·Review·

Cod liver oil: a potential protective supplement for human glaucoma

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Abstract

• Glaucoma is one of the leading causes of visual impairment and blindness. Improved knowledge of the pathogenesis of this disease has allowed the exploration of new therapeutic methods. In general, elevated intraocular pressure (IOP), oxidative stress, and vascular insufficiency are accepted as the major risk factors for the progression of glaucoma. Many natural compounds have been found beneficial for glaucoma. Nutritional therapies are now emerging as potentially effective in glaucomatous therapy. One nutritional supplement with potential therapeutic value is cod liver oil, a dietary supplement that contains vitamin A and omega-3 polyunsaturated fatty acids (PUFAs). Vitamin A is important for preserving normal vision and it is a well-known antioxidant that prevents the oxidative damage that contributes to the etiology and progression of glaucoma. Vitamin A is also a crucial factor for maintaining the integrity of conjunctival and corneal ocular surfaces, and preventing the impairment of ocular epithelium caused by topical antiglaucomatous drugs. Omega-3 fatty acids are beneficial for glaucoma patients as they decrease IOP, increase ocular blood flow, and improve optic neuroprotective function. In this article, we propose that cod liver oil, as a combination of vitamin A and omega-3 fatty acids, should be beneficial for the treatment of glaucoma. However, further studies are needed to explore the relationship between cod liver oil and glaucoma.

• KEYWORDS: cod liver oil; glaucoma; omega-3 fatty acids; vitamin A

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INTRODUCTION

Glaucoma is the second leading cause of blindness in the world. According to Quigley[1,2], by the year 2000, the number of people in the world with primary glaucoma was estimated at nearly 66.8 million, with 6.7 million suffering from bilateral blindness. This number is expected to increase to 79.6 million by 2020, and of these, 74% will have open angle glaucoma (OAG). The treatments available for glaucoma are still far from satisfactory; therefore, new therapeutic approaches continue to be sought.

Glaucoma is an optical neuropathy characterized by a specific structural alteration of the optic nerve head that leads to progressive deterioration of the visual field. Although increased intraocular pressure (IOP) is a major risk factor for primary open angle glaucoma (POAG), other factors also play important roles, including vascular insufficiency, glutamate-mediated toxicity, excess production of nitric oxide (NO), and oxidative stress [3]. Improved knowledge of the pathogenesis of the disease is now opening up new therapeutic strategies. Nutrition, a subject of interest in many fields of medicine, is also being viewed as a potential therapeutic path and ophthalmologists are beginning to seek possible ways to preserve vision through diet and supplements. For example, Mozaffarieh *et al*[4-6] have found that gingko, dark chocolate, tea, coffee, red wine, the anthocyanosides found in bilberries, ubiquinone, and melatonin are potential neuroprotective agents for glaucoma. Other avenues of treatment, such as magnesium, salt and udrocortisone, are already used by some physicians. Nutritional therapies are therefore emerging as potentially effective methods for preventing the progression of glaucoma.

Cod liver oil is used widely as a dietary supplement. It is a rich source of vitamin A, vitamin D, and essential omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) [7]. Because of its special

components, cod liver oil is generally accepted as good for human health. In previous studies, cod liver oil supplementation has been suggested to reduce cardio-metabolic risk factors [8], have anticancer effects [9], and ameliorate cognitive impairment induced by chronic stress[10]. To our knowledge, no study has yet investigated the potential beneficial effects of cod liver oil in preventing the progression of glaucoma. The aim of this article is to consider the hypothesis that cod liver oil is a potential protective compound for the treatment of human glaucoma. In the following, we present a body of evidence in support of a role for cod liver oil, as a source of vitamin A and omega-3 fatty acids, in glaucomatous therapy.

The Role of Vitamin A in Glaucoma Vitamin A is an essential fat-soluble vitamin. It is required for normal functioning of growth, vision, epithelial differentiation, immunity, and reproduction [11]. Vitamin A also has a vital role in ocular metabolism: it is essential for conjunctival and corneal epithelial maintenance, retinal phototransduction, and retinal pigment epithelial cell viability. A deficiency of vitamin A will lead to vision loss, keratomalacia, Bitot's spot, and dry eye. Night blindness results when the vitamin A pool in the eye becomes depleted, and the concentration in the rod cells is lowered. This condition is reversible with increased vitamin A intake or supplementation [12]. In short, vitamin A is important for maintaining normal vision.

