another important adaptation to CR is the reduction of plasma concentrations of inflammatory cytokines and a modest increase in circulating cortisol which translates into a reduction of systemic inflammation together with a protection against the deterioration associated with the aging of the immune function [35,36].

Other molecular effectors that have been shown to mediate the effects of CR include TOR, AMPK, sirtuins and NRF2 [35,36].

The energy and amino acids restriction causes an inhibition of mTORC1 activity which in turn improves autophagy, proteostasis and stem cell function [35,36].

AMPK is an enzyme that plays a critical role in cell homeostasis; it belongs to the serine-threonine kinase family. It is a fundamental regulator of energy metabolism.

AMPK is the most important enzyme regulated by AMP; AMPK responds to increased AMP by phosphorylating key proteins and modulating their activity. The increase in AMP can be caused by a decreased nutrient supply or by prolonged exercise. The action of AMPK increases the transport of glucose, the activity of glycolysis, the oxidation of fatty acids and reduces the synthesis of glycogen, fatty acids and cholesterol [37]. At the same time, in extrahepatic tissues the kinase stimulates liver gluconeogenesis to supply glucose to the brain.

AMPK is activated by high concentrations of AMP and low concentrations of ATP, exercise, the sympathetic nervous system or peptide hormones produced by the adipose tissue (leptin and adiponectin) [37].

The level of AMPK activation depends on the intensity of the exercise and changes in the AMP/ATP and creatine/phosphocreatine ratios.

Activation of AMPK in response to acute exercise inhibits ATP consumption pathways and activates the metabolism of carbohydrates and fatty acids to restore ATP levels in muscle [37].

In addition, AMPK also plays a role in the adaptive response of muscle to continued exercise by altering energy reserves and the expression of exercise-sensitive genes [37].

Recently, it has been shown that AMPK is also regulated by known hormones as adipokines, which have effects on all tissues including adipose tissue and liver (where energy reserves accumulate), hypothalamus (responsible for the control of hunger and thirst) and skeletal muscle (where the demand for energy substrates is constant for the contraction) [37]. In each of these tissues these hormones are able to modify the activity of the AMPK and trigger a response through it. In particular, at the level of the hypothalamus, AMPK is stimulated by a decrease in the glucose concentration and intestinal hormone ghrelin, resulting in increased nutrient intake [37].

On the contrary, AMPK is inhibited by leptin (hormone produced by adipose tissue), with consequent reduction of nutrient intake [37].

In response to reduced calorie intake, cells activate AMPK as a survival mechanism. This beneficial activation of AMPK vanishes when normal food consumption is resumed. Metformin can increase AMPK activity [37].

Sirtuins and eye

Sirtuins are a family of NAD+dependent deacetylase proteins, i.e. enzymes that remove the acetyl group from lysine residues of protein substrates or histones in the presence of the cofactor.

NAD+sirtuins (nicotinamide adenindinucleotide).

They play a key role in regulating many aspects of cellular metabolism, from energy to synthesis; they modulate the gene transcription of chromatin and regulate the activity of various transcription factors. They are metabolic sensors and mediators of cell survival in stressful conditions, such as CR and exercise, in which their transcription is, activated.

They are involved in metabolic processes that delay aging and increase lifespan, in the regulation of the cell cycle, in the inhibition of apoptosis, in glucose homeostasis and in insulin secretion (Figure 2).

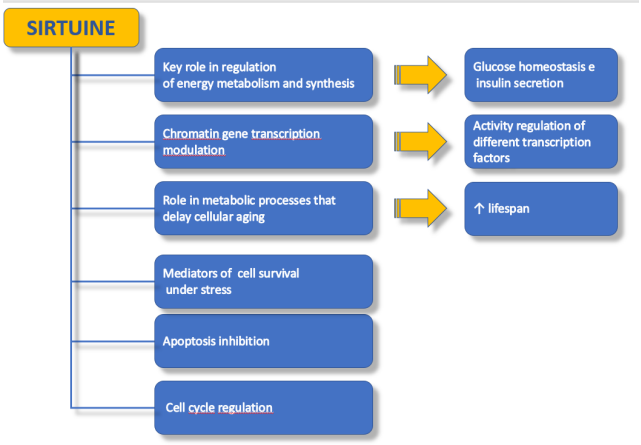

Figure 2: Roles of sirtuins.

