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Review of Nutritional Supplementation Options for the Anterior Segment: An Evidence Based Approach

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Introduction

The anterior segment of the eye is a metabolically active system, which includes the ocular surface of the eye and extends posteriorly to the crystalline lens.[1] Ocular surface diseases often disrupt the complex interplay of cornea, conjunctiva, meibomian glands, eyelids, and the lacrimal system, leading to diminished visual acuity and discomfort, and occasionally to frank pain. This can negatively impact the patient's quality of life. Other anterior segment diseases including keratoconus, glaucoma, and cataract may also affect visual acuity. Oxidative stress and inflammation have been investigated in pathogenesis of these diseases.[2] There has been an increase in the number of studies investigating various nutritional supplements benefiting the anterior segment structures. This review discusses the role of these supplements with supported clinical evidence.

Treatment Modalities for Ocular Surface Diseases

Autologous Serum Tears

Autologous serum tears have garnered significant interest within the realm of ocular surface health, emerging as a promising intervention for addressing various eye pathologies. Derived from the patient's own

blood, these unique tears contain a rich assortment of essential growth factors and bioactive compounds crucial for the regeneration and rejuvenation of compromised ocular tissues.[3] Clinical applications have explored different concentrations of serum, including 20%, 40%, and 50%. Hussain *et al.*[4] concluded that at 50%, serum tears are safe and effective for the long-term treatment of dry eye disease (DED). Encouragingly, multiple studies have demonstrated positive outcomes, affirming the effectiveness of autologous serum tears in mitigating discomfort associated with dry eye syndrome and various other ocular surface disorders. In a cross-over study, severe DED patients were randomized to receive 3 months of treatment with autologous serum eye drops 50% and 3 months with conventional therapy, and vice versa; symptoms and impression cytology of conjunctival epithelial cells improved significantly after treatment with autologous serum tears.[5-7] While systematic reviews and meta-analyses of randomized controlled trials (RCTs) indicate some benefits for patients with DED compared to artificial tears, further large-scale RCTs are warranted to validate these findings.[8]

Platelet Rich Plasma Eye Drops

Autologous platelet rich plasma (PRP) eye drops have been shown to be beneficial in various ocular surface disorders, including severe DED, neuropathic ulcers, LASIK-induced dry eye, recurrent corneal erosions, acute corneal chemical injury, and persistent epithelial defects.[9-13] Platelets play an important role in tissue regeneration and wound healing.[14] Metheetrairut *et al* have shown that PRP contains higher concentration of epitheliotropic factors like fibronectin, transforming growth factor-beta1(TGF- β1) and epidermal growth factor in PRP eye drops when compared to autologous serum drops.[15]

Recently, a meta-analysis and systematic review concluded that platelet-rich plasma significantly reduces the signs and symptoms of DED. This meta-analysis included 19 studies from different parts of the world including Spain, Italy, Egypt, India, and Columbia. Both evaporative and aqueous tear deficient dry eye were treated with PRP eye drops and improvement in tear quality, tear quantity and corneal staining, along with symptomatic improvement, was noted.[16]

Plasma Rich in Growth Factors (PRGF) Eye Drops

Plasma rich in growth factors has also been used for the treatment of DED. This technology activates the PRP using calcium chloride, which allows the release of biologically active proteins from platelets. In 2007, Rocha *et al* successfully used PRGF eye drops for neurotrophic ulcer following LASIK surgery.[17] Corneal healing with PRGF drops was reported by Lopez-Plandolit *et al.* in patients who were refractory to other medical treatments such as topical corticosteroids, autologous serum drops or amniotic membrane.[18] Successful treatment of rapidly progressive corneal melt with PRGF has also been noted in an isolated case report.[19] PRGF was noted to be effective and safe in refractory DED and neurotrophic keratitis stages 2 and 3 showing poor response to traditional treatments, with improvement in ocular symptomatology and signs of inflammation.[20-22]

Albumin, Fresh Frozen Plasma (FFP) and Heparin Eye Drops

Albumin eye drops can also be used for dry eyes as an alternative to serum eye drops. The compounded drops are available as human albumin 5% infusion solution.[23] Unlike autologous blood drops, these drops do not require individual extraction or centrifugation. Serum albumin is abundantly present in human serum and carries many physiologic roles. In therapeutic models, it has shown to rescue epithelial cells from apoptosis in dry eyes.[24] A clinical study conducted by Seki *et al.* showed statistically significant improvement in symptoms of keratoconjunctivitis sicca with the use of human albumin eye drops. The human albumin drops were well tolerated in 95% of the patients in their study with no adverse reactions.[25] Both FFP and heparin are used topically in treating ligneous conjunctivitis.[26,27]

