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Editorial

# Effect of diet on eye diseases and visual impairment

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The leading causes of visual impairment worldwide are cataract, age related macular degeneration (ARMD), diabetic retinopathy, glaucoma and dry eye disease (DED), etc. There has been an increasing interest in the benefits of nutrition and nutritional supplements against eye diseases. There are some reported evidences which shows that essential nutrients in the diet play an important role in maintaining structural integrity and cellular metabolism of ocular tissues. Deficiency of dietary nutrients may lead to altered metabolic states which affect immune-inflammatory mechanisms in ocular tissues causing pathogenesis and progression of various eye diseases. Thus, it is possible that dietary modifications may reduce both the prevalence and severity of eye diseases, hence reducing the risk of visual impairment.

## 1. Essential Nutrients for Healthy Eyes

### *1.1. Vitamins*

Important vitamins associated with ocular functions are vitamin A, vitamin $B_1$ (thiamine), vitamin C, vitamin D and vitamin E. Vitamin A (retinol) is an essential nutrient required in small amounts for normal functioning of the visual system, maintenance of epithelial cellular integrity and ocular immune function. Dietary sources of preformed vitamin A in animal products are milk and dairy products, liver, egg yolk and fish liver oil and pro-vitamin A (carotenoids) which are found in green leafy vegetables (e.g. spinach, amaranth etc.), yellow vegetables (e.g. pumpkins, carrots etc.) and yellow non-citrus fruits (e.g. mangoes, apricots and papaya, etc.). Vitamin A deficiency chiefly affects the retina, conjunctiva and cornea leading to biochemical/ functional changes (night blindness) and structural changes (e.g. fundus xerophthalmicus, conjunctival xerosis, Bitot's spots, corneal xerosis, and keratomalacia).[1]

Carotenoids are naturally occurring pigments synthesized by plants, algae and photosynthetic bacteria. Alpha carotene and beta carotene are provitamins. Some can be converted into retinol while some Carotenoids like lutein, lycopene and xeaxanthin cannot be converted into retinol. Dietary sources are orange and yellow vegetables and spinach etc. Carotenoids have antioxidant properties and anti-carcinogenic properties. Lutein and xeaxanthin directly increase macular pigment density and protect the macula from sunlight damage and is thus associated with lowering the risk of AMD.[2]

Vitamin $B_1$ (thiamine) is a water-soluble vitamin of the B complex family. Common sources are dried peas, beans and dried yeast etc. It plays an important role as a cofactor for trans-ketolase, alpha ketoglutarate dehydrogenase and pyruvate dehydrogenase enzymes. Intracellular accumulation of thiamine may lead to anemia, retinal abnormalities, visual disturbance, optic nerve atrophy and retinal dystrophy (cone-rod dystrophy).[3]

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Vitamin C (ascorbate) is an essential nutrient for the biosynthesis of collagen and L-carnitine. Ascorbate is found in many citrus fruits and other fruits like cherries, kiwi, mango, papaya, strawberries and vegetables like cabbage, broccoli, cauliflower, tomatoes, etc. Diurnal animals and humans have the highest concentration of ascorbic acid in aqueous and least in the retina. Roles of ascorbic acid in ocular tissues have not been well described. It acts as a strong reductant and scavenger of free radicals like superoxide, thus protecting ocular structures from oxidative damage.[4] In trabecular meshwork, ascorbic acid modulates the production of fibronectin and laminin, which are components of basal lamina and is involved in synthesis of glycosaminoglycan.[5] Ascorbic acid promotes corneal wound healing and affects arachidonic acid metabolism in the iris, ciliary body and cornea.[6] In the lens and retina, it protects against (UV) ultraviolet irradiation. It also prevents cataractogenesis.

