Obesity, Lutein Metabolism, and Age-Related Macular Degeneration: A Web of Connections

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Age-related macular degeneration (AMD) is a major cause of visual impairment in the United States. Currently there is no effective cure for this disease. Risk factors include decreased lutein and zeaxanthin status and obesity. Obesity is also an increasing public health concern. The alarming increase in the prevalence of obesity further exacerbates the public health concern of AMD. The mechanism by which obesity increases the risk of AMD may be related to the physiologic changes that occur with this condition. These include increased oxidative stress, changes in the lipoprotein profile, and increased inflammation. These changes would also result in an increased destruction and a decreased circulatory delivery of lutein and zeaxanthin to the macula of the eye. Therefore, the mechanism by which obesity is related to AMD risk may be through indirect effects on changes in lutein and zeaxanthin status and metabolism.

Risk Factors for Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a disease that affects the central vision. In the aging US population, AMD is a major cause of visual impairment and blindness. The prevalence of AMD increases dramatically with age. Nearly 30% of Americans over the age of 75 have early signs of AMD and 7% have late-stage

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disease, whereas the respective prevalences among Americans 43 to 54 years of age are 8% and 0.1%.[1-3] This number is expected to triple with the increase in the aging population in the next 30 to 40 years.[4] Because there are currently no effective treatment strategies for most patients with AMD, attention has focused on efforts to stop the progression of the disease or to prevent the damage leading to AMD.[5] Risk factors for AMD include age; female gender; family history; smoking; sunlight exposure; low dietary, serum, and tissue levels of lutein and zeaxanthin[5]; and increased adiposity.[6,7] Of these factors, only lutein and zeaxanthin status and adiposity are modifiable. To date, the roles of lutein and zeaxanthin status and adiposity in AMD risk/prevention have been considered individually. This review will evaluate the roles of lutein and zeaxanthin in AMD prevention, as well as obesity as a risk factor for AMD. The influence of obesity on lutein and zeaxanthin metabolism will also be evaluated as a possible mechanism by which obesity is related to risk of AMD.

Biological Rationale and Clinical and Epidemiologic Evidence for AMD Prevention

Lutein and zeaxanthin are compounds belonging to a large class of plant pigments known as carotenoids. Their presence in human blood and tissues is entirely due to the ingestion of food or supplement sources. The two foods that are known to have the highest amount of lutein are kale and spinach (Table 1). Other major sources include broccoli, peas, and brussels sprouts. These dihydroxy-carotenoids (or xanthophylls) selectively accumulate in the retina and are particularly dense in the foveal region, or macula, where they are the main components of the macular pigment (Figure 1). The macula is located in the posterior portion of the retina and possesses the highest concentration of cone photoreceptors, which are responsible for central vision and high-resolution visual acuity.[2] Lutein and zeaxanthin are known to function as antioxidants and as blue light filters, and may protect the macula from light-initiated oxidative damage to the retina and retinal pigment epithelium (RPE).[3-6]

Oxidative stress is high in the eye due to the intense

Table 1. Lutein and Zeaxanthin Content of Foods (from US Department of Agriculture. USDA-NCC Carotenoid Database for U.S. Foods-1998[61])

Food	Lutein/Zeaxanthin Content
	μg/100 g wet wt*
Kale, cooked	15,798
Spinach, raw	11,935
Spinach, cooked	7053
Lettuce, raw	2635
Broccoli, cooked	2226
Corn, sweet, cooked	1800
Peas, green, cooked	1350
Brussels sprouts, cooked	1290
Cabbage, white, raw	310

*Edible portion.

light exposure and the high rate of oxidative metabolism in the retina.[6] It is generally believed that cumulative oxidative damage is in part responsible for aging and therefore may play an important role in the pathogenesis of AMD. The appearance of oxidation products of lutein and zeaxanthin within the retina is consistent with the suggestion that lutein and zeaxanthin function as antioxidants in the eye.[7] Recent studies in quail exposed to bright light provide evidence that long-term zeaxanthin supplementation leads to increased retinal zeaxanthin and reduced photoreceptor death.[8,9]