The most studied sirtuin is SIRT 1, mainly located in the nucleus, in response to particular stimuli or physiological conditions. SIRT 1 is implicated in many cellular processes such as lipid and carbohydrate metabolism, mitochondrial biogenesis, inflammation, autophagy, circadian rhythm, resistance to stress and chromatin silencing [38-40]. Another important metabolic function is the regulation of glucose homeostasis: it increases glucose up-take inducing the overexpression of GLUT4, reduces the expression of enzymes involved in gluconeogenesis and increases adiponectin levels, all conditions that increase insulin sensitivity. The expression of SIRT 1 varies according to the physiological conditions and, in particular, is induced during a low energetic state and repressed in conditions of high energetic state. For this reason, SIRT 1 expression is increased in fasting conditions or low-calorie diets, while in high calorie diets its expression is reduced (Figure 3) [38-40].

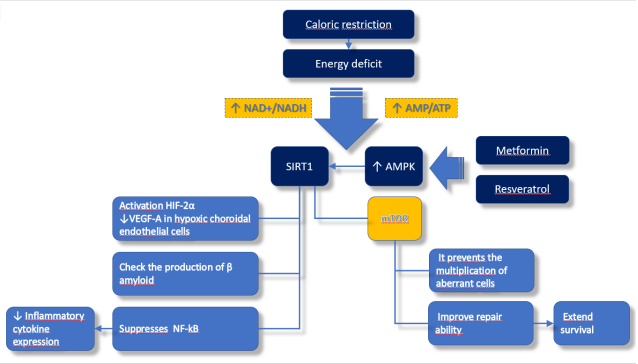

Figure 3: Pathway activated by CR.

Furthermore, many studies in the literature describe the importance of the role of polyphenols in the activation of sirtuins [41,42]. In 2003, the Sinclair team described 18 molecules derived from plants that can activate sirtuins in yeasts and studied their effects on SIRT1 [43-45]. The flavones quercetin and fisetin, the stilbeni piceatannol and resveratrol and the buteincalcone stimulated SIRT1 from 5 to 13 times. The most powerful activator is resveratrol, a compound synthesized by a large number of plants in response to stress and present in appreciable quantities in grapes and red wine. This molecule is already known for its protective role against numerous pathologies, including cardiovascular, neoplastic and neurodegenerative ones [46-49]. Another pivotal molecule involved in the regulation of SIRT 1 is the AMPK that, as previously mentioned, is activated in conditions of energy deficit, nutritional depletion or by all those substances that activate SIRT1 *via* the AMPSK signalling. Once activated, AMPK increases the ATP levels and stimulates the increase in NAD acting positively on SIRT1 [49]. These two proteins reduce mTOR activation.

The inhibition of mTORC1 activity induces two protective effects:

(a) It preserves the function of stem cells in numerous tissues, improving their repair capacity and, ultimately, delays the progression of age-related diseases and prolongs survival

(b) Prevents the multiplication of aberrant cells [50-53]. The enzymatic activity of SIRT 1 depends on the presence of NAD+, for this reason it is clear that the activity of this protein is directly linked to the metabolic state of the cell.

Confirming what has just been described, almost all Sirtuins have a role in regulating energy metabolism and homeostasis, often helping the cell to adapt to low energy intake situations.

Many studies have shown that in conditions of glucose excess there is a decrease in the activity of SIRT 1, while in conditions of energy deficiency an increase of it [51].

In addition, further studies have highlighted the role of SIRT 1 in lipid metabolism showing that in conditions of energy depletion the activity of SIRT 1 is highly stimulated.

Except for SIRT5, all sirtuins are expressed in the human retina [43,44]. The retina is a photoreceptive tissue whose energy consumption varies based on exposure to light.

Jaliffa and colleagues demonstrated that SIRT1 is expressed in the mouse cornea, in the lens, iris, ciliary body, inner nuclear layer (INL), outer nuclear layer (ONL) and retinal ganglion cell layer and appears to play a role in ocular morphogenesis [51-53].

SIRT2 is expressed in non-pigmented ciliary epithelium, extern and internal plexiform layer, nerve fiber layer, inner and outer nuclear layer and RPE [48]. It is also expressed in inflammatory cells of the limbo and iris stroma in cases of retinoblastoma.

SIRT3 is highly expressed in the lacrimal gland and in the neural retina of mice, mainly in the retinal ganglia and photoreceptor cells [54].