Vitamin D (ergocalciferol, vitamin D2 & cholecalciferol, vitamin D3) is fat soluble vitamins synthesized by plants (vitamin D2) and by human skin (vitamin D3) after sunlight exposure (UV B). Now food items fortified with vitamin D2 or D3 are available in the market. Vitamin D plays an important role in reducing the risk of ARMD and dry eye disease (DED) through its anti-inflammatory properties. Vitamin D inhibits proliferation of T- helper cells, T-cytotoxic cells and natural killer cells and increases T-suppressor cell activity. It also decreases the production of pro-inflammatory biomarkers such as IL-2, IL-6, IL-8, IL-12. Vitamin D reduces C-reactive protein, which is a marker of systemic inflammation. Vitamin D, being a potent inhibitor of angiogenesis, might protect against ARMD.[7]

Vitamin E (alpha–tocopherol) is a fat-soluble vitamin with strong antioxidant properties. Natural sources are-asparagus, egg, milk, almonds, nuts, green leafy vegetables and whole grain etc. Alpha-tocopherol possesses anti-proliferative and protein kinase C suppressing effects which exerts intraocular pressure lowering effects. Vitamin E plays a prophylactic role against sunlight-induced cataractogenesis, retinal photodeterioration and photocarcinogenesis. Neurodegeneration in glaucoma is due to compromised glutamate homeostasis. Glutamate transporter activity is mediated via alpha-tocopherol via diacylglycerol- PKC pathway.[8]

### *1.2. Minerals*

The common nutritionally essential mineral elements required for healthy eyes are manganese, selenium and zinc.

Manganese (Mn) is a constituent of some enzymes and an activator of other enzymes. Manganese Superoxide dismutase (MnSOD) is the main antioxidant enzyme in the mitochondria. It catalyzes the conversion of superoxide radicals produces during ATP synthesis into hydrogen peroxide which can be reduced to water. Pyruvate carboxylase is a manganese containing an enzyme and phosphoenol pyruvate carboxykinase (PEPCK) is a manganese activated enzyme. Dietary sources of manganese are oatmeal, cereal, brown rice, pineapple, almonds, peanuts and spinach etc.

Selenium is a trace element required in very small amounts (adults, 55mcg per day). The richest sources of selenium are seafood, organs and muscles, meat, grains, salmon and brown rice etc. It is required for the function of selenium dependent enzymes (selenoprotreins). Glutathione peroxidase (Gpx) is selenium containing an antioxidant enzyme which reduces harmful reactive oxygen species (ROS) such as hydrogen peroxide and lipid hydroxiperoxidase.[9] Synthesis and production of biologically active thyroid hormone (triiodothyronine or T3) requires selenium dependent iodothyroninie deiodinase enzyme. Thus, selenium is essential for normal growth and metabolism.

Zinc is the second most abundant trace element in the human body. Common dietary sources of zinc are oysters, red meat, nuts, eggs, milk products, bread, fish, cereals, etc. Zinc concentration in ocular tissues is unusually higher than other tissues.[10] Cherry red maculopathy and visual impairment have been reported in patients with Crohn's disease with zinc deficiency and visual improvement was found after zinc supplementation.[11] It has been reported that zinc deficiency in alcoholism and hepatic cirrhosis is associated with abnormal dark adaptation and diminished scotopic retinal response.[12,13] Zinc is highly concentrated in the retina and its effect on retinal function is through vitamin A metabolism.In retinal pigment epithelium zinc induces the synthesis of metallothionin which is scavenger of hydroxyl radicals.[14]

### *1.3. Fatty Acids (FA)*

Fatty acids may be saturated (no double bonds between carbon atoms) or unsaturated FAs (one or more than one double bonds between carbon atoms). Depending on the location of $1^{st}$ double bond between carbon atoms, polysaturated FA (PUFA) are divided into omega -3 and omega- 6 series. Linoleic acid (LA) is present in the omega-6 series and alpha- linoleic acid (ALA) is present in the omega-3 series. Both are essential FAs because they cannot be synthesized by mammals and must be supplemented through diet.

