Dietary fatty acids and lipoproteins on progression of age-related macular degeneration

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SUMMARY: Age-related macular degeneration (AMD) is a medical condition of central loss vision and blindness. Numerous studies have revealed that changes on certain dietary fatty acids (FAs) could have useful for AMD management. This review summarizes the effects of dietary omega-3 long-chain PUFAs, MUFAs, and SFAs, and lipoproteins on AMD. Findings are consistent with the beneficial role of dietary omega-3 long-chain PUFAs, while the effects of dietary MUFAs and SFAs appeared to be ambiguous with respect to the possible protection from MUFAs and to the possible adverse impact from SFAs on AMD. Some of the pathological mechanisms associated with lipoproteins on AMD share those observed previously in cardiovascular diseases. It was also noticed that the effects of FAs in the diet and lipoprotein on AMD could be modulated by genetic variants. From a population health perspective, the findings of this review are in favour of omega-3 long-chain FAs recommendations in a preventive and therapeutic regimen to attain lower AMD occurrence and progression rates. Additional long-term and short-term nutrigenomic studies are required to clearly establish the role and the relevance of interaction of dietary FAs, lipoproteins, and genes in the genesis and progression of AMD.

KEYWORDS: Age-related macular degeneration; Dietary fats; Fatty acids; Lipoproteins; Olive oil; Retina

RESUMEN: *Efecto de los ácidos grasos y lipoproteínas de la dieta sobre la progresión de la degeneración macular relacionada con la edad.* La degeneración macular asociada a la edad (DMAE) es una condición patológica caracterizada por pérdida de visión central y ceguera. Numerosos estudios han revelado que ciertos cambios en los ácidos grasos de la dieta podrían tener efectos beneficiosos en el manejo de la DMAE. En esta revisión se recogen los efectos de los ácidos grasos de la dieta poliinsaturados omega-3, monoinsaturados y saturados, y de las lipoproteínas en la DMAE. La literatura es consistente en el papel beneficioso de los ácidos grasos polinsaturados omega-3 de cadena larga, mientras que se muestra ambigua con los efectos de los ácidos grasos monoinsaturados y saturados de la dieta, respecto al posible papel protector de los ácidos grasos monoinsaturados como al posible efecto adverso de los ácidos grasos saturados en la DMAE. Además algunos mecanismos patológicos que asocian las lipoproteínas con la DMAE son los mismos observados previamente en las enfermedades cardiovasculares. Hacen falta estudios nutrigenómicos a corto y largo plazo para establecer el papel y la importancia de los ácidos grasos de la dieta, y las lipoproteínas en la aparición y progresión de la DMAE.

PALABRAS CLAVE: Aceite de oliva; Ácidos grasos; Degeneración macular asociada a la edad; Grasas de la dieta; Lipoproteínas; Retina

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1. INTRODUCTION

Age-related macular degeneration (AMD) was first described by Haab in 1888 (Haab, 1888), though Verhoeff and Grossman suggested that features of AMD might have been observed in 1875 (Verhoeff and Grosman, 1937). Nowadays, more than 2 million people in United States of America are affected by AMD, the main cause of vision loss in adults (Saade and Smith, 2014). The two manifestations of AMD consist of "wet" AMD, exudative AMD, or choroidal neovascularization (CNV), and "dry" AMD or geographic atrophy (GA) (Jager *et al.,* 2008). In the first states of AMD, most patients have drusen, lipid-rich deposits under the retinal pigment epithelium (RPE). The diffusion and growth of drusen determine the detachment of RPE with a damage of photoreceptors in the macula and subsequent vision loss. Dysfunction of the choroid, Bruch's membrane, and the RPE are the principal mechanisms involved in the onset of AMD (Lee *et al.,* 2015). Environmental and genetic factors influence the events underlying the disease and modifying the individual risk factors of developing AMD (Ersoy *et al.,* 2014). In line with this concept are the shared risk factors between AMD and cardiovascular disease (CVD), which suggests a mutual pathological mechanism. Several researchers suggested that an atherosclerosis-like process might contribute to the formation of CVN, eventually leading to retinal dysfunction and the onset of AMD (Klein *et al.,* 2007; Klein *et al.,* 2013). In accordance with the importance of dietary fatty acids (FAs) and lipoproteins in CVD, previous studies have sought to underline their role on the fat metabolism as a risk factor for the onset of AMD. Taken the public health relevance of AMD, it is crucial the development of effective prevention measures. It is conceptually attractive that evaluating the influence of dietary FAs and lipoproteins on AMD could help to identify new targets for AMD management.

