

Pathogenesis and Prevention of Worsening Axial Elongation in Pathological Myopia

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Purpose: This review discusses the etiology and pathogenesis of myopia, prevention of disease progression and worsening axial elongation, and emerging myopia treatment modalities.

Introduction: Pediatric myopia is a public health concern that impacts young children worldwide and is associated with numerous future ocular diseases such as cataract, glaucoma, retinal detachment and other chorioretinal abnormalities. While the exact mechanism of myopia of the human eye remains obscure, several studies have reported on the role of environmental and genetic factors in the disease development.

Methods: A review of literature was conducted. PubMed and Medline were searched for combinations and derivatives of the keywords including, but not limited to, “pediatric myopia”, “axial elongation”, “scleral remodeling” or “atropine.” The PubMed and Medline database search were performed for randomized control trials, systematic reviews and meta-analyses using the same keyword combinations.

Results: Studies have reported that detection of genetic correlations and modification of environmental influences may have a significant impact in myopia progression, axial elongation and future myopic ocular complications. The conventional pharmacotherapy of pediatric myopia addresses the improvement in visual acuity and prevention of amblyopia but does not affect axial elongation or myopia progression. Several studies have published varying treatments, including optical, pharmacological and surgical management, which show great promise for a more precise control of myopia and preservation of ocular health.

Discussion: Understanding the role of factors influencing the onset and progression of pediatric myopia will facilitate the development of successful treatments, reduction of disease burden, arrest of progression and improvement in future of the management of myopia.

Keywords: pediatric myopia, axial elongation, myopia maculopathies, scleral remodeling, myopic foveoschisis, atropine in the treatment of myopia (ATOM) study, macular buckle

Introduction

Pediatric myopia is a global public health concern affecting 22.9% of the world population,¹ and a leading cause of visual impairment with a prevalence of 0.9% to 3.1% worldwide. Asian populations are known to have a higher predominance in comparison to white populations, with a visual impairment prevalence rate of 0.2% to 1.4% and 0.1% to 0.5%, respectively.² In recent years, myopia has drastically increased globally, but its prevalence is generally highest in East Asian populations including Taiwan,³ Hong Kong,⁴ Korea,⁵ and China.⁶

Although school age myopia is becoming more common in Asian and Western countries, the pattern of the disease differs in onset, prevalence and severity. In

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typical cases of school age myopia, the disease onset appears in children of late primary or early secondary school years around ages 8–14. Further disease progression occurs over the next 10–15 years until stabilization of the refractive error.⁷ While many nations follow these patterns, myopia onset in East Asian countries occurs in children of much younger ages.^{8–12} As the prevalence of myopia increases, the age of disease onset decreases, which allows more time for myopia to progress before stabilization and increases the chances of progression into high myopia.¹³

In the past decade, research has focused on halting the progression of myopia and ameliorating the future of the eye. It was once viewed as a benign refractive condition, but has now been proven to be a significant risk factor to future eye diseases such as retinal detachment, glaucoma, cataract, macular degenerative scars, and choroidal neovascularization and other chorioretinal abnormalities, in addition to its hindering effects on vision and quality of life.¹⁴ The approximate economic impact of distance vision impairment due to uncorrected refractive error is estimated to be a loss of \$ 202 billion of gross domestic product annually.¹⁵ Influenced by factors such as visual function, economic burden, psychology, academic performance and aesthetics, the quality of life in patients with myopia is significantly impaired.^{16,17}

Until recent years, the universal therapeutic intervention of choice is to correct the refractive error by spectacles, contact lenses, or rarely, refractive surgery. While these treatment modalities improve visual acuity and prevent amblyopia, they do not impact the growth of the eye, axial elongation, or progression of myopia.

Furthermore, progression and acceleration of myopia in adolescence may preclude future refractive surgery options. This review emphasizes the pathogenesis and etiology of myopia, as well as the mechanics of the different treatment modalities for proper and precise control of myopia to preserve ocular health.

Methods of Literature Search

The MEDLINE and PUBMED Library databases were searched for peer-reviewed publications relevant to the topic of the etiology and pathogenesis of Pediatric Myopia, and its treatment modalities. An in-depth search of the available literature was performed using keywords including, but not limited to, “pediatric myopia”, “refractive error”, “axial elongation”, “atropine”. While it would not be feasible to include a comprehensive list of all

relevant search terms use in the preparation of this article, combinations and derivatives of the following words provided most of the manuscripts that were reviewed for inclusion in the article: pathological myopia, pediatric myopia, refractive error, axial elongation, scleral remodeling, accommodation, emmetropization, atropine, pirenzepine, muscarinic antagonists, muscarinic receptors, anti-hypoxic drugs, formononetin, salidroside, posterior pole, myopic maculopathies, myopic foveoschisis, choroidal neovascularization, macular holes, single vision lenses, multifocal lenses, myovision lenses, Progressive Addition Lenses, orthokeratology, ATOM study, ATOM2 study, L-DOPA, dopamine, visual deprivation, positive lenses, negative lenses, primates, chicken, guinea pig, macular buckle, and posterior scleral reinforcement. Searches included all literature published in the English language before August 2018. The abstracts of the resulting articles were carefully reviewed for suitability and inclusion, and the articles that were not relevant were discarded. We selected prospective studies including Randomized Control Trials, Case–Control studies, Cohort studies, Survey studies, Systematic Reviews, Animal model studies, and Meta-Analyses. Case reports or case series were excluded. The bibliographies of all identified literature were reviewed to track additional relevant references, including some that were not published in the English language.