In humans, the INL has shown a weak expression of SIRT3 throughout the retina [54].

In the human retina, the retinal pigment epithelium (RPE) expressed SIRT4, SIRT6 and SIRT7. SIRT4 and SIRT7 were strongly positive in the macula and peripheral retina but not in the ONL.

In humans, SIRT6 is expressed in macula, unpigmented body ciliary epithelium, ciliary muscle, RPE, optic nerve fiber and sensorineural retina except for the internal limiting membrane. The expression of SIRT6 has been observed in retinoblastoma [55].

In a study of hypoxic choroidal endothelial cells, SIRT1 was found to regulate vascular endothelial growth factor-A (VEGF-A) through the activation of HIF-2 α. The increase in the levels of VEGF in hypoxic cells and the consequent decrease after the activation of SIRT1 establish a relationship between SIRT1 and HIF-2 α [48].

Cao et al. have shown that one of the components of drusen is beta amyloid (A β) (controlled by SIRT1 activation) induced by inflammation in AMD [39]. Beta amyloid induced changes in retinal pigment epithelial cell morphology while barrier integrity was balanced by SIRT1 activation by suppressing the nuclear factor kappa-B (subunit p65). The reduction in the activation of the nuclear factor kappa-B further reduced the inflammatory expression of the cytokines interleukin-8 (IL-8), interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9). The current data therefore support the concept that modulating the activity of sirtuins to provide neuroprotection in these diseases can have therapeutic implications. However, drug release still remains one of the biggest challenges in ocular treatment, particularly for diseases affecting the posterior and anterior segment of the eye. Systemic administrations fail to reach a therapeutic concentration due to the presence of blood-aqueous and retinal barriers [48]. On the contrary, intravitreal administration may allow to reach a higher concentration of drug for the treatment of posterior segment diseases, but the process is very painful and suffers from poor patient compliance. The inventors have demonstrated prolonged retinal ganglion cell survival and neuroprotection by administering resveratrol incorporated in biodegradable polymer such as polylactic-glycolic acid (PLGA) and intend to use this formulation for the treatment of posterior segment disorders such as AMD and macular edema. Future studies are needed to better understand and clarify the molecular role of sirtuins and identify their substrate partners/

cofactors and the intracellular pathways that regulate their activity in different disease models. However, it is essential and plausible to develop and test (clinical studies) specific pharmacological activators or sirtuin inhibitors that can mediate neuroprotection and serve as a beneficial strategy for the treatment of neurodegenerative eye diseases.

CR mimetics

Although CR can have beneficial effects on humans, it is very difficult to implement and maintain it.

Therefore, alternative methods were evaluated to have the same benefits as CR, without imposing the strict guidelines required by the same.

Considering the molecular mechanisms involved in CR, some chemical compounds or natural products could mimic their effects.

Candidate compounds include several polyphenols, lactoferrin, astaxanthin, lipoic acid (α-lipoic acid or ALA) and deoxy-glucose (or 2-DG), as well as drugs currently in use such as metformin.

In particular, used for the treatment of diabetes improves the sensitivity of insulin receptors on the surface of metformin muscles and fat cells.

Metformin activates genes that reduce glucose production and reduces gene expression of enzymes that increase the oxidation of fatty acids, which correspond to the same actions as the genetic effects of CR [18].

Similar to CR, these compounds modulate numerous inflammatory pathways throughout the body and also in the eyes.

Several CR mimetics have been tested on various age-related eye conditions and these compounds have shown promising results in delaying the disease onset [18].

Polyphenols (including resveratrol, quercetin, anthocyanin and curcumin) and other candidate CR mimetics (such as lactoferrin, lutein and eicosapentaenoic acid) have been the most frequently studied in eye diseases.

Resveratrol is a polyphenol present in the peel of red grapes and other fruits and is a popular mimetic of CR [56].

In the eye, resveratrol suppresses vascular lesions associated with diabetic retinopathy and decreases inflammation of the innate retina in endotoxin-induced uveitis [56]. In diabetic retinopathy, AMPK activation is the known mechanism for the suppression of vascular lesions and the effects of resveratrol have been reproduced with the activator AMPK 5-aminoimidazole-4-carboxamideribonucleoside (AICAR) [57-59]. Resveratrol also has a neuroprotective effect in light-induced retinopathy [57-59].