Amniotic Membrane Extract Eye Drops (AMEED)

Similar to cryopreserved amniotic membrane, amniotic membrane extract also contains a high concentration of growth factors and inhibitory proteases that prevent inflammation, scarring, and angiogenesis.[28] AMEED can be prepared by different methods yielding different concentrations of bioactive components.[29] Studies conducted by

Perez *et al.* and Sabater-Cruz *et al.* show promising results in severe ocular surface pathologies including limbal stem cell deficiency, neuropathic ulcer, and DED.[30,31]

Vitamin A

Limited clinical evidence exists in the literature on the efficacy of topical Vitamin A. Kim *et al.* compared the efficacy of Vitamin A and cyclosporine A 0.05% eye drops in DED and found both treatments to be effective.[32] Another study compared Vitamin A to placebo and found Vitamin A ophthalmic solution (500 IU/mL) was safe and effective for the treatment of patients with dry eye.[33] The role of Vitamin A has also been studied in corneal healing. A study by Chelala *et al.* concluded that Vitamin A eye ointment did not affect re-epithelialization time, postoperative pain, corneal haze formation, or visual outcomes following PRK.[34]

Vitamin B

No direct study has evaluated the role of Vitamin B12 supplementation to treat neuropathic pain. However, Ozen *et al.* did find that Vitamin B12 deficiency was related to neuropathic ocular pain in DED patients.[35]

Compounded Testosterone, Lactoferrin and Selenoprotein P

There is limited evidence in the literature to support the benefits of topical testosterone in improving the quality of meibum in patients with meibomian gland disease.[36] Clinical evidence is limited for use of oral lactoferrin and selenoprotein P in DED.[37,38]

Omega-3 Fatty Acid Supplementation

Oral omega-3 fatty acids, often derived from fish oil, have become quite popular as a nutritional supplement in patients with dry eye. There are different formulations available, with a particular focus on the ratio of docosahexaenoic acid (DHA) to eicosapentaenoic acid (EPA). A large, multicentre, prospective, and double-masked clinical trial (DREAM study) was conducted to assess the efficacy and safety of 3000 mg of oral omega-3 fatty acid supplementation (2000 mg EPA, 1000 mg DHA) vs olive oil (1000 mg) as placebo for the treatment of dry eye, and did not show any difference in either of the groups.[39] We believe olive oil may not have been the best choice for a placebo as polyphenols found in the olive oil can reduce the risk of cardiovascular diseases, and omega-9 oleic acid is an anti-inflammatory agent.[40] An updated systematic review and meta-analysis indicates that omega-3 supplementation helps in improving the symptoms of DED. In contrast to the DREAM study, this review included studies with other sources of omega-3 such as krill and flaxseed oil. Also, the placebo included wheat germ oil, safflower oil and sunflower oil in addition to olive oil.[41] In addition, to reduce the risk of coronary vascular disease, the American Heart Association recommends a daily intake of 3 grams of omega-3 fatty acids in healthy adults and 1 gram in patients with documented coronary heart disease.[42]

Cataracts and Nutritional Supplements

Many recent RCTs that have studied the role of nutritional supplements show no significant results in preventing or halting cataract development.[43-46]

Glaucoma and Nutritional Supplements

Although there is much evidence supporting the role of oxidative stress in glaucoma, the meta-analysis done by Ramdass *et al.* did not show strong evidence to support the role of nutritional supplements in preventing glaucoma.[47]

Vitamin D

The association of Vitamin D with anterior segment disorders have been explored. It has been noted that patients with DED and keratoconus have lower levels of Vitamin D.[48-50] Although the evidence is still a work in progress, Gorimanipalli *et al.* offer valuable insights into the existing evidence and practical guidelines for incorporating Vitamin D into the management of keratoconus and dry eyes.[51]

Conclusion

The focus of this paper was to review the current evidence for nutritional supplementation in the management of anterior segment diseases. Our conclusions are that, while there is evidence suggesting a role for nutritional supplements in managing anterior segment disorders of the eye, especially for DED, further research is warranted to solidify these findings. Studies with larger sample sizes and more prospective, double-blinded RCTs are essential to enhance the evidence base and provide clearer guidance for healthcare professionals and patients alike. As our understanding of the relationship between nutrition and eye health continues to evolve, continued investigation into the efficacy and

safety of nutritional supplements will be crucial in optimizing treatment strategies and improving outcomes for individuals affected by anterior segment disorders.

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