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A novel approach to health care?

Paul B. Freeman, O.D.

May has been designated “Older Americans Month.” Established in 1963, the purpose of this designation was to “acknowledge the contributions of past and current older persons to our country, in particular those who defended our country.”1 I would submit that the contributions of many older Americans will continue to fashion the fabric of America, even into the future. As optometrists, to support the goal of helping older Americans continue to be visually viable, we need to redefine our efforts at listening to our seniors, and then addressing their needs.

Interestingly, in any conversation about senior eye care, the question usually comes up, “What is so different about evaluating a senior other than, say, evaluating someone who is middle-aged?” Other than finding the obvious normal aging vision changes, as well as the potential increased likelihood of ocular pathology, such as cataracts or macular degeneration, the difference oftentimes lies in the ability to communicate effectively.

Although listening to our patients seems obvious, consider some basic characteristics of doing so carefully. Encourage older patients to talk, and be prepared to really listen to what they have to say. In one of my recent editorials, I mentioned the distinction between asking “How are you doing?” vs. a more specific question like “How is your reading?”2 Asking specific questions is more likely to elicit more well defined concerns which we can address. But, be prepared to really listen to the response, as it is sometimes necessary to read between the lines. Sometimes patients will equate functional improvement with the expectation of being as visually vibrant as they were years before, or as sometimes said, “visually normal.”

After clarifying the needs or problems a patient may have, it may be helpful to modify the pace or extent of the examination; with young patients the pace might need to be slowed down a bit (and sometimes abbreviated), with the patient directing the pace. Then, once the exam is complete, we must use whatever we have in our armamentarium to address the patient’s needs, including lenses, prisms, contact lenses, vision therapy, low vision rehabilitation, nutritional counseling, lighting and glare control, etc., or to treat those pathologies that are within our scope of practice, and, when necessary, make the appropriate referral for those medical and/or functional interventions that we as individual practitioners do not perform. Care for seniors should all be done without using age as a limiting criterion for treatment.

One consistent source of positive feedback that anyone who works with seniors receives is based on actually talking to the senior patient, rather than initially to a family member, spouse or caregiver, who might have accompanied the patient (although they, too, typically have an opportunity to “share” information once the patient’s concerns are addressed). It should not be assumed that aging and the inability to understand or respond go hand in hand. That said, however, we should be cognizant that “… even when neurological disease is not present there is a progressive and gradual loss of some intellectual functions that become evident starting from the seventh or eight decade of life and increasingly evident after the ninth decade.”3 With more recent information that suggests that “cognitive decline is already evident in middle age (age 45-49),”4 it should make the doctor, in the patient-centered interaction, more acutely aware of how best to address the concerns and questions of the patient. Recognizing this apparent fact will go a long way to helping a senior patient understand what the evaluation is about, what options there are to solve the patient’s chief complaint, and in helping the patient understand the importance of compliance of treatment options. This type of care in the larger medical arena has recently been defined as “Patient-Centered Medicine,” and is carried out by “focusing on the individual patient’s needs and concerns, rather than the doctor’s….”5 What a novel approach: listening to the patient!

Optometrists, by and large, have always embraced the notion of listening to patients and spending time trying to sort out their visual needs; now there is actually a term for that. Recognizing the importance of attending to the visual needs for seniors is not new and was, I believe, helpful in our gaining Medicare parity, for as Congressman Claude Pepper (D-FL), commented on HR 3009 and 3010 in 1984, “Vision is the single most important sense upon which the nation’s elderly depend. Certainly its deterioration or loss dramatically reduces the quality of life and seriously threatens the ability of the aged to function independently.” Who better than optometrists to support the vitality of seniors?

In time, we will each be someone’s patient. As we age, the odds of that happening go up considerably. The question we must ask ourselves is “do we want our care to be patient-centered or doctor-centered?” And then, remember the Golden Rule….

References
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Trends in the use of diagnostic glaucoma testing were evaluated for patients with open angle glaucoma (OAG) and for glaucoma suspects. Ancillary glaucoma tests included the use of visual field (VF), fundus photography (FP), and other ocular imaging (OOI). Confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography were considered OOI.

Between 2001 and 2009 169,917 subjects with OAG and 395,721 glaucoma suspects over age 40 years were reviewed. The mean subject age was 55.1 years; 79.4% of subjects were white, 10.7% black, 6.2% Latino, 2.8% Asian, and 53.6% were female.

The use ofVF testing in subjects with OAG decreased over time, reaching a 44% decrease by 2009. Contrary to this, there was a significant increase of 147% in the use of OOI by 2009. The use of FP showed a smaller, more stable increase of 8%. Initially in 2001, optometrists and ophthalmologists were similar in VF testing for OAG (66% and 65% respectively), but by 2009 optometrists were less likely to perform VF (44%) compared to ophthalmologist (51%).

For glaucoma suspects, the trend was an overall decrease in VF testing for optometrist (57% in 2001 decreased to 24%, 2009) and ophthalmologist (50% decreased to 28%, 2001 to 2009). For OOI, optometrist’s were initially less likely to perform them, but by 2009 trends were similar for both optometrist (47%) and ophthalmologist (46%). The overall increased trend to perform OOI was significantly higher for optometrist (153% increase) compared to ophthalmologist (100% increase). FP saw minor changes over time, but optometrists demonstrated an increased probability to perform FP.

Overall optometrist and ophthalmologist demonstrated increased use of OOI and decreased use of VF testing in OAG and glaucoma suspects. By 2008, the probability of using OOI had increased to nearly the same for VF for ophthalmologist, but for optometrist, OOI use had exceeded that of VF. The authors express concern that OOI may be utilized as replacement, and not adjunct testing for glaucoma patients. They propose this may be due to the quick, easy technique of OOI, the objective test methods, and the increased patient comfort and preference as compared to VF and FP.

The authors suggest that if these trends of relying on OOI instead of VF continue, the following OOI limitations need to be addressed: current normative databases often do not include a diverse race and ethnicity representation; tilted discs, moderate to high myopia, small or large optic nerve head are challenging to image with OOI; software used to detect and quantify progression over time needs more research and validation; the quick turnaround of newer equipment models must be compatible to older models so patients can be monitored over time; and the high cost of OOI may limit availability to providers of lower income, racial minorities, and other high-risk groups that may not have adequate funding.

Khadija Shahid, O.D.
Ocular Contusion with Microhyphema and Commotio Retinae

Melissa Misko, O.D.

Abstract

**Background:** Blunt force trauma can affect all structures in the eye, frequently causing complications such as hyphema or microhyphema. A hyphema is defined as bleeding in the anterior chamber that layers and forms a visible clot. A microhyphema occurs when the red blood cells are suspended in the anterior chamber, and do not form a layered clot. Microhyphema is a rarely reported, visually significant complication. Ocular trauma is the second most common cause of visual impairment, and appropriate management must be executed swiftly and efficiently to maximize a patient’s visual potential.

**Case Report:** A 21-year-old Indian male presented after ocular contusion to the right eye. His visual acuity was reduced at initial presentation. Pertinent clinical findings included red blood cells in the anterior chamber and ecchymosis of the orbital adnexa, with associated conjunctival injection. Subsequently, the patient developed commotio retinae.

**Conclusion:** It is important for clinicians to take a detailed case history of the event, perform a thorough ocular exam, select proper treatment/therapy, monitor the patient closely, and make appropriate referrals as needed. This case report discusses the clinical findings, treatment, and management of 1 patient with an ocular contusion resulting in microhyphema and commotio retinae.

**Introduction**

With approximately 2.4 million eye injuries recorded per year in the United States, ocular trauma is second only to cataracts as the most common cause of visual impairment. According to the United States Eye Injury Registry (2000), eye injuries are the leading cause of monocular visual impairment. Most injuries occur at home (34-40%), and 13-15% are sports related,1-3 with the more significant ocular complications resulting from smaller, faster projectile sports (paintball, racquetball, hockey, baseball).4,5 Males are affected significantly more than females, with a reported incidence of 60-80%.1,3,5-8 Age also appears to be a risk factor, with ocular trauma impacting persons most frequently in late adolescence/early adulthood (median = 26 years1) and persons over age 70.5.

Acute complications of ocular trauma include hyphema, commotio retinae, retinal tears/breaks, and vitreous hemorrhages. While not frequently encountered, hyphemas occur in up to 33% of blunt trauma cases1-2 and may present as a macroscopic hyphema or microscopic hyphema. Due to the self-limiting nature of commotio retinae, frequency of occurrence is not well reported.

**Case Report**

A 21-year-old Indian male presented for an emergency ocular examination following blunt trauma to the eye while playing racquetball. He reported being hit by the ball in the right eye, approximately 1 hour prior, with resulting pain, decreased vision, nausea and dizziness. The patient subsequently vomited during the exam. No eye protection was being worn at the time of injury, although he was wearing disposable Biomedics® toric soft contact lenses. His ocular history was negative for any other ocular trauma or surgery; however, he had a history of physiologic anisocoria OD>OS. His medical history was unremarkable and he denied any current medications, ocular or systemic. He did report a positive sulfa drug allergy, and a family history of diabetes. The patient was a non-smoker and denied alcohol, recreational or IV drug use. He was oriented to time, place, and person.

At the time of presentation, the patient’s uncorrected visual acuity was hand motion at 2 feet OD. Pinhole acuity at distance was 20/200 OD. The patient reported that his contact lens was lost during the injury. Corrected visual acuity at distance OS was 20/20. Pupils were unequal in size (OD>OS) and unequal in reactivity to light (OS>OD), although no afferent pupil defect was noted in either eye. The patient reported confrontation fields were blurry, but he could identify hand motion in all quadrants OD. The peripheral visual fields were full to finger count OS. Extraocular muscles were unrestricted in all gazes with no pain OU. Slit lamp examination OD revealed 2+ ecchymosis, chemosis, and edema of the upper lid,1+ ecchymosis, chemosis and edema of the lower lid, intact conjunctiva with 3+ injection, intact and clear cornea, dense and diffuse 4+ red and white blood cells in the anterior chamber (see Figure 1), flat iris with no apparent tear, and 4/4 anterior chamber angles by Van Herrick estimation. Lids, lashes, conjunctiva, cornea, anterior chamber, and iris were clear OS, and anterior chamber angles were 4/4 by Van Herrick estimation OS. Intraocular pressures were 9 mm Hg OD and 15 mm Hg OS with Goldmann applanation tonometry. Dilated evaluation OD revealed a clear lens, but fundoscopy was challenging due to a hazy media. The optic nerve was pink and distinct with a cup-to-disc ratio of 0.7 round. No pallor or edema could be appreciated. Retinal vessels appeared normal with an arterial-venous ratio of 2/3. The macula was positive for a foveal reflex, with no apparent elevation. No cells or blood were noted in the vitreous. The peripheral retina was negative for any apparent hemorrhages, tears, breaks, or holes 360° OD.
Evaluation of the posterior segment OS was unremarkable for signs of trauma. The disc was flat, pink and distinct, with a cup-to-disc ratio of 0.7 round, macula was clear and flat, with a positive foveal reflex, retinal vessels were normal with an arterial-venous ratio of 2/3, lens was clear, and the vitreous and peripheral retina were clear.

Based on the exam findings, the patient was diagnosed with a microhyphema OD secondary to a contusion. He was educated on the self-limiting condition, the long-term complications associated with ocular trauma (such as cataracts, glaucoma, and retinal detachment), the importance of follow-up and future eye care, and the importance of eye protection during sports. The patient was also strongly advised to limit activity, and to discontinue vigorous activity to decrease the risk of further bleeding. Avoiding aspirin and other nonsteroidal anti-inflammatory medications was also discussed to decrease the risk of further bleeding. The patient was educated that a rebleed can carry serious complications including reduced vision, corneal staining, increased ocular pressure, and the need for a surgical intervention. It was recommended that the patient monitor his vision, as a decrease in vision can indicate a rebleed, and that he should keep all follow-up appointments.

Further instructions were given to discontinue contact lens wear until otherwise notified, to keep his head elevated at a 30-45 degree angle while sleeping, and to use cool compresses OD as needed to minimize ecchymosis and edema. The patient was given a sample of OmnipredTM 1% (prednisolone acetate, Alcon) ophthalmic suspension to use one drop every 3 hours OD and homatropine 5% ophthalmic solution 1 drop 2 times per day in OD. The patient was advised to follow up the next day or to contact the doctor on call sooner if vision decreased, pain increased, or if he experienced flashes or floaters.

The following day, the patient returned for follow up. His visual acuity had improved to 20/25+ OD. Anterior segment examination was stable from the previous day, with intraocular pressures measuring 8 mm Hg OD and 16 mm Hg OS. Fundoscopy revealed an area of commotio retinae nasal to the disc (see Figures 2 & 3). The macula was positive for a foveal reflex and a 1.5 DD area of Berlin’s edema extending inferior nasally (see Figure 3). No cells or blood were observed in the vitreous. The peripheral retina was negative for any apparent hemorrhages, tears, breaks, or holes 360° OD; however 2 areas of commotio retinae were noted inferior temporal (see Figure 4) and superior nasal (see Figure 5). Spectral Domain Optical Coherence Tomography (OCT) supported a diagnosis of Berlin’s edema showing areas of hyper-reflectivity in the outer segments of the photoreceptors (see Figure 6).

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**Figure 1** Photograph illustrating the author’s hazy view of the anterior chamber OD. Details of the iris are obscured secondary to suspended red blood cells in the anterior chamber.

**Figure 2** Posterior segment photograph of commotio retinae nasal to the optic nerve OD.

**Figure 3** Posterior segment photograph of commotio retinae nasal to the optic nerve OD and Berlin’s edema (commotio retinae of the macula) OD.

A diagnosis of commotio retinae (including Berlin’s edema) secondary to an ocular contusion OD was added to the patient’s original diagnosis of microhyphema. The patient was instructed to continue to keep his head elevated at a 30-45
degree angle while sleeping, to use cool compresses OD as needed, to minimize vigorous activity, to avoid aspirin or other nonsteroidal anti-inflammatory medications, and to continue current ophthalmic medications (OmnipredTM 1% ophthalmic suspension 1 drop every 3 hours OD and homatropine 5% ophthalmic solution 1 drop 2 times per day OD). The patient was advised to follow up the next day or sooner if vision decreased, pain increased, or if he experienced flashes or floaters.

The patient was seen every 1-2 days over the course of the next week. During that time, the commotio retinae resolved; however, the microhyphema persisted for an additional 2 weeks. The patient was followed thereafter every 3-4 days. Homatropine was discontinued after the first week. The patient was slowly tapered off of the steroid after resolution of the microhyphema. A taper schedule of qid x 4 days, bid x 2 days, qd x 2 days was utilized. At 2 weeks and 4 days after the initial injury, the patient had discontinued all topical medications, and all injuries had resolved without complication. He was approved to resume contact lens wear. Final visual acuity after complete resolution was 20/20 OD.

Discussion

Ocular trauma can be divided into closed globe injuries and open globe injuries. Open globe injuries are those with a full thickness wound in the eye wall (cornea and sclera) such as lacerations, or ruptures. Closed globe injuries include contusions, superficial foreign bodies, and partial thickness wounds (for example, a lamellar laceration), with blunt trauma (contusions) accounting for 40% of ocular traumas. Damage from blunt trauma is caused by three mechanisms: coup, contre-coup, and ocular compression. The coup mechanism is defined as trauma directly at the site of injury. Contre-coup refers to injury across from the site of impact or on the opposite side of the eye. For example, the retina is affected by the contre-coup mechanism after an object collides with the eye and shock waves carry the impact posteriorly. Lastly, ocular compression is defined as an initial globe deformation caused by the impact of an object, and a rebound, with an overexpansion before returning to its original shape. Most anterior segment injuries are a result of the coup and compression mechanisms including orbital fractures, lid ecchymosis, conjunctival hemorrhages, corneal abrasions, angle recession, hyphaema, traumatic cataracts, and lens dislocation. Commotio retinae, retinal holes/tears, vitreous hemorrhages, and orbital fractures are among the posterior complications caused by the contre-coup mechanism.

Hyphemas occur in up to 33% of blunt trauma cases and may present as a macroscopic hyphema or microscopic hyphema. A macroscopic hyphema (also known simply as a hyphema) is present when accumulated blood layers in the anterior chamber. This layered clot can often be seen without the use of a microscope, lending to its name as a macroscopic hyphema. There are two methods commonly used to grade a hyphema. One method is based on the volume of blood in the anterior chamber - grade 1 is less than 1/3 of the anterior chamber, grade 2 is between 1/3 and ½ of the anterior chamber, grade 3 is more than 1/2 but less than the entire anterior chamber, grade 4 is the entire anterior chamber, also known as a total or “8 ball” hyphema. The second grading method uses millimeters to measure the height of the blood layer. A microscopic hyphema, or microhyphema, is defined as blood in the anterior chamber that will not layer. A microscope is used to assess the amount of circulating erythrocytes in the anterior chamber and graded in a similar fashion to anterior uveitis: 1+ (5-10 cells/field), 2+ (11-20 cells/field), 3+ (21-30 cells/field), 4+ (>30 cells/field). The source of the erythrocytes suspended in the anterior chamber is damaged tissue. As the eye is indented by the source of trauma, the intraocular pressures rises, and the ocular tissues are stretched equatorially resulting in small tears in the blood vessels of the iris and ciliary body.

Both macroscopic and microscopic hyphemas may present with symptoms similar to traumatic uveitis – including pain, photophobia, and blurry vision. Minimal literature can be found on microhyphemas, so treatment and management is rooted in guidelines for traumatic macroscopic hyphemas. Treatment is designed with 3 goals in mind: to improve patient comfort, to prevent rebleeding, and to monitor for complications including increased intraocular pressure and corneal staining. In most cases, microhyphemas will resolve without further intervention.
cases, patients diagnosed with a hyphema do not need to be hospitalized. Circumstances requiring consideration for hospitalization include children with hyphema, patients presenting with total hyphema, patients who may have issues being compliant with medications and/or guidelines for recovery, increased or uncontrolled IOP, patients with sickle cell, and patients with other ocular injuries or severely decreased vision. It is important to determine whether the patient’s home environment is safe and conducive to healing and whether or not the patient is capable of adhering to the medication and follow-up schedule. Due to the propensity of bleeding complications, blood work should be discussed for patients with a spontaneous hyphema or with a personal or family history of blood dyscrasias (sickle cell disease, leukemia, Von Willebrand’s disease), bleeding disorders (hemophilia), thrombotic disorders, etc.12

To improve patient comfort, a topical mydriatic (atropine, scopolamine) is recommended 1 to 3 times daily to decrease pain, photophobia, and inflammation secondary to ciliary body spasm.5,11 A topical corticosteroid (prednisolone acetate 1%) is also used between 4 times daily to hourly to decrease inflammation. In addition, research supports the use of a topical corticosteroid to reduce the risk of a rebleed.12 Along with the dosage of a mydriatic, bed rest and limited activity (for 3 to 5 days after the initial injury) is recommended to aid healing and decrease the risk of a rebleed.5,11 A rebleed, or secondary hemorrhage, has occurred when examination reveals new blood. For a macrohyphema, this can be observed as a brighter layer of blood over the older, darker clot, or if new, unsettled red blood cells can be detected in the anterior chamber above the settled clot, or simply if the size of the hyphema increases.12 For a microhyphema, an increase in the suspended red blood cells indicates a rebleed. The risk of rebleed is highest 3 to 5 days after the onset of injury.11 Notably, rebleeds are usually much larger than the initial bleed.11

Rebleeds have been reported in up to 38% of traumatic hyphema cases.5 However, the incidence is much lower in microhyphemas, with only 1.9 to 3% of patients experiencing a rebleed, which may indicate that microhyphemas are the result of a less severe injury.11 Regardless of the extent of the initial hyphema, long-term visual prognosis is worse in cases of rebleeds.1,13 Along with bed rest and limited activity, topical and/or oral medications may decrease the risk of a rebleed. Topical cycloplegics are often used to increase patient comfort. However, they may also have the benefit of reducing rebleeds, and possibly delay clearance of the settled clot, or simply if the size of the hyphema increases.12

Rebleeds have been reported in up to 38% of traumatic hyphema cases.5 However, the incidence is much lower in microhyphemas, with only 1.9 to 3% of patients experiencing a rebleed, which may indicate that microhyphemas are the result of a less severe injury.11 Regardless of the extent of the initial hyphema, long-term visual prognosis is worse in cases of rebleeds.1,13 Along with bed rest and limited activity, topical and/or oral medications may decrease the risk of a rebleed. Topical cycloplegics are often used to increase patient comfort. However, they may also have the benefit of reducing rebleeds, especially in patients using aspirin, as shown in one study.12 In other literature, the rate of rebleeds (along with final visual acuity, and rate of clot absorption) was not statistically different between groups using a topical mydriatic, miotic, neither, or both.12 Oral antifibrinolytic medications have been proven to lower the rate of rebleeds, and possibly delay clearance of the hyphema.12,13 Most commonly studied antifibrinolytics are Amicar® (e-aminocaproic acid) and Cylklokapron® (tranexamic acid), however, both medications are off-label for hyphema use.12 Although Amicar has been documented to decrease the rate of rebleeds from 22-33% to 0-4%,12 use of the drug produces unpleasant systemic side effects including nausea, vomiting and diarrhea in 25% of patients, and postural hypotension and dizziness in 6-18%.12,13 Recently, a topical aminocaproic acid preparation has been developed called Caprogel™. In a study of 51 patients by Pieramici. et al, rebleeding occurred in 30% of the untreated group and only 8% of the treated group.13

Patients with microhyphemas or total hyphemas were excluded from the study. Patients reported less systemic side effects with the topical preparation as compared to oral antifibrinolytic agents. Patients also noted minimal ocular irritation. However further research is needed as the study was terminated due to recruitment problems.