Molecular Concepts Underlying Myopia and Refractive Error Scleral Remodeling

As the prevalence of myopia increases, researchers have hypothesized on various biological mechanisms of myopia development and progression. The major structural change and determinant in myopic eyes is axial elongation, due to which alterations in the scleral extracellular matrix (ECM) are likely to result in changes in scleral shape.

The human sclera is composed of a single layer of fibrous connective tissue with fibroblasts and myofibroblasts in an encompassing collagenous extracellular scleral matrix.^{18,19} Collagen is the major component of total scleral protein.²⁰ Fibroblasts secrete Type I collagen, which represents the highest expression of collagen subtypes and acts as a major component of the scleral architecture.^{18,19} However, collagen gene expression in tree shrew sclera reveals 11 collagen subtypes (I, III, V, VI, VII, VIII, IX, XIII, XV, XVI, and XVII) in the total

scleral collagen composition.²¹ Collagen type I mRNA expression was reduced in sclera of myopic eyes, while the levels of subtypes III and V remained relatively similar to normal sclera. The reduced collagen subtype ratio (III/I and V/I) alters the collagen accumulation, degradation and synthesis in myopia.²¹

The sclera of the myopic human eye is described as thinning of collagen fiber bundles as well as a reduction in the size of the individual collagen fibrils, with an increase in the dispersion of the range of fibril diameters averaging below 60–70nm.²² Additionally, studies reveal an increase in abnormal star-shaped fibrils and a predominantly lamellar arrangement of collagen fibers in myopic eyes in comparison to tighter interwoven collagen fibers in emmetropic eyes.^{22,23} Such microscopic structural alterations in the human myopic sclera suggest a disruption of collagen fibril growth and organization.

The biomechanical properties of sclera are primarily dependent on the components of the scleral extracellular matrix. In accordance with studies, the ultramicroscopic changes to scleral collagenous structure are thought to be a result of a significant reduction in scleral glycosaminoglycans (GAG) synthesis in myopic eyes, especially in the posterior pole.^{24,25} Such findings were reported in myopic experimental models in tree shrews, which are mammals closely related to primates. Deprivation myopia was induced in tree shrews with occluders in front of the eye, and the ocular growth was modulated to adjust to the defocus of the eye.^{26,27} The tree shrew models have revealed reduced levels of scleral hydroxyproline and sulfated glycosaminoglycans at the posterior pole. This suggests a reduced collagen accumulation and proteoglycan content in myopic eyes, which allows the sclera to be more distensible and permitting axial elongation and resultant myopia.²⁸ The results from the studies in tree shrews reaffirm that an internal mechanism for ocular growth and scleral remodeling occurs to increase the axial length of the eye.

Myopia inducing experiments, such as visual form deprivation, have revealed that the majority of the molecular scleral changes may be reversed upon termination of the experiment. In the recovery period, the expression of mRNA levels of scleral collagen and the levels of GAG synthesis reverted to baseline levels.^{24,29} Such experiments provide sufficient grounds for salvaging the myopic sclera through intervention at molecular levels.

While fibroblasts secrete Type I collagen, myofibroblasts are contractile cells that arise from a trans-differentiation of

fibroblasts.^{18,19} A study by Wu et al reported that scleral hypoxia plays a pivotal role in myopia induced scleral remodeling.³⁰ The triggers for scleral hypoxia are multifold. The retina contains the highest consumption of oxygen in the body and has continuous light exposure, which is highly susceptible to generating Reactive Oxygen Species (ROS).³¹ Oxidative stress is a result of an imbalance between such free radical production and anti-oxidant defenses, which result in oxidative damage and ultimately hypoxia. Hence, damage to the retina by oxidative stress is highly likely to be linked to myopia.³²

Additionally, it is suggested that decrease in choroidal blood flow resulting from external visual stimuli may lead to myopia. A high choroidal blood flow is a required force for diffusion of oxygen and nutrients through the retinal layers. The ocular pulse amplitude decreases along with the choroidal blood flow. Since the retina is thinner in myopic eyes, the high driving force is no longer needed, resulting in a decrease in the choroidal blood flow. Such vascular modifications result in circulatory disturbance causing hypoxia in myopia.^{33,34}

Visual signals are conveyed to the retina and choroid, which produce mediators that result in myofibroblast trans-differentiation and resultant remodeling in the sclera. Scleral hypoxia is induced by Hypoxia-Inducible Factor-1 α (HIF-1 α), which triggers a signaling cascade for myofibroblast trans-differentiation resulting in scleral extracellular matrix (ECM) remodeling in worsening myopia. Wu et al postulated that hypoxia-induced myofibroblast trans-differentiation down-regulates type I collagen synthesis, which results in scleral structural changes, thus emphasizing the potential role of hypoxia in myopia.³⁰

Scleral architecture alterations with resultant staphyloma are detected using color fundus photography, ultrasonography, 2-dimensional Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), and more recently a 3-dimensional MRI. The new high-resolution 3D MRI with volume rendering techniques analyzes the entire shape of the eye to delineate the posterior staphyloma in highly myopic eyes.^{35–37} Using the 3D MRI, Ohno-Matsui reported posterior outpouching of the eye, suggestive of staphyloma, in 50.5% of highly myopic patients with mean axial length of 30.0 ± 2.3 mm.³⁵ In addition, Ohno-Matsui utilized a combination of 3D MRI and Optos to analyze the morphological features and structural changes observed in staphyloma in highly myopic patients in Japan and Spain with mean axial length greater than 26.5mm.³⁸ It was reported that more staphylomatous

eyes had additional features such as patchy chorioretinal atrophy and myopic choroidal neovascularization than eyes without evident staphyloma.³⁵ It is suggested that myopic eyes with staphyloma and other structural modifications have a worse prognosis for visual acuity and other degenerative changes in the eye.

