An evidence-based update on myopia and interventions to retard its progression

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SUMMARY

Myopia is the most common human eye disorder. With its increasing prevalence and earlier age-of-onset in recent birth cohorts, myopia now affects almost 33% of adults in the United States, and epidemic proportions of 85% to 90% adults in Asian cities. Unlike children in Western populations, where the prevalence of myopia is very low (less than 5%), Asian children have prevalences as high as 29% in 7-year-olds. In addition to the direct economic and social burdens of myopia, associated ocular complications may lead to substantial vision loss. This workshop summarizes the current literature regarding myopia epidemiology, genetics, animal model studies, risk factors, and clinical treatments. Published treatment strategies to retard the progression of myopia in children, such as pharmacologic agents, progressive addition lenses, and neural adaptation programs, are outlined.

Myopia, or near-sightedness, is the state of refraction in which parallel rays of light are brought to focus in front of the retina of a resting eye. It is measured by the spherical power in diopters of the diverging lens needed to focus light onto the retina, which can be expressed as the spherical equivalent, that is, sphere + half negative cylinder. Most commonly used definitions of myopia in epidemiologic studies include spherical equivalent of at least −0.50 D, −0.75 D, and −1.0 D. Myopia is the most common human eye disorder in the world, affecting 85% to 90% of young adults in some Asian countries such as Singapore and Taiwan, and between 25% and 50% of older adults in the United States and Europe. Epidemiological studies in Western populations have collectively shown the prevalence of myopia to be low (<5%) in children aged 6 years or younger. However, studies in Asian children suggest a significantly higher prevalence of myopia, affecting 9% to 15% of preschool children and 29% of primary school children in Singapore. A study of 10,000 Taiwanese school children found that the prevalence of myopia was 6% in 6-year-olds, with the prevalence increasing to more than 70% by age of 15 years.

With its increasing prevalence and earlier age of onset in recent birth cohorts, myopia now affects 33% of adults in the United States. Between 1999 and 2004, the prevalence of myopia was two thirds higher than it was between 1971 and 1972. The National Health and Nutrition Examination Survey also showed a higher prevalence in women (39.9%) than in men (32.6%), in younger than older persons, and in whites (35.2%) than African Americans (28.6%) or Mexican Americans (25.1%). Myopia is a significant global public health concern. Along with cataract, macular degeneration, infectious disease, and vitamin A deficiency, myopia is 1 of the most important causes of visual impairment worldwide. Severe or high-grade myopia is a leading cause of blindness because of its associated ocular comorbidities of retinal detachment, macular choroidal degeneration, premature cataract, and glaucoma. The yearly incidence of retinal detachments had been estimated as 0.015% in patients with less than 4.74 D myopia and increases to 0.07% in patients with myopia greater than or equal to 5 D and 3.2% in patients with myopia greater than or equal to 6 D. Myopes also have increased risks of developing macular choroidal neovascularization, ranging from 2 times for patients with 1 D to 2 D of myopia, 4 times with 3 D to 4 D of myopia, and 9 times for −5 D to 6 D. The Blue Mountains Eye Study showed that glaucoma was present in 4.2% of eyes with low myopia and 4.4% of eyes with moderate to high myopia, compared to nonmyopic eyes.

Ample evidence supports heritability of the nonsyndromic forms of this condition, especially for high-grade
myopia, commonly referred to as myopic spherical refractive power of 5 D to 6 D or higher.28

Epidemiology
Recent epidemiological data has identified outdoor activity as a key environmental determinant of myopia. In both Singaporean and Australian children, total time spent outdoors was associated with less myopic refraction, independent of indoor activity, reading, and engagement in sports.29,30 A comparative study of Chinese children in Singapore and Sydney also revealed a protective effect of outdoor activity.31,32

Previous reports of rural–urban differences in myopia prevalence have also been confirmed, with inner-city urban areas having higher odds of myopia than outer suburban areas. This data suggested that small to moderate environmental differences may affect myopia development, even within a common predominantly urban environment.33