Lutein, a carotenoid belonging to the group of xanthophylls, is concentrated in the macula (center of the retina) and is indicated as a macular pigment in humans. Based on the results of clinical trials, lutein is thought to prevent the development and progression of AMD and has been investigated as part of a very large prospective study, Age-Related Eye Disease Study 2 (AREDS2) [60]. Initial results from the Age-Related Eye Disease Study (AREDS) indicated that supplementation with antioxidants (β-carotene and vitamins C and E) and zinc was associated with a reduced risk of AMD progression [61]. The AREDS2 follow-up study, designed to improve upon the earlier formulation, tested the addition of lutein, zeaxanthin, and ω-3 fatty acids. The AREDS2 formulation with 10 mg lutein/d and 2 mg zeaxanthin/d is now the standard of care for reducing the probability of advanced AMD in patients with substantial risk factors for progression to severe visual loss, and there is even some evidence that subjects receiving AREDS2-type supplements could have stabilization and improvement of best-corrected visual acuity [62,63]. However, the AREDS2 failed to show that fish oil supplements had any benefits, and the β-carotene of the original AREDS formula is no longer generally recommended because of potential lung cancer risks.

Carotenoid can suppress retinal neuronal degeneration in diabetic retinopathy, innate retinal inflammation in endotoxin-induced uveitis and neurodegeneration in light-induced retinopathy [63].

In a non-randomized comparative clinical study, the influence of antioxidant supplementation on the retinal function of patients with age-related maculopathy was evaluated by recording focal electroretinograms (FERG).

The focal electroretinogram of patients undergoing oral antioxidant supplementation (lutein, 15 mg; vitamin E, 20 mg; and nicotinamide, 18 mg, daily for 180 days), showed an increased amplitude compared to patients not undergoing dietary supplementation during the same period. The results suggest that increasing level of antioxidants in the retina could influence macular function in the early stages of the disease process, as well as in normal aging [64].

Saffron supplementation also leads to a significant improvement in retinal function in the early stages of AMD. The major constituents of saffron, (derived from the pistils of Crocus sativus,) crocin and crocetin, which are derivatives of carotenoids, are powerful antioxidants, with antiapoptotic characteristics [65].

Crocins are able to activate metabolic pathways to protect cells from apoptosis and to reduce light-induced death in isolated photoreceptors, whereas crocetin increases oxygen diffusivity through liquids, such as plasma.

Daily supplementation of 20 mg/d saffron for 90 days was associated with statistically significant changes in the macular FERG parameters (amplitude and modulation threshold) in patients with early AMD [66,67].

Saffron can therefore play a role as a retinal neuroprotector against oxidative damage.

Further recent studies confirm that saffron treatment is extremely effective in reducing the effects due to neurodegenerative processes both in the animal model and in human diseases in which oxidative stress and neuroinflammation are heavily involved [68-70].

The visual performance in patients treated with saffron remains stable while in patients treated with the AREDS protocol they

deteriorate, confirming the hypothesis of an added value of the saffron treatment compared to the pure antioxidant treatment.

Saffron could activate a resilience mechanism in response to oxidative and inflammatory stress.

Numerous clinical studies are needed to confirm this promising result.

Saffron acts directly at different levels as an antioxidant, but also by regulating many genes and protein synthesis. Neuronal death, neuroinflammation and morphological disorganization are reduced and the progression of degenerative pathology is slowed down.

Many natural products with antioxidant capacity have been tested. Compared to the others, saffron seems very promising in slowing the progression of AMD which means that low doses and extended treatments increase the probability of a positive outcome [71-75]. Microarray experiments have shown that saffron is capable of modulating gene expression modified by damage induced by the retina [73]. Saffron treatment modulates the expression of the metalloproteinase and the enzymatic activity and reduces the disorganization of the external matrix. The greater efficacy of saffron treatment is probably related to the activation of multiple pathways.

Eicosapentaenoic acid (EPA) is an omega-3 polyunsaturated fatty acid (PUFA), abundantly present in fish, and is also being studied in AREDS2. Daily dietary supplementation with EPA suppressed the development of laser-induced choroidal neovascularization in a mouse model of AMD (Table 1).

Table 1: CR Mimetics.