Etiology of Myopia

Although numerous etiological studies have been conducted, the exact mechanism of myopia has been a historical dilemma and hitherto remains unknown. It has been suggested that both genetic and environmental factors play a significant role in its development. Myopia prevalence varies according to different ethnic and geographic populations.

It is evident that Asian populations, specifically East Asian, have the highest prevalence rates of myopia. In China, the prevalence of pediatric myopia in an urban Chinese population increased from 5.7% in 5 year-year-olds to 78.4% in 15-year-olds.⁹ The prevalence in rural China in junior high children increased from 36.8% in 13-year-olds to 53.9% in 17-year-olds.³⁹ In India, the prevalence of pediatric myopia in the urban population increased from 4.68% in 5-year-olds to 10.8% in 15-year-olds.⁴⁰ In rural India, the prevalence of pediatric myopia increased from 2.8% in 7-year-olds to 6.72% in 15-year-olds.⁴¹ Similarly in Taiwan from 1983 to 2000, the myopia prevalence rate increased from 5.8% to 21.0% in 7-year-olds, 36.7% to 61.0% in 12-year-olds, 64.2% to 81.0% in 15-year-olds, and 74% to 84% in 16 to 18-year-olds.⁴² In Korea, the prevalence of myopia increased from 50% in 5 to 11-year-olds to 78% in 12 to 18-year-olds, and decreased to 45.7% in high school children.⁴³ In Hong Kong, the prevalence of myopia in Chinese school children was 18.3% for 6-year-olds and 61.5% for 12-year-olds.

While it is known that East Asian populations have a higher prevalence rate of pediatric myopia, the prevalence and trend vary among the Non-Asian populations. In the United States, the prevalence of myopia among ages 12 to 54 increased from 25.0% in 1971–1972 to 41.6% in 1999–2004.⁴⁴ In Australia, the prevalence of myopia was 1.43% in 6-year-olds.⁴⁵ In the United Kingdom, the prevalence of myopia in a predominantly white population was 2% in 6 to 7-year-olds and 15% in 12 to 13-year-olds.⁴⁶

The recent Multi-ethnic Pediatric Eye Study of preschool children aged 6–72 months revealed the prevalence of 1.2%

in non-Hispanic White, 3.7% in Hispanic, 3.98% in Asians and 6.6% in African American children.^{47,48} The incidence of myopia increases with advancing age as demonstrated by multiple studies, including the multi-ethnic observational study conducted on older children aged 5–17 years reveals an overall 9.2% of myopia in the study subjects with 4.4% in non-Hispanic whites, 6.6% in African Americans, 13.2% in Hispanic and 18.5% in Asian children.^{49–51} The high prevalence of myopia in children and adolescents indicates that refractive error and its associated health concerns are a major public health concern that visually incapacitates children in educational, recreational and social settings.

Studies have also demonstrated that myopia risk increases with the number of myopic parents. In comparison to children with non-myopic parents, children with one myopic parent are 2.91 times more likely to have myopia while those with 2 myopic parents have 7.79 times elevated risk. The associated development risk rates are 7.6% for non-myopic parents, 14.9% for one myopic parent and 43.6% for 2 myopic parents.^{52,53} Zadnik et al reported that children with two myopic parents have longer axial lengths and less hyperopic refractive error, suggesting that the premyopic eye in children with a family history of myopia resembles to the elongated myopic eye.⁵⁴ Additional studies reveal that the annual axial length increases with the number of myopic parents: 0.20mm for no myopic parents, 0.26mm for one, and 0.37mm for two myopic parents.⁵⁵ Furthermore, myopia recurrence risk increases with the number of myopic siblings.⁵⁶ Therefore through sharing of genes and environmental factors, the probability of inheriting myopia is suggested to be significantly higher in families with myopia. Ghorbani Mojarrad et al reported that the number of myopic parents was a weak predictor of the refractive error in children since it reveals information regarding the shared environmental risk factors for myopia. Hence, it is suggested that a genetic risk score was better at detecting children at risk of myopia.⁵⁷

The investigation of genetic influence on refractive error and myopia is demonstrated in numerous Genome Wide Association Studies (GWAS) conducted over the past decade. Major development in myopia genetics occurred from the international Consortium for Refractive Error and Myopia (CREAM) study and from the genotyping company 23andMe. The CREAM study identified 24 chromosomal loci associated with refractive error between subjects of European ancestry and Asians, and uncovered a tenfold increase in the risk of myopia among these alleles.^{58,59}

Similarly, the genome-wide association study conducted by 23andMe company conducted a survival analysis on the age of myopia onset obtained from questionnaire data, and identified 20 novel chromosomal loci. The study's findings reveal multiple genetic factors and complex interactions, such as interactions between extracellular matrix remodeling, neuronal development and visual signals from the retina, in the development of myopia.^{59,60} In total, both studies identified the same 25 chromosomal loci that are associated with refractive error.⁵⁹ The collective inference from GWAS performed in the past decade has explained a portion of the genetic variants associated with refractive error. **Table 1** reveals the genes identified in experimental myopia studies. Further investigation of the mechanism by which the various loci affect the refractive error indicates potential to identify genetic targets for treatment and prevention strategies for adequate myopia control.