In the absence of a secondary hemorrhage, light activity can usually be resumed 2 weeks after the trauma.11 Along with limiting activity, patients should also be instructed to discontinue use of aspirin, NSAIDs, and other blood thinners (e.g. Coumadin®), wear an eye shield while sleeping, and keep the head elevated approximately 30 degrees above the horizontal.6,12 The importance of continued follow-up should be stressed to the patient. A gonioscopy exam and dilated fundus exam with scleral depression should be performed after resolution of the microhyphema or hyphema or within 2-6 weeks of injury. To reduce the risk of a rebleed, neither should be completed within 2 weeks of the original injury, unless hypotony or elevated IOP necessitates otherwise.1,11,12

The third goal of treatment is to prevent increased intraocular pressure and corneal staining. Acute intraocular pressure increases or spikes occur due to fibrin, red blood cells, and/or platelets that become lodged in the trabecular meshwork.11 In a patient without sickle cell disease or trait, beta blockers, alpha agonists, and carbonic anhydrase inhibitors are all adequate topical therapy options. Since mydriasis has been shown to be beneficial, miotics should be avoided in all (both non-sickle cell and sickle cell) patients as a pressure lowering option. The literature is divided on the use of prostaglandin analogs, which may increase inflammation and should be used with caution.5,14 Carbonic anhydrase inhibitors are contraindicated in sickle cell patients as they lower oxygen tension in the anterior chamber and lead to red blood cell sickling, causing further trabecular meshwork deposition and decreased aqueous outflow.5 Corneal staining (endothelial toxicity) in combination with elevated IOP can result in blood breakdown products entering the stroma. Because corneal staining is more common in hyphema patients with rebleeds or periods of elevated IOP, these patients should be monitored closely.12 Cornical blood staining, which causes decreased visual acuity, occurs in approximately 2-11% of hyphema patients, with the incidence rising to 33-100% in total hyphema cases.12 A daily slit lamp examination is needed to detect early corneal staining, seen as a light yellowing of the deep stroma. Surgical intervention should be considered at this point to prevent gross blood staining, which causes decreased vision, and can take 4-6 months to resolve. This period of decreased vision is an even greater concern in younger patients as the risk for deprivation amblyopia increases.12 Surgical intervention (irrigation, vitrectomy, trabeculectomy) to remove the clot should be considered when one of the following criteria has been met: IOP ≥ 60 mm Hg for 48 hours with max medical therapy in a non-sickle cell patient (due to risk of optic atrophy/central retinal artery occlusion (CRAO)), IOP ≥ 50 mm Hg for 4 days with max medical therapy in a non-sickle cell patient (due to risk of optic atrophy/CRAO), IOP ≥ 24 mm Hg during the first 24 hours or repeated IOP spikes of ≥ 30 mm Hg in a sickle cell patient (due to risk of optic atrophy/CRAO), total hyphema with IOP ≥ 25 mm Hg for 5 days (due to risk of corneal blood staining), or hyphema ≥ 50% with IOP ≥ 25 mm Hg for ≥ 6 days (due to risk of corneal blood staining), hyphema ≥ 50% for ≥ 8 days (due to risk of synechia formation).12
Commotio retinae, an acute, self-resolving retinal opacification, can occur minutes to hours after a blunt trauma. Some literature reports the mid-peripheral retina is the most commonly affected area, and the macula the least affected. Others argue that the area surrounding the optic disc and macula are most susceptible areas secondary to their perpendicular nature to the original insult. Regardless of the area affected, commotio retinae is the most common retinal sign of an ocular contusion.

Commotio retinae of the macula is called Berlin’s edema. Berlin first described this post-traumatic retinal whitening in 1873, hypothesizing that the retinal whitening was a result of extracellular edema. However, we have since learned that there is no actual extracellular or intracellular edema in commotio retinae. In vivo research has shown that the disruption and disorganization of the outer segments of the photoreceptors, combined with RPE damage, is the true cause of commotio retinae. Flourescein angiography performed 30 minutes after trauma has revealed staining of the retinal pigmented epithelium corresponding to areas of commotio retinae. This further confirms the lack of vessel leakage and edema. Patients presenting for evaluation after an injury may or may not have decreased visual acuity in association with commotio retinae. However, the visual acuity usually recovers quickly. In most cases, the retinal whitening will also resolve without treatment in 4 to 7 days. Retinal pigmented epithelium hyperplasia or atrophy may be left behind.

New advances with optical coherence tomography have illustrated commotio retinae as areas of increased reflectivity in the area of the photoreceptor outer segment. These areas of hyper-reflectivity represent the photoreceptor disorganization. This was demonstrated in our patient's horizontal and vertical macular OCT scans taken at follow-up #1 (see Figure 6). The arrows OD point to the regions of hyper-reflectivity as compared to the well defined alternate layers of coloring, shown by arrows OS.

After a traumatic event to the eye, patients are at risk for several visually devastating delayed complications including traumatic cataracts, glaucoma, and retinal detachments. Traumatic cataracts may develop months to years after the blunt insult, slowly compromising vision. Most commonly, ocular contusions produce anterior or posterior subcapsular cortex spokes or a 'sunflower cataract.' Treatment (surgical removal) relies largely on the level of visual impairment caused by the cataract.

The 6-month incidence of developing post-traumatic glaucoma, as reported by Girkin et al, was 3.39%. The report also went on to associate angle recession with the development of glaucoma. Angle recession is thought to occur when the impact of the trauma compresses the eye, pressing the iris against the lens and consequently forcing trapped aqueous to rupture the ciliary body at its scleral spur insertion. Additionally, angle recession has been found in 70-100% of eyes with a history of hyphema. Glaucoma secondary to angle recession stems from damage sustained by the trabecular meshwork. Over time, scar tissue develops, thus decreasing the aqueous outflow and elevating the intraocular pressure. Literature reports up to 6-9% of patients with angle recession will develop glaucoma, with the risk increasing proportionally to a larger area of recession.

Due to the contre-coup mechanism, and the compression and expansion of the ocular tissues upon impact, the vitreous and retina can be pulled away from the retinal pigmented epithelium.

Figure 6 Optical Coherence Tomography with arrows indicating the regions of hyper-reflectivity representing disorganization of the photoreceptors OD; as compared to the well defined layer of photoreceptors, shown by arrows OS.
resulting in retinal dialysis, retinal tears, and posterior vitreous detachments that evolve to retinal detachments.\textsuperscript{1,5} These complications further emphasize the importance of regular gonioscopy and dilated fundus examinations on patients with a history of blunt trauma.\textsuperscript{5,11}

**Conclusion**

Ocular trauma is the second most common cause of visual impairment and the leading cause of monocular visual impairment.\textsuperscript{1,2} The detrimental visual effects of these accidents could be prevented or minimized with appropriate eye protection. According to the U.S. Department of Health and Human Services, only 39.7\% of adults (18 years and over) used eye protection during sports and other potentially harmful situations in, around, or outside the home in 2008. As primary eye care providers, it is our responsibility to educate patients on the vital need for eye protection.\textsuperscript{20}

Ocular contusions may result in a wide array of complications that can affect both the anterior and posterior segment. This case report discusses the clinical findings, treatment, and management of one patient with an ocular contusion resulting in microhyphema and commotio retinae. Appropriate diagnosis and treatment is essential in managing these patients to prevent visually significant sequelae.

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Corresponding author: Melissa Misko, O.D., 510 NW 84th Ave, Apt 617, Plantation, FL 33324. Email: mm2388@nova.edu.
Central corneal thickness measurements obtained with anterior segment spectral domain optical coherence tomography compared to ultrasound pachymetry in healthy subjects

Lori Vollmer, O.D., Joseph Sowka, O.D., Joseph Pizzimenti, O.D., and Xinha Yu, Ph.D., M.S.

Abstract

**Introduction:** Central corneal thickness (CCT) imparts information about an individual’s risk of conversion to glaucoma from ocular hypertension, progression of established glaucoma, and the likelihood of developing structural and functional abnormalities in patients with ocular hypertension. Most typically, CCT is measured through ultrasound (US) pachymetry. Currently, optical coherence tomography (OCT) has the ability to image the anterior segment, cornea, and anterior chamber angle. With this ability comes the option of determining CCT. The purpose of this study is to ascertain any significant difference in CCT measurement results as well as quantify the reproducibility of measurements of the two technologies. In addition, by measuring CCT both with traditional US pachymetry as well as spectral domain (SD) OCT technology, we sought to determine if CCT measurement by SD-OCT is an accurate, comparable and viable option.

**Methods:** Eighty eyes of forty healthy volunteers were used to determine CCT with both SD-OCT and US pachymetry. Three consecutive measurements were collected with each method on every eye.

**Results:** CCT measurements made by US pachymetry and SD-OCT were similar and consistent \((r=0.99\) for both methods). CCT measurements made by SD-OCT were consistently thinner by approximately 12 micrometers than measurements made by US pachymetry \((p<0.001)\). Repeated measurements of CCT obtained by SD-OCT were more reproducible and had less variability than measurements obtained by US pachymetry. The mean within-subject standard deviation among SD-OCT was significantly smaller than that in US pachymetry \((1.92 \text{ SD-OCT} \text{ vs.}\ 2.04 \text{ US pachymetry}, p=0.036)\).

**Conclusions:** Measurement of CCT by SD-OCT compares favorably with and is at least as accurate as measurements made by US pachymetry. Repeat measurements of CCT by SD-OCT have less variability than those obtained by US pachymetry, are more reproducible, possibly more reliable, and may better represent actual CCT.

**Introduction**

A congenitally thin central cornea has been established as a risk factor for glaucoma. In the Ocular Hypertension Treatment Study (OHTS), it was seen in multivariate analyses that baseline factors predicting conversion to primary open angle glaucoma (POAG) from ocular hypertension included older age, larger vertical cup-disc ratio (C/D), higher intraocular pressure (IOP), greater pattern standard deviation, and thinner central corneal measurement (CCT). Patients in the OHTS with the thinnest CCT measurement who additionally had higher IOP and greater vertical C/D ratio measurement had the greatest conversion to POAG.\(^1\,^2\)

Additionally, studies have also associated thin CCT with increased prevalence of diagnosed glaucoma as well as glaucomatous structural and functional changes. Henderson and associates evaluated patients with ocular hypertension in an attempt to correlate retinal nerve fiber layer thickness as measured by scanning laser polarimetry with CCT measurement and found that patients with thin CCT measurements also had significantly thinner retinal nerve fiber layer measurements compared to those with thicker CCT measurements and normal control patients, thus suggesting a relationship between thin CCT measurements and retinal nerve fiber layer structural abnormalities.\(^3\)

Kim and associates examined a case-control patient population with various forms of open-angle glaucoma and concluded that visual field progression in these patients was significantly associated with thinner CCT.\(^4\) Hong et al studied patients with chronic primary angle-closure glaucoma and found that those with a thinner cornea were at greater risk for visual field progression even if they maintain a low IOP after treatment.\(^5\) Medeiros and associates examined 98 eyes of 98 patients with pre-perimetric glaucomatous optic neuropathy and saw that those patients that did eventually develop repeatable visual field abnormalities during follow-up had a significantly thinner CCT measurement than those that maintained clear visual fields over the study period (mean follow-up time of 4.3 +/- 2.7 years).\(^6\) The Los Angeles Latino Eye Study surveyed a large population of Latinos and discovered that persons with thin CCT had a significantly higher prevalence of open-angle glaucoma than did those with normal or thick CCT at all levels of IOP.\(^7\)

Ultrasound (US) pachymetry is the technology most commonly used in the clinical measurement of CCT and is considered the gold standard in measuring corneal thickness. It utilizes acoustic pulses to locate and measure the corneal layers and interfaces at the location where the speed of sound differs. US pachymetry requires topical anesthetic. Spectral domain optical coherence tomography (SD-OCT) is a non-invasive test that does not require topical anesthetic. It is based on measuring...
the delay of infrared light reflected from the tissue to determine the depth and thickness. SD-OCT produces a cross-sectional “in vivo” visualization of the tissue for which a caliper can be used to determine the thickness of the cornea image. The central cornea can be determined using the reflectivity profile or by marking the center of the pupil. The corneal cross-section is used to place the measurement of the calipers, making it easier to assure that the measurement is located at the central cornea.

There have been previous studies comparing CCT measurement obtained with US pachymetry and OCT. Many of these studies were performed with the time domain (TD) retinal imaging technology rather than the anterior segment spectral domain technology. The difficulties included attempting to image the anterior segment, namely the cornea, with a device primarily designed for retinal imaging as well as the lesser tissue resolution and longer acquisition time associated with time domain imaging. Despite these limitations, it was felt that the CCT measurements obtained with TD-OCT were accurate, reliable, and reproducible and results from each technology were similar, accurate, comparable and reproducible, though not necessarily interchangeable.

Subsequent studies have compared CCT measurements obtained by anterior segment SD-OCT in comparison to measurements obtained by US pachymetry. Similarly, there was strongly agreement in the measurements by the different technologies. In some instances, it was found that the CCT as measured by SD-OCT was thinner than that measured by ultrasound pachymetry. It was felt that while CCT measurements by each technology were accurate and reliable, they should not be considered interchangeable.

A high degree of reproducibility on subsequent testing is likely indicative of reliable results being obtained. There are questions of reproducibility of CCT results obtained by US pachymetry, even by trained observers. Shildkrot and associates examined reproducibility of CCT measurements by trained observers using US pachymetry. In this study CCT was measured by US pachymetry (mean of 15 measurements for each eye) on 2 separate occasions at least 1 month apart. It was seen that measured CCT values differed by more than 20 microns in 20.4% of test subjects and 40 microns in 5.1%. The authors felt that factors affecting CCT measurement by US pachymetry, such as examiner error or true alterations in corneal thickness by the technique, required continued investigation.

Wickham et al evaluated the measurement of CCT by US pachymetry in a cohort of glaucoma patients over a 3-month period. They found that measurements by a trained observer showed fluctuation over the 3-month period, with a mean difference in corneal thickness of 9.6 ± 26.9 microns in the right eye and 19.0 ± 29.2 microns in the left eye, with a bias towards increased corneal thickness being recorded at the second reading in both eyes. They concluded that measurements of CCT taken by US pachymetry within a clinical setting by a trained observer may show significant variability. They had suggested that more than 1 measurement of CCT reading may be required. Failure to do so may result in an inaccurate assignment of risk.

Beyond assessment of risk for glaucoma, accuracy and reproducibility of corneal thickness measurement is especially important for the ongoing evaluation of corneal thinning disorders such as keratoconus and conditions of corneal edema such as disciform keratitis where response to treatment may be contingent on reduction of tissue thickness.

**Methods**

Central corneal thickness measurements in 80 eyes of 40 healthy adult volunteers between the ages of 21-45 were obtained using both US pachymetry (Sonogage Corneo-Gage Plus™, Cleveland, OH) and SD-OCT (Cirrus 4000™, Carl Zeiss Meditec, Dublin, California). Exclusion criteria included contact lens wear within 1 month of testing, history of corneal surgery (including LASIK or any refractive procedure) and any history or identification of corneal disease through examination. All subjects were determined to have normal corneal health by biomicroscopic examination. The appropriate Institutional Review Board approved this study and informed consent form was obtained from each participant before testing.

The sample size was determined based on the average differences of the two methods. Assuming a difference of 20 micrometers is clinically significant with a standard deviation of 10 micrometers, it was estimated that 80 eyes were needed for this study. The sample size gives 80% power at the 0.05 level of significance (2 sided, paired) and also allows the adjustment for co-variables.

Paired repeated measure design was used in this study. For each test subject, the CCT of both eyes was measured using the 2 methods (US pachymetry and SD-OCT) on the same day. In every case SD-OCT was performed first. This was done to remove any possible induction of artifacts by topical anesthesia used in the performance of US pachymetry. Each measurement for each technology was obtained 3 times with the patient repositioned between each measurement. For consistency, 2 investigators conducted all of the measurements (LV for US pachymetry and JP for SD-OCT). Each examiner was blind to the results of the other to eliminate bias. Measurements with each modality were performed according to written guidelines from each manufacturer. For US pachymetry, topical anesthetic was used. For SD-OCT imaging, the corneal center was determined using the center of the pupil and the corneal cross-section used to mark the central cornea. The device’s internal caliper-measuring system was used to determine thickness at this location.

Additionally, as an ancillary test to examine potential inter-observer variation in measuring, 6 individuals were tested by the same investigators with each using both methods. It was seen that the CCT measurements obtained with SD-OCT and US pachymetry methods were comparable, despite which examiner was performing the tests. There were no adverse events noted during the study.

**Statistical Analysis**

The main outcome in this study is the difference in measured CCT results between the 2 methods. Two eyes were measured for each study subject using each method. A preliminary examination found that even though the corneal thickness measurements are highly correlated between 2 eyes for both methods (r=0.99 for both methods), the average difference between the 2 methods were not correlated between two eyes (r=0.25, p=0.12). In addition, when assessing the 2 methods, we did not consider a person as a cluster
variable because the focus of the study is the comparison of 2 measurements matched by eyes. Thus, the unit of analysis was eyes.

The agreement between these 2 methods was assessed using the Bland-Altman plot. That is, the difference between these two methods for each eye was plotted against the average value of these 2 methods. Under the null hypothesis that the 2 methods are equal, the differences should be around zero and no systematic pattern exists.

The reliability as assessed by reproducibility of each method was analyzed by comparing the variation of 3 repeated measures for each method for each eye. The distribution of the within-subject coefficient of variations (WSCV: standard deviation divided by mean for each eye) of the 2 methods was plotted. Because the 2 methods are paired by eyes, a Wald test was used to determine whether the 2 CVs were statistically significantly different.

Furthermore, multivariate analysis was employed to assess the differences of these 2 methods and adjust for co-variables including age, race, sex and laterality. To take into account of matching by eyes, we used a repeated measure model with the eye as the cluster variable (Generalized Estimate Equation population average model, GEE). In the multivariate analysis, the intra-class coefficient in the model for each method is also a measure of reliability. All analyses were done in Stata 11.1 (Stata Inc., College Station, TX) and SAS 9.2 (Proc Mixed) (SAS Inc., Cary, NC).

Table 1 presents the basic characteristics of the study subjects and the univariate analysis of the 2 measurements. The study subjects are young and predominantly white. The mean CCT for US pachymetry is 535.3 micrometers for right eyes and 538.2 micrometers for left eyes, which are thicker than mean SD-OCT measurement of 523.0 micrometers for right eyes and 523.3 micrometers for left eyes, respectively. The unadjusted mean differences between the 2 measures are 12.2 micrometers for right eyes and 14.9 for left eyes, respectively.

Given that the difference between the 2 methods was uncorrelated between 2 eyes, each eye was treated as a separate unit in the following analysis. The distributions of the 2 measures are shown in Figure 1a and 1b. Both measures had symmetric distributions and did not have any outliers.

Figure 2 presents the Bland-Altman plot to examine the agreement between the 2 methods, matched by eyes. It shows that regardless of the actual cornea thickness, the US pachymetric measurements were always thicker than SD-OCT measurements.

Table 1  Characteristics of study subjects.

<table>
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<tr>
<th>Characteristics</th>
<th>OD (micrometers)</th>
<th>OS (micrometers)</th>
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<tr>
<td>Total (N)</td>
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<td>Age (mean, SD)</td>
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<tr>
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<tr>
<td>OS (micrometers)</td>
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<td>523.3</td>
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<tr>
<td>OCT (Mean SD)</td>
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<td>OS (micrometers)</td>
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Figure 1a and 1b  Distributions of OCT and pachymetric measures.

Results

Table 1 presents the basic characteristics of the study subjects and the univariate analysis of the 2 measurements. The study subjects are young and predominantly white. The mean CCT for US pachymetry is 535.3 micrometers for right eyes and 538.2 micrometers for left eyes, which are thicker than mean SD-OCT measurement of 523.0 micrometers for right eyes and 523.3 micrometers for left eyes, respectively. The unadjusted mean differences between the 2 measures are 12.2 micrometers for right eyes and 14.9 for left eyes, respectively.

Figure 2 presents the Bland-Altman plot to examine the agreement between the 2 methods, matched by eyes. It shows that regardless of the actual cornea thickness, the US pachymetric measurements were always thicker than SD-OCT measurements.
On average, the mean difference is 13.9 micrometers (SD: 3.9 micrometers) between US pachymetry and SD-OCT measurements.