Genetics of Ocular Refractive Components
Refraction is determined by coordinated contributions of ocular biometric components such as axial length (AL), anterior chamber depth (ACD), corneal curvature (keratometry readings in diopters), and lens thickness. The inverse relationship of AL and ACD to refraction is well documented (the longer the eye, the more myopic the refractive error). Myopes have longer axial lengths, deeper vitreous chambers, thinner lenses, and flatter corneas.34-36 In the vast majority of cases, the structural cause of myopia is an excessive axial length of the eye, or more specifically, the vitreous chamber depth. AL is estimated to be the greatest determinant of refractive error; heritability estimates for AL range from 40% to 94%, and most recently were reported to be 81% in a whole genome twin study in Australia.37 This study was the first to identify a locus implicated in ocular axial length, on chromosome 5q, and it identified additional regions with suggestive multipoint logarithm of the odds ratios on chromosomes 6, 10, and 14 linked to axial length.37

Twin Studies
Twin studies provide the strongest conclusive evidence that myopia is inherited, as background contributions are diminished. Many studies have noted an increased concordance of refractive error as well as refractive components (AL, corneal curvature, lens power) in monozygotic twins compared to dizygotic twins. Most recently, Dirani and colleagues38 reported the first evidence for a genetic component in adult-onset myopia within a large cohort study of white twins. He and colleagues39 estimated a high genetic contribution to axial length, anterior chamber depth, and angle opening distance in twins from the Guangzhou Twin Registry.

Myopia Loci
See e-Supplement 1 (available at jaapos.org) for several recently identified loci with linkage to myopia (Pang CP, Lam CY, Tam PO, et al. Poster 1397-2007, American Society of Human Genetics, 2007).40-49

Candidate Gene Studies
The list of hypothesized candidate genes for myopia is based largely on the current understanding of the pathophysiology of syndromic myopia.50 The majority of the work examining the relationship between myopia and individual polymorphisms in candidate genes has been performed on single candidates at a time, to the exclusion of other independent or interacting genes. The results for many of the candidate myopia genes are promising and may have biological plausibility, but most are not conclusive and could not be replicated in other studies. Functional SNP effects have not been implicated for all of these candidate genes, and it is unclear how ethnic differences play a role in the degree of associative significance.50

Animal Models
One impediment to correlating genotypic data with tissue histopathology in human myopia is that the tissue of interest (ie, retina/sclera) cannot be directly sampled. Animal models of myopia have been developed to be used as surrogates, although it is unclear how correlative induced myopia in animals may be to physiologic myopia in humans. Animal studies over the past 30 years in juvenile and newborn monkey, tree shrew, and chick models have revealed an active emmetropization mechanism that normally achieves and maintains a match of the ocular AL to the eye’s optical power so that the photoreceptors are in focus for distant objects. Thus genes expressed in retina, retinal pigment epithelium, choroid, and/or sclera that control this emmetropization process, if irregularly expressed, could cause the eye to elongate and become myopic. The emerging picture is 1 of complex interaction, in which mutations in several genes likely act in concert. The majority of myopia cases are not caused by defects in structural proteins, but by defects involving the control of structural proteins.

The first knockout mouse model for relative myopia was based on form-deprivation experiments in chickens, mice, and rhesus macaque monkeys.51 This model involved the immediate early gene transcription factor ZENK (also known as Egr-1), which is up-regulated in retinal amacrine cells when axial eye growth is inhibited by positive lens wear, and is down-regulated when axial growth is enhanced by negative lenses, suggesting that ZENK is linked to an axial eye growth inhibitory signal. ZENK knockout mice had longer eyes and a myopic shift relative to heterozygous and wild-type mice with identical genetic background.51

Zhou and colleagues52 provided a helpful record of refraction, corneal curvature, axial components, and the correlations between refraction and ocular growth during...
emmetropization in C57BL/6 mice. Refraction was most myopic at day 25 and then shifted in the hyperopic direction to reach a peak at 47 days.

Hyperopic defocus, where the conjugate point of the object of regard is behind the retina, was been shown in early animal models to stimulate eye growth that moves the retina toward the conjugate point. Myopic defocus was reported to inhibit axial elongation, more robustly in the chick than in the mammalian eye, with the choroid of the chick pushing the retina forward toward the myopic focal point. Later studies showed that animal eyes respond bidirectionally to a level of defocus greater than its distance from emmetropia. The bidirectional modulation of eye growth by hyperopic and myopic defocus in disparate species suggests that the same may occur in children.