While it is evident that genetic factors play a role in myopia development, rapid growth in incidence and prevalence is likely due to associated environmental factors. Numerous studies have identified environmental influences such as higher education, scholastic performance, and near work to contribute to myopia development and progression.

It has been suggested that adults with higher education, near work-related occupations and accordingly higher incomes are more likely to have longer axial lengths and higher myopic refraction. For example, individuals with 10 years of more of education could be expected to have 0.60mm longer axial lengths and 1.50 diopters more myopic refraction than those with fewer years of education. Similarly, individuals with near work occupations could be expected to have 0.28mm longer axial lengths and 0.71 diopters more myopic refraction.^{61,62} It is suggested by Mendelian randomization that every additional year of education was associated with a more myopic refractive error of -0.18 diopters per year.⁶³ Williams et al displayed that education was significantly associated with myopia, as the age-standardized prevalence was 25.4% for those completing primary education, 29.1% for secondary education and 36.6% for those who completed higher education. However, it is suggested that education levels act as an additive rather than explanatory factor for increased myopia prevalence.⁶⁴ Based on these and additional study results, higher education has been closely associated with high refractive error as a result of axial elongation.

Similarly, studies have attempted to display a more direct association between reading and near work activity by

measuring the number of books read by children per week. Saw et al observed that myopic children spend more time reading than non-myopic children, and that the proportion of children with more than -3.00 Diopters of myopia was higher if children read more than 2 books per week.⁶⁵ Studies further report that highly myopic children spend more time reading, studying and in near work activities, than in outdoor activity. In a sample of Australian school children, it was reported that children of European Caucasian ethnicity spent 26.0 hrs a week in near work activities and children of East Asian ethnicity spent 32.5 hrs per week. As a result, activities such as near work, close distance reading and continuous reading are strongly associated with myopic refractive error.⁶⁶ Furthermore, myopic discordant twin studies confirm these findings and show additional findings on the impact of outdoor activity on myopia development or progression.⁶⁷

Outdoor activity has been associated with a protective effect on myopia in several epidemiological studies. While it remains independent of the amount of time spent in near work activities such as reading, the type of outdoor activity has also remained irrelevant. Studies reveal that time spent in outdoor activities is inversely correlated with myopic refraction in children. It is hypothesized that distant stimuli effect on vision for 2 to 3 hrs neutralizes the effects of 9 to 12 hrs of hyperopic defocus experienced during near work activity.⁶⁸⁻⁷¹ Additionally, it is suggested in experiments of form-deprivation myopia that outdoor light exposure exerts a protective effect of normal vision by stimulating dopamine release from the retina. This is known to inhibit eye growth and inhibit progression of myopia.⁷² Hence, it is of public health concern to promote outdoor activity in school curriculums to exert its protective effects on normal vision in children.

Animal Models Influence on Current Understanding

To better understand the etiological factors of myopia, researchers have relied on a variety of animal models for studies in stringently controlled environments. Animal studies widely report that while genetics determine myopic susceptibility, environmental factors significantly modulate the growth of the eye. Researchers have reported that intervening with the visual experience of animal models results in alterations in the growth of the eye. In 1978, Raviola and Wiesel first described that visual deprivation by eyelid suture or corneal opacification of primates

Table 1 Genes Analyzed in Experimental Myopia Studies

Authors	Year	Chromosome Location	Candidate Genes	Methodology	Study Ethnicity
Young et al ¹⁶⁰	1998	12q 21-23	TNL	Linkage Study	E
Young et al ¹⁶¹ Scavello et al ¹⁶²	2001	18p 11.31	TGIF	Linkage Study	A & E
Paluru et al ¹⁶³	2003	17q 21-22	Unidentified	Linkage Study	En & Cn
Hammond et al ¹⁶⁴	2004	11p 13 3q 26 8p 23 4q 12	PAX6	GWLS	E
Stambolian et al ¹⁶⁵	2004	22q 12.3	Unidentified	GWLS	AJ
Zhang et al ¹⁶⁶	2005	4q 22-27	RRH	Linkage Study	A
Paluru et al ¹⁶⁷	2005	2q 37.1	SAG DGKD	GWLS	E
Wojciechowski et al ¹⁶⁸	2006	1p 36	~189 genes	GWLS	AJ
Zhang et al ¹⁶⁹	2006	Xq 23-25	Unidentified	Linkage Study	A
Nallasamy et al ¹⁷⁰	2007	10q 21.1	Unidentified	Linkage Study	E
Ciner et al ¹⁷¹ Paget et al ¹⁷²	2008	7p 15	~170 genes	GWLS	AA E & Af
Lam et al ¹⁷³	2008	5p 15.33-15.2	IRX2 IRX1 POLS CCT5 CTNND2 LOC442129	GWLS	A
Ciner et al ¹⁷⁴	2009	20, 11	Unidentified	Linkage Study	AA & W
Yang et al ¹⁷⁵	2009	14q 22.1-24.2	Unidentified	GWLS	A
Hysi et al ¹⁷⁶	2010	15q 25	TNL	GWAS	E
Solouki et al ¹⁷⁷	2010	15q 14	GJD2 ACTC1	GWAS	D
Ma et al ¹⁷⁸	2010	5p 13.3-15.1	CDH6 CDH10 CDH12 PDZD2 GOLPH3 ZFR	GWLS	A
Guo et al ¹⁷⁹	2010	Xq 28	Unidentified	Linkage Study	A
Rydanicz et al ¹⁸⁰	2011	7p 22.1-21.1 7p 12.3-11.2 12p 12.3-12.1	TNL	Linkage Study	P
Han et al ¹⁸¹	2011	1P 36.6 4q 12	FRAP1 PDGFRA	GWAS	A

(Continued)

Table I (Continued).