An association between oxidative stress and POAG has already been reported [13-15]. Tezel found that oxidative stress takes part in the neurodegenerative process[14]. Welge-Lussen and Birke [14] concluded that oxidative stress can induce characteristic glaucomatous trabecular meshwork (TM) changes, and speculated that the prevention of oxidative stress exposure to the TM may help to reduce the progression of POAG. According to Feilchenfeld *et al*[15] oxidative injury also occurs in blood vessels and astrocytes in the pre-laminar optic nerve head in human POAG. Further studies have concluded that oxidative stress may contribute to the etiology and progression of POAG. Therefore, the potential is great for antioxidant supplementation to minimize TM changes, protect the optic nerve and the ocular vessels [5, 6, 14]. If increasing total dietary antioxidant intake is to succeed as an effective therapeutic strategy, this would be a promising means of primary prevention for POAG.

Vitamin A, provitamin A, and carotenoids are well-known antioxidants. However, humans cannot synthesize vitamin A and must obtain it from their diets. Cod liver oil is a good source of vitamin A supplementation, as the dose of vitamin A is moderate and the quality of vitamin A is excellent. The antioxidant activity of vitamin A and related carotenoids is conferred by the hydrophobic chain of polyene units that can quench singlet oxygen, neutralize thiyl radicals, and combine with and stabilize peroxyl radicals. The majority of research performed to date has examined the antioxidant effects of vitamin A and carotenoids. The observation by Das *et al* [16] suggested that vitamin A and its metabolites exhibited an antioxidant effect even greater than that produced by vitamin E. It is extensively suggested that vitamin A supplementation can exert protective effects against neurodegenerative and cardiovascular diseases, since oxidative stress play a major role in the pathogenesis of such conditions [17, 18]. However, using data from two large prospective cohorts, Kang *et al* [19] found little evidence that an increase total intake of vitamin A substantially reduced the risks of POAG. Further research, experiments, and clinical trials are still necessary to investigate the potential association between the antioxidant properties of vitamin A and their effects on glaucoma.

Topical IOP lowering drugs for glaucoma must penetrate across the tissues of the eye to reach their therapeutic targets. Frequently, these tissues are the first to show signs and symptoms of drug toxicity and adverse effects such as eyelid dermatitis, malpositions, lacrimal system scarring, ocular discomfort upon instillation, tear film instability, conjunctival inflammation, subconjunctival fibrosis, conjunctival epithelium changes, and corneal surface and endothelial impirment [20]. Many studies have demonstrated that long-term use of ocular hypotensive medications can cause significant changes to the ocular surface[21, 22]. Vitamin A is essential for conjunctival and corneal epithelial maintenance and it plays a vital role in ocular epithelial growth and differentiation. It is a crucial factor for regulating mucin production of the ocular surface epithelium, which is known to be an important part of the ocular surface defense [23]. A randomized controlled experimental study in rabbits concluded that vitamin A palmitate could promote the repair of mechanical defects in the corneal epithelium and the development of intracellular conjunction; and it also could promote regeneration of conjunctival goblet cells and re-establish intracellular conjunction of the conjunctival epithelium [24]. Base on this evidence, vitamin A not only can maintain ocular surface integrity, but it also can prevent impairment of the ocular epithelium caused by antiglaucomatous drugs.

However, the intake of large doses of vitamin A can cause nausea, vomiting, headache, and dry scaly skin. More severe health problems can arise from storing excess vitamin A in the body, including liver damage, osteoporosis, and nervous system disorders. For these reasons, the total vitamin A intake is recommended as less than 3000μg per day from

retinol[25]. Supplementation of moderate amounts of cod liver oil appears to be relatively safe.

The Role of Omega−3 Fatty Acids in Glaucoma Not all fatty acids can be synthesized by the human body. Those that cannot be synthesized and must be obtained from the diet are known as "essential fatty acids." There are two known families of "essential fatty acids": omega-3 and omega-6 fatty acids. Of these, two long-chain omega-3 fatty acids, EPA and DHA, are particularly important nutritional components. Both EPA and DHA are concentrated in the phospholipids of cell membranes throughout the human body, but especially in the brain, heart, retina, and testes.