Although 3 earlier studies in humans suggest that increases in accommodative lag occur before the onset of myopia, the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error Study concluded that increased hyperopic defocus from accommodative lag may be a consequence rather than a cause of myopia. Increased accommodative lag relative to model estimates of lag in emmetropes did not occur in children who became myopic before the onset of myopia or during the year of onset.

Evidence that excessive accommodation does not cause myopia includes the fact that visual deprivation myopia can be induced in the young of many animal species, including primates after ciliary ganglion destruction, Edinger-Westphal nucleus destruction, or following optic nerve section. Recovery from refractive errors induced by the wearing of minus or plus lenses can also occur when accommodation has been surgically abolished.

More recently, studies on infant monkeys suggest that the peripheral retina can play an important role in modulating overall eye growth and axial refraction. While studies strongly suggest an association between relative peripheral hyperopia and the development of myopia in humans, a causative role for the former has yet to be confirmed. It may still be that the relative peripheral hyperopia observed in eyes that become myopic is simply associated with the more prolate or less oblate shape of the eye.

Interventions to Retard the Progression of Myopia

Many interventions aimed at slowing myopia progression have been proposed; however, few have been subjected to the scientific rigors of randomized controlled trials. The rest of the studies have been retrospective case series, non-randomized controlled trials, and uncontrolled clinical trials.

Medication

Atropine Eye Drops

Atropine is a nonselective muscarinic antagonist. It was first used for myopia treatment by Wells in nineteenth century. Subsequent studies have shown some clinical effect on the progression of myopia in children. In addition, atropine inhibits myopia in tree shrew and monkey myopia models and blocks form deprivation myopia or lens-induced myopia in chicks.

In contrast to the mammalian eye, the avian eye contains striated intraocular muscle and atropine has neither mydriatic nor cycloplegic effect in birds, indicating a nonaccommodative mechanism for anti-myopia activity of atropine in chick.

Unlike early atropine treatment studies for myopia, which had various methodological shortcomings such as lack of regular and detailed follow-up examinations, absence of appropriate clinical controls, absence of masking of participants and investigators, the Atropine in the Treatment of Myopia study (ATOM) was a randomized, double-masked, placebo-controlled trial involving 400 Singapore children (Figure 1). It showed that 1% atropine eye drops instilled nightly in 1 eye over a 2-year period reduces myopic progression significantly in children by 77% (0.28 D in the control group vs 1.2 D in the atropine group). The atropine group’s mean axial length remained essentially unchanged, whereas the placebo group’s mean axial length increased 0.39 ± 0.48 mm. The topical atropine was well tolerated. Multifocal electroretinogram testing of the ATOM study subjects at 2 or 3 months after cessation of atropine or placebo treatment revealed no significant effect on retinal function.

Side effects of atropine include photophobia due to mydriasis and decreased near vision due to cycloplegia. As a result, if atropine is used in both eyes, the patient needs photochromatic, progressive additional lenses. The ATOM study reported no systemic side effects, although possibilities include dry eye, dry mouth, dry throat, flushed skin, constipation, and difficulty with micturition. In addition, there appears to be an initial increased rate of myopia progression following the cessation of atropine treatment in the ATOM study subjects (−1.14 ± 0.8 D in the atropine group vs −0.38 ± 0.39 D in the control group, p < 0.0001). This “rebound” phenomenon is probably related to the strong cycloplegic effects of atropine. However, after 3 years of participation in the trial (with 2 years on atropine treatment), eyes randomized to atropine have less severe myopia than other eyes. Spherical equivalent was −4.29 ± 1.67 D in the atropine-treated eyes compared with −5.22 ± 1.38 D in the placebo-treated eyes (p < 0.0001).

Other issues to be addressed include determining the mechanism of action in retardation of myopia progression and possible long-term effects like ultraviolet-light–induced damage to lens and retina. The psychological effects of such a regimen on children need to be taken into consideration too. Finally, the optimal concentration and desired duration of drug application need to be established.