Authors	Year	Chromosome Location	Candidate Genes	Methodology	Study Ethnicity
Yu et al ¹⁸²	2012	11q 24.1 5p 15.2	TNL CTNND2	Association Analysis	C
Abbott et al ¹⁸³	2012	6q 13–16.1 5q 35.1–35.2	TNL	QTL Linkage Study	W
Fan et al ¹⁸⁴	2012	1q 41	ZC3H11A SLC30A10 LYPLAL1	GWAS-Meta	A
Mishra et al ¹⁸⁵	2012	4q 12	PDGFRA	Meta-Analysis	Au
Cheng et al ¹⁸⁶	2013	1p 34.3 3q 12.1 6q 22.33 15q 14 22q 12.1 1q 32.2 12q 13.3 2q 37.1 1q 41	RSPO1 C2orf26 LAMA2 GJD2 ZNRFB3 CD55 MIP ALPPL2 ZC3H11B	GWAS-Meta	E & A
Guggenheim et al ¹⁸⁷	2013	4q 12	PDGFRA	GWAS	E
Wang et al ¹⁸⁸	2014	1p 22.2	ZNF644	Association Analysis	C
Chen et al ¹⁸⁹	2015	15q 25.1	RASGRF1	Meta-Analysis	C & J
Wang et al ¹⁹⁰	2016	5p 35.5	GRM6	CC Association Analysis	C
Liao et al ¹⁹¹	2017	6q 13	KCNQ5	Case-control study	C
Musolf et al ¹⁹²	2017	11p	TNL	Linkage Study	W
Musolf et al ¹⁹³	2018	10q 26.13	TNL	Linkage study	C
Wojciechowski et al ¹⁹⁴	2018	12q 24 4q 21	TNL	GWLS	Am, AA, AJ & W

Notes: Characters in Bold denote Chromosome number

Abbreviations: TNL, Too Numerous to List; GWAS, Genome Wide Association Studies; GWLS, Genome Wide Linkage Scan; QTL, Quantitative Trait Locus; CC, Case-control Study; A, Asian; AA, African American; Af, African; AJ, Ashkenazi Jews; Am, Old Order Amish; Au, Australian; C, Chinese; Cn, Canadian; D, Dutch; E, European; En, English; J, Japanese; P, Polish; W, Caucasian.

induced axial elongation and high degrees of deprivation myopia. These results initiated parallel animal studies showing that stimulation of the retina with blurred image results in alteration of growth signals within the eye.^{73–75}

Additional animal studies show that using both positive and negative lenses triggers the eye to alter its axial length to accommodate according to the lens placed in front of the eye. This mechanism is reversible when the visual stimuli are removed and can even occur when the optic nerve is severed, which reveals that the mechanism involved lies within the eye itself. Moreover, chicken eye models demonstrated the signaling cascade of growth modulators such as acetylcholine, dopamine, vasoactive

intestinal polypeptide and glucagon as they trigger retinal, choroidal and scleral growth.^{27,74,75}

There is extensive evidence suggesting that deprivation myopia in animal models result in a reduction in retinal dopamine levels, suggesting that retinal dopamine release is linked to visual stimuli and axial growth of the eye.^{76–78} Studies report that direct intravitreal injections of dopamine in rabbit eye models hinder the ocular changes in form deprivation myopia such as myopic shift, vitreous chamber and axial elongation.^{79,80} Dopamine molecules interact with its receptors D₁ to D₅ to exert their pharmacological action. The D₁-like family receptors (D_{1R}) include D₁ and D₅, which mediate responses by activating adenylate cyclase.

Contrastingly, D2-like family receptors (D2R) include D₂, D₃, and D₄, which inhibit adenylate cyclase.⁸¹ A large body of evidence suggests that stimulation of dopamine release in addition to activation of D2-Dopamine receptors exerts protective effects of normal vision against form-deprivation myopia in animal models.^{72,82,83} Contrastingly, a study by Zhang et al demonstrated that D1R activation inhibited, while D2R activation enhanced form-deprivation myopia in guinea pigs.⁸⁴

In addition to dopamine, there is sufficient evidence in support of the role of neuropeptides such as Substance P, Vasoactive Intestinal Peptide (VIP) and Calcitonin gene-related peptide (CGRP) in experimental myopia in animal models. Substance P and VIP, which are localized in amacrine cells, were among the first neuropeptides investigated for its role in modulation of eye growth in myopia.^{85–87} Primate study reports that the immunohistochemical reactivity of the retina for VIP was higher in the myopia inducing fused eyes than the open eyes. The same was not reported for Substance P.⁸⁵ Additionally, the ophthalmic sensory nerve fibers that innervate the choroid contain vasodilatory substances such as Substance P and CGRP.⁸⁸ Studies have investigated the influence of these sensory fibers on choroidal blood flow in deprived chick eye models.^{89–91} It is suggested that the vasodilatory effect of the neuropeptides may play a role in sensing changes in ocular temperature and consequently modifying the choroidal blood in myopic eyes.⁸⁸

Based on animal models, we assume that experimental manipulation of eye growth resembles the myopic changes in the human eye. Accordingly, interventions such as progressive-addition lenses, bifocals, and pharmacological interventions such as atropine eye drops have been attempted on human subjects to reduce myopic progression. Fortunately, the changes in axial growth and myopic refraction in human eyes were consistent with the predictions based on animal models.

