

Lutein Supplementation for Diabetic Macular Edema

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ABSTRACT

Lutein is a natural component of the retina that is acquired in the diet; One of its multiple functions is to capture reactive oxygen species and promote their elimination. People with Diabetes Mellitus have a significant increase in oxidative stress due to protein glycation and activation of the polyol pathway; as a result, they develop diabetic retinopathy that can progress to macular edema and cause severe visual disturbances including central blindness. The lack of lutein in people with macular edema is evident, therefore, they require additional consumption to prevent and reduce the complications. We decided to undertake a review in order to learn more about this supplement, its properties and its beneficial effect on the eyesight of individuals with Diabetic Macular Edema.

Keywords

Carotenoids, Diabetes complications, Zeaxanthin.

Introduction

Diabetic Macular Edema (DME) represents the most frequent cause of blindness in individuals aged 20 to 74 years [1]. This can start to develop at least 7 years before the diagnosis of Type 2 Diabetes Mellitus [1,2]. Studies in Mexico report a prevalence of Diabetic Retinopathy of 33.3% (29.9% with Non-Sight Threatening Retinopathy and 3.4% with Sight Threatening Retinopathy) of which, more than half suffer from DME [3,4]. Currently, existing therapies are limited to invasive pharmacological treatments, however, recent studies have shown efficacy in the treatment of DME after the administration of natural supplements derived from carotenoids. This article provides an overview about Lutein and evidence of its use as an alternative for the treatment of Diabetic Retinopathy and DME.

Carotenoids and their Properties

Carotenoids are natural compounds found in different plant structures and in a great variety of animals, algae, fungi and bacteria. These pigments are responsible for the coloration of

flowers and fruits (in order to favor pollination and the scattering of seeds), or animal structures such as feathers and the beaks of certain birds, the exoskeletons of crustaceans and the muscles or skin of certain types of fish [5].

These compounds are considered to be essential to life, owing fundamentally to the functions they carry out in relation to photosynthesis (harvesting light pigments, photoprotection) [5,6].

There are two types of carotenoids: carotenes, which contain no oxygen in their terminal rings (example: β -carotene, lycopene) and xanthophylls, which contain oxygen in their terminal rings (example: lutein and zeaxanthin). These four are the most abundant in human blood [7,8]. However, the one found in the greatest proportion in plasma is lutein, which also makes up 90% of the pigment in the macula (central zone of the retina and area of greatest ocular vision) [9] (Figure 1).

Carotenoids are isoprenoids (unsaponifiable simple lipids) that have properties of light-absorption through the presence of 7 or more conjugated double bonds and its principal benefit is the absorption of ultraviolet light (high-energy light, originating from

the sun and electronic appliances that harms the cells of the retina, causing macular degeneration; this is where its importance to the visual function is derived from [5,10].

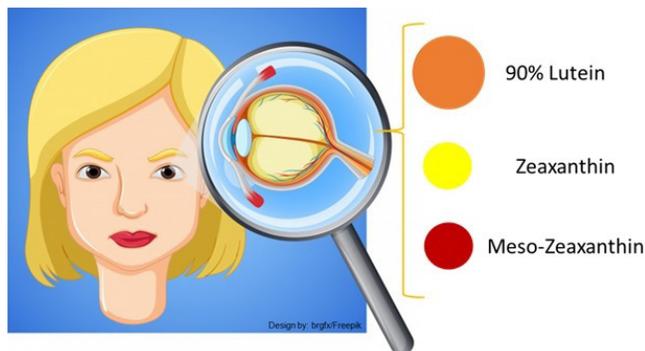


Figure 1: The retinal carotenoids: The 90% of the macular pigment corresponds to lutein; while the remaining 10% by its precursors: Zeaxanthin and Meso-zeaxanthin [5].

Lutein and biological functions

Lutein is the most common carotenoid found in nature, as well as that principal xanthophyll of the protein complex. It is a dihydroxylated derivative of α -carotene, which, having substituted beta-rings, has no provitamin A activity. In addition, human beings cannot synthesize this nutrient, so it must be acquired through the consumption of foods such as egg yolk, broccoli, orange or chard spinach [11].

Lutein is a yellowish-orange pigment with a dual mechanism, inactivating singlet oxygen (energetically excited forms of molecular oxygen) and trapping free radicals. It also possesses anti-inflammatory and neuroprotective properties [12]. Its neuroprotective function lies in the preservation of levels of synaptophysin, a synaptic vesicle protein that is important for the release of neurotransmitters and activity of the synaptic network. This protein is abundant in the inner plexiform layer of the retina. In addition, lutein suppresses the activation of the extracellular signal-regulated kinases (ERKs), a kinase that degrades Synaptophysin [12].

Anti-inflammatory function is achieved through the induction of changes in the expression of genes related to inflammation, demonstrated in the retinal pigment epithelium (RPE). Antioxidants inhibit the retinal increase in the redox-sensitive nuclear transcription factor-B (NF- κ B, a transcriptional factor that controls the expression of many genes involved with inflammation) and what prevents the development of diabetic retinopathy [12].