Several studies have provided evidence that macular pigment attenuates light damage in the human retina. It has been reported that the age-related decline of retinal sensitivity of the short-wavelength (blue) cones is reduced in areas where macular pigment levels are highest.[10] Bull's eye maculopathy, a clinical condition associated with photosensitizing drugs, is characterized by retinal degeneration in the annular pattern that surrounds but significantly spares the macula (the area of greatest lutein and zeaxanthin concentration).[11] Furthermore, the photic damage from operating microscopes resulting in lesions has the least damage in illuminated regions that overlap the macular pigment.[12,13] Greater age-related loss of sensitivity to blue light in retinal regions with lower macular pigment density and in older adults with lower macular pigment density has been interpreted as additional evidence of protection by this pigment.[5]

Epidemiologic and case-control studies suggest that the risk for AMD is inversely related to lutein and zeaxanthin concentrations in the diet. Lower risk for AMD has been associated with the consumption of food sources of lutein and zeaxanthin (Table 2). Intakes of approximately 6 mg/d of lutein and zeaxanthin are related to a decreased risk of AMD.[14] In a study comparing postmortem retinas from persons with AMD with those from control donors, the amounts of macular pigment were lower for those diagnosed with AMD (Figure 2).[13]

Recent studies suggest that lutein supplementation may improve visual function in AMD patients. Falsini et al.[15] evaluated the influence of short-term antioxidant supplementation on retinal function in age-related maculopathy patients and in control subjects (54–84 yrs) by recording focal electroretinograms. The supplementation regimen included 15 mg/d lutein for 180 days. These investigators reported a significant increase in amplitude change of the focal electroretinograms in patients and controls with antioxidant supplementation. It was concluded that increasing the level of retinal antioxidants, and therefore antioxidant capacity, may influence macular function early in the disease process as well as in normal aging. In another study of AMD patients (n = 59; ~75 years of age) supplemented with 10 mg of lutein resulted in positive effects on visual function, including improved contrast sensitivity, glare recovery, and visual acuity.[16]

Obesity and the Risk of AMD

In 2000, the prevalence of obesity among US adults was 19.8%,[17] which reflects a 61% increase since 1991. In 2001, this value increased to 20.9%. In 2000, 39.8 million US adults met the classification of obesity, defined as having a body mass index (BMI) of greater than 30 kg/m². Currently, more than 44 million Americans are considered obese. This reflects an increase of 74% since 1991. Several studies have reported an increased risk of AMD with increase in BMI (Table 3). For example, in a recent prospective study involving 261 participants with some sign of non-advanced AMD, it was reported that higher BMI increased the risk for progression to the advanced forms of AMD.[18] Relative risk was 2.35 (95% confidence interval [CI], 1.27–4.34) for a BMI of at least 30 and 2.32 (95% CI; 1.32–4.07) for a BMI of 25 to 29 relative to the lowest category (<25) after controlling for other factors (P = 0.007 for trend). Furthermore, a higher waist-to-hip ratio (i.e. higher abdominal obesity) was also found to increase the risk for progression to
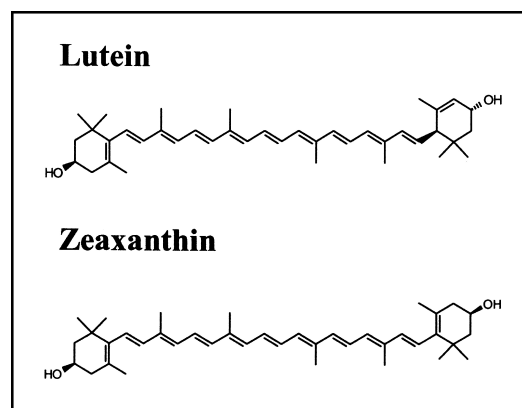

Figure 1. Structures of lutein and zeaxanthin.

Table 2. Lutein and Zeaxanthin Intake and Risk of Age-Related Macular Degeneration (AMD)

Study	Subjects	Outcome	Intake	Odds Ratio (95% CI)
Mares-Perlman et al.[62]	Age 40–59; 3829 controls; 51 cases	Early AMD*	Low vs high quintile	10.0 (3.3–10.0)
	Age 60–79; 3012 controls; 15 cases	Late AMD	Low vs high quintile	10.0 (1.1–>20)
Snellen et al.[63]	Age 60; 66 controls; 72 cases	Neovascular AMD	• Lowest vs highest quartile	5.3 (1.5–18.4)
			• Low vs highest quartile	3.6 (1.0–12.9)
			• High vs highest quartile	3.4 (0.9–12.3)
Seddon et al.[14]	Age 55–80; 520 controls; 356 cases	Late AMD	• Highest vs lowest quintile	2.3 (1.4–5.0)
			• High vs lowest quintile	1.3 (0.8–2.0)
			• Mid vs lowest quintile	1.2 (0.8–2.0)
			• Low vs lowest quintile	0.9 (0.6–1.4)