Previous reviews have discussed the role of omega-3 fatty acids in prevention and therapy of various diseases (cardiovascular diseases, cancer, depression, neurological diseases, *etc*.) as well as their mechanisms of action [26, 27]. Dietary omega-3 fatty acids have also been shown to be beneficial to the outcome of ocular diseases such as decreasing risk for age-related maculopathy (ARM) [28]. According to Ren *et al* [29], patients with POAG have an abnormal blood fatty acid composition that is characterized by a reduction in EPA, DHA, and omega-3 fatty acids. Therefore, we predict that omega-3 fatty acids should display potential beneficial effects on glaucoma.

Among the factors involved in the pathogenesis of glaucoma, elevated IOP is the major risk factor. The final consequence of IOP elevation is retinal cell loss, which leads to a specific structural alteration of the optic nerve head and progressive deterioration of the visual field. Results of a large-scale and long-term clinical trial have provided convincing evidence that lowering IOP prevents progression at both the early and late stages of glaucoma[30]. The IOP is determined by the balance between aqueous humor production and outflow.Nguyen *et al* [31] demonstrated that an increased consumption of omega-3 fatty acids leads to decreased IOP through an increased aqueous outflow facility [31]. The exact mechanism of the aqueous outflow increase is via prostaglandins (PGs), which are metabolites of omega-3 fatty acids [32]. These reduce IOP by enhancing uveoscleral and trabecular outflow via direct effects on ciliary muscle relaxation and remodeling of extracellular matrix [33]. The PGs are powerful ocular hypotensive agents that can be used for the treatment of elevated IOP. Cod liver oil that contains both EPA and DHA has been demonstrated to lower IOP in experimental animals[34].

Vascular insufficiency is also recognized as another important risk factor, in addition to IOP. Circumstantial evidence points to an association between vascular insufficiency and glaucoma. Recent findings indicate a role for vascular deficits in the pathogenesis of glaucoma [35], suggesting that treatments designed to improve ocular blood flow may be of benefit to glaucoma patients. A study done by Hamard *et al* [36] on POAG patients and normal tension glaucoma (NTG) patients showed that the optic nerve blood flow velocity was reduced and the ability of the red blood cells (RBCs) to aggregate was increased, leading to increases in the local viscosity within the papillary capillary network. Decreased blood flow velocity and increased blood viscosity will lead to vascular insufficiency. Evidence has been shown that blood viscosity is significantly and uniformly lowered in subjects who receive omega-3 fatty acids. The potential mechanism is thought to relate to the ability of omega-3 fatty acids to enhance cell membrane fluidity, decrease platelet aggregation, and reduce serum cholesterol concentrations by decreasing the synthesis of very low density lipoprotein and low-density lipoprotein[37]. Omega-3 fatty acids appear to increase blood fluidity by at least two independent mechanisms: changing red cell deformability possibly by altering the cell membrane composition, and lowering plasma viscosity possibly by altering the protein pattern of the plasma [38]. However, the therapeutic potential of omega-3 fatty acids for improving ocular circulation needs to be explored more thoroughly.

Previous studies have found that omega-3 fatty acids are beneficial for the treatment of glaucomatous optic neuropathy (GON). Omege-3 fatty acids function in the treatment of GON by preventing retinal cell structural degradation and by decreasing glial cell activation induced by the elevation of IOP [39]. Caramazza *et al* [40] also demonstrated that polyunsaturated fatty acids, acting on nerve cell trophism, helped to preserve nerve fiber function in GON. Omega-3 fatty acids are considered an efficacious supportive therapy in the prevention and treatment of GON[41].

CONCLUSION

Base on the above literature review, we find evidence to support the idea that vitamin A and omega-3 fatty acids can play a protective role in the treatment of glaucoma. Cod liver oil, as a combined supplement of vitamin A and omega-3 fatty acids, should be more effective than single supplement formulations. However, the true efficacy of cod liver oil has not yet been solidly determined and further studies are needed to clarify its true benefits. Properly controlled, long-term clinical trials are needed to determine whether supplementation with cod liver oil would be therapeutically beneficial as a treatment for glaucoma. We hope that this study will encourage others to investigate the effects of cod liver oil on glaucoma.

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