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Review

Nutritional modulation of age-related macular degeneration

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ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly worldwide. It affects 30–50 million individuals and clinical hallmarks of AMD are observed in at least one third of persons over the age of 75 in industrialized countries (Gehrs et al., 2006). Costs associated with AMD are in excess of $340 billion US (American-Health-Assistance-Foundation, 2012). The majority of AMD patients in the United States are not eligible for clinical treatments (Biarnes et al., 2011; Klein et al., 2011). Preventive interventions through dietary modulation are attractive strategies because many studies suggest a benefit of micro- and macronutrients with respect to AMD, as well as other age-related debilities, and with few, if any, adverse effects (Chiu, 2011). Preservation of vision would enhance quality of life for millions of elderly people, and alleviate the personal and public health financial burden of AMD (Frick et al., 2007; Wood et al., 2011). Observational studies indicate that maintaining adequate levels of omega-3 fatty acids (i.e. with 2 servings/week of fish) or a low glycemic index diet may be particularly beneficial for early AMD and that higher levels of carotenoids may be protective, most probably, against neovascular AMD. Intervention trials are needed to better understand the full effect of these nutrients and/or combinations of nutrients on retinal health. Analyses that describe effects of a nutrient on onset and/or progress of AMD are valuable because they indicate the value of a nutrient to arrest AMD at the early stages. This comprehensive summary provides essential information about the value of nutrients with regard to diminishing risk for onset or progress of AMD and can serve as a guide until data from ongoing intervention trials are available.

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1. Introduction and definition of AMD

High resolution vision is possible due to the high density of photoreceptors in the macula of the retina. Photoreceptors receive light signals and convert them to chemical and then electrical impulses that are sent to the brain. In the advanced stages of age-related macular degeneration (AMD) the central field of vision is distorted or lost due to damage or loss of photoreceptors in the macula/fovea located near the center of the retina (National Eye Institute, 2010). Photoreceptors are exposed to an extensive amount of oxidative stress in the form of light and oxygen (Zarbin, 1998) (also see below, and articles by Handa (2012), Jarrett and Boulton (2012) and Sparrow et al. (2012)). Each night, the outer 10% of segments of photoreceptors are shed and engulfed by the retinal pigment epithelium (RPE), which lies posterior to the photoreceptors (Sung and Chuang, 2010). Due to the requirement of one RPE cell to service 30 photoreceptors, the RPE has among the highest degradative burden in the body. In addition to the digestion of photoreceptors and their associated debris, the RPE are also involved in maintaining the nutriture of the photoreceptors. Nutrients from the choroidal blood supply must cross Bruch's membrane, a pentalaminar structure composed of several layers of elastic and collagen, to enter the RPE and photoreceptors (Zarbin, 1998). The flow of nutrients into the retina, and debris out of the retina through the RPE is crucial, since photoreceptors do not have their own blood supply (Shakib and Zinn, 1973; Sivaprasad et al., 2005). Adequate nutritional support to the RPE also facilitates efficient turnover of photoreceptors. This is consistent with a requirement for proper nutrition for maintaining healthy vision. While we stress the function of the RPE as supporting photoreceptors, it is not clear that RPE damage is a unique initiating insult for AMD. Data also indicate that insults may occur in neural Muller cells and photoreceptors (Marc et al., 2008; Sullivan et al., 2007).

The chemical nature of nutrients should help predict which nutrients are crucial for the retina. Being a highly lipophilic tissue that is subject to environmental and age-related oxidative stress, one might anticipate that maintaining adequate levels of lipophilic antioxidants (polyunsaturated fatty acids, carotenoids, vitamin E) would bring salutary effects. To some extent this is borne out in the results discussed below. However the situation is far more complex, with hydrophilic compounds such as sugars also apparently playing significant roles in retinal homeostasis and damage.

The combination of inadequate nutrition with the inability to properly degrade and dispose of cellular debris may contribute to the formation of deposits in the RPE–Bruch's membrane region. Basal laminar deposits are those which accumulate in the RPE cell, between the RPE basement membrane and the RPE plasma membrane. Basal linear deposits accumulate between the RPE basal lamina and the inner collagenous layer of Bruch's membrane (Curcio and Millican, 1999). As the health of the RPE deteriorates, basal laminar deposits accumulate. These are thought to precede the formation of drusen, clinical indicators for early AMD (Al-Hussaini et al., 2009; Ding et al., 2009; Jager et al., 2008; Wang et al., 2009).

Drusen are often found between the RPE and the choroid. Mass spectrometric analysis indicates that drusen contain a variety of lipids, proteins, including ubiquitin and advanced glycation end products, as well as inflammatory mediators (Ding et al., 2009) (also see review by Shang (2012)). Early AMD is indicated by small (<63 μm) and/or a few medium-sized (<125 μm) drusen. The transition from early AMD to more advanced stages is characterized by an increase in drusen size and number as well as an increase in damage to the RPE. This damage can manifest as an increase in areas of the retina with too much or too little pigment (Davis et al., 2005a; Smiddy and Fine, 1984). If the RPE are damaged by drusen or other stressors, they may lose their ability to efficiently turn over the photoreceptors in the macula. Consequently, patients in the intermediate stages of AMD will notice a slight blur in their central field of vision.

Late AMD can manifest in two forms, geographic atrophy (also called dry AMD) and neovascular (also called wet AMD). Geographic atrophy is diagnosed when there is depigmentation in the RPE as observed by fundus photography. This depigmentation is often focal, round with sharp margins, and choroidal vessels may be visible underneath (Davis et al., 2005b). Along with this depigmentation, there is often large and abundant drusen as well as death of RPE and photoreceptors in the macula. Consequently, patients with geographic atrophy experience significant vision loss. Damaged photoreceptors and RPE cells may also accumulate and accelerate the formation of drusen, further exacerbating disease. There are currently no therapies to treat the dry form of AMD (Smiddy and Fine, 1984).

Another form of late stage AMD is manifested by formation of exudates and/or neovascularization of the retina. The latter is characterized by the development of aberrant blood vessels, originating from the choroid, that penetrate Bruch's membrane causing damage to the RPE and overlying photoreceptors. These aberrant vessels are prone to leak: thus, the designation "wet AMD". Such bleeding can cause the macula to bulge, causing straight lines to appear curved (AREDS, 2001). On a fundus photograph, the presence of subretinal fibrous tissue, RPE detachment, subretinal hemorrhage, or serous sensory retinal detachment would suggest that neovascular AMD is present (Davis et al., 2005b).