Currently, the decision to use atropine eye drops for retarding myopia progression should strike a balance between known short-term benefits of reducing myopia...
progression and the risks of side effects of atropine. It may be a viable option for children with rapidly progressive, high myopia and strong family history of high myopia and its comorbidities such as retinal detachment.

**Pirenzepine 2% Gel**

Pirenzepine 2% gel is a selective M-1 antagonist with a long history of oral use to treat dyspepsia and pediatric endocrine disorders in Europe and Asia. Unlike atropine, which is equipotent in binding to M3 (accommodation and mydriasis) and M1 muscarinic receptors, pirenzepine is relatively selective for the M1 muscarinic receptor and thus is less likely than atropine to produce mydriasis and cycloplegia. In the US pirenzepine 2% gel applied twice a day slowed myopia progression over 2 year (0.58 D vs 0.99 D). In Asia the mean increases in myopia were 0.47 D, 0.70 D, 0.84 D in twice daily–once nightly control groups over 1 year. Pirenzepine 2% gel applied twice a day and nightly reduced myopia progression by 50% and 44%, respectively (Figure 1). Currently development of pirenzepine as an anti-myopia therapeutic has ceased due to regulatory and financial obstacles.

**Optical Treatment**

**Bifocals**

Reports in animal and human studies suggest that increased retinal defocus is a factor in the pathogenesis of myopia. High accommodative lag has been associated with myopia. It was postulated that bifocals or multifocals could provide clear vision over a range of viewing distances, reduce retinal defocus, and slow the progression of myopia. However, randomized, clinical trials in the US, Finland, and Denmark showed no significant slowing of myopia (Figure 1).

**Progressive Additional Lenses**

The use of progressive addition lenses has produced relatively small treatment effects (Figure 1). In particular, the correction of myopia evaluation trial (COMET), a multicenter, randomized, double-masked clinical trial, concluded that the overall adjusted 3-year treatment effect of 0.20 ± 0.08 D was statistically significant (p = 0.004) but not clinically meaningful. All the treatment effect occurred in the first year. Additional analyses showed that there were more significant treatment effects in children with larger lags of accommodation in combination with near esophoria (0.64 ± 0.21 D), shorter reading distances (0.44 ± 0.20 D), or lower baseline myopia (0.48 ± 0.15 D). Although statistically significant, these differences over a 3-year period are not clinically meaningful.

**Contact Lenses**

Although anecdotal reports have suggested that the use of soft contact lenses speeds up myopia progression, resulting
in a phenomenon of “myopic creep,” randomized trials reported no significant difference in progression between soft contact lens and spectacle wearers. On the other hand, soft contact lenses and rigid gas permeable lenses (RGP) were not shown to be effective in retarding myopia progression either (Figure 1).59-61

In the Contact Lens and Myopia Progression study, subjects were randomized to wear either RGP or soft contact lenses for 3 years.62 Results showed a statistically significant difference in myopia progression in the RGP versus soft lens group (−1.56 ± 0.95 D for RGP wearers vs −2.19 ± 0.89 D for the soft lens group, p < 0.001) with most of the treatment effect found in the first year (Figure 1).59 Corneal curvature steepened significantly less in the RGP group (0.62 ± 0.60 D) compared to the soft lens group (0.88 ± 0.57 D, p = 0.01).63 Three-year axial elongation was not significantly different between treatment groups. These results suggest that the slowed myopia progression was mainly due to corneal flattening, which may be reversible with discontinuation of RGP lens wear. In the absence of differences in axial elongation, the authors concluded that RGP lenses was not effective for myopia control.63

Orthokeratology
In overnight orthokeratology—also known as OOK, OK, ortho-k, and corneal reshaping—the patient wears reverse geometry lenses overnight to temporarily flatten the cornea and provide clear vision during the day without any glasses or contact lenses.64 Reduction in the myopia (up to −6 D) is achieved by central corneal epithelial thinning, midperipheral epithelial, and stromal thickening. More than 100 cases of severe microbial keratitis related to orthokeratology have been reported since 2001.65

