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Review Article

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Hypertrophy of the Eye Focusing Ciliary Muscle in Glaucoma and Beneficial Effect of Nitric Oxide

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Abstract
Biophysical and biochemical factors influence progression of myopia and glaucoma. Such factors include degree and duration of controlled eye focusing, and metabolism that sustains muscular contraction. Autonomic innervations regulate contractile tissue, adjusting the rate of aqueous outflow. Individual variations are compounded by instrument and examiner factors, all of which alter repeatability of measured intra-ocular pressure. Drainage of aqueous humor via the alternate, uveo-scleral pathway appears to be amenable to agents such as nitric oxide. The modality by which nitric oxide exerts a beneficial effect is by increasing inter-fiber spacing within the ciliary muscle, reducing density, so aqueous can leave the anterior chamber and permeate into venous circulation. It is hoped that future case-control clinical research studies shall deploy dietary and topical agents to reduce ciliary muscle hypertrophy, soon after a suspected diagnosis. Until then, eye doctors are encouraged to assess near focusing stress and prescribe optical compensatory lenses in accordance with accommodative demand, with under-correction of myopia for patients that do not drive moving vehicles. Ultrasound imaging studies of ciliary muscle for various stages of glaucoma appear to be warranted.

Keywords: Accommodation, Aqueous, Myopia, Outflow, Nitrate, Pressure

1. Introduction

Clinical measurements of internal fluid pressure are universally considered a primary method for helping to manage eyes diagnosed with glaucoma. Elevated intra-ocular pressure (IOP) is managed by topical eye-drops, by systemic diuretic agents, by Laser ablation, and by surgical implants. Pressure elevation has been attributed to pigment dispersion and age-related changes in the conventional "trabecular" drainage pathway, located at the edge of the posterior cornea adjacent to the peripheral iris. A secondary route by which aqueous fluid exits the eyeball is via inter-fiber spaces of the "ciliary" muscle. Sustained contraction of this "eye focusing" muscle can reduce the volume of fluid that exits the eye per unit time, leading to elevated IOP. Nitric oxide (NO) is a powerful mediator of muscle relaxation, and amino acid such as L-arginine is known to make NO physiologically accessible [1,2]. To date, studies deploying oral nutrition supplements that promote ciliary muscle relaxation, as a supportive therapy for glaucoma, have not been published. The main objective of this review is to encapsulate information on the internal eye-focusing muscle, alongside nitric-oxide, myopia, and glaucoma, so university-clinic sponsored case-control studies, similar to ones that have been conducted for dietary interventions in gastric infection, and immune dysfunction, might be planned and executed [3,4].

2. Relevant Aspects of Optometry and Ophthalmology

The traditional mandate of optometry: Testing and compensating for errors of refraction, has been attempted even for the poorest at a world-wide scale [5]. This is thanks to the efforts of the various councils and colleges serving the profession, and to social entrepreneurship: A tradition that goes back many years to the origins of the nursing profession [6-8]. However, full correction of myopia tends to increase habitual ciliary muscle contraction for intermediate distances and for near objects, so thereby myopia and glaucoma are often found in the same eye and can be hard to distinguish [9].

Management of glaucoma brings challenges not just for optometry,[10] but also for ophthalmology [10,11]. Treatment for glaucoma prior to the 1990's was the sole responsibility of ophthalmologists. However, optometrists as primary eye-care providers in private practice today, especially in the USA, are able to use advanced technology and methods in service of their patients, including eye-drops to lower IOP. Viewing distance, stress factors such as photophobia, and auto-immune dry eye, are frequently evaluated by optometrists. However, attacks of acute glaucoma are better served by ophthalmologists, especially those who are able to administer "parenteral" intra-venous viscous fluid (mannitol) drip, and those able to perform Laser ablation surgery to anterior pigmented anatomical structures (e.g. peripheral iridotomy and trabeculoplasty).

3. Accommodation, Ciliary Muscle and Aqueous Outflow

Hypertrophy of the ciliary muscle has been described as reducing fluid outflow via inter-fiber spaces of the ciliary muscle [12-15]. Ciliary muscle thickness increases with near accommodation contraction, and decreases on far focusing relaxation [16]. Post-accommodation anatomical parameters demonstrate hysteresis effects, with a delayed return to original dimensions [17-19]. Ocular indentation also exhibits hysteresis effects, and various methods for tonometric measurement of eye pressure are currently used in eye clinics [20,21]. Habitual, sustained near focusing accommodation can predispose to development of myopia, and this could perhaps be mitigated by environmental exposure to broad spectrum daylight and outdoor activity [22]. During near accommodation, ciliary muscle thickness increases notably more in myopic eyes compared with emmetropic eyes [23]. Further, myopic eyes tolerate a greater "lag" of accommodation,[24] and exhibit reduced ciliary muscle movement [24,25]. On the brighter side, transient near focusing increases the surface area of Schlemm's canal and this is posited to improve aqueous outflow in children, with diminishing rewards for adults [26].