Drug	Function	Mechanism and AMD	References
Metformin	Oral hypoglycemic agent that strengthens the sensitivity of insulin receptors on the surface of muscles and fat cells;	They increase AMPK activity SIRT 1 reduces inflammatory cytokine expression its are associated with a reduced chance of developing AMD.	[18,19]
Polyphenols: Resveratrol, Anthocyanin, Quercetin, Curcumin	They have antioxidant and anti-inflammatory properties.	They increase AMPK activity SIRT 1 reduces inflammatory cytokine expression They are associated with a reduced chance of developing AMD.	[56]
Lutein	Carotenoid belonging to the group of xanthophylls, concentrated in the macula. It has antioxidant properties.	It suppresses neuronal degeneration in particular, due to its ability to neutralize oxidation reactions in photoreceptor cells. It prevents development and progression of AMD.	[60]
Saffron	Crocin and crocetin (main components of saffron, derived from carotenoids) are powerful antioxidants, with anti-apoptotic characteristics.	Crocins are able to activate metabolic pathways to protect cells from apoptosis. It reduces the effects due to neurodegenerative processes in which oxidative stress and neuroinflammation are heavily involved. Saffron play a role of retinal neuroprotector against oxidative damage in AMD and it seems very promising in slowing the progression of AMD.	[62,65,67,68,72]
Eicosapentaenoic acid (EPA)	EPA is an omega-3 polyunsaturated fatty acid (PUFA). It has antioxidant properties.	Daily dietary supplementation with EPA suppressed the choroidal neovascularization in a mouse model of AMD.	[60]

Animal model studies have shown that CR delays age-related decline in ocular functions by alleviating oxidative stress.

Now that CR mimetics are known to control ROS in a similar way to CR, clinical trials with dietary supplements can be performed.

It is expected that compounds based on the CR mechanism, including sirtuin activators and AMPK up regulators, will be developed to allow for the wide application of the benefits of CR in the clinical setting.

A recent study, the first observational study examining the association of metformin and AMD, showed that metformin, an oral hypoglycemic agent, was able to stimulate glucose metabolism in the retina and protect retinal photoreceptors and RPE from hereditary mutations or oxidative stress in preclinical mouse models [19]. The study also demonstrated that metformin was protective through the activation of AMPK in the retina. Recent works suggest that systemic treatment with metformin activates AMPK in the retina and causes an increase in the number of copies of mitochondrial DNA and ATP production. In contrast, AMPK mutations in neuroretin cause retinal degeneration and accelerate the aging of phenotypes in mice [19]. In addition to the diabetes drugs, we wanted to examine the effect of several commonly prescribed drugs that could have an association with AMD to rule out any effects from these drugs. Studies suggest that statins, a class of drugs used to reduce lipid levels, may be associated with a lower chance of developing AMD.

This study suggests that metformin is associated with a reduced chance of developing AMD [19]. Other studies have shown that the use of metformin, but not other drugs for diabetics, is associated with a reduction in the probability of glaucoma, retinal vein occlusions in diabetes mellitus, and diabetic retinopathy. These results suggest that metformin itself has an important protective role.

Recent studies using preclinical models suggest that metabolic dysregulation may play an important role in the pathogenesis of AMD [76]. Retina is one of the most metabolically active tissues in the body with on the highest energy needs.

However, some studies have found that diabetes is associated with an increased chance of developing AMD [77].

Due to limitations in the data, in the above study it has not been shown the effective dose of metformin or the duration of therapy. Since for a large number of patients (1333 out of a total of 1947 cases) it was not specified whether macular degeneration was wet or dry, no conclusions were drawn on any form of AMD. There may be further confounding factors that have not been considered in the analysis. Other risk factors such as family history, smoking or genetics have not been taken into account. As smoking and genetics are important risk factors for AMD, the inability to explain these variables could be confusing. The effects of metformin on the incidence or severity of AMD must be prospectively tested in large multicenter clinical trial. A blinded, randomized phase II clinical trial is currently underway to evaluate the safety and efficacy of the use of metformin to reduce the progression of geographic atrophy in a small group of non-diabetic patients with dry AMD. Future prospective studies should further investigate the protective effect of metformin on AMD in large-scale multicenter clinical trials.