Figure 3 shows the comparisons of within-subject coefficient of variations (WSCV) within each eye between the 2 methods to examine the reliability of the 2 measures. The average WSCV for OCT is 0.49% (SD: 0.56%) and 0.45% (SD: 0.50%) for ultrasound pachymetry (p=0.35 for comparison). However, among OCT measures, there are 29 eyes (36%) that had a zero WSCV value for OCT measures suggesting that OCT may be more reliable than pachymetry. In fact, the mean within-subject standard deviation among OCT is significantly smaller than that in pachymetry (1.92 in OCT vs. 2.04 in Pachymetry, p=0.036).

Finally, after controlling for race, age, sex, and laterality in the multivariate GEE analysis results, the average difference between two methods is 12.3 micrometers (95% Confidence Interval: 11.0-13.7, p<0.001). Race, age, and sex were not related to the cornea thickness while left eye has slightly higher value than right eye (mean difference: 2.6 micrometers, p=0.001), possibly due to operational techniques used by examiners.

**Discussion**

Since the realization that thin CCT imparts a greater risk of glaucomatous damage, the determination of CCT has become commonplace in glaucoma management. While measurement of CCT typically has been obtained with US pachymetry due to the ease, accuracy, and low cost of the technology, practitioners are increasingly using other methods to measure CCT. One such method is SD-OCT, which has evolved to a level where anterior segment structures such as the cornea can be easily and accurately imaged. With this enhanced imaging and caliper-based measuring tools within the SD-OCT software, the thickness of the cornea can be easily determined. It is necessary to examine the accuracy and reproducibility of these alternate forms of CCT measurement in order to determine if these measurements are correctly assessing glaucomatous risk. Additionally, conditions that cause corneal thinning, such as keratoconus, as well as corneal thickening, such as disciform keratitis, can possibly be followed more objectively if corneal thickness measurements can be easily obtained with a high degree of accuracy and reproducibility. Currently, SD-OCT is used to quantify effects of anti-angiogenic therapy for macular edema. Similarly, SD-OCT can potentially be used to quantify corneal therapeutic effects in conditions such as disciform keratitis if it can be determined that the measurements of corneal thickness by this technology is accurate, reproducible, and comparable to the current gold standard of US pachymetry.

Leung and associates noted CCT measured by SD-OCT and US pachymetry to be highly correlated. They felt that SD-OCT is a reliable alternative for CCT measurement. Similar to the study results presented here, Prospero Ponce et al found that SD-OCT CCT measurements were reproducible but always thinner than US pachymetry in normal and keratoconus-suspect eyes. Zhao and colleagues also noted that CCT measurements by SD-OCT were thinner than that determined by US pachymetry.

There are several possible explanations for SD-OCT consistently measuring CCT thinner than US pachymetry as well as being more reproducible on repeat measurements. US pachymetry uses a probe held by hand in space. Thus, it is incumbent on the examiner to visually localize the cornea center. Factors such as patient changing fixation, hand movement, and examiner placement of the probe at slightly off-center positions on repeat examination can contribute to higher intra-test variability with US pachymetry. In contrast, SD-OCT has an internal fixation target. Additionally, once the anterior segment has been imaged, it is inherently easier to identify the cornea center for caliper based determination of thickness.

It is critically important when measuring CCT with US pachymetry to touch the probe perpendicular (or as close as possible) to the cornea when obtaining measurements. If the probe is not perfectly perpendicular, there exists the possibility that the off axis position allows for the sound waves to
essentially travel through more corneal tissue, thus giving the false impression of the cornea being thicker than it really is. SD-OCT, by nature of the head and chin rest, positions the patient’s cornea perpendicular to the measuring interferometer. Assuming a normal head position of the patient, the corneal image should better represent the most orthogonal position for measurement. This could explain the consistently lower CCT readings for SD-OCT and that the true CCT is actually better reflected by the measurements obtained by SD-OCT, as pachymetry probe-position artifacts can lead to an overestimation of the true CCT.

The strength of this study is its relatively large sample size as we planned this study based on careful sample size calculation. In addition, homogeneity of subjects (i.e., all are young, and most of them are white) allowed us to focus on the measurement difference. Confounding factors due to age and race were significantly reduced. Furthermore, we also used multivariate GEE analysis to take account of subject and eye differences.

One weakness of our study is the homogeneous subjects. We could not examine the difference due to age, race and other eye conditions. In addition, only 2 investigators were involved in measurements. This was done to ensure consistency in measurements. We were unable to explore variations due to examiners as part of this study, however, a small subset of 6 subjects were tested by the same investigators using both methods, with the results of SD-OCT and US pachymetry methods being comparable, despite which examiner was performing the tests. Future study should specifically address this issue.

Conclusions

To assess glaucomatous risk, it has become increasingly important to measure CCT. Traditionally, this has been done through US pachymetry. However, this technique has been noted to potentially have significant inter- and intra-examiner variation. Such variations could possibly lead to an incorrect assessment of risk. SD-OCT technology has evolved to the point where the anterior segment structures can be imaged. With accurate imaging of the cornea, CCT can be easily determined, potentially without the artifacts that can be induced by hand-held US pachymetry. It has been shown that CCT measurement by SD-OCT is comparable to that measured by US pachymetry, though the results are not necessarily interchangeable, mostly due to SD-OCT measuring thinner.

In our study, the cornea thickness measured by SD-OCT is about 12 micrometers thinner than that obtained with US pachymetry. Both methods are considered reliable; however the reproducibility of repeat measurement is greater with SD-OCT than US pachymetry. This may indicate greater reliability of measurement with SD-OCT. The CCT measurements obtained by SD-OCT were consistently thinner than that obtained with US pachymetry. This may reflect probe-position artifact in US pachymetry leading to an overestimation of CCT. Based upon our results, it appears that CCT obtained by SD-OCT is acceptable to use in glaucoma assessment. The greater reproducibility of repeat measurements also makes SD-OCT a better tool by which to follow other corneal disorders characterized by thinning or thickening, especially when monitoring therapeutic response. Finally, the consistently thinner reading obtained with SD-OCT may better reflect the true corneal thickness as the corneal center is more accurately determined and measurements are being made perpendicular through the minimal amount of corneal tissue.

Disclosure and Acknowledgements

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Corresponding author: Lori Vollmer, O.D., Associate Professor of Optometry, Nova Southeastern University, 3200 S. University Drive, Fort Lauderdale, FL 33328. Email: lvollmer@nova.edu.
Normalization of Retinal Nerve Fiber Layer with Stratus Optical Coherence Tomography after Bilateral Diabetic Papillopathy

Richard J. Zimbalist, O.D.

Abstract

Background: Diabetic papillopathy is a benign optic neuropathy with a favorable predictable visual outcome, found in Type 1 and Type 2 patients with diabetes mellitus. The condition manifests with optic disc edema and minimal optic nerve dysfunction. Previous reports have described several similarities between diabetic papillopathy and non-arteritic anterior ischemic optic neuropathy; however, there are clinical differences that make them unique conditions.

Case Report: A 62 year old Caucasian male with Type 2 diabetes manifested bilateral optic disc edema without visual dysfunction. The patient was diagnosed with diabetic papillopathy after an extensive systemic evaluation which did not reveal any contributory etiologies. The patient was followed with serial retinal nerve fiber layer scans using optical coherence tomography over the course of one year. The optical coherence tomography measurements demonstrate normalization of retinal nerve fiber layer following optic disc edema resolution.

Conclusions: Presented is a case report demonstrated the normalization of retinal nerve fiber layer following bilateral diabetic papillopathy. The use of optical coherence tomography is helpful in both documenting progression and differentiating from similar clinical entities.

Introduction

Diabetic papillopathy (DP) was first described in 1971 as the onset of optic disc edema (ODE) in juvenile Type 1 diabetics without significant visual acuity or field loss. Since its initial description, multiple reports have also documented DP in older Type 2 diabetic patients. There remains discordance amongst clinicians as to whether DP is a distinct entity or an extension of non-arteritic anterior ischemic optic neuropathy (NAION). This report supports DP as a unique and separate condition from NAION based on both clinical resolution and serial nerve fiber layer measurement with Optical Coherence Tomography (Stratus OCT3; Carl Zeiss Meditech, Dublin, California, USA) through one year of follow up examinations.

Case Report

A 62 year old Caucasian male presented to the clinic with a chief complaint of gradual decreasing vision at distance and near, moderate photophobia, and persistent frontal headaches. Known ocular history included borderline ocular hypertension, incipient cataracts, and non-exudative macular degeneration.

Medical history was notable for previous alcohol dependence, hyperlipidemia, peripheral neuropathy, depression, hypertension, gout, pyrosis, erectile dysfunction, chronic headaches, and Type 2 diabetes mellitus. The patient had known diabetes for five years with a recent reduction in hemoglobin A1C from 10.0% to 7.4% over a three month period. Medications at the time of the examination included amitriptyline, amlodipine besylate, cyanoalamin, HCTZ 25/ Lisinopril 20, insulin aspart, insulin glargine, metformin, naproxen, omeprazole, pravastatin, quetiapine fumarate, tramadol, and a daily multivitamin. Examination showed best corrected visual acuities of 20/25 OD, 20/30 OS with refractive errors of +2.25-1.25x120 OD and +3.50-0.75x075 OS. Pupils were equal, round and reactive without an afferent pupillary defect in either eye. Slit lamp examination was remarkable for trace nuclear sclerotic lenticular changes. Intraocular pressures were 21 mm Hg OD, 20 mm Hg OS by applanation. Fundus examination of the right eye revealed multiple macular hard drusen and a cup-to-disc ratio of 0.1 with few retinal hemorrhages and mild optic disc edema (ODE). Fundus examination of the left eye revealed multiple macular hard drusen and a cup-to-disc ratio of 0.1 without ODE. There was no diabetic retinopathy in either eye. The mildly decreased visual acuity was consistent with macular degeneration findings in both eyes. Optical coherence tomography (OCT) showed a significantly thickened nerve fiber layer in the right eye with an average thickness of 175.22 microns (Range: 86.0-107.6 µm for age matched Caucasians). Blood pressure was 150/88 RAS at time of evaluation.

Lab work was obtained to rule out giant cell arteritis (GCA) given the optic nerve appearance and persistent frontal headaches. Inflammatory markers were slightly elevated with an ESR of 33 mm/hr (Range: 0-31 mm/hr) and CRP of 1.5 mg/dL (Range: 0.1-0.82mg/dL). Complete blood count with differential showed mild anemia without thrombocytosis. The patient was started on 40 mg of prednisone with adjustment of insulin while on oral steroids. A right temporal artery biopsy was performed within two weeks with a negative finding. Shortly after the biopsy, the patient self discontinued the prednisone because there was no symptomatic improvement in his headaches and he was experiencing polyphagia with weight gain. A biopsy was not performed on the left temporal artery, since the patient had minimal systemic symptoms and suspicion for GCA was rather low. An additional medical workup including hemoglobin A1C, syphilis serology, lupus panel, bartonella henselae titer, angiotensin converting enzyme, lyme titer and MRI of the orbits with and without contrast were all

KEYWORDS
diabetic papillopathy, optical coherence tomography (OCT), non-arteritic anterior ischemic optic neuropathy (NAION), retinal nerve fiber layer (RNFL), optic disc edema (ODE)
within normal limits. Complete blood counts were obtained at follow up visits, which revealed a consistent mild anemia and moderate eosinophilia (Ranging from 0.7 - 1.6k/cmm with reference high of 0.6 k/ccmm). A lumbar puncture was performed and revealed an opening pressure of 19 cm with clear fluid (Range: 5-20 cm). There was no growth of bacterium or fungus observed over the course of four weeks.

Follow up examinations revealed increased ODE with peripapillary hemorrhages and cotton wool spots in the right eye on day 32 (Figure 1a). A similar clinical appearance developed in the left eye on day 62 (Figure 1b). OCT measurements were performed on days 4, 32, 62, 251, and 372 after initial presentation. Retinal nerve fiber layer (RNFL) thickness averages were as high as 236.91 microns OD and 229.95 microns OS (Figure 2). Follow up on day 372 showed normal appearing optic nerves and nerve fiber layer thicknesses of 125.02 microns OD and 122.89 microns OS. (It is important to note there was no evidence of optic atrophy in either eye consistent with anterior ischemic optic neuropathy.) SITA-Standard 24-2 visual field testing (Humphrey-Zeiss Systems, Dublin, CA, USA) was performed on day 62, and showed a shallow localized defect supero-nasally in the right eye and scattered depressed points without clusters in his left. Repeat testing the following year was similar with the exception of a slightly enlarged blind spot OD (although high fixation losses on testing) and an isolated cluster OS. (Figure 3a, 3b) The patient’s visual acuities, pupillary response, and non-contributory retinal findings remained stable throughout all visits.

Discussion

This case presents several interesting findings associated with a final diagnosis of diabetic papillopathy. The current diagnosis criteria for DP includes the presence of Type 1 or Type 2 diabetes mellitus, unilateral or bilateral disc edema, absence of substantial optic nerve dysfunction, and lack of ocular inflammation or elevated intracranial pressure. DP typically demonstrates hyperemic edema or dilation of the inner optic disc microvasculature.

Diabetic papillopathy presents with ODE that persists for a period ranging from 3 months to 1 year. The optic nerve returns to its pre-edematous appearance with healthy appearing rim tissue after resolution. Although many have reported minimal optic nerve dysfunction following DP, there have been no reports that discuss the anatomical changes to the RNFL throughout disease progression. Figures 1a, 1b, and 2 illustrate the progression of the patient’s ODE and RNFL findings throughout the course of one year of follow up exams. There is a notable lack of optic atrophy and RNFL thinning after resolution of the ODE. The OCT data illustrates the trend towards normalization of the retinal nerve fiber layer with resolution of DP.

The pathogenesis of diabetic papillopathy is largely a supposition despite years of reports and hypotheses. The Diabetes Control and Complications Trial documented worsening of diabetic retinopathy with improved metabolic control. It has since been speculated that DP may also be the result of rapid tightening of blood glucose. A recent report has documented the development of DP in several patients who had a small cup-to-
disc ratio and a large change in Hemoglobin A1C over three months. The development of diabetic papillopathy was statistically correlated with a drastic reduction in A1C, averaging -2.5% amongst the identified cases. Studies also show that strict glycemic control is associated with a significant reduction in retinal vein volumetric flow rate five days after insulin initiation in 64% of patients. It is postulated that intensive insulin therapy results in retinal hyperperfusion with subsequent increased vascular leakage and venous congestion. Previous theories of DP pathogenesis have proposed toxicity and compressive effects of axonal components as primary etiologies. Slagle proposed that capillary vasostasis, retention of cellular waste, and reabsorption in the capillary bed lead to localized edema of the optic nerve head vasculature. While the above factors may contribute to the development of DP, additional research is needed to substantiate these theories.

Several therapies to expedite the resolution of ODE in diabetic papillopathy have been attempted despite the self-limiting nature of the condition. There has been no observed benefit after purposeful elevation of glycemic control, based on the aforementioned mechanism discussed above. Local corticosteroids have been shown to improve ODE and visual acuity in case reports of Type 2 diabetics; this suggests the anti-inflammatory and anti-angiogenic properties may aid in the resolution of ODE. Use of anti-VEGF intravitreal bevacizumab has also shown improvement of ODE as early as three weeks after injection. Future randomized clinical studies may be beneficial in determining a definitive treatment modality for DP.

Reports have attempted to delineate diabetic papillopathy as a unique and separate identity from NAION. There are notable differences in the symptoms, natural progression and clinical outcomes between the two entities. DP is typically asymptomatic and has healthy nerve tissue after resolution of ODE, whereas patients with classic NAION experience sudden vision loss and unilateral ODE followed by optic atrophy within three months. Contreras examined the retinal nerve fiber layer of 27 patients with unilateral NAION for one year with optical coherence tomography. At the time of presentation, the initial RNFL thickness was increased in the area of ODE. Normalization of the RNFL was noted at 6 weeks which corresponded to the resolution of ODE. The RNFL thickness was decreased and thinned at months 3, 6, and 12 in atrophic segments of the optic nerve.

The development of NAION is believed to be due to acute ischemia of the short posterior ciliary arteries (PCA) that supply the anterior optic nerve. Transient non-perfusion or hypoperfusion of the PCA’s is the primary etiology although embolic lesions have also been demonstrated histopathologically.

**Figure 2** RNFL change over follow up visits as measured by Stratus OCT. Note: On 11/24/10 visit, RNFL scan was decentered inferiorly resulting in suggesting thinning superior right eye.
Figure 3a  Visual field of right eye on Day 62 and Day 372.

Figure 3b  Visual field of left eye on Day 62 and Day 372.
Evidence indicates that NAION develops due to localized ischemia of ganglion cell axons resulting in axoplasmic flow stasis and optic nerve swelling. The edematous tissue compresses local capillary beds causing further ischemia and a cyclical pattern due to the tight orientation of ganglion cell axons. Systemic conditions that have been linked to NAION include nocturnal hypotension, diabetes mellitus, arterial hypertension, ischemic heart disease, arteriosclerosis, hyperlipidemia, sleep apnea, migraine, and carotid dissection. Ocular risk factors consist of a crowded optic disc, angle closure glaucoma or any markedly elevated intraocular pressure, optic nerve drusen, and cataract extraction.

The Ischemic Optic Neuropathy Decompression Trial evaluated the safety and efficacy of optic nerve sheath decompression surgery for non-arteritic ischemic optic neuropathy. Patients who were solely monitored showed greater improvement in visual acuity when compared to surgical intervention. Additionally, patients that had undergone decompression had a significantly greater risk of losing three or more lines of vision at 6 months. High dose oral corticosteroid therapy with systematic taper has been shown to improve visual acuity and visual field improvement in NAION. Patients with initial visual acuity worse than 20/70 and moderate to severe visual field loss showed greater benefit of oral therapy. Although corticosteroid therapy shows promise for the treatment of classic NAION, the accepted primary therapeutic intervention continues to be the control of systemic and ocular risk factors.

Hayreh reported a new entity regarded as incipient NAION which may be the mildest form of ischemic optic neuropathy. The criteria for the diagnosis of incipient NAION are shown in Table 1. Review of the criteria identifies several shared clinical characteristics similar to that of diabetic papillopathy. There is a notable greater incidence of classic NAION development in the affected or fellow eye when compared to previous reports of diabetic papillopathy. Our patient exhibited two findings which support a diagnosis of diabetic papillopathy over incipient NAION. Criteria (i) was not met as the patients initial ODE presentation for each eye revealed diffuse, mild ODE with thickened RNFL superior and inferior to the optic nerve. Hayreh also found that the ODE associated with incipient NAION persists for an average of 9.5 weeks and 8.9 weeks in diabetics with and without interventional steroid. Our patient demonstrated significant worsening of the ODE bilaterally as shown on day 62 (8.8 weeks) as seen in Figure 1a,b. It can be assumed the ODE would have persisted for a significantly longer duration given the worsening of edema at 8.8 weeks. Unfortunately, the patient was lost to follow up between day 62 and day 251 which prevented documentation of the true timing and pattern of resolution. The prolonged duration of ODE is consistent with DP rather than incipient NAION.

### Table 1 Summary of Criteria for Diagnosis and Natural History of Incipient NAION

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
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<tbody>
<tr>
<td>(i)</td>
<td>Marked optic disc edema in one portion of the optic nerve, similar to the pattern of edema with classic NAION.</td>
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<tr>
<td>(ii)</td>
<td>No subjective or objective decrease in vision from classic NAION.</td>
</tr>
<tr>
<td>(iii)</td>
<td>All other etiologies of optic disc edema are excluded such as hematologic, neurologic, endocrine, neoplastic, and autoimmune conditions. Patient should be evaluated by primary care physician or internist for systemic abnormalities.</td>
</tr>
<tr>
<td>(iv)</td>
<td>The contralateral eye has demonstrated classic NAION in 55% of patients with incipient NAION.</td>
</tr>
<tr>
<td>(v)</td>
<td>Incipient NAION progressed to classic NAION throughout follow-up in 25% of patients.</td>
</tr>
<tr>
<td>(vi)</td>
<td>Classic NAION developed in the same eye after complete resolution of incipient NAION in 20% of patients during a mean follow-up period of 5.8 weeks.</td>
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</table>

OCT has been widely used for the evaluation of optic nerve disorders, however, there are no previous reports documenting the longitudinal changes to the RNFL in diabetic papillopathy. The OCT measurements throughout the visits showed normalization of the RNFL thickness without atrophy following ODE. Diagnosis of DP must meet the set criteria but clinicians should also consider using retinal scanning technology to monitor progression of the RNFL until resolution. This case report demonstrates how optical coherence tomography is valuable for monitoring RNFL and can be used to help differentiate between the similar clinical entities of DP and incipient NAION.