Lifetime Risks of the Myopic Eye

The definition of pathological myopia, though inconsistent, is commonly associated with refractive error greater than -6.00 D with an axial length greater than 26 mm. This signifies a high degree of myopia and accounts for up to 33% of the myopic population.⁹² The increased axial elongation of the eye results in degenerative changes in the retina and associated maculopathies, such as posterior staphyloma, choroidal neovascularization, RPE atrophy, macular holes, and foveoschisis.^{93,94}

Choroidal neovascularization (CNV) is the formation of abnormal blood vessels under the retinal pigment epithelium capable of penetrating the Bruch membrane and extending into the subretinal space.⁹⁵ It is a vision-threatening complication of myopia and has been estimated to develop in 5–10% of patients with high myopia and is frequently associated with lacquer cracks or RPE tears and atrophy. Due to the excessive elongation of the myopic eyeball, there is mechanical stretching of the retina leading to an imbalance between pro-angiogenic and anti-angiogenic factors.⁹⁶

Myopic CNV is classified into 3 stages: active, scar and atrophic. In the active stage, a small, grey, fibrovascular membrane forms around the lesion with occasional bleeding, and patients present with rapid decrease in central vision, often with central scotoma or metamorphopsia. In the scar stage, there is formation of a scar and absorption of the bleeding, which may result in temporary improvement of vision. In the atrophic stages, there is regression of the neovascularization and presence of an area of chorioretinal atrophy, which leads to further deterioration of the vision.

A study by Yoshida et al reported that the long-term visual outcome of myopic CNV is extremely poor as chorioretinal atrophy develop around the regressed CNV in 96.3% of the patients at 5 and 10 years after CNV onset.⁹⁷ Peripherally located CNV is usually asymptomatic, while CNV located centrally present with symptoms such as metamorphopsia, scotoma, and reduced visual acuity. The visual prognosis of myopic macular CNV is poor, as patients have visual acuity of 20/200 or worse in 5 years; therefore, ophthalmologists should consider active interventions for early myopic treatment.^{92,93,98}

Myopic foveoschisis is increasingly prevalent as a vision-threatening complication. It is characterized by the splitting of retinal layers in the macula, which is more frequently seen in myopic eyes of greater than 8 diopters.⁹⁹ With progressive elongation of the highly myopic eye, patients develop posterior bulging of the globe resulting in a posterior staphyloma. Based on 3-dimensional MRI scans of the entire eye, Ohno-Matsui classifies posterior staphyloma according to its location and distribution.³⁵ This abnormal contour contributes to abnormal vitreous traction and posterior vitreous detachment.^{48,49} Additionally, it is hypothesized that the inner retinal layers are less flexible than the outer retinal layers as a result of the adherent vitreous cortex to the retina, the epiretinal membrane and the internal limiting membrane.^{100,101} Such traction on the inner retinal layers

results in splitting of the retina leading to retinoschisis and subsequent retinal detachment at the fovea.

Takano and Kishi reported in the first study that myopic foveoschisis was detected using time domain OCT in 11 out of 32 eyes of patients with severe myopia.⁹⁹ A study by Panozzo and Mercanti reported that foveoschisis occurred in 34.4% of 218 eyes in patients with severe myopia ranging from 8 to 26 diopters.¹⁰² Myopic foveoschisis is reported to contain variations of foveal architecture such as foveal cysts in 47%, lamellar hole in 29% and foveal detachment in 29% of cases.¹⁰³ Consequently, the prognosis is poor and early diagnosis is a challenge due to a slow visual decline, which is usually gone unnoticed by patients in early stages.^{48,49}

Myopic foveoschisis in its later stages may result in the formation of a macular hole from the abnormal vitreous traction and the foveal detachment. Studies show that protein, collagen, and hyaluronic acid content of vitreous humor was considerably lower in patients with myopia compared with those without myopia, suggesting that myopic eyes are affected by the degenerative process in comparison to non-myopic eyes. Additionally, the volume of the vitreous cavity is increased in highly myopic eyes, which may explain the early development of vitreous degeneration and macular holes.^{104,105}

With a myopic macular hole, patients experience severe vision loss, and an eventual retinal detachment if left surgically untreated. Regrettably, patients may require multiple surgeries, as reopening of the macular hole and retinal re-detachment are not uncommon.^{93,104}

Treatment of Myopia

Optical Correction

Single Vision Lenses

The most common therapeutic intervention for myopia utilized by clinicians is single vision lenses (SVLs) with periodic alteration of the spectacle prescription to correct the increasing refractive error. SVLs emulate the process of emmetropization by regulating the refractive error of cornea and the axial length of the eye to focus the rays on the retina. While this enhances visual outcomes, it does not interrupt the myopic progression or axial elongation of the eye. As described previously, animal studies have shown compensatory growth of the eye in spectacle induced emmetropization, which negates SVL use as it may increase progression of myopia.^{106,107} Additionally, animal studies have implied that under-correction of the

refractive error reduces the axial growth of the eye and progression of myopia. Based on the results of animal models, clinical trials on human subjects prescribed SVLs under corrected by 0.5 to 0.75D in order to reduce axial growth and myopia progression. In a 2-year clinical trial, Chung et al demonstrated that under correction speeds up myopia development and axial elongation, which is contrary to the animal studies. At the end of the clinical trial, the progression of myopia in the under-corrected group was 0.5 D per year, while that of the fully corrected group was 0.38 D per year.¹⁰⁸ Adler et al confirmed the results by reporting that under-correction produced a slight increase of 0.17 D progression of myopia over the 18-month trial period, compared to the full-correction.¹⁰⁹ Such studies report that under-correction is not an effective manner of slowing the rate of myopic progression. Additionally, while SVLs attend to the refractive error and vision complaints of the child, it does not have a protective role in the health and growth of the eye that the myopia epidemic entails.

