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The role of omega-3 and micronutrients in age-related macular degeneration

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ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the United States, Europe, and other developed countries. Although the pathogenesis of AMD remains unclear, current evidence suggests a multifactorial aetiology. Nutrition may play an important role in the development and progression of AMD. There have been several epidemiological studies suggesting that omega-3 fatty acids could have a protective role in AMD, but a beneficial effect remains to be demonstrated in randomized controlled trials. There also exists a substantial body of evidence suggesting that protection against AMD may be provided by specific micronutrients (vitamins and minerals and antioxidants). The identification of risk factors for the development and progression of AMD is of particular importance for understanding the origins of the disorder and for establishing strategies for its prevention. We examine the relationship between dietary omega-3 intake and the incidence and progression of AMD, as well as the role of omega-3 supplementation in the prevention of the disorder, and also explore the role of other micronutrients in AMD.

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the United States, Europe, and other developed countries. Early AMD, the most common form, involves lipid deposits (drusen) outside the retinal pigment epithelium (RPE), or pigment abnormalities in the RPE, without visible choroidal vessels, and is not associated with marked vision impairment.[14,27] Late, or advanced, AMD involves progressive lipidization as well as degenerative changes of the RPE, Bruch membrane, and choriocapillaris and is usually associated with severe vision loss.[14,27] Dry AMD, also referred to as geographic atrophy, starts with a sharply demarcated round or oval hypopigmented spot in which large choroidal vessels are visible. Wet or exudative AMD initiates with serous or hemorrhagic fluid that causes the neuroretina or the RPE to detach from Bruch is membrane.

The prevalence of AMD is known to increase with age, with one study showing a prevalence of early AMD of approximately 30% among those aged 75 years or older,[29] with a smaller percentage of individuals (6–8%) in this age group having the advanced form of AMD that includes geographic atrophy (dry AMD) and choroidal neovascularization (exudative or wet AMD). Strikingly, in the population-based Rotterdam Study, of the 825 participants aged 80 years or older, 64% showed signs of early or late AMD.[14]

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The pathogenesis of AMD remains unclear, but current evidence suggests that it is most likely a multifactorial disorder, with both environmental and polygenic components.[19,32,48,52] A genetic component has been demonstrated by familial aggregation and twins studies, with linkage studies also identifying several DNA regions of interest.[17,19,24,28,32,46,48,55,56]

Nutrition has also been shown to be associated with AMD.[9,13,16,31,47,50,62] Studies have indicated that vitamin and mineral supplementation may reduce the risk for progression to the advanced forms of AMD and subsequent visual loss,[2] and dietary sources of antioxidants also appear to be important,[13,61] as do lutein and zeaxanthin.[9,37,47,61] Moreover, numerous studies have indicated that people with dietary intakes higher in various carotenoids, antioxidants, and omega-3 fatty acids may have a lower risk of developing AMD.[9,16,31,45,47,52,58,62]

1.1. *The potential role of omega-3 fatty acids*

Omega-3 and omega-6 fatty acids are important components of tissue lipids, particularly cell membrane phospholipids. The major dietary omega-3 polyunsaturated fatty acid is docosahexaenoic acid (DHA). This makes up only a small fraction of the fatty acids in most tissues, but is present at high levels in the retina, where it is a major structural lipid.[4,33] As a result of its biophysical and biochemical properties, DHA may affect the permeability, fluidity, thickness, and lipid phase properties of the photoreceptor membrane,[41] and may also be involved in signaling cascades, acting to enhance activation of membrane-bound retinal proteins, and may be involved in rhodopsin regeneration. There is evidence that tissue DHA insufficiency is associated with changes in retinal function.[41] Eicosapentaenoic acid (EPA) ($C_{20:5\ \omega\text{-}3}$), the precursor to DHA as well as other major dietary omega-3 fatty acids, can exert similar actions to DHA.[41]

Dietary omega-3 fatty acids have also been shown to be beneficial in inflammatory diseases and where those taking omega-3 report less joint stiffness, swelling, tenderness, and fatigue.[25,30,60] Dietary omega-3 fatty acids have been shown to reduce the inflammatory response by competing with arachidonic acid metabolism and altering the eicosanoid profile. EPA and DHA have been shown to decrease CD4+ T-cell activation and cause the inflammatory environment to switch from a pro-inflammatory to an anti-inflammatory one; a mechanism by which omega-3 fatty acids can alter inflammation-related signaling cascades is through disrupting plasma membrane organization, increasing the molecular order of lipid rafts and suppressing lipid second messengers and proteins required for activation of T-cells (Fig. 1).[54] These anti-inflammatory actions may be beneficial in the retina, inflammation may play a role in the development of new choroidal vessels in exudative AMD.[3,13,18,35,51]

Early studies investigating a potential relationship between dietary fat intake and AMD revealed that this might not be straightforward. Results of initial studies suggested that higher intake of some fatty acids, and possibly elevated blood cholesterol levels, may be related to an increased risk of AMD.[49,53] More specifically, results suggested that higher intake of specific subtypes of lipids (cholesterol, monounsaturated, polyunsaturated fats, omega-6 fatty acid, linoleic acid) rather than total fat intake may be associated with a greater risk for progression of AMD. In contrast, diets high in omega-3 fatty acids and fish were found to be inversely associated with risk for AMD when intake of linoleic acid was low.[49,53]

Since this time, there have been several epidemiological studies suggesting that omega-3 or polyunsaturated fatty acids DHA and EPA could have a protective role in AMD, particularly exudative AMD.[22] Furthermore, there is evidence to suggest that omega-3 fatty acids have cytoprotective and cytotherapeutic actions, giving rise to anti-angiogenic and neuroprotective mechanisms within the retina.[41]

2. Objective and methodology

The identification of risk factors for the development of AMD is of particular importance for understanding of the origins of

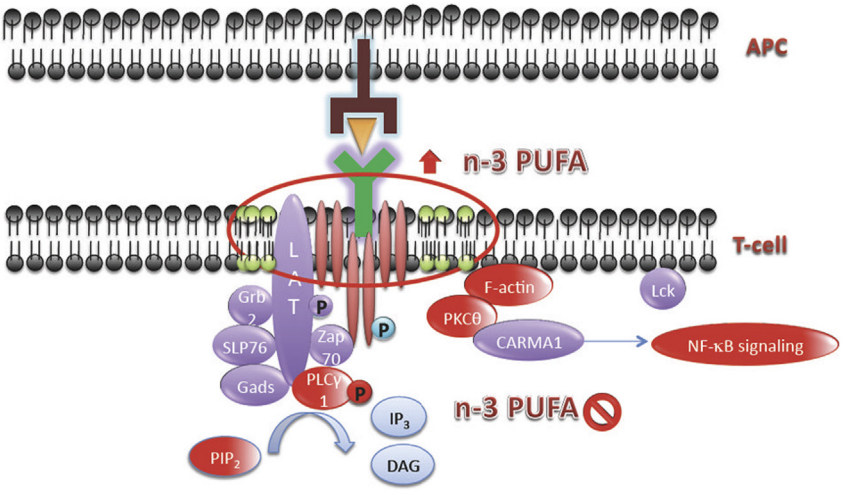

Fig. 1 – The action of omega-3 fatty acids on lipid membranes and T-cell signaling processes. (Reproduced from Shaikh et al[54] with permission of Elsevier.)