Food sources of omega 6 FAs are: (i) linoleic acid (vegetable oils, such as soyabean, safflower, corn oil, nut seeds, etc.) (ii) Arachidonic acid (present only in animal products, meat, eggs).

Dietary sources of omega-3 fatty acids: (i) Alpha linolenic acid (ALA)- flax seeds, walnuts, canda oil and mustard oil (ii) Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)- fish like salmon, oysters, tuna and crab.

DHA is essential structural component of the retinal membranes. Long chain omega 3 fatty acids protect vascular and neural retina against oxygenic, inflammatory and age associated retinal pathology.[15,16] DHA may also help in regeneration of rhodopsin.[17]

### *1.4. Proteins*

Proteins are polymers of amino acids (essential and non-essential). Essential amino acids must be present in our diet. Proteins are major source of energy, these are part of enzymes useful in cellular metabolism and are major structural components of ocular tissues. Proteins also play important role as antibody, hormones and transport/storage function. Glutathione is an ubiquitous tripeptide molecule consisting of cysteine, glutamic acid and glycine. Glutathione enhances the immune system (multiplication of lymphocytes), acts as antioxidant and free radical scavenger and detoxifying agent (detoxification of carcinogens / harmful metabolites). It regulates other antioxidants such as vitamin C and E.

### *1.5. Carbohydrates*

Carbohydrates are the most abundant organic compounds found in living organisms. Carbohydrates are basically classified as simple carbohydrates, complex carbohydrates (starch) and fiber. All carbohydrates behave quite differently in our body. They have different glycemic index (GI). Low GI carbohydrates produce only small fluctuations in blood sugar and insulin levels.

## 2. Nutritional Supplements and Eye Diseases

### *2.1. Diet and dry eye disease*

Dry eye disease (DED) or keratoconjunctivitis sicca (KCS) is a multifactorial disease with symptoms of discomfort, visual disturbance and tear film instability. It has been found that prevalence of DED is increasing with age and is more prevalent among post-menopausal women due to hormonal status. Recent concepts of pathogenesis have shown that DED seems to be caused by inflammation mediated by T-cell lymphocytes.[18] It has been reported that supplementation of naturally occurring PUFA of omega 3 (n-3) fatty acids have beneficial effects in DED.[19] Rashid S reported beneficial effects of topical application of ALA omega-3 fatty acids in which, they found reversal in signs of DED and underlying inflammatory changes.[20]

Vitamin D supplementation has shown to improve dry eye disease. Vitamin D plays multifactorial role in ocular surface disorders through its anti-inflammatory and extracellular matrix remodeling properties. Calcitriol (1,25(OH)2 D3) inhibits hyperosmotic stress- induced cellular inflammation in corneal epithelium. Vitamin D also modify the toll- like receptor (TLR)- mediated inflammation and suppress the release of pro-inflammatory cytokines in cornea.[21,22]

### *2.2. Diet and glaucoma*

Glaucoma is the second leading cause of irreversible blindness characterized by progressive death of retinal ganglion cells with subsequent peripheral visual field loss. Intraocular pressure (IOP) remains the major modifiable risk factor for glaucoma thus primary aim of treatment is reducing IOP.

Lillico and associate reported increase in the risk of glaucoma associated with excess selenium intake by cancer patients.[23] Conley et al. conducted a study to investigate the mechanisms of selenium induced changes in homeostasis of human trabecular meshwork (HTM) cells. Selenium affects the secretion of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). They concluded that selenium induced changes in MMP-2/TIMP-1 may lead to imbalance of extracellular matrix turnover in aqueous outflow pathway and causes raised IOP that leads to glaucoma.[24]

Latanoprost, travoprost are prostaglandin F2 alpha analogues which are potent IOP lowering drugs used in glaucoma. The dietary intake of n-6 fatty acids may lead to greater availability of prostaglandin F2 alpha which helps in maintaining IOP levels that are less harmful to optic disc.[25]