Its function as an antioxidant in human tissue decreases the risk of cardiovascular disease and certain kinds of cancer; however, it presents the greatest benefit in ocular problems, especially those concerning retinal affections, it being a tissue with a high exposure to oxidative stress [13]. The retina is the neurosensory tissue of the eye and is extremely rich in membranes with polyunsaturated lipids, a feature that makes it especially sensitive to the deleterious action of free radicals derived from oxygen and nitrogen [14]. An event that led to the discovery of the effects of this antioxidant on

the human body took place in 1904, when a Japanese bacteriologist, Inawashiro Noguchi Seisaku, uncovered the causal agent of trachoma (*Chlamydia trachomatis*), which causes a contagious granular conjunctivitis that can lead to blindness. Alongside this investigation, he studied syphilis; whereby he discovered the spirochaete *Treponema pallidum*, which was found in the brain and in the spinal cord of those affected and came up with a method of diagnosis that consisted of a modification of the Wassermann reaction with lutein, a method which was dubbed the Noguchi reaction with lutein in his honor [15].

From that point on, studies were made on the functions of lutein, with allowed for its commercialization in powder form and its use as an additive in certain foods, as well as its use as a supplement in capsules for eyesight.

Lutein for Diabetic Macular Edema.

Currently, lutein is used to prevent Age-Related Macular Degeneration (ARMD), however, there is evidence supporting its efficacy in reducing diabetic macular edema. Bo-Jie Hu, et al. (16) proved its effects by carrying out an intervention on 30 patients suffering from non-proliferative diabetic retinopathy, to which they administered 6 mg of lutein and 0.5 mg of zeaxanthin orally over a span of three months, and made a comparison with a second group that did not receive lutein, but did have non-proliferative diabetic retinopathy, and a control group of healthy people; the results showed that foveal thickness diminished in 83% of patients after medication [16].

L. Brazionis et al., reported that people with diabetes have lower plasma concentrations of α -Carotene β -Carotene, Lutein, zeaxanthin, Lycopene, compared to control group [17]. M. Moschos et al, confirms that the Macular Pigment Optical Density (MPOD) and Contrast Sensitivity (CS) increase after the carotenoid supplementation [18].

Likewise, F. Granado et al. tried supplementation with capsules of α -tocopherol, cis-lutein and trans-lutein in order to find out if plasma lutein concentrations are related to oxidative stress, in his study he reports a non-significant decrease of plasma lutein levels in Type 1 diabetics, probably influenced by the lipid's metabolism of each person [19] (Table 1).

Future directions and challenges

This supplement would represent an excellent therapeutic option for individuals suffering from diabetic macular edema, since treatment for this pathology is currently limited to intravitreal injections of antiangiogenic pharmaceuticals or corticosteroids and laser; however, these therapies are only effective in less than a third of those who undergo them and all this at a high cost [20,21].

Basing ourselves on these investigations, we have decided to carry out clinical studies in Mexico to compare the effects of this natural antioxidant to existing therapies for treating Diabetic Macular Edema. It is necessary that these clinical trials become the foundation on which to carry out new studies that prove the

Author	Year	N	Population of study	Duration	Treatment	Results			
						Plasma Concentrations	OCT (µm)	BCVA	HbA1c (%)
M. Moschos et al. [18]	2017	60	Type 2 Diabetes without diabetic retinopathy	2 years	One capsule a day with: -lutein (10 mg) -zeaxanthin (2 mg) -meso-zeaxanthin (10 mg)	-----	↑ Macular pigment density = 157.1 ± 14 to 163.4 ± 13.2 (p≤0.001)	no changes (≥ 9/10)	-----
Hu BJ et al. [16]	2011	90	Nonproliferative diabetic retinopathy	3 months	One capsule a day with: -Lutein 6mg/d -Zeaxanthin 0.5mg/d	DR Group: ↑ L/Z (0.5409 µg/mL and 0.2816 µg/mL). Control Group: 0.0701 µg/mL and 0.0224 ± µg/mL (p =0.001)	↓ Foveal thickness= 286.50 ± 134.185 (p=0.05)	Control Group= 7.9 vs DR= 8.8 (p=0.018)	-----
L. Brazionis et al. [17]	2009	111	Type 2 Diabetes		Not taking carotenoid supplements, only measurements	↓L/Z (mmol/L) 0.36 vs DR 0.34 (p=0.736)	-----	-----	Control Group= 7.9 vs DR= 8.8 (p=0.018)
F. Granado et al. [19]	2002	18	Type 1 Diabetes	21 days	One capsule a day with: -12 mg all-trans-lutein - 3 mg of 13/15-cis-lutein - 3.3 mg of α-tocopherol	↑Lutein (nmol/L) 20.76 ± 13.72 vs DM1= 21.29 ± 14.43 (p= NS)	-----	-----	Control Group= 4.8 ± 0.5 vs DM1= 7.7 ± 2

Table 1: Summary of studies investigating the relationships among, Diabetes, Diabetic Retinopathy, supplementation of Lutein/analogs & derivatives. BCVA: Best corrected Visual Acuity, DR: Diabetic Retinopathy, L/Z: Lutein / Zeaxanthin, DM1: Type 1 Diabetes Mellitus, NS: Non significant, OCT: Optical Coherence Tomography.

usefulness of Lutein so it can be opportunely used in cases of Diabetic Retinopathy and Diabetic Macular Edema.

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