There is still no evidence for long-term efficacy of orthokeratology in reducing myopia progression. The often quoted Longitudinal Orthokeratology Research in Children involved 35 children in Hong Kong who wore OK lenses for 2 years.66 Although results of the study showed that the axial length in the orthokeratology group increased by 0.29 mm versus 0.54 mm for the control group, a major scientific flaw was that the control group was actually a historical control group of children wearing single vision lenses. More recently, the Corneal Reshaping and Yearly Observation of Nearsightedness Pilot Study compared 28 subjects with corneal reshaping contact lenses with soft contact lens wearer from another myopia control trial.67 The annual rate of change in axial length was 0.16 mm per year less (p = 0.00004) for corneal reshaping lens wearer than soft contact lenses. However, limitations of this study included high dropout rate (30%), the choice of soft contact lenses as control group, and the small numbers.68

A gold standard randomized controlled trial with sufficient subject numbers still needs to be conducted to definitively determine whether orthokeratology is effective for slowing myopia progression.

Undercorrection
The literature on myopigenesis suggests an active emmetropization mechanism regulated by optical defocus. Strong evidence is provided by compensatory ocular growth in response to lens-induced defocus in different species of animals.69 A myopic defocus, where the optical image is formed in front of the retina, results in a growth response toward hyperopia in animals. Only 1 masked, randomized clinical trial involving 94 children has been conducted to compare undercorrection by 0.75 D with full correction with single vision lenses.70 Two-year progression in the fully corrected group was 0.77 D, significantly less than the 1.0 D in the undercorrected group (p < 0.01) (Figure 2). Contrary to animal studies, myopic defocus speeds up myopia progression rather than retarding it. This means that myopes may have an abnormal mechanism for detecting the direction of optical defocus of the retinal image.

Part-Time Lens Wear
Patterns of lens wear in myopes patients can vary from full-time wear, to the use of lenses for distance viewing only, to nonwear of prescribed lenses. Preliminary data of 43 subjects suggest that there is no effect of the pattern of lens wear on the progression of myopia. Three-year refractive shifts were not significantly different among the 4 groups71: (1) full-time wearers, (2) myopes who switched from distance to full-time wear, (3) distance wearers, and (4) nonwearers. A randomized clinical trial using a large sample of children randomly assigned to a lens wear regimen was warranted.

Commercial Products and Techniques

NeuroVision
The term perceptual learning describes a process whereby practicing certain visual tasks leads to an improvement in visual performance. Brain plasticity in visual functions has been shown in various studies. The NeuroVision technology is a noninvasive, patient-specific, Internet-based perceptual learning program based on visual stimulation.72,73 It facilitates neural connections at the cortical level using Gabor patches, which are are local gray-level gratings with spatial frequencies of 1.5 to 12.0 cycles per degree modulated from a background luminance of 40 cd/m2. They are widely used in visual neurosciences and have been shown to efficiently activate and match the shape of receptive fields in visual cortex. Gabor patches are used in different configurations, with different levels of spatial frequency, contrast, orientation, spatial location, distance, displacement, task order, and exposure duration.

The patient is shown 2 consecutive displays in random order. Each display has some arrangement of Gabor patches with subtle differences. The patient is asked to identify the correct display as determined by the instructions for the specific task. If the patient answers correctly,
the target contrast will be reduced and the task will become more difficult. On the other hand, incorrect answers will trigger the program to increase the contrast and the task becomes easier. NeuroVision improves neuronal efficiency and contrast sensitivity function by reducing the noise, increasing signal strength, and thereby reducing the signal-to-noise ratio of neural activity in the primary visual cortex.106,107

Although NeuroVision has been shown to improve unaided visual acuity and unaided contrast sensitivity in adults with low myopia, it does not alter refraction or accommodative amplitudes.107,108 Children with highly progressive myopia often use undercorrected glasses and experience poor vision. A pilot study on 31 children aged 7 to 9 years showed that NeuroVision resulted in improvement in mean undercorrected visual acuities and mean undercorrected contrast sensitivity function (Chua WH, Hong CY, et al. Poster 52, 12th International Myopia Conference, 2009). After 1 year, the progression of myopia in this group was 0.5 D, which was less than the average progression in the age-matched normals from the Singapore Cohort Study of Risk Factors for Myopia study (0.944 D). A randomized controlled trial is needed to scientifically support these findings. In the meantime, NeuroVision should not be used for retardation or prevention of myopia.