MyoVision Lenses

MyoVision Lenses are novel spectacle lenses that were designed to reduce the peripheral hyperopia and have reported to be effective in preventing myopia progression in subgroup of children in China and more recently Japan.^{110,111} The study reported no statistically significant difference in the rate of myopia progression between children wearing the MyoVision lenses and the control group. However, an unplanned subgroup analysis revealed a possible effect in children with myopic parents.¹¹⁰ However, such results have not yet been replicated in other studies. MyoVision lenses were utilized to reduce relative peripheral hyperopia on myopia progression in Japanese children. However, the mean-adjusted change in spherical equivalent refraction and the axial elongation were not significantly different in the MyoVision Lenses group in comparison to the control group wearing Single Vision Lenses.¹¹¹ This mandates additional studies to examine the efficacy of the MyoVision lenses as well as studies to design lenses that can more effectively reduce the peripheral hyperopic defocus and reduce myopia progression.

Multifocal Lenses

Multifocal lenses have largely been investigated to slow the progression of myopia and the axial elongation of the eye. The theoretical mechanism of action of these lenses is to decrease the accommodative effort for near vision,

reduce peripheral hyperopic defocus and ultimately decrease rate of myopic progression. Multifocal lenses and the newer, more aesthetically pleasing Progressive Addition Lenses (PAL) have been widely explored by studies such as the Correction of Myopia Evaluation Trial (COMET) study—a 3-year multicenter, randomized double-masked clinical trial. The COMET study compared myopia progression in children treated with PALs versus SVLs, where progression was measured by cycloplegic autorefraction and A-Scan ultrasonography axial length. The cumulative 3-year treatment result of the trial was statistically noteworthy, as the mean increase of myopia in children treated with PALS was $1.28 \pm 0.06\text{D}$ compared to $1.48 \pm 0.06\text{D}$ for those treated with SVLs. Since these results spanned over a treatment period of merely 3 years, however it was considered clinically insignificant.^{106,112} Additionally, patient compliance may pose problems regarding cosmetic acceptance and adaptability. Future large population based, and long duration studies may substantiate the significance of the multifocal lenses in preventing the progression of myopia.

Rigid Gas Permeable Contact Lens

Contact lenses are accepted for optical correction with cosmetic benefits, and has largely been utilized to treat pediatric myopia, retard its progression and decrease axial elongation. Several options are available for myopia correction and slowing of progression such as rigid gas permeable contact lens, soft bifocal contact lens and orthokeratology contact lens.

Studies such as Contact Lens and Myopia Progression (CLAMP) study investigated the impact of contact lenses on myopic progression. CLAMP study evaluated the progression of myopia in 8 to 11-year-old children over a period of 3 years and demonstrated that rigid gas permeable contact lens wearers experienced reduced progression vs soft lens controls. Walline et al reported that rigid gas permeable lens wearers progressed $-1.56 \pm 0.95\text{D}$ in 2 years in comparison to soft contact lens wearers who progressed to $-2.19 \pm 0.89\text{D}$.^{14,113} Unfortunately, upon cessation of lens wear, myopia progression increased. Similarly, the 3-year Houston study of rigid gas permeable contact lenses compared 100 myopic children of ages 8–13 years who were fitted with Paraperm oxygen plus contact lenses with 20 spectacle wearers. The study reported that the average progression of myopia was statistically and significantly different with 0.48D progression for Rigid gas permeable contact lens wearers and -1.53D progression for spectacle

wearers.⁵⁰ The study and several others revealed that the temporary decrease in progression was a result of altering the corneal curvature, and not the axial length.^{113–115} Contrastingly, a larger randomized Singapore study involving 383 children aged 6–12 years revealed a lack of significant difference in the myopia progression rate or axial length for the contact lens and spectacle-wearing group.¹¹⁶

Soft Bifocal Contact Lens

Soft bifocal contact lenses have been designed for distance in the center with additional power in the periphery, or vice versa. Some studies have demonstrated that soft bifocal contact lenses slow myopic progression due to decrease in accommodation effort and axial length. These contact lenses are designed to correct central myopia while reducing relative peripheral hyperopia. Walline et al conducted a study among 40 participants aged between 8 and 11 years, who were fitted with soft multifocal lenses with a -2.00D add versus 40 children wearing soft single-vision contact lenses. A-scan ultrasound and cycloplegic autorefraction were performed at baseline, after 1 year, and after 2 years. It was found that the average myopic progression at 2 years was $0.41 \pm 0.03\text{D}$ for the single-vision contact lens wearers and $0.29 \pm 0.03\text{D}$ for the soft multifocal contact lens wearers.¹¹⁷ Anstice and Phillips used a contralateral eye study design, and demonstrated that the eye wearing soft bifocal contact lens has a slower axial growth when compared to the eye wearing soft single-vision contact lens.¹¹⁸ This warrants the need for further large-scale investigations on the effect of soft bifocal contact lenses on myopic progression and axial elongation, and a comparison to rigid gas permeable contact lenses.