2. STRUCTURE OF THE RETINA: A BRIEF DESCRIPTION

The sensory retina is arranged into layers of neurons. The light conversion into chemical signals happen in the outer segments of the cone (responsible for colour vision and image-forming daylight) and rod (responsible for vision under low illumination) photoreceptors in the neural retina (Wang *et al.,* 2014). Encoded retinal signals are integrated through visuals networks and finally cross to the optic nerve. Retinal blood vessels that arise from the central retinal artery supply the blood to the neural retina. Endothelial tight junctions control the transport through retinal blood vessels (inner blood–retinal barrier) (Promsote *et al.,* 2014). The next monolayer is the RPE, which has pivotal roles in the integrity for homeostasis in the retina and the photoreceptor layer (Sonoda *et al.,* 2009). Behind the RPE is the Bruch membrane, an elasto-collagenous and thick extracellular matrix. Together, the Bruch membrane and the RPE constitute the outer blood–retinal barrier, which protects the entrance of immune cells and macromolecules from the choroid into the retinal layers. Located posterior to the Bruch membrane, the choroid has an intricate network of choriocapillaris, blood vessels that supplies nutrients and oxygen to the optic nerve, outer retina, and RPE. The fenestrated choroidal endothelium allows the transport of molecules to the RPE (Baltmr *et al.,* 2014; Demeestere *et al.,* 2015).

3. AGE-RELATED MACULAR DEGENERATION

AMD is a growing retinal pathology characterized by the failure of vision as a direct result of damage into the macula. Despite the fact that the main causes of AMD are fully uncertain, a number of environmental and genetic risk factors have been linked with the AMD (Fritsche *et al.,* 2013). Moreover, factors such as gender, race, advanced age, and smoking are well recognized to substantially increase the risk of AMD. Factors such as hypertension, obesity, and malnutrition (e.g. high intake of cholesterol and dietary fats or low intake of dietary vitamin D, zinc, and antioxidants) may also play a role in the pathogenesis of AMD (Clemons *et al.,* 2005; Dasari *et al.,* 2011; Millen *et al.,* 2015; Parekh *et al.,* 2009; Sui *et al.,* 2013). Furthermore, AMD has been recently associated with retinal low-grade inflammation linked by the infiltration and activation of immune cells and production of inflammatory mediators into the site of retinal damage (Nita *et al.,* 2014; Whitcup *et al.,* 2013).

The deposition of drusen between the choroid and the RPE is the main early hallmark of AMD onset. Drusen are constituted by glycoprotein vitronectin, apolipoprotein E (ApoE), ApoJ (clusterin), amyloid P component, albumin, coagulation factor X, Alzheimer's Aβ-peptide, and tissue inhibitor of metalloproteinases 3 (Johnson *et al.,* 2002; Mullins *et al.,* 2000). Interestingly, these components are unspecific to drusen, and are usual into extracellular deposits related with other disorders, such as atherosclerosis and other CVD (Mullins *et al.,* 2000). Moreover, over 40% of drusen have lipid components, mainly phosphatidylcholine and cholesterol (Wang *et al.,* 2010). In agreement with the hypothesis that oxidative stress promotes to AMD pathology, compounds of lipid oxidation are highly abundant in AMD drusen (Chiras *et al.,* 2015).

Advanced AMD exists in two clinical manifestations: neovascular and non-neovascular AMD (Pascolini and Mariotti, 2012). CNV, involving aberrant growth of immature chroroidal blood vessels through the outer blood-retinal barrier, is the

hallmark of neovascular AMD, also termed as exudative or "wet" AMD. Due to the formation of newly choroidal blood vessels, the sub-retinal space is exposed to blood components. Thus, in this manifestation of AMD are also detected sub-retinal fluid accumulation, lipid deposition, haemorrhage, RPE detachment, and fibrotic scar. Importantly, while neovascular AMD only affect to 10%–15% of AMD patients, this manifestation may progress rapidly and lead the most severe vision loss (Celkova *et al.,* 2015). In addition, GA within the macula, implying a cell death and thereby a diminution of functional RPE and photoreceptors, is the hallmark of non-neovascular, non-exudative or "dry" AMD.