“EyeRelax”
“EyeRelax” is a microscope-like device purported to improve the vision of emmetropes, myopes, and even presbyopes, to prevent the worsening of myopia and to treat amblyopia. The retail price is around US$580. Users are to peer into the eyepieces of the device for 5 minutes per eye, where they will see a kaleidoscope of brightly colored lights that focus and defocus. However, there is no evidence that it can retard the progression of myopia.

“Vision Therapy Eyewear”/Pinhole Glasses
“Vision Therapy Eyewear”/Pinhole Glasses are black opaque lenses that have multiple small holes in them. A 10% to 20% improvement in vision—even elimination of myopia—is advertised. However, there is no evidence that this can retard myopia progression. What it actually uses is the pinhole effect, where only coherent rays of light pass through. As the pinhole blocks most of the light rays, there is a smaller circle of blur on the retina.108

Bates Method
Dr. William H. Bates (1860-1931) attributed nearly all sight problems to habitual strain of the eyes and published a book entitled Perfect Sight Without Glasses, also known as The Cure of Imperfect Sight by Treatment Without Glasses.109 The Bates method is based on his book and teaches techniques such as palming and sunning. The child is to register together with a parent for the workshop run by various companies, for a fixed sum of money. “Good habits of natural perfect sight” are taught, with some of the advertised benefits being “relaxed vision with better eye-mind coordination; improved memory and concentration; improved color vision and depth perception.” However, the principles behind the Bates technique are very different from conventional teaching and understanding. Bates’ anecdotal reports of improved vision have not been evaluated in trials.

Recommendations
The search for an effective intervention to slow the progression of myopia remains hampered by the lack of clear understanding of the exact pathogenesis of myopia. In searching for a clinically validated and effective therapy to retard myopia progression, future research should take into consideration the role of environmental factors to genetic influences, such as interactions of early-age nearwork or outdoor activity and genotype. Consideration also needs to be given to the identification of phenotypes indicating etiologically homogeneous subgroups, for example, early age-of-onset, with/without retinal degenerative changes, or classification by individual response to treatments that reduce accommodation to near objects, such as progressive addition lens use.

Steady progress has been made in the field of human myopia genetics, but there is much still to be done. For example, no results have implicated more that just a single gene, or have expanded into an analysis of a specific pathway. This may implicate additional genes in a pathway also shown to be risk factors for myopia in validation studies and point to potential haplotype-specific treatments. No candidate genes have been shown to account for even a modest
fraction of the familial risk of myopia, and most of the data are conflicting about whether a true association exists. Candidate gene studies underscore that myopia is very complex, in fact, so complex that single candidate gene studies are unlikely to demonstrate the type of relationships needed to account for the majority of susceptibility genes. Thus there is a need for a genome-wide approach, incorporating candidate genes but not restricted to the study of candidate genes, to explore the relative contributions and interactions between known candidate genes and possibly novel genes in increased myopia susceptibility.

Randomized clinical trials of a variety of interventions such as bifocal lenses, progressive additional lenses, and contact lenses have yielded disappointing results of marginal clinical significance (Figure 2). To date, topical atropine 1% is the most promising. However, its short-term side effects, such as photophobia, have decreased compliance and possible long-term effects like ultraviolet-light–induced damage to lens and retina have limited its clinical use for retarding myopia progression. It is a viable option for high-risk children with rapidly progressive myopia. Although topical pirenzepine, a selective M1-muscarinic antagonist, has also been shown to retard myopia progression, it is no longer commercially available. With regard to optical correction, current evidence suggests full correction. As for commercial devices, the anecdotal accounts of “improvement” or reduction of myopia may be related to pseudomyopia, which often occurs in children because of their high accommodative facility.

As several large studies conducted in different parts of the world have reported that the prevalence of myopia in children with more outdoor activity hours is lower than in children with fewer hours, a promising but yet to be tested therapy could just simply be increased outdoor play. Peripheral refractive interventions to retard myopia progression may also be possible in the near future.

References