KETOGENIC DIET AND RETINIC DAMAGE

Numerous studies agree that the ketogenic diet elicits a neuroprotective function. For almost 90 years, the ketogenic diet has been used successfully for the treatment of patients with intractable epilepsy. The ketogenic diet includes a diet rich in fat and low in carbohydrates and proteins. During prolonged exposure to the ketogenic diet, energy is mainly derived from the oxidation of fatty acids in the mitochondria, rather than from glucose: fatty acids are oxidized at high speed, with consequent overproduction of acetyl-CoA. The overproduction of acetyl-CoA therefore leads to the synthesis of ketone bodies, such as β-hydroxybutyrate, acetoacetate and acetone, mainly in the liver. These ketone bodies act as energy substrates and there is evidence that they can improve neuronal survival in some pathological conditions, including hypoxia, anoxia or ischemia. Acetoacetate and β-hydroxybutyrate have recently been shown to produce a significant dose-dependent neuroprotective effect on retinal ganglion cells in a rat model of NMDA-induced neuronal damage. The ketogenic diet has been shown to exert neuroprotective effects in brain trauma, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Furthermore, the anticonvulsant effects have been well documented, which is consistent with its therapeutic use in the treatment of refractory epilepsy [78,79]. In light of the literature data, the ketogenic diet can exert a therapeutic benefit in ocular pathologies associated with neurodegeneration [80-84].

During a ketogenic diet, the main ketone body produced by the liver is β-hydroxybutyrate (βHB); in addition to being used as an alternative source of energy especially by neurons, the latter can act as a signalling molecule through binding with hydroxyl carboxylic acid (HCAR) receptors [83]. Stimulation of HCAR by βHB improves neuroinflammation through inhibition of the formation of the NLRP3 inflammasome in the retina. Furthermore, treatment with a ketogenic diet reduces the phlogistic process through another mechanism: the inhibition of AMPK. More generally, in addition to acting as a metabolic sensor, AMPK activates NF-κB signalling and subsequently induces a pro-inflammatory response. In summary, treatment with a ketogenic diet improves phlogistic-metabolic processes through [85]:

(a) Inhibition of AMPK,

(b) Stimulation of the HCAR1 receptor that inhibits neuroinflammation mediated by the NLRP3 inflammasome,

(c) Increase in neuronal mitochondrial biogenesis with consequent increase in metabolic efficiency,

(d) Increase in glutathione levels and consequent improvement of antioxidant efficiency,

(e) Activation of the Kinurenic acid pathway which acts as a neuroprotective agent.

(f) Better neuronal energy efficiency carried out by ketone bodies compared to glucose.

GLYCEMIC INDEX AND AMD

Over the past two decades, numerous studies have shown that the total amount of carbohydrates and even more the glycemic index are associated with visual health [86-91]. This relationship was also evaluated in mice in order to clarify the etiological relationships between food glucose, visual health and genetics [91-93]. Abundant epidemiological evidence indicates associations between GI and AMD in people without diabetes. The retina is the most metabolically active tissue in the human body, with double blood supply and rapid consumption of glucose and oxygen [94]. It is not surprising that glucose homeostasis in the retina plays an important role in retinal health and disease.

In people with diabetes, failure to regulate blood sugar leads to biochemical abnormalities in cells and tissues. Diabetic retinopathy (DR) is the most common microvascular complication [95]. Although the detailed pathogenesis of DR has not been fully understood, extensive epidemiological studies have shown that hyperglycaemia is an underlying cause of this disease [96,97]. However, similar damage also occurs to people without diabetes and in AMD. The range of pathological lesions in the retina and other vascular beds differs between age-related diabetic and non-diabetic lesions. This may be due to differences in the extent or duration of hyperglycemic exposure and/or related biochemical and metabolic abnormalities.

Epidemiological studies indicate that a low glycemic index diet is associated with a reduced risk of AMD, but intervention studies have not been conducted on this topic.

A higher GI diet is associated with an increased risk of large drusen.

A prospective analysis of the AREDS AMD study indicated that the consumption of a low glycemic index diet increased the protective effects of the AREDS formula (antioxidants such as Vitamin C and Vitamin E, zeaxanthin, lycopene plus zinc) and DHA/EPA against the progression towards advanced AMD [98].

Other studies have shown how postprandial hyperglycemia depresses serum antioxidants, including lycopene and vitamin E low GI diets could reduce damage from oxidative stress. Even more interesting is the fact that with small changes, the first benefits can already be observed, such as the replacement of 5 slices of white bread with whole grain bread. The GI-AMD relationship was further confirmed in a 10-year follow-up in the Blue Mountains Eye Study (BMES) [99].