### Conclusion

References


Corresponding author: Richard Zimbalist, O.D., Harry S Truman Memorial Veterans Hospital Eye Clinic, 800 Hospital Drive, Columbia, MO 65201. Email: Richard.Zimbalist@va.gov.
Current Status on the Development and Treatment of Myopia

Jeffrey Cooper M.S., O.D., Erica Schulman, O.D., and Nadine Jamal O.D.

ABSTRACT

This is a review of the current literature describing the effect of atropine, bifocals, and/or contact lenses on slowing the progression of myopia. Cumulative data from a number of studies have demonstrated atropine instilled once a day in myopic eyes resulted in a 90% average reduction of myopia progression, as compared to untreated eyes, i.e., from 0.50 D/year to 0.05 D/year. Pirenzepine, a muscarinic pharmacological agent, has a minimal effect on pupil size and accommodation, and it has been shown to slow myopia by 44%. Bifocals and progressive lenses, which have been used for years to slow the progression of myopia, have recently been shown to produce, on average, only small, clinically insignificant treatment effects. However, their effectiveness is increased in children who are esophoric and have a large lag of accommodation, reducing myopia progression to between 0.25 and 0.40 D/year. Traditional correcting soft and gas permeable contact lenses, as well as novel spectacle lens designs, have not been shown to be effective in reducing myopic progression. Under-correction of the refractive error has been shown not only to be ineffective in slowing myopia, but has also been associated with an increased rate of myopia progression. Orthokeratology, using reverse geometry designed lenses, has been shown to be moderately effective in decreasing the progression of myopia by between 30 to 50% in a number of short-term, well-controlled studies, reducing myopia progression to between -0.25 and -0.35 D/year. Recently, there have been pilot studies using novel peripherally correcting soft contact lenses to slow the progression of myopia. Two of those lens designs have been shown to be moderately effective in slowing the progression of myopia, both of which had a 30% efficacy, reducing myopia progression to 0.35 D/year. In summary, myopia control is entering a new era with the use of contact lenses and pharmaceutical agents to effectively slow its progression with minimal side effects.

Myopia

Myopia is a common refractive condition affecting approximately 100 million people in the United States. Its prevalence has increased over the past decades, leading to a growing concern among the public and scientific community. The prevalence of myopia varies in different parts of the world. Generally speaking, myopia is more prevalent in industrialized countries and in cities as compared to rural areas. The prevalence of myopia in Taiwan and Singapore is 20% to 30% in children 6 to 7 years of age, increasing to 60% to 80% in young adults. The rapid increase in the prevalence of myopia provides strong evidence that current environmental factors must have a considerable influence on the development of myopia that can not be explained by a genetic model. Understanding how the environment influences eye growth should be central to preventing the progression of myopia.

The widespread prevalence and rapidly increasing rates of myopia make it a significant public health concern. Persons with higher degrees of myopia have a greater risk of developing sight-threatening complications i.e., permanent visual impairment (or “blindness”) from myopic macular degeneration, cataract, glaucoma, retinal holes and tears, and retinal detachments. Myopia has been implicated as the sixth leading cause of vision loss. Retarding the progression of myopia in children could ultimately impact the lives of approximately 42 million adults in the United States.

Thus, finding an effective method of slowing myopia progression is important in decreasing the morbidity associated with this condition.

Myopia has been broadly classified by age of onset as pathological, school age, or adult onset. Pathologic myopia, which usually presents before six years of age, is caused by abnormal and extreme elongation of the axial length of the eye, generally does not progress, and is usually associated with retinal changes. School age myopia occurs between 6 and 18 years of age and is thought to progress and stabilize by the late teens or early twenties. This type of myopia is associated with higher IQ scores, more time spent reading, and less hours of exposure to sunlight as compared to non-myopic patients. In Singaporean children, the prevalence and magnitude of myopia correlates with the time spent in education. In addition, school-age myopia is found more commonly in urban areas (versus rural areas), and industrialized countries. Adult onset myopia occurs between 20 and 40 years of age (early adult onset) or after 40 years of age (late adult onset). It has different characteristics as compared to the school age onset myopia, particularly in that it is associated with accommodative anomalies and near vision dominated occupations. Myopia progression in all three groups is due to the elongation of the axial length, which is primarily due to the elongation of the vitreous chamber depth of the eye.

If myopia is to be controlled during development, the rate of eye growth must be slowed. The rate of myopia progression is highest for young children with an average age for stabilization of childhood myopia at 16 years of age. Once myopia begins...
to develop, the mean rate of progression in children 8 to 13 years of age is 0.55 D/year for Caucasian children;\textsuperscript{33} between 0.63 D/year for Hong Kong Chinese children;\textsuperscript{34} and 0.82 D/year determined for Asian children by meta analysis.\textsuperscript{35} For an average baseline age of 9 years, estimated annual progression (combined ethnicities) was 0.80 D/year for females, and a significantly slower 0.71 D/year for males.\textsuperscript{35}

The etiology, pathogenesis, and treatment of myopia have been debated for decades, and the exact mechanism of the development of myopia still remains unclear. Both environmental and genetic factors have been associated with the onset and progression of myopia.\textsuperscript{2,19,22} The strongest evidence for genetic factors comes from comparing the prevalence of myopia in uniovular versus binovular twins. Uniovular twins have a higher prevalence of myopia as compared to binovular twins, thus supporting the genetic influence on the development of myopia. In addition, Angle and Wissman\textsuperscript{36} found that near work explained only a small part of the variance in teenagers, and thus concluded that genetics is the most important factor in determining the development of myopia. Studies have also shown that having one or two nearsighted parents is a risk factor for the development of myopia.\textsuperscript{37-40} However, this does not completely explain the role of genetics since parents share both genetic and environmental factors with their offspring.

The concept that myopia evolved from the use and abuse of the eyes during near vision activities has been credited to Cohn in 1886 and has been traced back to Kepler.\textsuperscript{41} More recent studies demonstrate a positive correlation between the presence of myopia and the following: intelligence,\textsuperscript{24,42,43} academic advancement,\textsuperscript{44,16,42} avocations requiring near vision use,\textsuperscript{45,46} after professional school,\textsuperscript{31,47} caged versus free-ranging animals\textsuperscript{48} and people confined to restricted spaces such as submarines.\textsuperscript{49} The implication of most of these studies is that the greater the time spent performing near work results in an increased incidence of myopia.\textsuperscript{50-52} Zylberman,\textsuperscript{53} while studying children in religious schools, noted that the incidence of myopia was much higher in Orthodox Jewish males who spent approximately 16 hours per day studying as compared to Jewish females who did not study as much. The incidence of myopia in Jewish females was similar to other Jewish male cohorts who attended non-religious schools. Zylberman\textsuperscript{53} suggested that both groups of males had similar genetic make-ups, but the group that studied more became more myopic. In both groups, the females who studied a similar amount developed a similar amount of myopia.

The assumption in most use and abuse theories is that accommodation is somehow indirectly responsible for axial length elongation. There is some indirect evidence for this since myopes exhibit greater lags of accommodation,\textsuperscript{54,55} higher ACA ratios,\textsuperscript{56,57} more esophoria even when they are still emmetropic,\textsuperscript{58} reduced accommodative amplitudes,\textsuperscript{59} worse accommodative responses,\textsuperscript{60,61,62} and deficient positive relative accommodation.\textsuperscript{63} However, the difference in accommodative function between emmetropes and myopes is not great enough to explain the development of myopia. Secondly, it is difficult to determine which came first, the abnormal accommodative function or the myopia. Abnormal accommodative findings have lead to a host of treatment methods including bifocals, progressive addition lenses (PALs), base-in prism, atropine therapy, and vision therapy.

Mutti and Zadnik\textsuperscript{64} recently challenged the near vision theories by noting that recent epidemiological studies suggested that the amount of time spent outside in sunlight is more closely related to the development of myopia than the amount of time spent reading, studying, or working on a computer.\textsuperscript{55,66,67} In animals the level and/or amount of illumination during the day can affect refractive development.\textsuperscript{68,69,70} A number of studies have documented a strong negative correlation between the amount of time children spend outdoors and their refractive error, i.e., myopia becomes more common in children who spend less time outdoors.\textsuperscript{27,65,66} However, this finding has not been observed universally.\textsuperscript{71,38,72} Guggenheim et al.\textsuperscript{73} in a recent study determined that the amount of time spent outdoors was predictive of incident myopia independently of physical activity. They reported that the association of myopia observed for time outdoors and “sports/outdoor activity” is related to time outdoors rather than to the level physical activity.

The mechanism of sunlight has been ascribed to the pinhole effect causing a reduction of peripheral blur, UV exposure affecting cross-linking of the sclera, and/or alteration of the focusing shell when looking from distance to near. The prevalence of myopia varies minimally across geographical latitudes, that exhibit a wide range of both the length of day and the amount of ambient light.\textsuperscript{74} Thus, Guggenheim et al.\textsuperscript{73} concluded that it is likely that light levels regulate the eye’s “gain” response to the visual cues that guide emmetropization rather than exerting a direct effect on eye growth. Mutti and Zadnik\textsuperscript{64} makes a point of stating that the time spent outdoors is an independent variable, not the inverse of near work. When looking at epidemiological studies, one must be cognizant of the cohort being studied. For example, many of the studies involving amount of sunlight exposure were performed on school-aged myopes and may not be relevant to adult onset myopia. At the same time, most of the studies on accommodation used college aged students versus younger children (between the ages of 8 and 13 years).

The most compelling studies implicating the impact of the environment on myopia come from animal studies in which the environment has been manipulated to produce myopia, hyperopia, or astigmatism in visually immature animals. Wiesel and Raviola\textsuperscript{58,75} sutured the lids of monkeys, allowing a minimal amount of light to penetrate. Form deprivation resulted in the animals developing myopia secondary to axial elongation of the vitreous chamber. They concluded that form deprivation disrupts the feedback mechanism for emmetropization and resulted in myopia across all species including humans. Similar myopiogenic effects were observed when translucent diffusers were placed over an eye rather than suturing the lid closed. However, myopia did not develop if the animal was patched with a totally opaque occluder or reared in total darkness, since total darkness eliminates any signal for visual feedback.\textsuperscript{76,77}

Wallman et al.\textsuperscript{78} used hemi-retinal sector occluders to create regional diffusion of light. Hemi-retinal diffusers result in a clear image on one half of the retina and diffused unfocused light on the other half. Myopia, with axial elongation, occurred only in the field in which the occluders diffused the light, i.e., asymmetrical elongation of the globe (see Figure 1). Myopia occurred in the occluded half of the retina, in the presence of equal illumination in both halves of the retina, and in the absence of accommodation. Smith and his associates reported similar results.\textsuperscript{79} Lastly, these changes occurred in the absence of an intact optic nerve, demonstrating that changes were local to the eyeball.\textsuperscript{80,81} Varying the amount of illumination by the degree of frosting resulted in varying the degrees of myopia. In a similarly designed experiment, Diethe\textsuperscript{82} used hemi-regional plus and
minus lenses to induce local retinal blur, which caused a localized change in axial length in young chicks. Diether suggested that these results provide further evidence that accommodation is not responsible for axial elongation. Schaeffel and his associates\textsuperscript{93,94} used plus and minus contact lenses to create artificial hyperopia or myopia. When lenses between -10.00 and +15.00 were placed on primates' eyes, the growth of their eye(s) compensated for the focal length created by the lens in an attempt to eliminate blur. (It should be noted that the eye responded accurately to the direction of the error.) These studies demonstrate that emmetropization is driven towards the direction that results in a clear, higher contrast image. It has been postulated that near visual activity either disrupts the normal pathway of emmetropization or results in a change in ocular growth in order to adapt to the near environment.\textsuperscript{85}

Animal studies using positive and negative lenses have demonstrated that optical defocus can cause directionally controlled eye growth.\textsuperscript{84,86-88} Thus, it would not be unreasonable to presume that hyperopic retinal blur from a larger lag of accommodation during near viewing could cause myopia progression in children\textsuperscript{63,89,90} and the larger the amount of hyperopic defocus, the faster the rate of myopia progression.\textsuperscript{91} In support of this hypothesis, Gwiazda et al.\textsuperscript{57} reported an elevated lag of accommodation two years before the onset of myopia. Conversely, Mutti et al.\textsuperscript{92} reported that accommodative lag in pre-myopic children was not elevated until a year after the onset of myopia. Rosenfield et al.\textsuperscript{93} reported that young adults who became myopic had a smaller lag of accommodation before and after the onset of myopia. While there is no consensus regarding lag of accommodation prior to the onset of myopia, there is a consensus that the lag of accommodation is larger after the development of myopia.\textsuperscript{94-96} Recently, Bernsten et al.\textsuperscript{97} investigated the relationship between accommodative lag and the rate of myopia progression in a large sample of children; they reported that foveal hyperopic retinal blur during near viewing could not explain school-age myopic progression. Thus, the relationship of lag of accommodation in causing myopia is at best controversial.

Previously, the macula (including the fovea), which dominates cortical vision in primates, was thought to be responsible for the process of emmetropization. However, recent animal studies have demonstrated that the peripheral retina has a greater influence than the macula over emmetropization and ocular growth.\textsuperscript{98-102} For example, form deprivation causes primate eyes to become myopic, when only the peripheral retina is deprived. If peripheral form deprivation is eliminated during the critical period, the vitreous cavity decreases in size and the eye becomes more emmetropic.\textsuperscript{103} This even occurs in the absence of an intact fovea after ablating the macula with a laser.\textsuperscript{99} Myopia progression results in the peripheral posterior pole of myopic eyes to become relatively hyperopic relative to the central retina due to the round shape of the globe.\textsuperscript{103} (See Figure 2.)

It has been suggested that this relative hyperopic defocus may actually act as a signal for axial elongation.\textsuperscript{101} Hoogerheide et al.\textsuperscript{104} noted that emmetropic or hyperopic airline pilot trainees were most at risk for becoming myopic when the relative peripheral refractive error was more hyperopic. In addition, Schmid\textsuperscript{105} observed that there was a correlation between temporal retinal steepness and the development of myopia in humans. Monkeys reared with centrally unrestricted vision (plano lens) and -3.00 D in the periphery produced similar myopia as a full field lenses of -3.00 D of power; demonstrating that peripheral blur caused axial elongation irrespective of whether central vision was corrected.\textsuperscript{98} (See Figure 2.) Liu and Wildsoet\textsuperscript{106} used peripherally designed lenses in young chicks to create myopia which resulted in a reduction of axial growth. These findings support the hypothesis that eye shape, associated with peripheral defocus, is one of the factors influencing axial eye growth. (See Figure 3.)

In the Orinda Longitudinal Study of Myopia, which included predominantly Caucasian subjects, Mutti et al.\textsuperscript{107} reported that myopic children had relative peripheral hyperopia, whereas emmetropic and hyperopic children had relative peripheral myopia. Relative peripheral hyperopia results in a more prolate

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**Figure 1** Regional Deprivation Causes Localized Axial Elongation

Panel 1 One of the following was placed in front of the nasal field of a visually immature animal's eye resulting in a blurred image on the temporal retina: occluder, translucent lens, or minus lens.

Panel 2 The blurred image on the temporal retina over time causes localized elongation of the eyeball.\textsuperscript{205,79} This occurs even when the optic nerve is severed, demonstrating that cortical feedback is not necessary for localized elongation.\textsuperscript{81}

**Figure 2** Peripheral Blur Drives The Eye to Elongate

If either the macula is ablated, a multifocal lens is placed over an eye (center plano, peripheral -3.00), or a diffuser placed over the peripheral portion of the eye while the center is unobstructed, the eye will elongate in response to the peripheral blur. This occurs across species (including those with and without fovea).\textsuperscript{98,176}
ocular shape in myopic eyes, in which the axial length exceeds the equatorial diameter. Similar findings have been reported in Chinese subjects with myopia.\textsuperscript{107-111} Chen et al.\textsuperscript{109} reported that relative peripheral refractive errors (RPRE) in Chinese children and adults with moderate myopia, low myopia, emmetropia, and low hyperopia were different. They reported that RPRE for the moderate myopic group had a relative hyperopic shift while subjects with low hyperopia demonstrated a relative myopic shift. The RPRE profile for the moderately myopic group was different for adults as compared to children. Adult eyes had a greater amount of hyperopic change. Thus, the periphery of a prolate shaped eye would experience hyperopic defocus, which might result in the onset and progression of myopia.\textsuperscript{98,99}

The preceding findings have resulted in a renewed interest in orthokeratology and novel spectacle and contact lens designs to correct the hyperopic peripheral defocus in order to eliminate the local retinal signal for elongation (to be discussed later). In addition, the neuro-retinal signal for ocular elongation is thought to have a biochemical basis.\textsuperscript{19} Thus, if one can block the signal, then one might slow or stop myopia progression. Atropine\textsuperscript{112-138} and pirenzepine\textsuperscript{139-147} have been shown to slow the progression of myopia via this presumed mechanism.

In summary, there is ample, solid evidence for both genetic and environmental factors producing myopia. It may be presumed that the genetic predisposition for myopia is triggered by environmental factors such as diet, amount of reading time, occupation, and amount of light. Currently, genetic make up cannot be altered, but the environmental factors can be. Thus, understanding the methodology of emmetropization is important in developing methods to control myopia.

**TREATMENT: SPECTACLE CORRECTION**

**Bifocals and Multifocal Lenses**

Optometrists first began using bifocal lenses to attempt to slow myopia progression in the 1940s.\textsuperscript{148} The rationale was that if accommodation caused an increase in myopia, then bifocals or multi-focals would reduce the accommodative response and thus slow myopia progression. A more recent alternate theory suggested that myopic children do not accommodate as well as emmetropic children.\textsuperscript{57} This inaccurate accommodation somehow creates a retinal blur that acts as a signal for myopia progression, similar to the blur-induced myopia that can be experimentally produced in animals.\textsuperscript{54,55,60} Gwiazda et al. reported that myopic children with esophoria have a greater lag of accommodation than other myopic children and that myopic children have a greater lag of accommodation than emmetropic children.\textsuperscript{54,55,60} A greater accommodative lag would cause retinal blur and possibly a stronger stimulus for myopia progression. Thus, the elimination of a lag of accommodation is thought to slow the progression of myopia.

Goss\textsuperscript{199} performed a retrospective analysis of children between 6 and 15 years of age from three optometry practices to assess the effect of bifocal lenses on the rate of myopia progression. Sixty children wore bifocal lenses with an add power that varied between +0.75 D to +1.25 D, and 52 children wore single vision lenses. Children in the bifocal group displayed either esophoria at near, a low amplitude of accommodation, negative relative accommodation (NRA) and positive relative accommodation (PRA) which were more plus and/or less minus than normal values, a subjective refraction showing more minus than static retinoscopy, or a reported symptom of intermittent distance blur. As a group there was no statistically significant difference in progression between the bifocal group (0.37 D/year) and the single vision group (0.44 D/year). However, when Goss looked only at the esophoric children, there was a statistically significant decrease in myopia progression for children wearing bifocal lenses as compared to single vision lenses, 0.32 D/year versus 0.54 D/year, respectively. Myopia progression was also analyzed based on lens type and near cross cylinder findings. For children with a near cross cylinder finding greater than or equal to +0.50 D, there was also a statistically significant difference in myopia progression for children wearing bifocal glasses as compared to single vision glasses; 0.25 D/year versus 0.48 D/year, respectively.

Grosvenor et al.\textsuperscript{150,151} randomly placed 207 children between the ages of 6 and 15 years into three treatment groups; single vision glasses, +1.00 D bifocals, and +2.00 D bifocals. At the end of the three year study, Grosvenor et al.\textsuperscript{151} reported that for the 124 children who completed the study, there was no significant difference in myopia progression in children wearing single vision glasses or bifocal lenses. Goss\textsuperscript{199} re-analyzed Grosvenor’s data, looking only at the esophoric children, and reported that for this group, there was 0.20 D/year less myopia progression for the bifocal wearers compared to single vision lens wearers.
Fulk et al.\textsuperscript{152,153} conducted a prospective, randomized study of 82 esophoric children, (age 6 to 13), to evaluate whether bifocals (+1.50 D add) were effective in slowing myopic progression over 30 months. The authors noted that during at least one of five follow-up examinations, 33% of the bifocal wearers were observed to read over the top of their bifocals. Fulk reported that there was a 20% reduction in myopia progression for esophoric children wearing bifocal lenses as compared to single vision, a difference of 0.25D over 30 months. Fulk observed that if the outliers were excluded, which consisted of the five children who progressed more than 2.00 D over 30 months, then there was a 44% reduction in myopia progression for esophoric patients wearing bifocals. Myopia progression was 1.25 D or more in 25% of the bifocal group as compared to 44% of the single vision group, a 0.49 D difference over 30 months. The number of patients who demonstrated more than 2.00 D of myopia progression was similar in both groups. The authors concluded that improper bifocal use was associated with faster myopic progression; 67% of the children who progressed by more than -1.25 D were observed to look over the top of their bifocal on at least one of five follow-up visits.