*Macular pigmentary abnormality.

advanced AMD with a relative risk of 1.84 (95% CI; 1.07–3.15) for the highest tertile compared with the lowest (P = 0.02).[18]

Obesity, Oxidative Capacity, and Risk of AMD

Increased body weight has been reported to result in increased oxidative stress.[19] It has been shown in a large community-based cohort of otherwise healthy indivduals (~3000 participants) from the Framingham Heart Study that increased urinary F2-IsoP formation in both men and women was strongly associated with increasing BMI. These findings are supportive of two smaller studies in which overweight/obesity was associated with enhanced oxidant stress.[20,21]

Multiple mechanisms likely play a role in the association between obesity and oxidative stress. For example, the rennin-angiotensin system is upregulated in obesity.[22] Angiotensin II has been shown to induce NADPH oxidase in various tissues, with a resulting increase in superoxide production.[23] Angiotensin II has also been shown to increase low-density lipoprotein (LDL) uptake by macrophages, resulting in enhanced lipoprotein oxi-
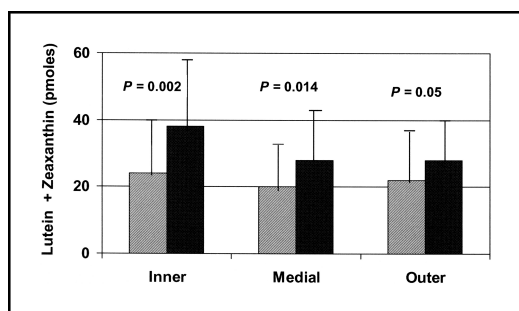

Figure 2. Lutein and zeaxanthin content of human retina from subjects with age-related macular degeneration (gray bars) and from control subjects (black bars). Inner retinal region is 0 to 5°; medial region is 5° to 19°; outer region is 19° to 38°. From Bone et al.[13]

dation.[23] Furthermore, obesity has been shown to be associated with reduced antioxidant defense mechanisms, including decreased erythrocyte glutathione and glutathione peroxidase.[24]

There is a general consensus that cumulative oxidative damage is in part responsible for aging and may therefore play a role in the pathogenesis of AMD. The retina is an ideal environment for the generation of reactive oxygen species for several reasons: 1) oxygen consumption in the retina is much greater than in any other tissue[25]; 2) the retina is subject to high levels of cumulative irradiation; 3) photoreceptor outer segment membranes are rich in polyunsaturated fatty acids, which are readily oxidized[26]; 4) the neurosensory retina and the retinal pigment epithelium contain an abundance of photosensitizers[27-29]; and 5) the process of phagocytosis by the retinal pigment epithelium is an oxidative stress and results in the generation of reactive oxygen intermediates.[30]

If oxidative stress is involved in the etiology of AMD, then the aging of retinal pigment epithelium and the development of AMD could be prevented or delayed with an increased antioxidant capacity of the retinal pigment epithelium. As mentioned above, several studies have found correlations between increased intake of the antioxidants lutein and zeaxanthin and decreased risk of AMD (Table 2). The Age-Related Eye Disease Study (AREDS) found that antioxidant supplementation delayed the progression of early-stage AMD.[31] A recent report from the Framingham Study provides evidence that increased systemic oxidative stress may be an important mechanism by which obesity increases atherosclerotic cardiovascular disease.[19] A similar mechanism may exist for obesity and AMD.[32]

Obesity, Inflammation, and AMD Risk

Markers of inflammation are associated with increased BMI.[33-35] For example, in a group of 316 men and

Table 3. Body Mass Index (BMI, kg/m^2) and Risk of Age-Related Macular Degeneration (AMD)