The relevance of fiber in the association between GI risk and AMD should also be considered.

In a prospective study, GI was shown to play a more important role in individuals with bilateral AMD progression (i.e., those who are more sensitive to AMD progression) than in those with unilateral AMD progression, especially in the later stages of AMD [90].

This finding implies that the interaction between AMD susceptibility and GI affects the risk of AMD progression and that this interaction plays a more important role in the later stages. The nature of this susceptibility remains unclear. Genetic susceptibility may be an important component of the basic relationship between GI and AMD.

Like diabetes and CVD, an intervention study evaluating the effect of GI on the clinical outcomes of AMD would be difficult to perform because feeding people with high glycemic index diets for prolonged periods may not be ethical and the study would be very expensive.

Interventional data are not available, there are only observational and epidemiological studies that support this thesis (moreover not all studies agree with the results).

With aging, the external segments of the photoreceptors become convoluted and lipofuscin accumulates in the internal segment of the photoreceptors. RPE cells decrease in number, become pleomorphic and undergo atrophy, hypertrophy, hyperplasia and cell migration. Bruch's membrane becomes thickened, basophilic and hyaline and the lipid content increases. RPE is unable to cope with the phagocytosis of the external segments and its own high metabolic needs. The drusen formed by metabolic debris further interfere with the metabolic process of RPE. Eventually, this leads to cell death [100].

Although the histopathological characteristics and chemical composition of these deposits are documented, their precise role in the etiology of AMD has only partially been resolved.

Carbohydrates have been found to be important components in drusen and BLD and play an important role in the pathogenesis of AMD [101]. Drusen and, to a lesser extent, BLDs have deleterious effects on RPE function and lipofuscin accumulation in RPE with age [102].

Some sources in the literature indicate that the retina is particularly susceptible when a hypoxic condition coincides with hyperglycaemia. In a fairly recent study, a new hyperglycemic and hypoxia-inducing pathway called HIF (HYPOXIA INDUCIBLE-FACTOR) is proposed, to complete current theories regarding the pathogenesis of hyperglycaemia: HIF is a transcriptional complex that responds to the decrease oxygen in the cellular environment. Under conditions of hyperglycaemia, HIF has been shown to increase the expression of HIF-inducible genes, such as vascular endothelial growth factor (VEGF). We suggest that HIF can also be described as an inducible hyperglycaemia factor. In hypoxic conditions (as in aerobic respiration) the 4 pathways linked to glycolysis and the HIF pathway should be seen as interconnected and independent mechanisms.

These 4 glycolytic pathways are: intracellular production of AGE precursors, increased flow through the polyol pathway (the most important for the retina), PKC activation, increased activity of the hexosamine pathway.

Epidemiological data indicate that the consumption of diets with a high glycemic index is associated with a higher prevalence and greater progression of AMD; even when diets contain the same amount of total carbohydrates [86-88]. People in the highest quintile of GI intake had an increased risk of large drusen, neovascularization and geographic atrophy compared to the lowest quintile [88]. The work of other groups confirms that diets with a high glycemic index increase the risk of AMD, including soft drusen [99].

Chronic hyperglycaemia, as would be expected from consuming a high glycemic index diet, can lead to glucose oxidation or glycation.

AGEs accumulate in tissues during aging in both animals and humans. Using an antibody that recognizes a particular change in age (MG-H3), AGEs accumulate in human lenses and in the mouse brain with aging [3,103].

Animals fed high-glycemic index diets as well as having a greater risk of metabolic alterations such as impaired glucose tolerance also have an increase in retinal lesions consistent with an AMD phenotype [91,93]. Retinal changes such as increased basal laminar deposits and decreased basal inflections in mice fed high glycemic index diets were observed. Basal laminar deposits have also been observed in humans with AMD [104]. A recent work indicates that the consumption of foods with high AGE content leads to metabolic syndrome and impaired cognitive function suggesting that AGEs in the diet are harmful *in vivo* [105].

Fructose-rich diets are also associated with health problems [106]. A possible mechanism could be that fructose is able to form AGE at a faster rate than glucose [107]. Therefore, fructose toxicity may be due to its ability to form AGE. However, fructose *in vivo* is not more glycant than glucose in a yeast model and a recent study suggests that fructose alone is not correlated to compromised health that cannot be attributed to an increased total calorie intake [108,109]. Therefore, it is unclear whether fructose glycating activity is more harmful *in vivo* than glucose. Given the abundance of fructose in our diets, the relationship between fructose consumption and AMD risk deserves further attention.