The World Health Organization (WHO) estimates that worldwide, 285 million people representing about 4% of the total population may be currently affected by some form of visual disability, including AMD as one of the main clinical issues in developed countries (Pascolini and Mariotti, 2012). It has been recently reported that the global prevalence of AMD may reach 8.7% of people after the age of 45 years (Rassoulinejad *et al.,* 2015). The problem is being worse in Europe, because about 18% of all people 45 years of age or over is likely afflicted from one of the two clinical manifestations of AMD. In people aged between 70–79 years, the prevalence of AMD may reach 32%, increasing to 45% in people over 80 years. These observations suggest that nearly one in two people develop AMD at elderly age. It is expected that this will happen in 59 millions Europeans by 2020 and in 70 millions by 2040 (Wong *et al.,* 2014).
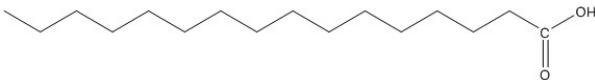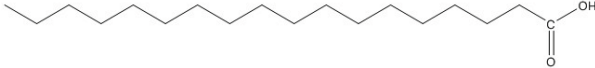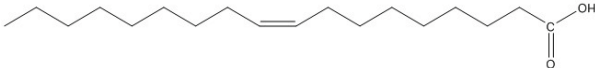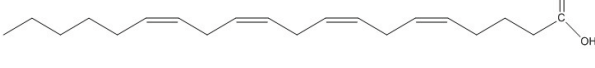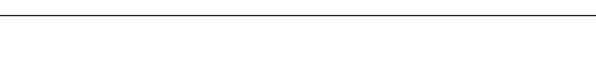
4. DIETARY FATTY ACIDS IN AGE-RELATED MACULAR DEGENERATION

Several studies have attempted to elucidate the effects of dietary habits on susceptibility to AMD. The risk for AMD has been shown to increase in individuals ingesting lower amount of certain nutrients than in individuals ingesting higher amounts. This is the case for the intake of omega-3 long-chain polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA), carotenoids lutein and zeaxanthin, and zinc (Weikel *et al.,* 2012a). However, these observations can be dramatically affected by differences in various aspects of study design, including populations and classification systems used. Dietary patterns have also an effect on risk for AMD. For example, individuals who consume diets with a high glycemic index (GI) are more prone to developing AMD (Weikel *et al.,* 2012b). In contrast, lower GI diets are protective against AMD, most notably against early signs of disease. Western-type diets, which typically contain more red and processed meats, high-fat dairy products, and refined grains also increase the risk for AMD when compared to diets rich in vegetables, fruits, legumes, seafoods, and whole grains (Chiu *et al.,* 2014). It is noteworthy that several efforts have been made in defining the relationship between dietary fat intake and AMD. Fats are composed of FAs, which are carboxylic acids that often have long unbranched aliphatic chains. Based on their structural and chemical properties, FAs can be classified as saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and PUFAs. The major dietary FAs are palmitic acid (16:0), stearic acid (18:0), oleic acid (18:1n-9), linoleic acid (18:2n-6), dihomo-γ-linolenic acid (20:3n-6), α-linolenic acid (18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3), and DHA (22:6n-3) (López *et al.,* 2014). The chemical structures of principal FAs in retina are displayed in Table 1.