Study	Subjects	Outcome	BMI	RR
Seddon et al.[18]	Age >60 (n = 261)	Geographic atrophy and neovascular AMD	>30 vs <25 25–29 vs <25	2.35 2.32
Delcourt et al.[64]	POLA study; age 60–95 (n = 2584)	Late AMD	>30 vs lean	2.29
AREDS Research Group[65]	AREDS (n = 4519)	Neovascular AMD	≥31 vs >23.6	1.68
Smith et al.[66]	Blue Mountain Eye Study (n = 3652)	Early AMD	>30 vs 20–25	1.78
Schaumberg et al.[54]	Physician's Health Study (n = 21,121)	Dry AMD	≥30 vs 22–24.9 25–29 vs 22–24.9 <22 vs 22–24.9	2.15 1.24 1.43

AREDS = Age-Related Eye Disease Study; RR = Relative risk.

women 40 to 79 years of age, serum levels of C-reactive protein were significantly higher in the obese group than in their non-obese counterparts. Interestingly, serum levels of lutein and zeaxanthin were lower in these obese individuals.[33] Furthermore, weight loss in obese patients has been reported to induce a significant decrease of C-reactive protein and interleukin-6 concentrations.[36,37] In a recent study, plasma C-reactive protein levels showed positive and significant correlations with waist girth and visceral adipose tissue accumulation.[38] These results suggest that increased abdominal fat may be responsible for low-grade inflammatory states by providing a source of increased production of interleukin-6, a potent stimulator of hepatic C-reactive protein synthesis.[39]

It has been suggested that AMD represents an age-related inflammatory disease that is manifested in the eye.[40] C-reactive protein was found to be significantly higher among patients with advanced AMD than among those with no AMD.[40] After adjustment for age, sex, smoking, and BMI, C-reactive protein levels were significantly associated with the presence of intermediate and advanced stages of AMD, suggesting that an elevated C-reactive protein level is an independent risk factor for AMD. The possibility that low-grade chronic inflammation, such as has been linked to atherosclerosis and risk for cardiovascular disease,[41] could act to confound epidemiologic investigations has been tested by Kritchevsky et al.[42] In this investigation based on data from 4557 non-smoking, 25- to 55-year-old subjects participating in the Third National Health and Nutrition Examination Survey (NHANES-III), circulating inflammatory markers (C-reactive protein, fibrinogen, and white blood cell counts) were tested for correlation with serum levels of five commonly measured carotenoids (lutein, zeaxanthin, β-carotene, α-carotene, β-cryptoxanthin, and lycopene).

After adjusting for several factors, all carotenoids were significantly lower in participants with elevated C-reactive protein. This association was relatively specific, in that neither fibrinogen nor white blood cell count was related to concentrations of most carotenoids studied. A key aspect of this study is the fact that the inverse association between C-reactive protein and carotenoid levels was observed in young non-smokers, in which the prevalence of chronic diseases was low. Therefore, this factor could not account for the observed inverse association. The most likely explanation for this observation is that a chronic low-grade inflammatory state leads to both an elevation in C-reactive protein and a reduction in serum carotenoids, which is consistent with the notion that inflammation is tightly linked to oxidative stress by virtue of a self-reinforcing cycle[41] and that chronic inflammation can lead to reduced levels of carotenoids.[43,44] To date, the relationship between markers of inflammation, antioxidant capacity, serum lutein and zeaxanthin, and macular pigment density has not yet been investigated. A systemic chronic low-grade inflammation may play a role in AMD by means of either a direct inflammatory/oxidative insult to the Bruch's membrane-retinal pigment epithelium-photoreceptor complex or by reducing the bioavailability of the lutein and zeaxanthin to the macula via depletion of the systemic pool, depletion of the intraretinal pool, or both.

Obesity and Lutein and Zeaxanthin Status

The biological mechanisms whereby body fat increases risk for AMD may in part be related to effects of increased adiposity on destruction of endogenous lutein and zeaxanthin and decreased delivery to the macula. A summary of these various relationships is found in Figure 3. In light of the discussion above, increased adiposity may affect the ability of lutein and zeaxanthin to

accumulate in the macula through one of four mechanisms: 1) adipose tissue acting as a "sink" for lutein and zeaxanthin; 2) increased oxidative capacity; 3) increased inflammation; or 4) increased LDL-to-high-density lipoprotein (HDL) ratio.