Bifocal lenses, as compared to progressive addition lenses, are not as cosmetically appealing, and do not vary in power for different working distances. Both progressive lens and bifocals fit high should improve the proper use of the reading addition. Leung and Brown\textsuperscript{154} conducted a clinical trial to evaluate the efficacy of progressive lenses on slowing myopia progression. Sixty-eight children between the ages of 9 and 12, who had myopia between 1.00 D and 5.00 D with less than 1.50 D of astigmatism, were fit with either progressive lenses or single vision lenses. The mean myopic progression over the 2-year study was 0.76 D for the +1.50 D add group, 0.66 D for the +2.00 D add group, and 1.23 D for single vision group. The progressive lens groups exhibited a statistically significant decrease in the amount of myopic progression associated with axial length changes as compared to the single vision lens group. There was no statistical difference between the two progressive lens groups. The axial lengths of the children in all groups increased with increasing degrees of myopia, and the majority of change occurred in the vitreous chamber. Leung and Brown noted that esophoric subjects wearing progressive lenses progressed 46% less than non-esophoric subjects wearing single vision lenses. The difference in myopic progression over 2 years between children with esophoria wearing single vision lenses as compared to progressive lenses was 0.71 D.

The Correction of Myopia Evaluation Trial (COMET), a 3 year prospective, randomized, double-masked clinical trial, evaluated the effect of progressive lenses (with a +2.00 D add) in 469 myopic children 6 to 11 years of age (spherical equivalent between -1.25 D and -4.50 D).\textsuperscript{155} After 3 years, there was a statistically significant, but clinically insignificant, 0.20 D reduction in myopia progression over 3 years for children wearing progressive lenses as compared to single vision lenses. Children with larger accommodative lags (greater than 0.43 for a 33 cm target) wearing single vision lenses had the most progression at the end of the 3 years. For children with both larger lags of accommodation and near esophoria, there was a statistically significant decrease in myopia progression in children wearing progressive lenses as compared to single vision lenses: 1.08 D verses 1.72 D, respectively. However the 3 year treatment effect decreased after 5 years to 0.49 D/year.\textsuperscript{156} (Though, progressive lenses are more effective when one or both of the parents are myopic, there are no long-term data for this sub-group.)

A more novel use of multifocal glasses involves the use of specially designed glasses to correct for the central myopic error while, at the same time eliminating the peripheral hyperopic refractive error induced by traditional glasses.\textsuperscript{109} This residual error results in a blur which is believed to be the stimulus for increased myopic progression. Sankaridurg et al.\textsuperscript{157} reported on the effect of correcting peripheral hyperopic defocus on myopia progression in 210 Chinese children after 12 months of wear of one of three novel spectacle lenses designs. The myopic children were randomized into one of four groups: wearing either one of three peripheral correcting spectacle lens designs or a conventional, single-vision spectacle lens. Both central and peripheral cycloplegic auto-refractions, and axial length were measured at 6 and 12 months. Myopic progression in eyes wearing special peripherally correcting lenses and traditional spectacle lenses at 6 and 12 months was 0.55 D ± 0.35 D and 0.78 ± 0.50 D, respectively. There was no statistically significant difference in the rates of progression with the peripherally correcting lenses as compared to traditional spectacle lenses. However, in one sub-group, the authors reported that the younger children (6 to 12 years) with parental history of myopia, had significantly less progression (0.68 D ± 0.47 D vs. -0.97 D ± 0.48 D) with one type of lens compared to traditional spectacles (mean difference of 0.29 D). One of the major problems with spectacle glasses is the inability to control where the patient looks through the lens, thus inducing variability in correcting the optics of the eye.

Cheng D, Schmid KL, et al.\textsuperscript{158} measured myopic progression in a group of Chinese Canadian children, who were progressing more than 0.50 D/year as determined with cycloplegic refraction and ultrasonography. In this unmasked study subjects were placed in one of three lens treatment groups: myopic progression averaged 0.77 D/year in the single-vision lenses group, 0.48 D/year in the +1.50 executive bifocal group, and 0.35 D/year for prismatic bifocal group (+1.50 add with 3 prism base in prism in each eye): axial length increased proportionally to the refractive changes. Cheng et al.\textsuperscript{159} concluded that bifocal lenses with and without BI prism can slow myopic progression in children with high rates of progression after 2 years of wear by approximately 45%. They reported that the effect of the bifocals was not related to any of the other concurrent variables measured: myopic duration before trial, lag of accommodation, hours of close work conducted per week, hours of outdoor activities per week, near phoria, and /or parental myopia.

Cheng W, Woo, and Schmid\textsuperscript{159} argue that the difference between their positive results and other studies, which did not show such a large effect, might be related to the lack of consideration for the proper add based on lag of accommodation, the lack of correction of the esophoria induced by relaxing accommodation with a near add, and/or the use of high fitting executive bifocals to ensure the use of the near reading add. A +1.50 add was chosen since it was close to the average lag of accommodation, and the BI prism prescribed was the average required to correct the esophoria measured at near. Cheng et al.\textsuperscript{159} suggested that previous studies using multifocal progressive lenses suffered from the problem in not knowing what part of the lens the children viewed through. They felt that the prescription of a high fitting bifocal would eliminate this problem. (The practitioner needs to be aware of the cosmetic
problem that executive bifocals impose.) One must be careful in the interpretation of this data in light of the COMET study, which demonstrated a 5 year loss of the early effect of treatment with progressive lenses. Lastly, the most effective treatment with bifocals occurred in a very specific group of subjects who were children of Chinese origin, who progressed rapidly, and wore bifocals.154,158,159

The major benefit of any progressive lenses, bifocals, or novel peripheral correcting lenses, is the low risk of complications or adverse effects and their effectiveness in esophoric myopic children, which constitute about 30% of myopic children.152 The major disadvantages of progressive lenses are cost, lack of strong scientific support of efficacy in the majority of non-esophoric myopic patients, and poor long-term data.

**Under correction**

Under-correction has been a popular method advocated by professionals to slow down the progression of myopia. In two separate studies, under-correction was associated with either an increase in the progression of myopia or no change compared to fully corrected controls.160,161 Thus, under-correction is associated with a faster progression of myopia, and should no longer be advocated.

**CONTACT LENSES**

**Single vision contact lenses**

Randomized clinical trials comparing soft contact lenses to spectacle lenses to slow the progression of myopia found no significant difference in myopia progression.162 Walline et al., in the Contact Lens and Myopia Progression (CLAMP) Study, performed a randomized trial to determine if rigid contact lenses (RGP) would affect myopia progression.163 They found that children wearing RGP lenses had less myopia progression as measured by refraction than children wearing soft contact lenses. However, it was found that only the corneal curvature of RGP wearers was flatter than that of soft contact lens subjects; there was no significant difference in axial length in either cohort. Thus, refractive changes were most likely due to a temporary flattening of the cornea and did not represent a true slowing of myopia. In another randomized clinical trial by Katz et al.,164 there was no significant difference in refractive error between RGP lens wearers and spectacle wearers. These studies suggest that RGP do not reduce the progression of myopia as previously thought.

**Orthokeratology**

Orthokeratology (also called OK, ortho-k, corneal reshaping, corneal refractive therapy or CRT, and vision shaping treatment or VST), first described by Jessen in the 1960s, uses reverse geometry rigid gas-permeable contact lenses to reshape the cornea resulting in a temporary elimination of refractive error. There has been a resurgence in prescribing this treatment over the past decade due to better oxygen permeability of lens materials and improvement in the fit of the lenses.165,166 The reverse geometry design flattens the central cornea while creating mid peripheral steeping which theoretically corrects hyperopic peripheral defocus, and in turn is thought to slow myopic progression. In 2003, Reim and his associates167 performed a retrospective chart review of myopia progression in children between the ages of 6 and 18 with myopia between 0.50 D and 5.25 D. These subjects were fit with the DreimLens orthokeratology lens. In his cohort, 253 eyes were examined after one year of wearing the DreimLens, and 164 eyes were examined after 3 years of wearing the DreimLens. They reported a mean increase in myopia of 0.39 D over the 3 years, or 0.13 D/year. This was significantly less than the average reported progression of myopia, -0.50 D/year with single vision spectacle lenses.

Walline and associates,166 in the Children’s Overnight Orthokeratology Investigation (COOKI) pilot study, evaluated refractive error, visual changes, and biomicroscopy findings before and after 6 months of overnight orthokeratology in 29 subjects who were between 8 and 11 years of age, with 0.75 D to 5.00 D of myopia and less than 1.50 D of corneal astigmatism. Subjects were fit with Paragon corneal refractive therapy contact lenses. At the 6-month visit, the mean uncorrected visual acuity was 20/25, and the mean spherical equivalent refraction was -0.16 ± 0.66 D in each eye. During the morning visits, 58.8% of the children showed mild corneal hydration, and only 35.3% of children showed mild corneal hydration at the afternoon visit. No lasting adverse visual effects from corneal-reshaping contact lens wear were reported; thus Walline et al. concluded “overnight corneal reshaping contact lenses was efficacious for young myopic patients.”

Cho and associates,168 in the Longitudinal Orthokeratology Research in Children (LORIC) study, compared the axial length of the eye measured with A-scan ultrasound in subjects between the ages of 7 and 12 with myopia between 0.25 D and 4.50 D, with less than 2.00 D of astigmatism. The children were fit with either corneal reshaping contact lenses (N=35) or prescribed single vision spectacles. The single vision spectacle control group was selected from another study. Eighty one percent of the children completed the study. There was a significant slowing of eye growth in the ortho-k group, reflected in less of an increase in axial length (AL) and vitreous chamber depth (VCD) measurements; i.e., AL increased in the ortho-k group by mean 0.29 ± 0.27 mm, and by 0.54 ± 0.27 mm in the spectacle group. Similar results were found for VCD; i.e., 0.23 ± 0.25 mm increase for the ortho-k and 0.48 ± 0.26 mm increase for the control groups. The average myopic reduction was 46%, however, there was substantial variability in the amount of eye elongation for any subject, suggesting that there is no way to predict the effect of orthokeratology on myopia progression for any individual.

Walline and associates169 performed a study to determine whether corneal reshaping contact lenses slow eye growth in the Corneal Reshaping and Yearly Observation of Nearsightedness (CRAYON) Study. Forty children, 8 to 11 years of age, who had between 0.75 D and 4.00 D of myopia with less than 1.00 D of astigmatism, were fit with Corneal Refractive Therapy (Paragon Vision Sciences) contact lenses which they wore for 2 years. Seventy percent of the children completed the study; none of the dropouts were due to complications as most were due to lack of interest in wearing contact lenses. The control group subjects were selected from the Contact Lens and Myopia Progression (CLAMP) Study.170 Axial length was measured using A-scan ultrasound for both children fit in corneal reshaping contact lenses and a matching control group of children wearing soft contact lenses. In children wearing corneal reshaping contact lenses, as compared to soft contact lens wearers, the rate of change in axial length was on average 0.16 mm per year less and vitreous chamber
depth was 0.10 mm per year less. This represents a 38% reduction in myopic progression.

Kakita et al. recently conducted a study to assess the influence of overnight orthokeratology on axial elongation in children using spectacle lens wearers as a control group. Axial length was measured at the baseline exam, and repeated after 2 years using the IOL Master. After 2 years the axial length increased 0.39 ± 0.27 mm for the orthokeratology group and 0.61 ± 0.24 mm for the spectacle group; the difference was statistically significant. These findings demonstrated that orthokeratology slows axial elongation in myopic children by approximately 36%, and thereby slows the progression of myopia as compared to spectacle lens correction. In a similar study, Santodomingo-Rubido et al. compared axial length growth in white children myopia wearing OK lenses and distance single vision spectacles (SV) for a 2-year period. They reported that the axial length increased significantly over time for both the OK group (0.47 mm) and SV group (0.69 mm). The difference represented a reduction of myopia.

Swarbrick et al. compared changes in axial length and refractive error during overnight orthokeratology with daily wear rigid gas-permeable contact lens wear in myopic children. Twenty-six myopic children wore an overnight orthokeratology lens in one eye and a gas permeable lens for daily wear in the other eye for 6 months. After 6 months the lenses were reversed. Axial length was measured using the IOL Master and refraction was measured with an auto-refractor. Swarbrick et al. found that overnight orthokeratology lens wear inhibited axial length increase and myopia progression over a 12-month period. After 12 months, the orthokeratology eyes showed no change in axial length and a slight decrease in myopia, whereas the gas permeable eye showed increased axial length and myopic progression. Crossover of the orthokeratology lens with the gas permeable contact lens produced similar results and conclusions.

Kwok-Hei Mok and Sin-Ting Chung measured refractive error and central corneal curvature for 34 children wearing Ortho-K lenses and for 36 children who wore spectacles 6 years or a longer. All the Ortho-K patients had a washout period that was determined to occur when the keratometry findings at the end of the study matched the findings prior to beginning the study. Myopic progression was calculated as a change of myopia from the baseline to the final visit. Average myopic progression of the overnight Ortho-K contact lens was 0.37 ± 0.49 D (0.05 D/year) while average myopic progression of the single-vision spectacle group was 2.06 ± 0.81 D (0.29 D/year) after 7 years. Lastly, there was no incidence of microbial keratitis in their patients. It is of interest to note the reduced rate of progression of both the Ortho-K group and the spectacle group, as compared to other studies. There were no A scans nor cycloplegic refractions. However, this preliminary study does provide good pilot data demonstrating the long-term effect of Ortho-K.

Recently Hiraoka et al. published a 5-year, long-term study to compare axial length changes in myopic children receiving either overnight orthokeratology (OK) or spectacles as controls. There were 59 subjects who had axial length measured with an IOL Master. The increase in axial length during the 5-year study period was 0.99 mm ± 0.47 for the OK group and 1.41 ± 0.68 mm for the control groups. The difference was statistically significant for the first 3 years, but not for the fourth and fifth year. These findings are similar to the COMET bifocal study in which the treatment effect seems to diminish after 3 years. Thus, one needs to be careful to generalize short-term data to long-term conclusions. Like other OK studies the effectivity was approximately 30%.

It has been suggested that the peripheral retina plays a role in emmetropization, specifically that hyperopic peripheral defocus may stimulate axial myopia. In animal studies, peripheral form deprivation produces axial myopia. In both humans and animals, myopic eyes are relatively hyperopic in the periphery since the radius of the peripheral retina is shorter than that of the central retina. When traditional glasses or contact lenses correct the error at the posterior pole, relative peripheral retinal hyperopic defocus is created which has been implicated as a signal for local axial elongation. Orthokeratology flattens the central cornea, which results in a steepening of the mid-peripheral cornea. This mid-peripheral corneal steepening creates less peripheral defocus than single plane correction, which is the suggested mechanism for the effect on the progression of myopia. In support of this theory, Kang and Swarbrick, noted in a recent study that myopic children have relative peripheral hyperopia as compared to their central refraction. After 3 months of wearing orthokeratology lenses in one eye, hyperopic shifts in refraction were measured between 30 degrees in the temporal visual field and 20 degrees in the nasal visual field. Peripheral refraction was similar to center at all positions in the temporal visual field while remaining significantly myopic at all locations in the nasal visual field. On the other hand, there was no change in either central or peripheral refraction in the control eye, which wore a traditional gas perm contact lens. Kang and Swarbrick concluded that orthokeratology changes the relative peripheral hyperopia found at baseline to relative peripheral myopia after orthokeratology. They suggested that the induced myopic defocus in the periphery is thought to provide a mechanism for myopia control.

In summary, Ortho-K results in an approximately 40% reduction in the progression of myopia. Its advantages are that it both eliminates the need for daytime contact lens wear and reduces the progression of myopia. Its disadvantages include cost, risk of infection, discomfort, problems with insertion and removal, and reduced visual acuity as compared to glasses or daily wear contact lenses. In addition, it is difficult to determine which subjects will demonstrate slowing of their myopia and by how much. Lastly, there are no good controlled long-term studies demonstrating that the reduction continues after year one.

**Multifocal Soft Contact Lenses**

There have been two types of multifocal contact lens treatment strategies. The first involves the use of multifocal contact lenses, which are similar to progressive lenses to slow the progression of myopia. The second, more novel use, is that of multifocal lenses that are designed to eliminate the peripheral hyperopia induced with spherically correcting contact lenses.

The success of orthokeratology has led both researchers and the major soft contact lens companies to design soft contact...
lenses that might slow the advancement of myopia. Woods et al. performed an experiment to determine whether lens-induced myopia in chickens can be inhibited when the central minus power is combined with a hyperopic peripheral lens design. Chicks were fit unilaterally with peripheral correcting lenses, with the central power being a -10.00 D, or a conventional -10.00 D control lens of the same physical parameters as the test lens. Refractive error was measured by retinoscopy. This study showed that lens-induced myopia in chicks wearing conventional lenses can be reduced by using multifocal, peripherally correcting lenses. The difference in the induced myopia provides further evidence of the influence of peripheral retinal hyperopic defocus on eye growth.

Antsticke and Phillips tested the ability of an experimental Dual-Focus (DF) soft contact lens to reduce myopic progression. The experimental group wore a Dual-Focus lens that had a central zone that corrected refractive error and concentric treatment zones that created 2.00 D of simultaneous peripheral myopic retinal defocus during distance and near viewing. The control group wore single vision distance lenses with the same parameters but without treatment zones. Children wore the Dual-Focus lens in a randomly assigned eye (period 1) and the control lens in the other eye for 10 months. The lenses were then switched between eyes, and worn for another 10 months (period 2). Cycloplegic auto-refraction, axial length measured by partial coherence interferometry, and accommodation using an open-field auto-refractor, were measured at the end of each 10 month period. The mean change in spherical equivalent refraction with dual-focus lenses (-0.44 ± 0.33 D) was less than with the control lenses (-0.69 ± 0.38 D); mean increase in axial length was also less with Dual-Focus lenses (0.11 ± 0.09 mm) than with the control lenses (0.22 ± 0.10 mm). In 70% of the children, myopia progression was reduced by 30% or more in the eye wearing the Dual-Focus lens compared to that wearing the control lens. Visual acuity and contrast sensitivity with Dual-Focus lenses were similar to the control lenses. Dual-Focus lenses provided normal visual acuity and contrast sensitivity and allowed for normal accommodative responses to near targets.

Holden and The Vision CRC Myopia Control Study Group evaluated a soft contact lens designed to correct central vision but reduce relative peripheral hyperopia, which would slow the rate of myopia progression. Cycloplegic auto-refraction and axial length were measured after 6 months of wear of the experimental lens group and spherical lens control group. Progression of myopia with the experimental lens was significantly less than with the control, -0.26 ± 0.25 D versus 0.60 ± 0.29 D. Similarly, axial length increase was less with the experimental lens as compared to the control lens, 0.08 ± 0.11 mm versus 0.25 ± 0.12 mm. Holden et al. concluded that after 6 months of wear, progression of myopia with the experimental contact lens designed to maintain clear central vision but reduce relative peripheral hyperopia, was 56% less than that with standard spherocylindrical spectacles. They also concluded that “longer experience with wear of such contact lenses is needed, however the data are promising with regard to a new generation of contact lenses aimed at myopia control.”

In a subsequent study, Holden et al. measured central high and low contrast visual acuity with a log MAR chart (VA) and contrast sensitivity (CS) in subjects wearing peripherally correcting lenses and conventional lenses. Peripheral VA & CS were measured at 30° nasal and temporal eccentricity. There were no differences for high and low contrast VA and central CS between groups. However, there was a significant improvement in measurements of peripheral VA at both 30° nasal and temporal eccentricity equivalent to a 3 line improvement in the experimental lens design group. Also, CS improved at 30° temporal eccentricity.

Holden et al. reported that peripheral visual acuity was better with these lenses and that the improvement in peripheral vision was most likely due to a reduction in peripheral defocus. The authors concluded that these experimental lenses, designed to maintain clear central vision but reduce relative peripheral hyperopia, “have the capability of correcting central vision without blur, slowing the progression, and enhancing peripheral vision – a relatively unique and beneficial combination of effects.”

More recently, Chinese children, aged 7 to 14 years, with baseline myopia between sphere -0.75 to -3.50 D, were fitted with the novel contact lens designed to reduce relative peripheral hyperopia (n=45) and were followed for 12 months. Their findings were compared to a matched control group (n=40). The estimated progression at 12 months was 34% less, at -0.57 D, with the novel contact lenses as compared with -0.86 D for spectacle lenses. The baseline axial length was 24.6mm and after a year, the estimated increase in axial length (AL) was 33% less at 0.27 mm versus 0.40 mm for the contact lens and spectacle lens groups, respectively. The effectiveness was less in the second 6 months than the first six months. Most surprising was that almost 30% of the children dropped out of the study, due to discomfort of the lens. The 12 month data support the hypothesis that reducing peripheral hyperopia can alter central refractive development and reduce the rate of progression of myopia.