The needs of omega-3 long-chain PUFAs in patients with AMD is supported due to the fact that DHA accounts for 50–60% of the total FA content of photoreceptor outer segments, which are constantly replenishing. This process makes necessary an extraordinary input on dietary DHA or its precursors, since a deficiency of such FAs may predispose to the development of AMD (Evans and Lawrenson, 2014). Furthermore, omega-3 long-chain PUFAs play a role against oxidative stress, inflammation, and vascular dysfunction, which are closely associated to the pathogenesis of AMD (Bjelakovic *et al.,* 2012; Kishan *et al.,* 2011). There is evidence of a link between the consumption of cold-water fatty fish rich in omega-3 long-chain PUFAs and the reduction in the risk of developing AMD (Chong *et al.,* 2009; Christen *et al.,* 2011; Omenn, 2007; SanGiovanni and Chew, 2005). Similarly, individuals with moderate to high risk of progression to late-stage AMD under-reporting high consumption of omega-3 long-chain PUFAs had a 30% lower incidence rate of neovascular AMD comparing to those individuals who reported a low dietary consumption of such FAs (Tan *et al.,* 2009). The administration of a daily dose of EPA (350 mg) and DHA (650 mg) for 3 years has been shown to lower the risk of CNV in patients with early lesions of AMD, steadily achieving the highest tertile of omega-3 long-chain PUFAs in their red blood cell membranes (Souied *et al.,* 2013). As long-term biomarkers of omega-3 long-chain PUFAs (Gorusupudi *et al.,* 2016), red blood cell membranes with increased content of EPA and DHA (and plasma EPA) after dietary intake of seafoods are associated with a lower risk for neovascular AMD (Merle *et al.,* 2014). The combination of omega-3 long-chain PUFAs with intravitreal anti-vascular endothelial growth factor (VEGF) treatment also decreases vitreous VEGF-A levels in patients with AMD (Rezende *et al.,* 2014). However, if co-ingested with the Age-Related Eye Disease Study (AREDS) formulation (antioxidant vitamins C and E, beta carotene, and zinc), a daily dose of EPA (350 mg) and DHA (650 mg) for a period of time up to 5 years in people at high risk for progression to advanced AMD was reported not to offer an additional advantage in reducing the risk

TABLE 1. Chemical structures and food sources of the major fatty acids in human retinal membranes

Fatty acid (%) (Acar et al., 2012)	Food sources
16:0, palmitic acid (21%)	Palm oil, cotton oil, butter, chicken fat
18:0, stearic acid (20%)	Chocolate, butter, sesame oil, blood sausage, cookie, palm oil
18:1n−9, oleic acid (14%)	Olive oil, rapeseed oil, hazelnut, corn margarine, sesame oil, peanut oil
20:4n−6, arachidonic acid (11%)	Pork, veal, lamb, deer, chicken, beef
20:5n−3, EPA (2%)	Herring, mussel, salmon, trout, mullet, gilt-head bream
22:6n−3, DHA (15%)	Herring, swordfish, trout, salmon, albacore, mackerel

of developing advanced AMD (Age-Related Eye Disease Study 2 Research Group et al., 2013). A systematic review of nine studies, with a total sample of 88974 people that included 3203 AMD cases (1847 with early AMD and 1356 with late AMD), examining the link between fat consumption and AMD was reported by Chong et al. (2008). In this meta-analysis, not only a high dietary intake of omega-3 long-chain PUFAs was associated with a reduction (38%) in the risk for late AMD, but also the risk for both early and late AMD was diminished with only bi-weekly fish intake. While the authors concluded that dietary omega-3 long-chain PUFAs could be responsible for the lower rates of AMD progression, evidence-based dietary recommendations for consumption of omega-3 long-chain PUFAs among general population in AMD prevention require further research. An issue that deserves exploration is related with the relevance of interactions between environmental and genetic factors in the development and progression of AMD (Lim et al., 2012). As the major AMD-susceptibility genetic factor, accounting for approximately 30%–50% of AMD patients, the complement factor H (CFH) gene has been proposed to interact with lipid metabolism to affect AMD risk (Neale et al., 2010). Thus, while DHA (840 mg/day over 3 years) has been recently shown to exert protective effects against the occurrence of CNV in genetically non-risk patients with early lesions of AMD, a genetic predisposition to AMD conferred by the CFH Y402H (rs1061170) variant may limit these benefits of DHA supplementation (Wang et al., 2015). It is plausible that inconsistencies in estimating the benefits of omega-3 long-chain PUFAs on AMD are due in part to have missed the genetic component of the disease.

In the Melbourne Collaborative Cohort Study (Chong et al., 2009), higher intake of olive oil was reported to be inversely associated with late AMD. However, despite olive oil contains large amounts of oleic acid, it was unclear the contribution of MUFAs to this association. It is critical to contextualize the potential effects of dietary FAs for a number of retinal disorders, as MUFAs from beef, dairy fats, and partially hydrogenated vegetable oils, without additional adjustment for the intake of other fats, were associated with a higher risk for AMD in the Eye Disease Case Control Study (Seddon et al., 2001). No association of AMD progression with the intake of SFAs, MUFAs, omega-6 PUFAs or trans FAs was observed in the Cardiovascular Health and Age-Related Maculopathy Study (Robman et al., 2007) and in the Polanut Study (Delcourt et al., 2007). Solid vegetable fats containing omega-6 PUFAs were shown to have a direct association with AMD in the Carotenoids in Age-Related Eye Disease Study (Parekh et al., 2009), while MUFAs had protective effects. The first evidence of a potential effect of SFAs against AMD was provided by Mares-Perlman et al. (1995) who found an increased risk for early AMD in individuals with the highest intake of SFAs and cholesterol. More recent studies have also reported