Adipose tissue is a major storage organ for carotenoids due to the partitioning of carotenoids into fat.[45,46] Given that there are large variations in body fat percentages, the amount of body fat may have a strong influence among individuals with respect to the tissue distribution of absorbed carotenoid. Our research group, as well as others, has reported that increased body fat is associated with decreased serum and macular levels of carotenoids.[47-53] This may be due to the body fat acting as a "sink" for the dietary carotenoids, resulting in less lutein and zeaxanthin available to the macula of the eye.

Increased oxidative capacity is associated with increased BMI. Therefore, an increase in oxidative capacity from obesity will promote oxidative destruction of endogenous lutein and zeaxanthin, thus decreasing body stores that are potentially available to the macula.

Elevated C-reactive protein has been associated with high BMI.[35] C-reactive protein is inversely related to circulating concentrations of carotenoids.[42] This may be due to inflammation being tightly linked to oxidative stress. Therefore, an increase in inflammation with increased weight would result in more oxidative damage to endogenous lutein and zeaxanthin.

The associations between body fat and macular pigment density may be explained by other physiologic correlates of body fat, such as the different types and distributions of lipoproteins in lean and obese individuals, which are correlated with body fatness and abdominal obesity. A weight loss of 8 kg over a 12-week period has been shown to significantly decrease LDL and increase HDL in overweight men (mean body weight, 108 kg) and women (mean body weight, 89 kg).[54] Additionally, in 18 individuals who had been on calorie-restricted diets that resulted in a change in BMI from 26 ± 3 to 20 ± 2 kg/m^2, serum concentrations of HDL increased whereas concentrations of LDL decreased.[55] Lutein and zeaxanthin are transported within the blood primarily on the surface of HDL (about 53%), but also on LDL (about 31%), and very-low-density lipoproteins (VLDL) (about 16%).[56] When these lipoproteins reach retinal tissue, they are transferred to that tissue by means of lipoprotein receptors found at the surface of the retinal pigment epithelium and Muller retinal cells.[57,58] Although the precise mechanism has not yet been established, there is increasing evidence suggesting that HDL might be the most significant carrier for the retina. For example, within the plasma, most (>60%) of apolipoprotein-E is associated with the HDL fraction.[59] Recent evidence suggests that apolipoprotein-E can be synthesized directly within the retina (Muller cells) and binds to receptors on ganglion cells.[60] Thomson et al.[9] recently argued that the subspecies of HDL containing apolipoprotein-E (HDL-E) supplies lipids and lipid-soluble lutein and zeaxanthin to the retina. Thus, by increasing HDL levels, retinal lutein and zeaxanthin levels would be concomitantly increased.

Conclusion

AMD is a major cause of visual impairment in the United States, and there is currently no effective cure for this disease. Risk factors include decreased lutein and zeaxanthin status and obesity. Obesity is also an increasing public health concern. The alarming increase in the prevalence of obesity further exacerbates the public health concern of AMD.

The mechanism by which obesity increases the risk of AMD may be related to the physiologic changes that occur with this condition. These include increased oxidative stress, increased inflammation, and changes in lipoprotein profile. These changes would also result in an increased destruction and a decreased circulatory delivery of lutein and zeaxanthin to the macula of the eye. Therefore, the mechanism by which obesity is related to AMD risk may be through indirect effects of changes in lutein and zeaxanthin status and metabolism. Efforts to prevent obesity and improve lutein and zeaxanthin status may be important in the prevention of AMD.

Figure 3. Relationships among risk factors for age-related macular degeneration (AMD). (+) = Direct relationship; (–) = inverse relationship. *Xanthophylls are transported in blood on lipoproteins, primarily HDL.

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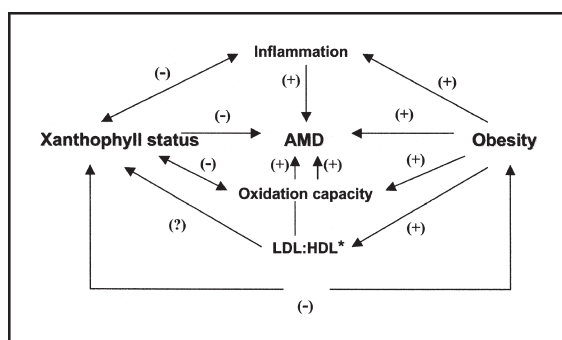
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