Yet, one needs to be careful in evaluating these results. In previous PAL studies, efficacy in the first year was 28%; however it decreased significantly in the second year to 17%. By the end of the study there was only a small difference between the PAL lenses and the single vision lenses over the longer duration of the study. The PAL study points to the importance of long term data before drawing broad general conclusions about a particular method of intervention. Lastly, none of these novel multi-focal contact lenses have been approved for wear. Currently approved contact lenses, that might conceptually correct both central myopia and relative peripheral hyperopia, include lenses designed to correct the distance centrally with a peripheral near add. The Biofinity multifocal D lens has a central optic zone that is fully corrected for distance. Beyond this central zone is an aspheric periphery that decreases myopic correction or increases hyperopic correction from the center moving outward in any direction. This design results in a clearer image focusing on the peripheral retina thus decreasing the amount of peripheral retinal blur. Although this specific lens has not been evaluated for its effect on slowing myopic progression, the hypothesis still applies. These lenses may ultimately be combined with atropine to compound their effect on myopia.

**ATROPINE**

Atropine is an alkaloid extracted from a variety of plants (Atropa belladonna, Datura stramonium, and Mandragora...
The name comes from the original use of dilating a woman's pupils during the 16th century to make them appear more attractive. Atropine is a non-selective muscarinic antagonist which causes maximum mydriasis within 40 minutes of the initial drop and cycloplegia within 5-48 hours after the first drop. The residual effects on accommodation last 10-14 days.\(^{184}\)

The first report describing the use of atropine to slow myopia progression was by Wells in the 19th century,\(^ {185}\) during which time atropine was used extensively to slow myopia progression.

### TABLE 1

Historical atropine studies are presented. It is apparent that in all of these studies, atropine is effective in slowing the progression of myopia. Though nearly all of these studies are retrospective, most do have some form of control. In these studies the researchers were not blind, and they were performed before sophisticated A-scan measurements. In spite of their limitations, the number of positive studies with minimal side effects is impressive. Also, there is some strong long-term data.

<table>
<thead>
<tr>
<th>Author</th>
<th># of children completed study</th>
<th>Treatment</th>
<th>Length of study</th>
<th>Control Group (mean progression)</th>
<th>Atropine Group (mean progression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gimbel(^ {106}) 1973</td>
<td>594</td>
<td>1gtt 1% atropine OU</td>
<td>3 years</td>
<td>-1.22D (over 3 years)</td>
<td>-0.41D (over 3 years)</td>
</tr>
<tr>
<td>Kelly et al(^ {175}) 1975</td>
<td>282</td>
<td>1gtt 1% atropine OU q.d. or b.i.d.</td>
<td>1 year</td>
<td>-0.52D (over 6 months)</td>
<td>+0.58D decrease in myopia (over 1 year)</td>
</tr>
<tr>
<td>Dyer(^ {110}) 1979</td>
<td>168</td>
<td>1gtt 1% atropine OU qhs</td>
<td>2-8 years (avg. 4.2 years)</td>
<td>Change in myopia: No change or improved: 2% -0.75D: 14% 1.00-1.75D: 35% 2.00-2.75D: 22% 3.00D: 27%</td>
<td>Change in myopia: No change or improved: 47% -0.75D: 34% 1.00-1.75D: 8% 2.00-2.75D: 7% 3.00D: 1%</td>
</tr>
<tr>
<td>Sampson(^ {107}) 1979</td>
<td>100</td>
<td>1gtt 1% atropine OU qhs +2.25D bifocal</td>
<td>1 year</td>
<td>NO CONTROL</td>
<td>Change in myopia: -0.25 to +0.50D: 79% +0.75D to +1.00D: 15% &gt;+1.00D: 6%</td>
</tr>
<tr>
<td>Bedrossian(^ {8}) 1979</td>
<td>90 children on atropine (62 followed for 2 yrs, 28 followed for 4)</td>
<td>1% atropine in 1 eye qhs x 1 year, next year atropine qhs in other eye</td>
<td>4 years</td>
<td>-0.82 D/Y (over first year, similar results during 4 years)</td>
<td>+0.21 D decrease in myopia (over first year, similar results during 4 years)</td>
</tr>
<tr>
<td>Gruber(^ {111}) 1985</td>
<td>200</td>
<td>1gtt 1% atropine OU qhs</td>
<td>1-7.5 years (mean treatment 1-2 years)</td>
<td>-0.28D/Y</td>
<td>-0.11D/Y</td>
</tr>
<tr>
<td>Brodstein(^ {109}) 1984</td>
<td>399</td>
<td>1gtt 1% atropine OU qhs +2.25D bifocal</td>
<td>1-9 years (median treatment 3 years)</td>
<td>-0.34D/Y</td>
<td>-0.12D/Y</td>
</tr>
<tr>
<td>Brenner(^ {113}) 1985</td>
<td>79</td>
<td>1gtt 1% atropine OU qhs</td>
<td>1-9 years (mean treatment 2.9 years)</td>
<td>NO CONTROL</td>
<td>Average refractive error at initial exam was -0.87D and increased over the nine years of maximum follow-up to an avg of -2.73D</td>
</tr>
<tr>
<td>Yen et al(^ {115}) 1985</td>
<td>96</td>
<td>1gtt1% atropine OU qhs bifocals</td>
<td>1 year</td>
<td>-0.91D/Y</td>
<td>-0.22D/Y</td>
</tr>
</tbody>
</table>

The effects of atropine on accommodation last 10-14 days.\(^ {184}\)

The first report describing the use of atropine to slow myopia progression was by Wells in the 19th century,\(^ {185}\) during which time atropine was used extensively to slow myopia progression.
The use of atropine declined after the turn of the 20th century due to paralysis of accommodation and photophobia.\textsuperscript{129}

During the First International Myopia Conference in 1964, Bedrossian and Gostin reported on the beneficial effect of atropine on slowing myopia progression. This report provided a renewed interest in the treatment of myopia progression with atropine.\textsuperscript{113} Seventy-five patients in an A-B cross over design between the ages of 7 and 13 were prescribed one drop of 1% atropine in one eye for the first year and then the other eye for following year. After 1 year of treatment, the eyes treated with atropine had an average decrease of 0.21 D of myopia, as compared to the control eyes that had an average increase of 0.82 D of myopia. After the second year, the eye that received atropine had an average decrease of 0.17 D of myopia. The control eyes (which one year before were treated with atropine) had an increase in myopia on average of 1.05 D. Of the 150 treated eyes, 112 showed either a decrease in myopia or no change, whereas only 4 eyes that were used as the control had a decrease or no change in myopia.\textsuperscript{114,117}

Recent studies using topical atropine have demonstrated both statistically and clinically significant reductions in myopia progression (See table 2). Chiang et al.\textsuperscript{187} performed a retrospective, non-comparative case series to evaluate the treatment of childhood myopia with the use of atropine and bifocal spectacle correction. Seven hundred and six Caucasian children from 6 to 16 years of age were treated with one drop of 1% atropine once weekly in both eyes for 1 month to 10 years (median 3.62 years). Seventy percent of the children were completely compliant with the regimen and 30% were only partially compliant. The most common reasons stated for the partial compliance were photophobia, inconvenience, or headache. The mean rate of myopia progression in the completely compliant group was -0.08 D/year, as compared to -0.23 D/year in the partially compliant group.

Kennedy et al.\textsuperscript{129} reported on 214 children aged 6 to 15 years old who were treated with one drop of 1% atropine once daily in both eyes for 18 weeks to 11.5 years (median 3.35 years). The mean myopia progression during atropine treatment was

<table>
<thead>
<tr>
<th>Treatment method</th>
<th>Percentage Reduction</th>
<th>Projected increase in myopia after 1 year</th>
<th>Projected increase in myopia after 8 years</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undercorrection</td>
<td>-8%</td>
<td>0.65</td>
<td>5.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spectacle control</td>
<td>0%</td>
<td>0.60</td>
<td>4.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripherally correcting glasses</td>
<td>1%</td>
<td>0.59</td>
<td>4.75</td>
<td>1, 10</td>
<td></td>
</tr>
<tr>
<td>Progressive glasses</td>
<td>4%</td>
<td>0.50</td>
<td>4.61</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>bifocals</td>
<td>16%</td>
<td>0.50</td>
<td>4.03</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Esophoria + bifocals</td>
<td>20%</td>
<td>0.48</td>
<td>3.64</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Periscope QD</td>
<td>34%</td>
<td>0.40</td>
<td>3.17</td>
<td>22</td>
<td>4, 8</td>
</tr>
<tr>
<td>Peripherally correcting CLs</td>
<td>40%</td>
<td>0.36</td>
<td>2.88</td>
<td>22</td>
<td>8, 9, 10</td>
</tr>
<tr>
<td>Orthokeratology</td>
<td>45%</td>
<td>0.33</td>
<td>2.64</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Atropine 0.25%</td>
<td>58%</td>
<td>0.25</td>
<td>2.02</td>
<td>22</td>
<td>9, 10</td>
</tr>
<tr>
<td>Atropine 0.1%</td>
<td>60%</td>
<td>0.24</td>
<td>1.92</td>
<td>22</td>
<td>9, 10</td>
</tr>
<tr>
<td>Atropine 0.1%</td>
<td>62%</td>
<td>0.23</td>
<td>1.82</td>
<td>22</td>
<td>7, 8, 10</td>
</tr>
<tr>
<td>Atropine 0.05%</td>
<td>65%</td>
<td>0.21</td>
<td>1.68</td>
<td>22</td>
<td>7, 8, 10</td>
</tr>
<tr>
<td>Atropine 0.05%</td>
<td>67%</td>
<td>0.20</td>
<td>1.58</td>
<td>22</td>
<td>7, 8, 9, 10</td>
</tr>
<tr>
<td>Atropine 0.05%</td>
<td>76%</td>
<td>0.15</td>
<td>1.35</td>
<td>22</td>
<td>7, 8, 9, 10</td>
</tr>
<tr>
<td>Atropine 0.5%</td>
<td>80%</td>
<td>0.12</td>
<td>0.96</td>
<td>23</td>
<td>5, 7, 8</td>
</tr>
<tr>
<td>Atropine 1%</td>
<td>90%</td>
<td>0.06</td>
<td>0.48</td>
<td>23</td>
<td>5, 7, 8</td>
</tr>
</tbody>
</table>

Table 2 presents the best estimate of the effectively in reducing the progression of myopia for each treatment. First, we determined the mean myopic progression rate per year for spectacle lenses from each study, then, we determined the mean myopic progression for all the other treatment modalities (D/year). We then corrected each treatment, i.e., if the mean rate of progression of the control was different than our calculated. Column 3 depicts the findings after 1 year. We then assumed a linear progression and calculated the amount of increased myopia after 8 years (column 4). Columns 5 and 6 present pros and cons of each treatment. 1 = Not effective, 2 = Expensive, 3 = Blur, 4 = Redness, 5 = Allergy, 6 = Infection, 7 = Mydriasis, 9 = Minimal scientific data, 10 = Not available, 21 = Inexpensive, 22 = Moderately effective, 23 = Very effective, 24 = Strong scientific data, 25 = Long term studies, 26 = Minimal side effects.

Subsequently, Gimbel,\textsuperscript{115} Kelly et al.\textsuperscript{186} Dyer,\textsuperscript{119} Sampson,\textsuperscript{116} Bedrossian,\textsuperscript{114,117,121} Gruber,\textsuperscript{111} Brodstein,\textsuperscript{118} Brenner,\textsuperscript{122} and Yen,\textsuperscript{124} from 1973 to 1989, reported in a number of studies that children using atropine had a reduction in the rate of myopia progression. These children demonstrated a range of progression, which varied from an increase of 0.22 D/year to a decrease of 0.58 D/year as compared to the control groups, which demonstrated an increase from 0.28 D/year to 0.91 D/year. Table 1 summarizes these studies. Most of the patients in these studies were between 6 and 13 years old, which is when the greatest progression of myopia occurs. 0.05 D/year, which was significantly less than the control subjects (0.36 D/year). Myopia progression after atropine was discontinued was calculated for 158 patients. Upon discontinuing atropine, children progressed 0.22 D/year, as compared to 0.13 D/year in the control group. However, this increase in myopia progression was not enough to offset the decrease in myopia progression during atropine treatment. The final refraction was still much lower in the atropine treated group.
Chua et al.\textsuperscript{133} performed a prospective, randomized, double-masked, placebo-controlled study on 400 children, ages 6 to 13 years, evaluating the use of atropine as a method for myopia control. This study, known as the Atropine for the Treatment of Childhood Myopia study (ATOM), evaluated the efficacy and safety of topical atropine in slowing both the progression of myopia and axial elongation in Asian children. One eye of each subject was randomly chosen for treatment (one drop of 1% atropine), while the other eye received an eye drop placebo once nightly for 2 years. All children were prescribed progressive, photochromic lenses. Three hundred forty-six children completed the study. After 2 years, the mean progression of myopia in the placebo-treated eyes was 1.20 ± 0.69 D and only 0.28 ± 0.92 D in the atropine-treated eyes. Over a 2-year period, there was a 77% reduction in the amount of myopia progression for children using atropine as compared to the control. The mean change in axial elongation in the placebo-treated eyes was 0.38 ± 0.38 mm, whereas in the atropine-treated eyes the axial length was essentially unchanged (decreased by 0.02 ± 0.35 mm). After 2 years, 65.7% of the atropine-treated eyes progressed less than -0.50D, whereas only 16.1% of the placebo-treated eyes progressed less than -0.50D. Only 13.9% of atropine-treated eyes progressed more than -1.00D whereas 63.9% of placebo-treated eyes progressed more than -1.00D.

This bar graph depicts the difference in percentage of children progressing less than -0.50D, whereas only 16.1% of the placebo-treated eyes progressed less than -0.50D. Only 13.9% of atropine-treated eyes progressed more than -1.00D whereas 63.9% of placebo-treated eyes progressed more than -1.00D.

**Figure 4** - Progression of Myopia in Eyes Treated or Not Treated with Atropine

This bar graph depicts the difference in percentage of children progressing less than -0.25 D in a year with either atropine 1% or a control, and those progressing more than -1.00 D with atropine or a control. It is readily apparent that atropine is effective at slowing the progression of myopia over a 2-year period of time.

Figure 4 compares the percentage of children who progressed less than -0.50 D and more than -2.00 D over the 2 years. The authors concluded topical 1% atropine was effective in slowing myopia progression.

Shih et al.\textsuperscript{128} evaluated the efficacy of various concentrations of atropine in slowing myopia progression. Two hundred children, 6 to 13 years of age, were randomly prescribed one drop of 0.5%, 0.25%, or 0.1% atropine, or 0.5% tropicamide (control treatment) in both eyes nightly. Children prescribed 0.5% atropine were given a bifocal (+2.00 add), children prescribed 0.25% atropine were undercorrected by 0.75 D, and children using 0.1% atropine were given their full distance prescription. Ninety-three percent of children completed the study. At the end of 18 months, the mean myopic progression was 0.42 ± 0.07 D in children using 0.5% atropine with multifocal glasses, which was significantly less than the 1.19 ± 0.07 D and 1.40 ± 0.09 D for children using placebo drops with multifocal glasses and single vision glasses, respectively. There was no significant difference between the last two groups, thus the authors concluded that the reduction of myopia progression was due solely to the use of atropine and not the multifocal spectacle correction. Approximately 50% of the children using atropine with multifocal glasses progressed less than 0.25 D/year and only 10% progressed greater than 0.75 D/year. Ten percent of the children using placebo drops with multifocal glasses progressed less than 0.25 D/year, while approximately 60% progressed greater than 0.75 D/year. Approximately 5% of children using placebo drops with single-vision lenses progressed less than 0.25 D/year and 70% progressed greater than -0.75 D/year. The progression of myopia in all the groups was highly correlated with an increase in axial length.

**Figure 4** - Progression of Myopia in Eyes Treated or Not Treated with Atropine

This bar graph depicts the difference in percentage of children progressing less than -0.25 D in a year with various concentration atropine (0.1%, 0.25%, 0.5%) or the control, and those progressing more than -1.00 D with atropine (0.1%, 0.25%, 0.5%) or the control. It is readily apparent that atropine is effective at slowing the progression of myopia over a 2-year period of time in Shih’s study, and the effect on progression varies with the concentration, though the results may have been affected by the different lenses worn by each group.\textsuperscript{128} A recent study suggests that the effectivity is not significantly dependent on the concentration.\textsuperscript{133}

Shih et al.\textsuperscript{128} compared the concentration of atropine in slowing myopia progression. The randomized clinical trial included 227 children, 6 to 13 years of age, placed into one of three groups: group one received 0.5% atropine daily with multifocal glasses, group two received a placebo drop daily with multifocal glasses, and group three received a placebo drop daily while wearing single vision glasses. One hundred and eighty eight children completed the study. At the end of 18 months, the mean myopic progression was 0.42 ± 0.07 D in children using 0.5% atropine with multifocal glasses, which was significantly less than the 1.19 ± 0.07 D and 1.40 ± 0.09 D for children using placebo drops with multifocal glasses and single vision glasses, respectively. There was no significant difference between the last two groups, thus the authors concluded that the reduction of myopia progression was due solely to the use of atropine and not the multifocal spectacle correction. Approximately 50% of the children using atropine with multifocal glasses progressed less than 0.25 D/year and only 10% progressed greater than 0.75 D/year. Ten percent of the children using placebo drops with multifocal glasses progressed less than 0.25 D/year, while approximately 60% progressed greater than 0.75 D/year. Approximately 5% of children using placebo drops with single-vision lenses progressed less than 0.25 D/year and 70% progressed greater than -0.75 D/year. The progression of myopia in all the groups was highly correlated with an increase in axial length.
the control group had no myopic progression. The authors defined fast myopic progression to be greater than 1.00 D/year. Four percent of children in the 0.5% atropine group, 17% in the 0.25% atropine group, and 33% in the 0.1% atropine group demonstrated fast myopic progression, whereas 44% in the control group showed fast myopic progression. The authors concluded that all three concentrations of atropine were effective in slowing myopia progression, with 0.5% being the most effective, although their results may have been confounded by the differences in lenses that each group used. (See Figure 5.)

Lu et al. investigated the effect of seasonal modifications in the concentration of atropine used on slowing the progression of myopia (n=120). The concentration was modified based upon season, sunlight intensity, and severity of myopia: 0.1% for summer, 0.25% for spring and fall, and 0.5% for winter for 63 children, while 57 children received no drops (control). For children less than 7 years of age with less than 0.50 D of myopia, 0.5% atropine was not used. The use of atropine was reduced to twice weekly for very low myopes (less than 0.75 D). Sunglasses with ultra-violet (UV) protection were prescribed for children to be used when outdoors, and progressive lenses were given for children who reported difficulty in the classroom. After one year, mean myopia progression was 0.28 ± 0.75 D for children using atropine and 1.23 ± 0.44 D for children in the control group. There was a 77% reduction in myopia progression for children using atropine as compared to the control group.

Lee et al. conducted a retrospective chart review of 57 Taiwanese children 6 to 12 years of age to evaluate the efficacy of 0.05% atropine in slowing myopia progression. Twenty-one children received one drop of 0.05% atropine in both eyes every night while 36 children were not treated (control). Mean progression of myopia was 0.28 ± 0.26 D/year in the 0.05% atropine group, as compared to 0.75 ± 0.35 D/year in the control group. The authors considered myopia progression less than -0.50 D/year to be relatively stationary, whereas greater than 0.50 D of myopia progression/year to be poorly controlled. Eighty-three percent of children in the treatment group had relatively stationary myopia progression, as compared to only 22.2% in the control group. In the 0.05% atropine group, 16.7% of children progressed greater than 0.50 D/year, whereas 77.8% of the control group progressed greater than -0.50 D/year. The authors concluded, “0.05% atropine regimen is a good starting point as medical treatment for the control of myopia progression.”

Fang et al. conducted a retrospective chart review of 50 Taiwanese children aged 6 to 12 years to evaluate the efficacy of 0.025% atropine for prevention of myopia onset in pre-myopic children (spherical equivalent refraction of less than +1.00 D, with cylindrical refraction of less than -1.00 D). Twenty four children received one drop of 0.025% atropine in both eyes every night and 26 children were untreated (control). Mean myopic shift was -0.14 ± 0.24 D/year in the 0.025% group, as compared to -0.58 ± 0.34 D/year in the control group. The authors considered a myopic shift greater than -0.50 D/year to be a fast myopic shift. Eight percent of children using atropine had a fast myopic shift, compared to 58% of the control group. The authors defined the onset of myopia as a change equal to or greater than 1.00 D in the myopic direction. Twenty one percent of children using atropine became myopic, as compared to 54% of children in the control group. The authors concluded, “topical administration of 0.025% atropine can prevent myopia onset and myopic shift in pre-myopic schoolchildren for a 1-year period.”

Recently the ATOM2 studies were performed to evaluate lower concentrations of atropine. The mean myopia progression at 2 years was 0.15 D/year for atropine 0.5%; 0.19 D/year for atropine 0.1%; and 0.24 D/year for atropine 0.01% groups. In comparison, myopia progression in ATOM1 at 2 years was -0.60 D/year in the placebo group and -0.14 D/year in the atropine 1% group. The authors found that differences in myopia progression (0.19 D) and axial length change (0.14 mm) between groups were small and clinically insignificant. Atropine 0.01% had a negligible effect on accommodation and pupil size, and no effect on near visual acuity. They concluded that atropine 0.01% had minimal side effects when compared with atropine at 0.1% and 0.5%, and retained comparable efficacy in controlling myopia progression. (See Table 2 for a comparison of each method of treatment over time.)