similar results on dietary SFAs and the risk for AMD (Cho *et al.,* 2001; Seddon *et al.,* 2003; Smith *et al.,* 2000). In line with this notion, the interaction of exogenous FAs, supplied into triglyceride-rich lipoproteins, with RPE cells causes pathogenic effects in a fatty acid-dependent manner, being MUFAs and omega-3 long-chain PUFAs much less harmful than SFAs (Montserrat-de la Paz *et al.,* 2016).

5. LIPOPROTEINS IN AGE-RELATED MACULAR DEGENERATION

The retina has been shown to uptake circulating low-density lipoproteins (LDL) through the RPE and Müller cells (Bretillon *et al.,* 2012). In this process, which is mediated by LDL receptors, neurons are provided with lipids to the maintenance or renewal of retinal ganglion cell axons and photoreceptor outer segments (DiBattista *et al.,* 2015). In the same sense, this shuttle involves high-density lipoproteins (HDL). ABCA1 transporter and SR-BI and SR-BII receptors are constitutively expressed in RPE cells (Ananth *et al.,* 2014). The ABCA1 transporter participates in apoE- and apoA1-dependent HDL biogenesis, whereas HDL uptake is mediated by scavenger receptors (SR-BI and SR-BII). Some correlations between AMD and HDL metabolism have been studied. For example, when transgenic mice expressing a dysfunctional form of human apoE3 (modelling human type III hyperlipoproteinemia) were subjected to a high-fat diet for a period of 9 months, all of them exhibited lipid deposits reactive for human apoE in the retina of both eyes. However, this abnormality was observed in only 33% of animals subjected to a normal diet or was absent in mice lacking apoE subjected to either diet. It is suggestive of a role for dysfunctional apoE in AMD development (Kliffen *et al.,* 2000). The major single nucleotide polymorphisms (SNPs) involved in HDL metabolism, the cholesteryl ester transfer protein (CETP) rs3764261, the lipoprotein lipase (LPL) rs12678919, and the hepatic lipase (LIPC) rs10468017 variants have been linked to AMD in a genome-wide association study (Merle *et al.,* 2015). After adjusting for the CFH gene, the CETP rs3764261 and LPL rs12678919 variants were found to be positively related to the risk of AMD, whereas the LIPC rs10468017 variant might be involved in a reduction of susceptibility to AMD (Haines *et al.,* 2005). These observations indicate potential interactions of diet, lipoprotein metabolism, and genes in the complement system linked to AMD. The metabolism of LDL, as a principal apoB100-containing lipoprotein, has been also involved in the pathogenesis of AMD. Mice expressing functional human apoB100 are more susceptible to lipid accumulation in sub-RPE deposits upon photo-oxidative stress and after a high-fat diet, a result alleviated by vitamin E pre-treatment (Espinosa-Heidmann *et al.,* 2004; Fujihara *et al.,* 2009). Increased secretion of apoB100-rich lipoproteins by RPE cells has been proposed as a mechanism for prevention of cell death through lipotoxicity. Sub-RPE lipid deposits are involved in the pathogenesis of AMD (Curcio *et al.,* 2009). Furthermore, a high-fat diet also promoted the occurrence of thickening, membrane-bound translucent particles, and immunolocalization of VEGF in Brunch's membrane of LDLR$^{-/-}$ mice, supporting the notion of accelerated AMD under decreased LDL clearance (Rudolf *et al.,* 2005). These studies suggesting that lipoprotein accumulation in RPE, synergistic with hyperlipidaemia and associated with a high-fat diet, is related to AMD pathogenesis.

6. CONCLUSIONS

The progression of AMD has social and economic implications. Due to the burden of this disease, efforts have been made to identify strategies that can delay the onset or progression of AMD. A growing body of evidence suggests that the dietary fatty acids and lipoproteins play a pivotal, yet underappreciated, role in the genesis and progression of AMD.

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