Oxidative stress may contribute to pathogenesis and progression of glaucoma. Oxidative process may lead to apoptotic death of retinal ganglion cells and damage of trabecular meshwork cells[26] Endogenous glutathione (oxidation-reduction agent) have protective role against glutamate-induced retinol toxicity. Antioxidant (vitamin A, C and E) supplementation may protect the optic nerve and trabecular meshwork. Increase dietary intake of vitamin E contributes in antioxidant defense mechanism in the aqueous humor by increasing concentration of glutathione.[27] Higher concentration of ascorbic acid in aqueous humor may offer IOP lowering effect by the depolymerization of hyaluronic acid component of trabecular meshwork's.[28]

### *2.3. Diet and diabetic retinopathy*

Diabetic retinopathy (DR) is a multifactorial, vision threatening complication of diabetes mellitus. In diabetes, increased oxidative stress in retina is one of the regulatory factor in development of DR. Vascular endothelial growth factor (VEGF), is a major angiogenic factor responsible for vascular abnormalities in DR. Diabetic retinopathy is also having an inflammatory component so leukostasis is also seen in diabetic retina. It has been observed that low-GI (glycemic index) diet and high antioxidant supplement may reduce the incidence of type-2 diabetes. Diet with high flavonoids (from fruits and vegetables) and omega- 6 PUFA might be associated with lower rate of DR.[29] Curcumin

(Constituent of turmeric plant) and green tea (rich source of flavonoids) having potent antioxidant and anti-inflammatory properties may be beneficial in management of DR.[29,30]

### *2.4. Diet and cataract formation*

Human lens is a biconvex, transparent structure within eye which helps in refraction of light and focussing it on the retina. With the increasing age, lens loses its transparency and result in cataract formation. Oxidative damage of lens protein is a key mechanism of catractogensis. The major risk factors for oxidative damage of lens are age, UVA rays exposure, diet with poor antioxidants and smoking etc. High dietary sodium and higher glycemic-index have also been linked to cataract progression. The recommendations for prevention of cataract formation are low-GI diet, increase intake of protein, omega-3 PUFA, carotenoids , antioxidants and vitamins A, B, C and E.[31,32]

### *2.5. Diet and prevention of age-related macular degenerations (AMD)*

Age-related macular degeneration (AMD) is the major cause of legal blindness in aging population. The exact pathogenesis of AMD is remains unknown. Oxidative stress and inflammatory mechanism may accounts for development of AMD.[33] Smoking habit and dietary factors are being the most common modifiable risk factors. Higher intake of saturated fats and cholesterol in individuals with a higher body mass index, increases risk of AMD.

The age-related eye disease study (AREDS) suggested that high dose supplement of Vitamin C, vitamin E, carotene and zinc was protective against progression of moderate to advanced AMD. The Supplemental beta-carotene increases the risk of developing lung cancer in heavy Smokers. However other carotenoids like Lutein, Zeaxanthin and lycopaine do not increase risk of lung cancer and can be used in high concentration. Lutein and Zeaxanthin are concentrated in macula and form the macular pigment which act as antioxidants and the blue light filters to protect the macula. Smoking is a major oxidative stress which may lower the bioavailability of Lutein / Zeaxanthin. Dietary fat modification may reduce the risk of AMD development. Higher dietary fish consumption/or long-chain omega-3 fatty acids associated with a lower likelihood of neovascular AMD. A lower GI diet has been associated with the decreased risk of AMD progression in AREDS trial.[34] Decreased zinc intake with antioxidants reduced risk of AMD progression in Blue Mountains Eye Study.[35] Vitamin D May reduce the risk of AMD by virtue of its anti-inflammatory and angiogenic properties. Combined dietary pattern, like Mediterranean-style diet found to be linked to a lower risk of neovascular AMD.[36]

Season Greetings !!

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