Prior to this paper, there had been two other reviews of various treatments for myopia. In each review the authors acknowledged the efficacy of atropine in slowing myopia progression. However, each author independently, without any supporting data from trial subjects, concluded that the benefit of atropine use for myopia control is outweighed by the possible systemic and ocular side effects.

These conclusions warrant a review of the side effects associated with atropine. Systemic side effects associated with topical atropine use can be divided into three types: fatal, serious, and mild. There have been 8 deaths associated with atropine, and only one since 1950. All the deaths, except one, were in children 3 years of age or younger suffering from congenital health conditions and who were ill at the time of presentation. The one child without congenital defects received a fatal dose of 18.1 mg of atropine within a 24-hour period. Thus, there have been no fatal occurrences in children over 3 years of age with appropriate atropine dosing.

Pupillary dilation and cycloplegia from atropine result in glare, photophobia, and near vision blur which are the most commonly reported side effects to atropine. These symptoms can be minimized with the use of photochromic progressive lenses, or the use of atropine in concentrations less than 0.025%. Serious systemic and central nervous system side effects occur at 20 times the minimum dose and include the following: hot and dry skin, facial flushing, dryness of the nose, loss of taste, constipation, difficulty swallowing, difficulty sleeping, drowsiness, excitement, changes in heartbeat, hallucinations, fever, headache, dizziness, nervousness, nausea, vomiting, and allergic reactions (rash, hives, itching, difficult breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue). Decreased salivation and drying of the mouth are usually the first signs of toxicity. The side effects of atropine are serious, but are fortunately short-lived, and have never been fatal, in healthy children over 2 years of age.

During the 2 year ATOM study that included 400 children, no serious adverse events were reported. Reasons for withdrawal were: allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical difficulties (3.5%) and others (0.5%). There was no decrease in best-corrected visual acuity. Glare and photophobia were minimized with the use of photochromic lenses.
Shih et al.\textsuperscript{128} reported the incidence of adverse effects due to the use of topical atropine in their study of 200 children (186 children completed the study). Seventy eight percent of the children using 0.5% atropine had no complaints of light sensitivity after 3 months. Fifteen percent of the children who used 0.5% atropine dropped out of the study: two children complained of severe light sensitivity, two children were fearful of long-term side effects, one child had recurrent allergic blepharitis, and four children were unable to consistently put drops in every night. Children who used 0.25% or 0.1% atropine reported no systemic or ocular complications. One hundred percent of the children who used 0.1% atropine, and 93% of children who used 0.25% atropine, did not complain of photophobia or blurred near vision after 4 weeks of using atropine.

In Kennedy’s study,\textsuperscript{129} of the 214 patients who were using 1% atropine, 40% reported photophobia, 10.7% reported blurred vision, 3.7% reported ocular discomfort, 3.7% reported ocular allergic reaction, 2.3% reported headaches, 2.3% reported bad taste in their mouth, 1.9% reported dry mouth, 1.4% reported dry eyes, 0.5% reported psychological problems, and 0.5% reported dizziness. Though the percentage of patients with side effects appears high, they did not result in a significant dropout rate. (The high percentage of photophobia reported by Kennedy was prior to today’s fast acting improving photochromic lenses which have eliminated most of the subjective complaints of photophobia.\textsuperscript{133})

In a study of 21 children who used atropine 0.05%, seven complained of photophobia in the morning, but only one had photophobia that continued into the afternoon, and only two children reported blurred near vision.\textsuperscript{134} No child reported irritation or an allergic reaction. In another study using 0.025% atropine,\textsuperscript{137} only four children in the treatment group and two children in the control group reported photophobia (24 and 26 children completed the study, respectively). None of the children reported blurred near vision nor had any systemic side effects.

In the Amblyopia Treatment Studies (ATS),\textsuperscript{195-197} 1% atropine was dosed unilaterally in a group of subjects being treated for amblyopia. In ATS1,\textsuperscript{195} which included 204 patients less than 7 years of age, at least one ocular side effect was reported for 26% of children, most commonly light sensitivity (18%), lid or conjunctival irritation (4%), and eye pain or headache (2%). Two patients reported facial flushing, one of who remained on atropine with no further problems and one was switched to homatropine. Atropine was not discontinued due to its side effects in any other patients. No other systemic side effects of atropine were reported. In ATS3,\textsuperscript{196} among 201 patients aged 7 to 13 years old, atropine was generally well tolerated. Four percent of patients discontinued treatment due to symptoms related to cycloplegia. Ocular side effects noted in ATS4,\textsuperscript{197} (most commonly light sensitivity), were reported by 13 (16%) of the children receiving daily atropine and 25 (29%) of the children receiving weekend atropine. However, these symptoms did not result in a change in compliance with the treatment regimen.

The ATOM study\textsuperscript{133} found that the paralysis of accommodation and the associated near vision blur secondary to atropine treatment was temporary and was reversible upon cessation of treatment. Six months after cessation of atropine, the measured amplitude of accommodation was larger than the pre-treatment level. In addition, at 6 months after terminating atropine, there was no significant difference in near visual acuity in the atropine-treated eyes as compared to placebo-treated eyes.\textsuperscript{133}

In summary, atropine has been used in both myopia control and amblyopia treatment studies with a minimal number of local side effects and no serious side effects. In none of the studies were the local side effects serious enough to cause a large number of patients to discontinue atropine treatment. (Anecdotally, the first author of this paper has used atropine for the last ten years on over 100 patients without any incident of a serious side effect, and notes that most children surprisingly tolerate atropine with minimal complaints.)

There is always concern of long-term effects when using any medication. Luu et al.\textsuperscript{198} assessed retinal function in children on atropine treatment, by performing multifocal electroretinograms (mERGs) on 48 children who received 1% atropine eye drops once daily for 2 years and 57 children who received placebo eye drops. Recordings were performed during the second and third month after the cessation of treatment. Both the response amplitude and implicit time of N1 and P1 and k21 were measured. The difference between the N1 and P1 amplitudes and implicit times between atropine-treated and placebo-treated eyes were not statistically significant. There was also no significant difference between k21 amplitude and implicit time between atropine-treated and placebo-treated eyes. The authors of this study concluded that since retinal function was not significantly affected soon after stopping atropine (when the concentration of atropine in the retina would be highest), that it is highly unlikely that there would be retinal impairment years later when the concentration of atropine would be less.

To assess whether the slower rate of myopia progression and axial length elongation would be maintained after stopping atropine, or if there would be a rebound effect that would eliminate the initial treatment effect, the patients from the ATOM study were evaluated up to 1 year after stopping treatment.\textsuperscript{136} Only a small number of children dropped out after the two years of treatment, i.e., 3% of the placebo group and 5% of the atropine group. After atropine was discontinued for 2 years, the mean myopic progression in the atropine-treated group was 1.14 ± 0.80 D over 1 year; whereas the progression in placebo-treated eyes was 0.38 ± 0.39 D. In the first half of the third year, the mean rate of myopia progression in the atropine-treated eyes was 1.51 ± 1.40 D/year, as compared to 0.40 ± 0.65 D/year in the placebo-treated eyes. Over the second half of the third year, the mean rate of myopia progression in the atropine-treated eyes was -0.76 ± 0.70 D/year, as compared to -0.38 ± 0.58 D/year in the placebo-treated eyes. For the atropine treated eyes, the rate of myopia progression was significantly less in the second half of the third year as compared to the preceding 6 months. Over the entire 3 year period, the eyes treated with atropine still showed much less myopia than the placebo-treated eyes. Although the effect of atropine on the final refractive status was reduced after cessation of atropine for 1 year, the change in axial length of the atropine-treated eyes was significantly smaller than of the placebo-treated eyes, and did not change as much as the refractive error. Over the 3 years, the increase in axial length of the atropine-treated eyes was 0.29 ± 0.37 mm, as compared to 0.52 ± 0.45 mm in the placebo-treated eyes. The authors suggested that most of the increase in refractive status was not...
due to a rebound effect but due to the more powerful cycloplegic effect obtained with atropine 1% as compared to cyclogel 1% which was used for measurements after termination of atropine.

In conclusion, since discontinuation of atropine had a small regression in refractive error but no effect on axial length, most of the change appears to be due to the difference in cycloplegic refraction achieved with cyclogel as compared to atropine. Atropine causes a greater cycloplegic effect than Cyclogel 1%, thus, the initial baseline for refractive error demonstrates more myopia with Cyclogel 1% than the amount measured immediately after beginning treatment with atropine 1%. This results in a greater perceived improvement of myopia control during the first year treatment and a falsely perceived rebound effect at the end of treatment. It is more important to note that axial length data did not change when atropine treatment was terminated. The study also showed that over the course of three years only 23% of atropine-treated eyes progressed more than 2.00 D as compared to 30% of placebo-treated eyes. Only 44% of atropine-treated eyes progressed more than 1.50 D as compared to 56% of placebo-treated eyes.

Atropine is a non-specific, muscarinic antagonist, which binds to muscarinic receptors on the ciliary muscle and thus blocks accommodation. Initially, atropine was suggested as a method for myopia control based on the thought that the act of accommodation influenced myopia progression; this presumed mechanism for control has since been disproven. McBrien et al. were the first to demonstrate that atropine reduces experimental myopia and axial elongation via a non-accommodative mechanism. McBrien et al. monocularly deprived (MD) chicks of pattern vision by placing a translucent occluder over the left eye, which has been found to cause an increase in axial elongation and myopia in human infants. Chickens, tree shrews, cats, gray squirrels, marmosets, and monkeys. Since the muscles of chicks contain only nicotinic receptors, atropine should not have had an effect on accommodation or pupil size. Chicks were treated with intravitreal injections of atropine or saline; after eight days of MD there was 20.9 D of experimentally induced myopia in saline-injected chicks, as opposed to only 2.8 D of myopia in atropine-injected chicks. This significant reduction in experimentally induced myopia in atropine-injected MD chicks was associated with a significant reduction in axial length elongation (0.21 mm versus 1.04 mm). Corneal iontophoresis of 10% carbachol, which binds to nicotinic receptors, induced the same degree of accommodation in both atropine-injected and saline-injected eyes, demonstrating that accommodation was not affected by atropine. Thus, the authors concluded that: “chronic atropine administration prevents experimentally induced myopia in chick(s) via a non-accommodative mechanism.”

Applying translucent lenses designed to deprive only part of the visual field in chicks results in local areas of axial elongation. Atropine blocks the effects of local elongation. Since it is not possible to accommodate different amounts in the same eye, some other mechanism besides accommodation, must be responsible for localized elongation. Emmetropization can still occur even when the optic nerve is severed, disrupting the feedback mechanism necessary for accommodation, which suggests that local retinal mechanisms may be sufficient for gross regulation of refractive error. It has also been demonstrated that experimental myopia can be induced in a species that does not possess a functional accommodative system. Lastly, experimental myopia can be produced in a species where the accommodative feed back loop has been blocked by bilateral destruction of the Edinger-Westphal nucleus. Since accommodation does not play a major role in myopia development, the obvious question then is how does atropine prevent myopia progression? Muscarinic receptors located in the retinal pigment epithelium are believed to be involved in the development of refractive error. However, the biochemical basis of how atropine inhibits axial elongation remains obscure, and there are doubts whether muscarinic receptors are involved at all. These findings have led to the search for other muscarinic drugs that do not affect accommodation or pupillary dilation.

Pirenzepine, an M1-selective muscarinic antagonist, has those attributes and has been used to retard the progression of myopia in animals without significantly affecting accommodation or pupillary size. In experimental studies on humans, Bartlett et al. demonstrated that pirenzepine caused minimal mydriasis or effect on accommodative amplitude. They concluded that the adverse events reported were mild or moderate (redness and irritation) in severity but resolved rapidly. Siatkowski et al. evaluated the safety and efficacy of 2% pirenzepine ophthalmic gel in school-aged children with myopia. The children, aged 8 to 12 years, had spherical equivalents from -0.75 to -4.00 D, and astigmatism of 1.00 D or less. At 1 year, there was a mean increase in myopia of -0.26 D in the pirenzepine group versus -0.53 D in the placebo group. Eleven percent of the patients in the pirenzepine group discontinued participation in the study because of adverse effects while none of the placebo group did. Pirenzepine was effective (50%) and relatively safe in slowing the progression of myopia during a one-year treatment period. In the 2 year follow-up study, Siatkowski et al. reported that the mean increase in myopia was -0.58 D in the pirenzepine group and -0.99 D in the placebo group. Only one more patient dropped out in the second year. They concluded that pirenzepine ophthalmic gel 2% was effective in slowing the progression of myopia over a 2 year period without significant side effects. It is of interest to note that axial length did not have a significant change in the treatment group. Pirenzepine unfortunately is not currently commercially available in the US.

Tan et al. evaluated the safety and efficacy of pirenzepine 2% ophthalmic gel in slowing the progression of myopia in school-aged children using a parallel-group, placebo-controlled, randomized, double-masked study. Subjects received 2% gel twice daily (gel/gel), 2% gel once daily (placebo/gel), or placebo twice daily (placebo/placebo) for one year. At 12 months, there was a mean increase in myopia in the gel/gel group by -0.47 D, placebo/gel group by -0.70 D, and placebo/placebo group -0.84 D. Eleven percent of the pirenzepine group discontinued participation in the study due to adverse events. Tan et al. concluded that pirenzepine gel 2% twice daily resulted in approximately 45% efficacy in slowing the progression of myopia over a 1 year treatment period and was a relatively safe treatment.

**DISCUSSION**

The purpose of this literature review is to provide an updated review of the current research in regard to slowing myopia progression and to provide the reader with unbiased information to help make appropriate clinical decisions. Atropine used once a day in both eyes is clearly the most...
successful treatment to slow the progression of childhood myopia. Cumulative data from a number of studies employing atropine 1% demonstrated up to a tenfold reduction in the rate of myopia progression as compared to untreated eyes, 0.05 D/year verses 0.50 D/year. Concentrations of less than 0.5% result in a decreased efficacy but still demonstrate a stronger effect on reducing myopia than other treatment regimens. Recent studies demonstrate that lower concentrations, i.e., 0.025% or 0.01% are more effective than Ortho-K or other soft lens designs.

The most common side effects of atropine include pupillary dilation, which leads to an increased sensitivity to light and UV radiation, and cycloplegia resulting in near vision blur. These problems have been minimized with the use of progressive lenses which incorporate photochromic properties, and UV filtration. The risk of other ocular and systemic side effects is minimal. In the studies included in this paper, more than 85% of children were able to tolerate the side effects, and continued with their assigned treatment protocol. The minimal local effects in most patients were not serious enough to cause discontinuation of atropine treatment. Previous reviews that state that atropine is not used or should not be because it is not tolerated by patients have no scientific basis. (Anecdotally, the first author, who has used atropine, progressive lenses, and contact lenses in the treatment of myopia, has had minimal problems with patient tolerance of atropine.) Only one of the long-term studies provided any evidence of rebound, while all of the others did not. However, this rebound effect was explained by the initial cycloplegic effect of atropine being greater than cyclogel. The exact mechanism of atropine in slowing myopia progression does not involve accommodation; it is presumed to block the signal stimulating the elongation of the globe via receptors at the retina.

The studies reviewed using atropine in children vary in methodology, inclusion criteria, number of subjects, duration and completeness of follow-up, and data analysis. Despite this, they all show that the progression rate of myopia with atropine use is significantly lower than in the control group and the ability to control myopia is far superior to any other treatment. No study to date has determined how long a child needs to be on atropine to slow myopia progression, or how fast the myopia will progress after cessation of treatment for longer than 2 years. Parents may be concerned that although atropine has been used for over 100 years for long durations in patients with uveitis and in multiple studies for 1 to 4 years, the long term effects on a large population of children is unknown. Clinicians may be concerned by the possibility of long term-increased toxicity due to light exposure; however, current lenses that incorporate UV filters and photochromic lenses mitigate the risk.

Children with a strong family history of myopia who are rapidly progressing in myopia should be given the option of atropine use. Figure 6 depicts the long-term history of a patient treated with progressive addition lenses and atropine 1% at night. The atropine stopped the progression with a paucity of symptoms. If symptoms do develop while using 1% atropine, then 0.5% can be used. Currently, 0.5% atropine is not commercially available, but can be formulated at compounding pharmacies upon request. Seasonal variation can be used to titrate the appropriate concentration for symptoms, i.e., lower concentration during the summer when children are not reading as much and the sun is stronger. More recent studies have shown that even lower dosages such as atropine .01% may be used alone or to supplement orthokeratology or any other method of myopia control if initial reduction is not adequate. Clinically, the biggest problem with the higher concentrations of atropine is that the social desire to eliminate glasses cannot be met due to loss of accommodative ability and need for compensatory lenses.

For those children in whom myopia is progressing more slowly, or there is a need to eliminate glasses for either cosmetic or functional reasons, the second choice might be orthokeratology. Orthokeratology has a high acceptance rate with children and provides a “wow” phenomenon, often seen with LASIK. Patients are appreciative of it’s ability to eliminate the need for glasses during the day and decreased the progression of myopia. It should be acknowledged that orthokeratology comes with its own risks of discomfort, keratitis, and potential corneal ulceration. Patients are often concerned about the risk of overnight wear of contact lenses. Even though the risk of complications with overnight wear of orthokeratology is appreciably less than with soft lenses, it still exists. The decreased risk is probably related to improved oxygen permeability of the lenses and reduced adhesion of either proteins or bacteria. Though not currently available, myopia-controlling soft multifocal contact lenses, which will attempt to correct for hyperopic peripheral retinal defocus, may have an exciting future. Since there are no currently FDA approved lens designs, the closest commercially manufactured lens today is either the Vistakon Oasis Presbyopic lens or the Cooper vision Biofinity Multifocal “D” lens. (See figure 7 for a comparison of each treatment.)

The last treatment recommended is progressive addition lenses for esophoric patients. Utilization of progressive lenses in other non-esophoric myopic patients provides minimal benefits, but

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**Figure 6** – Effect of Treatment Over Time Of Myopic Patient

This graph depicts the progression of myopia of a patient of one of the authors (JC). Progressive lenses initially slowed the progression of myopia in the first year but not in subsequent years. Once the patient was placed on atropine, the progression stopped. The patient, now 16 years old, was recently seen by (JC) without progression of his myopia. He has elected to stop using the atropine, and was recently fit with orthokeratology contact lenses without sequel. His unaided visual acuity in each eye is 20/20.
also minimal risk. In the end, patients should be informed of the current status of myopia treatment with either an explanation or literature to explain the options. Caregivers and patients should be provided unbiased risks and benefits of each treatment strategy to help make informed decisions. It is the obligation of both optometrists and ophthalmologists to properly educate patients. There is a true risk of not slowing myopia progression; both patient and doctor have to make appropriate, scientifically and clinically valid assessments regarding appropriate treatment. (See Figure 7 for a comparison of effectiveness of each treatment over time.)

As a general rule, the more sedentary the patient, the earlier the onset, the greater the risk factors (i.e., parents having myopia or family history of retinal holes or tears) the more likely that atropine will be suggested. Atropine dosage can be seasonally varied to reduce photophobia and blur complaints. On the other hand, patients who develop myopia later, associated with less progression, and/or are more athletic, the more likely that orthokeratology should be recommended. When parents have concerns about their children sleeping with contact lenses or using medications, a non-proven treatment using a CooperVision Biofinity Multifocal “D” +2.50 add, or Vistakon Oasys Multifocal lens is suggested. Lastly, there are those parents who are against the use of drops or contact lenses. If the child is esophoric, the use of progressive addition spectacle lenses can be recommended. Patients with myopia that want to slow the process but who require or desire traditional contact lenses should be prescribed UV filtering daily wear contact lenses. Ultimately, the decision of which treatment or combination of treatments to be used should be based upon the wants and needs of the patient.

CONCLUSION

In considering myopia treatment, remember what the 19th-century philosopher Arthur Schopenhauer said: “All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. And third, it is accepted as being self-evident.” Treatment of myopia with atropine is in the second stage, and orthokeratology is ending the second stage. Either atropine or orthokeratology will pass to the third stage or a better “atropine/orthokeratology” will come in to use. Atropine and orthokeratology are effective methods to slow the progression of myopia and should be in optometry’s armamentarium to fight the effects of this growing pandemic.

REFERENCES


Figure 7 – Progression of Myopia Over Time By Treatment
This is a cumulative graph, based on the results of numerous studies, of the projected treatment effects of each treatment to control myopia over time. It is assumed that yearly progression with traditional glasses is 0.60 D/year (mean rate), and that the progression rate is linear (which may not be true).