4. Focusing Effort and Autonomic Nervous Contro

In the eyes of young children, accommodation comes easily because the crystalline lens is pliable. As the lens grows with age, more and more muscular effort is required to meet the same near focusing demand, and the required muscular contraction force upon the tensile lens fibers at age 45 is many times greater, for the same focusing stimulus demand, than at age 15 [27]. Adverse effects on the person depend upon the combination of time spent and exerted lens power, termed as "diopter-hours," by Lane, now common parlance in myopia research [28-30]. Dietary factors might predispose to myopia and elevated IOP, in part from deficits of "energy-donor molecules" that are needed to sustain muscular metabolic function [31,32].

Changes in diameter of the eye pupil are mediated by light levels and by near focusing efforts. Autonomic nervous control of the pupil and accommodation, includes adrenergic (sympathetic) and cholinergic (parasympathetic) neurobiology that also regulates aqueous production and drainage [33]. Extensive observations on Adie's (tonic) pupil suggest that 90 percent of patients display impaired muscle stretch reflexes of the arms (triceps) and legs (ankles), and more than half are unable to maintain steady ciliary muscle tone for accurate focusing [34]. Causal factors include auto-immune neuropathic inflammation manifesting similarities with Sjogren's dry-eye and dry-mouth syndrome [35,36]. Unilateral ocular and facial pain with or without glaucoma can be an early sign of herpes zoster of the head [37]. Although grossly underreported, a viral etiology for chronic glaucoma is the subject of a recent review [38].

5. Eye-Related Nitric Oxide Physiology

Pharmaceutical companies are presently about to launch eye-drops that would lower intra-ocular aqueous fluid pressure by a nitric-oxide donor physiology [39,40]. As with any therapeutic modality, there needs to be adequate justification: With evidence in support of safety and efficacy [41,42]. Levels of nitrate ions, as tested in porcine tissue, are highly concentrated in the cornea and lacrimal glands, and once secreted into ocular surface tears, nitrate ions can be converted (with the aid of a reducing agent) into nitric oxide. Increased dietary intake of nitrates should reduce risk for primary open-angle glaucoma, and perhaps also deter macular degeneration [43-45].

Myopia and glaucoma have long been known to be connected physiologically and nitric-oxide mediated relaxation of the ciliary muscle is purported to slow myopic progression,[46] and improve uveo-scleral outflow of aqueous through the body of the ciliary muscle [46,47]. Muscle relaxation by NO is mediated biochemically through elevation of messenger molecule cyclic GMP, and by other ionic mechanisms [48,49]. Cyclic GMP activates intracellular protein kinase in response to binding of peptide hormones to the external cell membrane culminating in a decline of intracellular calcium ion concentrations and reduced contractile response from remaining calcium ions [50].

6. Amino Acid L-Arginine

Nitric oxide relaxes a hypertrophic ciliary muscle and allows aqueous to infiltrate and exit through the ciliary body out into venous circulation. Dietary proteins with high concentrations of amino acid L-Arginine would probably support muscle relaxation, by the same physiology. In young volunteers, oral supplementation with 125 mg L-homoarginine taken once daily, raised blood plasma levels 7-fold after 4 weeks with no adverse effects [51]. Importance of understanding downstream effects of orally administered nutrient supplements from intestinal absorption to the liver to the circulatory system and tissue is not to be understated [52]. In the absence of long-term safety data, it is probably wise to limit oral L-arginine (capsules) to a daily intake less than 1,500 mg (for an adult of 175 lbs).

Topical eye-drop pharmacology studies in rabbits, of L-arginine combined with other agents, have demonstrated notable IOP decrements, and such combinations might be safer than the best clinical options we have today [53, 54].

Patients suspected to have glaucoma can be evaluated by ultrasound to quantify ciliary muscle hypertrophy, but less invasive infrared methods are needed [55].

7. Concluding Remarks

It is hoped that the present review helps toward initiation of pilot studies in normal and glaucoma patients, for development of safe and effective dosages of oral nutrient supplements such as nitric- oxide donor molecule, L-arginine, and any other agents that are posited to relax a hypertrophic ciliary muscle. Teenage children should be taught regimens to relax their ocular focus and to habitually use larger text fonts and larger electronic display technology, held between 12 and 18 inches (30 cm to 45 cm) from the eye. Persons age 25 to 40 might be prescribed "plus addition" corrective lenses for extended hours of near focusing, despite normal amplitude of accommodation. Patients suspected to have glaucoma could be evaluated by ultrasound to quantify ciliary muscle hypertrophy.

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