

Editorial

Lutein and Zeaxanthin: An Overview of Metabolism and Eye Health

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The leading causes of blindness and vision impairment worldwide are age-related eye diseases including diabetic retinopathy, glaucoma, and age-related macular degeneration (AMD) [1]. It is estimated that these types of diseases affect over 9.1 million Americans aged 40 or older [2]. Vision loss is one of the most feared diseases among the elderly, and can reduce quality of life as well as incur serious economic burdens. Vision loss overtime is largely due to the irreversible loss of retinocytes, and subsequent degeneration of the retina of the eye, leading to AMD and other diseases [3]. While treatment is limited, nutritional interventions may be beneficial in improving eye health. Considerable research suggests that carotenoids, polyunsaturated fatty acids, and some vitamins may have an inverse relationship with AMD, by slowing the progression or preventing AMD and other age-related degenerative diseases.

Lutein (LUT) and zeaxanthin (ZEA) are two xanthophyll carotenoids found in dark green and yellow fruits and vegetables that have been associated with retino protective properties. An average US diet contains 1-3 mg/day of LUT and ZEA, while ~6 mg/day has been associated with lower risks of disease such as AMD and cataracts [4]. It is proposed that the retino protective capabilities associated with LUT and ZEA may be due to their unique chemical structure and their selective retinal accumulation. Hydroxyl groups, the large number of double bonds, and the polar nature of these compounds may contribute to the ability of LUT and ZEA to prevent oxidative stress associated with AMD by scavenging free radicals and transferring energy states [5]. Intake of LUT and ZEA and their selective retinal accumulation may increase macular pigment density which may slow or prevent AMD [6]. LUT and ZEA are considered an area of recent significant eye health research interest for these reasons.

The bioavailability and potential benefits of LUT and ZEA on eye health is dependent on the digestion, absorption, transport, retinal uptake, and storage of these carotenoids [7]. Multiple factors influence carotenoid bioavailability including the food matrix, processing conditions, and fat content [8]. In general, carotenoids are fat soluble compounds and follow lipophilic digestion and absorption pathways. Upon ingestion, food is mechanically and enzymatically broken down, carotenoids are released with help from dietary lipids, emulsified in the small intestine and incorporated and solubilized into micelles for

enterocyte absorption via passive diffusion or scavenger receptor class B type 1 (SR-B1)-facilitated diffusion. In the enterocyte, carotenoids are packaged into chylomicrons, transported to the liver, repackaged into lipoproteins and transported to extrahepatic tissues through the blood [9]. Along with LDL, HDL has been identified as a crucial xanthophylls transporter, observing that deficiencies in this lipoprotein may impair LUT and ZEA transport [10]. Although LUT and ZEA may accumulate in hepatic, adrenal, adipose as well as other tissues through various transport mechanisms, of greatest interest is the retinal accumulation and macular effect of these carotenoids [11].

LUT and ZEA make up about 80% of the total carotenoid content of the retina, a higher concentration than any other tissue of the human body [11, 12]. LUT and ZEA, as well as meso-zeaxanthin, a lutein metabolite, accumulate as a yellow spot in the macula of the eye, known as the macular pigment. This pigment has been suggested to contain antioxidant-like properties, reduce photoreceptor exposure to blue light, and protect the macula from light-induced oxidative stress [12-13]. Generally, the ratio of the macular carotenoids varies in different regions in the eye. Amount of LUT and ZEA tend to decrease from the fovea toward the periphery of the eye. In the fovea for example, less lutein is found compared to zeaxanthin, in a 1:2 ratio; however in the peripheral retina the ratio of LUT to ZEA is 2:1 [14]. As stated previously, higher intakes of LUT and ZEA have been associated with increased macular pigment densities. Significant research indicates that high macular pigment densities slow or prevent AMD, suggesting an inverse relationship between xanthophyll consumption and AMD [6]. Although the distribution of the macular pigment may vary, it remains unclear as to the transport governing the status, the regulation, and function of these carotenoids in the retina.

The retinal pigment epithelium (RPE) may be a transfer point of LUT and ZEA from the blood to the neural retina portion of the eye, involving specific xanthophyll-binding proteins (XBP) are involved in retinal uptake and macular concentration [15]. Many XBPs have been identified; however the exact mechanism of LUT and ZEA uptake is unclear. Glutathione S-transferase (GSTP1) is located in the macula preferentially interacts with ZEA and meso-ZEA, while more the steroidogenic acute regulatory domain 3 (StARD3) is partly responsible for retinal uptake of LUT [16,17]. Other research suggests that cell lines similar to RPE

are involved in LUT and ZEA uptake and are entirely dependent on SR-B1 transporters [15]. Different research indicates that carotene cleavage oxygenases (CCOs) mediate site-specific cleavage of double bonds forming apo-carotenoid metabolites, which may have important metabolic roles that differ from the original compound [18]. Mein and associates demonstrated that carotene-9'10'-monooxygenase, (CMO2), a CCO highly expressed in the RPE, cleaved LUT and ZEA at the 9,10 and 9',10' double bonds in ferrets [18]. No apo-carotenoid metabolites in the RPE have been identified from this CMO2 cleavage, however other LUT and ZEA metabolites have. The functional purpose of these metabolites remains elusive but includes: 3'-epilutein, 3-OH- β , ϵ -caroten-3'-one and aforementioned meso-zeaxanthin [19]. Although the functions of macular xanthophylls as preventers of AMD are promising, links between LUT and ZEA and diabetic retinopathy and other degenerative eye diseases are less established. Future investigations should consider the mechanisms of transport and regulation of LUT and ZEA in the retina, as well as identifying the function of these potentially biologically important apocarotenoid metabolites.

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