However, it has been hypothesized that the accumulation of AGE during aging and the consumption of diets with a high glycemic index lead to the disruption of protein homeostasis; this in turn can contribute to the development of protein conformational or amyloid diseases including AMD.

During aging and stress, the effectiveness of the proteolytic systems decreases [110]. This leads to an increase in the accumulation and aggregation of damaged proteins and toxicity due to the accumulation of aggregated proteins. Glycemic stress also leads to the accumulation of damaged and modified proteins, decreases the proteolytic turnover leading to a reduction in turnover of damaged proteins. We also observe the accumulation of high mass glycated proteins when the ubiquitin and lysosomal pathways are inhibited.

Thus, the existence of a vicious circle caused by diet and glycemic stress, induced by metabolism, accumulation of AGEs, attenuated cells and homeostasis and dynamics of the proteins of the tissues has been hypothesized.

Therefore, long-term consumption of high glycemic index diets can help reduce proteus poise and aggravate a number of diseases related to the precipitation of age-related proteins, including AMD.

CONCLUSIONS

Many studies on mouse models have shown that CR delays age-related decline in ocular functions by reducing oxidative stress. This type of intervention could also be effective in humans, but not easily applicable and for this reason it has not yet been studied extensively in the clinical setting. However, it is now known that the mimetics of CR can control ROS in a similar way to CR, therefore numerous clinical studies have been performed with food supplements. Still many studies need to be conducted to better clarify the molecular mechanisms underlying their beneficial effects. Clinical studies are currently underway to evaluate the safety and efficacy of the use of metformin in reducing the progression of geographical atrophy in patients with dry AMD but in the future other prospective studies should further investigate the protective effect of this hypoglycemic drug on incidence and/or severity of AMD. In the literature there are few data on the protective effect of the ketogenic diet on retinal neurodegeneration but cellular mechanisms have been identified in neurological studies focusing on the effects of the ketogenic diet on energy metabolism, GABA system, glutamate-mediated toxicity, antioxidant mechanisms, programmed cell death and enhancement of kynurenic acid production. Future studies are needed to better understand and clarify the molecular role of sirtuins and identify their substrate partners/cofactors and the intracellular pathways that regulate their activity in different disease models. To allow for the wide application of the benefits of CR in the clinical setting, mimetic compounds will be developed including the activators of sirtuins and AMPK. Finally, the role of the low glycemic index diet should not be underestimated. Since carbohydrates are our main source of energy, it is reasonable to argue that sugar metabolism plays a significant role in aging and disease. Recent scientific literature has revealed multiple epidemiological and bio-molecular data supporting the hypothesis that hyperglycaemia is associated with the risk of serious metabolic disorders, including type 2 diabetes, CVD and retinal diseases such as DR and AMD. Therefore, it remains crucial to re-evaluate the management of carbohydrate intake as a means of preventing the onset or progression of these diseases. A low glycemic index diet should be recommended for high risk individuals. Future studies should focus on the relation between low glycemic index diets and disease risk by investigating the underlying biochemical mechanisms. Understanding pathogenesis will improve therapeutic options. This manuscript aims to review the current literature of correlation between AMD and CR. Still many studies on a large population of patients must be conducted to demonstrate the effectiveness of CR, CR mimetics, ketogenic diet or simply a reduction of the glycemic index of the diet on the AMD prevention and/or progression.

In our opinion, the studies with the greatest chance to get reliable outcomes are those based on the use of antioxidants and mimetic drugs. Given the repeatedly confirmed role of metformin on the prevention of AMD, the studies on this antidiabetic drug should have priority.

AUTHOR CONTRIBUTIONS

Lucilla Gagliardi participated in drafting the article and revising it critically; Stefano Angelo Santini and Gaia Anselmi participated in the discussion and revision processes. Barbara Aquilanti, Giuseppina Matera, Gabriele Egidi, Sabrina Leone, Alessandra Giraldi, Valeria Velluti, Giacinto Abele Donato Miggiano, Angelo Minnella participated in the review of the literature. Prof. Falsini gave final approval of the version to be submitted.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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