We recognize that the studies varied in findings and with ethnicity, thus, we used mean number. Each treatment result was corrected using a correction based upon the control group to maintain uniformity of treatment results in regard to the rate of progression of the control. For example, if the control progressed by 0.80 D/year then the treatment progression was decreased by 0.60/.80 or 75%. Atropine has been collapsed into two groups Atropine 1% and .5%, and low concentration of atropine, which include atropine .01% to .25%. It is readily apparent that atropine is the most effective treatment of myopic progression, followed by orthokeratology, and lastly, progressive lenses. According to the graph, under-correction is not an appropriate treatment of myopia. Lastly, when interpreting these results, one must be cognizant that the progression of an individual may be very different than the mean.


Corresponding author: Erica Schulman, O.D., 40 Park Ave Apt 3F, New York, NY 10016. Email: erica.schulman@gmail.com.
New trends in early diagnosis of hydroxychloroquine toxic retinopathy  
Gary L. Vanderzee, O.D, and Douglas Tassi, O.D.

KEYWORDS  
Toxic maculopathy, hydroxychloroquine, bull’s eye maculopathy, spectral domain optical coherence tomography (OCT)

ABSTRACT  
Background: Toxic retinopathy is an uncommon sequella in the treatment of certain autoimmune diseases with hydroxychloroquine (HCQ). We present two cases of HCQ toxic retinopathy, as well as a discussion on how to diagnose and manage early toxicity findings.  
Case Reports: Two cases are presented of patients who experienced toxic effects of HCQ therapy. The first patient had bull’s eye maculopathy confirmed with visual field testing and optical coherence tomography (OCT). The second patient had early signs of toxic maculopathy validated by repeat visual field and OCT testing.  
Conclusion: Management of toxic maculopathy includes the cessation of hydroxychloroquine, continued monitoring of the toxic effects and optimizing the remaining vision. The irreversible and potential devastating effect of HCQ toxic maculopathy underscores the importance of early diagnosis and working with the patient’s rheumatologist.

Introduction  
In the US, the chronic use of hydroxychloroquine sulfate is for the treatment of autoimmune disorders, such as systemic lupus erythematosus and rheumatoid arthritis. Its more toxic predecessor, chloroquine, is currently not used very much in the US. The incidence of toxic maculopathy is low, but these patients are, nonetheless, at risk for the development of toxic maculopathy. Permanent visual damage happens with advanced toxic maculopathy often characterized by “bull’s eye” maculopathy. Visual morbidity may be avoided in these patients if early diagnosis is made and drug therapy is discontinued. Therefore, the key is early detection through appropriate screening methods.

Case 1  
An 85-year-old white man presented to the eye clinic for consultation. He was referred by a rheumatologist for routine hydroxychloroquine monitoring. This was his first time to our eye clinic. He had been followed every six months but had been delinquent the past couple of years. He reported that he had been on hydroxychloroquine for approximately 11 years but not sure of the exact duration. His initial complaint was that his right eye had been watering lately. The patient’s ocular history was positive for cataract surgery OU.

A review of his medical history showed he was taking: 200 mg hydroxychloroquine b.i.d. p.o. and methotrexate 25 mg/ml (inject. 8ml subcutaneously) every seven days for rheumatoid arthritis, diltiazem 240 mg daily for hypertension, 2 cap terazosin hcl 2 mg q.h.s. daily for benign prostatic hypertrophy, albuterol 90 mcg 200D oral inhaler 2 puffs q.i.d., Fluticasone HFA 220 mcg 120D oral inhaler, inhaling albuterol/ ipratropium nebulizer solution daily for asthma, nystatin oral suspension 2 tsp. q.i.d. p.r.n. for recurrent oral yeast infections, ½ tab tramadol hcl 50 mg tab b.i.d. for pain, and ½ tab furosemide 40 mg p.o. daily for fluid retention. He was also taking multivitamins, glucosamine, calcium, and folic acid. He reported no known drug allergies. His family history was non-contributory. He did not smoke or drink alcohol.

The patient’s best corrected distance visual acuities were 20/30 OD and 20/25- OS with a mixed hyperopic astigmatic correction. His pupils, extraocular motility, and color vision by Ishihara color plates were normal. Intraocular pressures were 15 mm Hg in each eye by Goldmann applanation tonometry. Biomicroscopy showed centered and clear posterior chamber intraocular lenses in each eye. Results of visual field testing with the Humphrey 10-2 (Carl Zeiss Meditec Inc. Dublin, CA) macular threshold showed bilateral paracentral scotomas with central 30 sparing (see Figure 1). Macular evaluation was performed with the Cirrus HD optical coherence tomographer (HD-OCT) (Carl Zeiss Meditec Inc. Dublin, CA) which revealed paracentral thinning of the retina, loss of the inner segment/outer segment (IS/OS) junction line in the macula with central sparing of both eyes (see Figures 2, 3). Also of note, a large retinal pigment epithelium (RPE)detachment was found between the macula and optic nerve OD. Dilated fundus evaluation was remarkable for macular RPE irregularity of both eyes that looked like a “bull’s eye.” (A fundus camera was not available, so retinal photos could not be taken.) The patient was counseled on hydroxychloroquine retinopathy and its permanent and sometimes progressive nature and the need for close follow-up. His rheumatologist promptly discontinued the hydroxychloroquine when notified of the findings.

He was scheduled and returned for a three-month follow-up appointment. His entering visual acuities were unchanged. All other findings appeared to be stable, with the exception of his macular threshold visual field test. It showed some slight progression in visual field loss OU. Photo documentation was done with the Canon CX-1 digital retinal camera (Canon USA, Lake Success, NY). The annular perifoveal hypopigmentation can be seen on the fundus images (see Figures 4, 5). Spectral domain optical coherence tomography (SDOCT) was repeated and found to be relatively unchanged with the exception of an improving pigment epithelial detachment OD.

Case 2  
A 65-year-old man presented to the eye clinic for his 6-month hydroxychloroquine follow-up. He had been followed every 6-9 months for the past nine years. He reported being on...
hydroxychloroquine for the past 10-11 years. He had no entering complaints and reported that his vision seemed to be stable. His ocular history was positive for cataract surgery OD. A review of his medical history revealed hypertension and rheumatoid arthritis. He smoked cigarettes and had an occasional drink.

His medications included 1 ½ tab atenolol 50 mg p.o. for blood pressure, 1 tab hydrochlorothiazide 25 mg q.a.m. p.o. for blood pressure, 1 tab hydroxychloroquine 200 mg b.i.d. p.o. for rheumatoid arthritis, ½ tab lisinopril 20 mg q.a.m. p.o. for blood pressure, 1 cap terazosin hcl 5 mg q.h.s. p.o. for blood pressure, and benign prostatic hypertrophy. Family history was positive for a sister and brother with diabetes.

His best corrected visual acuities were 20/20 OD and 20/20 OS with a low hyperopic astigmatic correction. Pupils and ocular motility were unremarkable, but color vision testing by Ishihara color plates showed only one out of seven plates seen by the right eye and left eye with no previous defect noted. Goldmann applanation pressures were 16 mm Hg in both the right and left eyes. Biomicroscopy disclosed a posterior chamber intraocular lens in the right eye and a 1-2+ nuclear sclerotic cataract OS. A Humphrey SITA-standard 10-2 central threshold visual field test revealed early paracentral annular scotoma of both eyes (see Figure 6). Confirmation of the visual field defect was attempted by performing SD-OCT macular scan and the 5 line raster scan. The 5 line raster on the Cirrus HD-OCT found a moth-eaten appearance to the IS/OS junction line in the paracentral retina OU (see Figure 7), and the macular scan found paracentral thinning in three quadrants OD and one quadrant OS (see Figure 8). Dilated fundus evaluation noteworthy findings were mild retinal pigmented epithelial irregularities and drusen noted in the macula OU (see Figure 9). The patient was informed of the findings which most likely pointed to early hydroxychloroquine retinopathy. His rheumatologist was informed of the findings and subsequently withdrew the hydroxychloroquine. The patient was informed of the importance of close follow-up to see if the retinopathy will progress. He was scheduled for another appointment for repeat 10-2 threshold visual fields and HD-OCT in 3 months. Testing done at the 3 month follow-up evaluation substantiated the visual field and OCT findings with no further evidence of progression.

Discussion

The incidence of hydroxychloroquine maculopathy in the literature is variable. In one study of 526 patients, the overall incidence was reported at 0.5%. The reported incidence increased to 3.4% of the patients if they were on the recommended dosage of hydroxychloroquine for more than six years.1 In one of the largest studies of 1207 patients, 5 patients developed toxic maculopathy. This is a rate of 0.4% of patients who were on the recommended dosage of 6.5 mg/kg.2 Marmor MF, et al., reported that the risk of toxicity increases toward 1% after five to seven years of use or a cumulative dose of 1000 g of hydroxychloroquine.3
Early hydroxychloroquine toxic retinopathy is often defined by two methods. One is the development of a persistent paracentral scotoma to threshold white stimulus. The other is a repeatable bilateral visual field defect on two separate visits. Early hydroxychloroquine retinopathy is considered when there is an acquired paracentral scotoma without corresponding fundus changes. Advanced retinopathy consists of scotomas in the presence of parafoveal RPE atrophy. This is what we would classically call bull’s eye maculopathy.4

Corneal changes in hydroxychloroquine treatment consist of the development of a vortex keratopathy. This drug-induced keratopathy is usually visually innocuous. In some cases, if the corneal verticillata are dense, this could cause halos and glare. The keratopathy develops in less than 10% of patients treated with hydroxychloroquine. Corneal deposits were found in 95% of patients treated with chloroquine.5 The vortex keratopathy is not related to dosage. This keratopathy is not associated with the level of risk of retinal toxicity and will resolve without complication if the medication is discontinued. This vortex keratopathy also appears with amiodarone treatment, chlorpromazine treatment, and Fabry’s disease. Other side effects may include decreased visual acuity, night vision problems, and color vision defects, especially in the blue-yellow spectrum. Rarely, vascular attenuation and optic atrophy may result.4

The exact mechanism of retinal toxicity is unknown. Previous studies have implicated outer retinal structures such as the photoreceptors and the retinal pigmented epithelium. The hydroxychloroquine molecule binds to the pigmented epithelium which disrupts lysosomal function and consequently there is lipofuscin accumulation. Therefore, photoreceptor loss may be attributed to this alteration in RPE metabolism. A recent study by Stepień, et al., using a prototype research ultra-high resolution optical coherence tomograph, found a diminished cone photoreceptor density in the affected perifoveal retina. This corresponded to the “moth-eaten” appearance of the IS/OS layer found by the OCT.6,7 Others suspected ganglion cells, the inner plexiform layer, or the nerve fiber layer.6,7,8,9 Some of the earlier animal studies pointed to inner ganglion cells or nerve fiber layer thinning as to the target for retinal toxicity. Korah and Kuriakose have OCT evidence pointing to loss of ganglion cell layers attributing to the thinning of the macula and parafoveal region.10 Pasadhika, et al., performed a study showing that chronic use of hydroxychloroquine is associated with thinning of the inner perifoveal retinal layers. This can be detected or found even in the absence of functional or structural clinical changes involving the photoreceptor or retinal pigmented cell layers. They feel this is the contributing factor in paracentral scotomas that can be observed as a first clinical sign.11 What is known is that there is loss of parafoveal retinal function which is due to associated retinal morphological or structural changes.

Currently, the greatest risk factor in hydroxychloroquine maculopathy is an accumulative dosage of the medication at or greater than 1000 grams. The recommended daily dosage of
hydroxychloroquine is 200 mg twice a day. Therefore, the highest risk for these patients presents at 6.8 years. Other risk factors include: duration of treatment greater than 5 years, dosage greater than 400 mg per day or exceeding 6.5 mg/kg/day based on lean body weight, age greater than 60 years, concomitant liver or kidney disease, and other retinal disease.\(^3,4\)

One must also note that many patients on hydroxychloroquine for rheumatoid arthritis may also be taking methotrexate which can cause renal and liver failure. Our patient in Case 1 was recently diagnosed with kidney failure and is taking subcutaneous methotrexate. Is it possible that the methotrexate caused the renal failure which contributed to the toxic retinopathy?

When it comes to retinal screening protocol there have been some changes recently due to some of the new technology that has come available. SDOCT has been noted to find abnormalities in the presence of normal ophthalmoscopy findings. There have been some patients reported with profound abnormalities with visual field testing and multifocal electroretinogram (mfERG) in the presence of normal macular appearance.\(^12\) In February 2011, the American Academy of Ophthalmology released new guidelines for the recommended examination schedule of patients on antimalarial medication. Those guidelines are as follows: A baseline examination is advised for patients starting these drugs to serve as a reference point and to rule out maculopathy, which might be a contraindication to their use. Annual screenings should begin after 5 years (or sooner if there are unusual risk factors).\(^3\) The American Academy of Ophthalmology released new testing guidelines for patients on antimalarial medication. The recommendations are as follows: BCVA (best corrected visual acuity), dilated fundus exam at
least within the first year of antimalarial drug use, 10-2 central threshold automated visual fields with a white target. Subtle, repeatable visual field defects are an indication to do objective testing. At least one of the following objective tests should be performed for routine screening if available: SDOCT, fundus autofluorescence (FAF), and mfERG. Newer testing, such as mfERG, SDOCT, and FAF can be more sensitive than visual fields. How often the patient should be evaluated in the first five years of treatment is up to the managing doctor based on individual patient risks and the doctor’s judgment. (The occurrence of toxic retinopathy in the first 5 years of treatment is not zero. There are documented cases of toxic retinopathy with cumulative doses of 760g and as little as 86g.) Annual screening is recommended after five to six years and more frequent examination with patients who have higher risk.

There is a lack of consensus for which test is the most diagnostically useful for toxic retinopathy secondary to hydroxychloroquine use. When determining which techniques or tests to perform on patients, one would ideally want instrumentation that is inexpensive, objective, quick, and non-invasive, as well as sensitive and specific for detecting early toxicity.

Visual field testing for hydroxychloroquine patients should consist of a threshold macular visual field test to detect reductions in retinal sensitivity. Macular toxicity will produce partial to total ring scotomas. These ring scotomas form in the parafocalzone of the visual field from 4 to 9 degrees. Of interest is the foveal sparing which occurs frequently in hydroxychloroquine retinopathy. The central 10-2 threshold visual field test is recommended by the American Academy of Ophthalmology for screening for HCQ maculopathy. Macular threshold visual fields may be the best way for the average clinician to determine early toxicity in patients without the availability of instruments like the SDOCT or mfERG. Amsler grid testing should not take the place of macular threshold testing.

Figure 5 Canon red free photographs of the right eye and left eye respectively of case 1. Note the darker fovea surrounded by slightly lighter circle and then the eventually lighter ring.

Figure 6 Humphrey 10-2 Central threshold visual field test of the left and right eye for case 2 shows paracentral relative scotoma 3-50 from fixation as noted by the pattern deviation.
visual fields in the evaluation of these patients. A disadvantage with threshold visual field testing is that there is a steep learning curve for the patients. Repeatable paracentral scotomas with white light are an indication to perform another more objective test such as mfERG, SDOCT, or FAF.

The mfERG is an objective but more difficult test to administer. There is also the issue of clinical availability, patient cooperation, and cost when it comes to the mfERG. However, the mfERG recently has shown promise in detecting early stages of retinal toxicity in hydroxychloroquine retinopathy. Kellner, et al., reports that mfERG can reliably detect retinal functional loss associated with CQ/HCQ retinopathy. In some patients, the mfERG showed reduced response amplitudes when other functional tests were normal (color vision, central visual field, and visual acuity) and morphological examinations were normal (FA, ophthalmoscopy). Spectral domain optical coherent tomography is positioned to become a very valuable technology in the management of patients on antimalarial medication. With recent advances in SDOCT, it is possible to obtain cross-sectional images of the retina with resolutions of 3-5 μm. In the future, with the use of adaptive optics, eliminating optical aberrations, HD-OCT may achieve resolution of an impressive 1 μm. The instrument potentially allows for an earlier diagnosis in an objective fashion with quick acquisition time. OCT functions as a type of optical biopsy in situ with resolution approaching that of excisional biopsy and histopathology. OCT findings in early hydroxychloroquine maculopathy include a distinctive discontinuity or “moth-eaten” area of the IS/OS junction line (see Figure 7). The “moth-eaten” appearance of the IS/OS junction line may be due to diminished cone photoreceptors in this area. The greatest area affected was the perifoveal retina where the cone density is the highest. This moth-eaten IS/OS junction can sometimes be detected before abnormalities appear with 10-2 central visual field testing. More advanced cases of maculopathy may have a complete loss of the IS/OS junction line. “Sink holes” form where displacement effects of the inner retinal layers fill space previously occupied by atrophic outer retinal layers (see Figure 3). This shift toward the RPE results in flattening of the perifoveal hump of tissue and loss of foveal depression. As “sink holes” form in the parafoveal area, the fovea takes on the appearance of a “mushroom cap.” Others have referred to this as producing the “flying saucer” sign. Irregularity of the retinal pigment epithelium layer can also be present and observed with the OCT (see Figure 3). These pathological signs or changes in morphological structure will be best visualized using the highest definition mode. With the Cirrus HD-OCT, this would be a 5 line or 1 line raster scan viewed in black and white. Chen, et al., found the SDOCT particularly useful in that they were able to diagnose early toxic retinopathy in the presence of normal ophthalmoscopy, autofluorescence, fluorescein angiography, and time domain OCT. The SDOCT showed thinning of the outer nuclear layer in the perifoveal region. Rodriguez-Patilla, et al., found that a
Fundus autofluorescence (FAF) is a recent technique that uses photography or scanning laser microscopy to detect and quantify the stimulated emission of light from naturally occurring fluorophores. An intense light flash (300-600 nm) excites the lipofuscin molecule and a weak light is re-emitted. The weak signal needs to be processed digitally for “noise” reduction and enhancement. The longer the wavelength of light, the deeper the penetration into ocular tissues. Lipofuscin, known as the aging pigment, is the most significant of these. It accumulates in post-mitotic neurons due to age, long-term phototoxicity, and from ocular disease. The RPE phagocytizes the cellular byproducts of the photoreceptors which contribute to the accumulation of lipofuscin. The toxic effects of hydroxychloroquine cause lipofuscin to accumulate in the RPE. Early on there is increased FAF in a pericentral ring around the macula.\textsuperscript{17}

Figure 8  Macular thickness cube on the Cirrus HDOCT of both the right and left eyes for case 2. Note the paracentral annular thinning of the retina, greater in the right eye as compared to the left eye. There is a distinct loss of the macular hump temporally in the right eye.

Figure 9  Canon photographs of the right eye of case 2. Color photograph displaying mild retinal pigmented epithelium irregularities and drusen of the macula consistent with early macular degeneration. (top right picture) red free photograph of the right eye showing only signs of early age-related macular degeneration. (Bottom left picture) FAF picture of the right eye. Note increased intensity of fluorescence in parafoveal retina consistent with early lipofuscin accumulation indicating increased retinal damage.
fovea and, as the toxicity advances, the ring of fluorescence will continue to broaden and intensify. Individuals with increased FAF often demonstrate decreased retinal sensitivity with microperimetry. Kelmenson et al., found correlation of increased FAF and retinal thinning on the OCT in the area of RPE dropout in more advanced toxic retinopathy cases. In later stages, there is an absence of FAF and a “bull’s eye” appearance becomes evident. Therefore, FAF is a technique that is capable of finding abnormalities in the RPE. In fact, FAF is more sensitive when screening for early RPE alterations in HCQ retinopathy as compared to ophthalmoscopy and fluorescein angiography. It therefore can be used as a reliable instrument to detect hydroxychloroquine retinal toxicity.

Progression of hydroxychloroquine retinopathy is variable and unpredictable after discontinuation of medication. There is a common misconception that once hydroxychloroquine has been discontinued the retinal disease process will not progress. This unfortunately is not the case. The binding of hydroxychloroquine to the pigment cells of the retinal pigment epithelium has a very long half-life, which is the reason for progression. If the retinal toxicity has been diagnosed early on, the chance of future progress is less severe. If the retinal toxicity is more advanced, there is a significant chance the retinal disease will progress despite discontinuation of the medication. The continued progression of the retinal disease has been reported up to three years after medication cessation. In one study consisting of eight years of long-term follow up after cessation of medication, it was determined that 63% of patients went on to have one or more lines of visual acuity loss and progression of visual field damage.

It is important to make an earlier diagnosis of macular toxicity before permanent functional vision damage occurs. Hydroxychloroquine toxic maculopathy is more likely to progress when diagnosed at later stages than when detected earlier in the disease process. Since the appearance of “bull’s eye” maculopathy is a late stage disease finding, diligent follow-up, appropriate testing, and assessing the patient's risk is imperative for prevention. With no known treatment for toxic maculopathy, the key to management is early diagnosis. A timely diagnosis can be made with the advent of new technologies, thus reducing the risk of visual morbidity from antimalarial medication.

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Corresponding author: Gary L. Vanderzee, O.D., Sioux Falls Veterans Affairs Health Care System, 2501 W. 22nd Street, Sioux Falls, SD, 57107. Email: Gary.Vanderzee@va.gov.