Based on the successful correlation between myopia and reduction of axial length with multifocal contact lenses, an ongoing clinical trial by Beasley et al aims to determine whether axial growth can be accelerated in children with hyperopia by imposing relative peripheral hyperopic defocus using center-near multifocal contact lenses.¹¹⁹

In a 2-year clinical trial on myopic children between ages 8–13, a newer lens design was evaluated for preventing myopic progression. A Defocus Incorporated Soft Contact (DISC) lens design applies concentric zones of alternating distance correcting and defocusing areas that cover the pupil. The correcting zones allow clear vision, while the defocusing zones simultaneously incorporate constant myopic defocus on the retina. The DISC lens was worn for 6–8 hrs per day. At the end of the 2 years,

DISC lens wearers reported 25% less myopia progression and 31% less axial elongation than those wearing SVLs.¹²⁰

Defocus Incorporated Multiple Segments (DIMS) Spectacle Lens

In a recent two-year Randomized Control Trial, Lam et al designed a concentric dual-power lens called Defocus Incorporated Multiple Segments (DIMS) spectacle lens to investigate if the spectacle lenses can slow myopia progression in school children. The DIMS lens provides the same optical stimulus as the DISC lens but avoids the disadvantages regarding contact lens wear and subject compliance. The subjects of the trial were instructed to wear the DIMS lens in full-time mode, except during sleeping and showering. With increased compliance and lens satisfactions, the DIMS lens proved to be more effective. The progression of myopia was 52% slower in children wearing the DIMS lens than those wearing SVLs, and had less axial elongation by 62% than in children wearing SVLs.¹²¹ The DIMS lens was applied to a recent study investigating the adaptability and the acceptance of the lens in a prospective, cross-over study using DIMS lens and SVLs in study with Chinese Children. The study reported a higher preference for the DIMS lens, with +3.50D defocus, in comparison to the SVLs, with minor complaints of mid-peripheral visual changes.¹²² Although early results display good tolerance, future investigation with a large sample size is warranted for accurate presentation of the lens acceptability in school children, and for determining the optimal amount of defocus for myopia control.

MiSight Lenses

MiSight soft contact lenses contain a dual-focus optic design for slowing juvenile onset myopia progression. The hydrophilic lens contains a 2D add power, producing a second focus in front of the retina, which creates a defocused image in the retinal plane that is superimposed with the distance vision image. The central correction zone of the contact lenses, which are surrounded by alternating concentric regions of near and distant powers, provide good distance visual acuity for the patient. The MiSight Assessment Study Spain (MASS) was a 2-year randomized clinical trial reported a slower progression of myopia in MiSight lenses compared with Single Vision Spectacles as control (0.45 D vs 0.74 D).¹²³ A recent 3-year, double-masked, randomized clinical trial at four investigational sites in four countries, and reported a change in spherical equivalent refraction of -0.73 D and axial length

change 0.32mm, which was 59% and 52% less, respectively, in the test group than control group.¹²⁴ In view of the MASS study, this study incorporates an ethnically diverse subject population to demonstrate the effectiveness of MiSight contact lenses in slowing change in spherical equivalent and axial length.

Orthokeratology

Orthokeratology contact lens is rigid contact lenses that flatten the cornea until its shape is altered to ultimately reduce myopia. The lenses are removed during the day and worn overnight to temporarily alter the corneal shape through central corneal thinning, thereby correcting the myopia for short periods of time. In the Berkeley Orthokeratology study, 80 subjects were randomized to orthokeratology versus the control group.^{125,126} The results displayed a significantly larger reduction of myopia in orthokeratology lens group compared to the control, but the study had overall minimal clinical significance.

The Longitudinal Orthokeratology Research in Children was a study conducted in Hong Kong, where children wore Orthokeratology lenses for 2 years. The results of the study reported that axial length in children wearing orthokeratology lenses increased by 0.29 mm, less than the 0.54mm observed in the control group.^{127,128} These studies are promising and demonstrate the demand for a large population-based study with adequate control groups and long-term follow-up of patients to reach clinical significance. The most serious complication of Orthokeratology lenses is microbial keratitis, which may lead to significant vision loss.^{129,130} While it is commonly used in East Asia due to its effectiveness, these lenses require proper lens fitting, compliance from the child, adherence to routine follow-ups, and proper and timely treatment of any complications for long-term success.

Pharmacological Management Atropine

Atropine is a non-selective muscarinic antagonist that has shown the most encouraging results for slowing the progression of myopia in children. Atropine was initially tested in animal models and was deemed effective in preventing myopia progression and reduction of axial length.

Studies have been devoted to understanding the pharmacological and molecular mechanism of action of muscarinic antagonists on the eye, and specifically on the signaling pathway of axial elongation. While there has

not yet been a confirmation on the precise mechanism, several theoretical mechanisms of actions have been postulated. Molecular studies have revealed the presence of muscarinic receptor (mAChRs) subtypes M_1 , M_2 , M_3 , M_4 , and M_5 in both human and mouse sclera, which carries a fundamental role in the biochemical and molecular regulation of scleral remodeling.¹³¹ Expression of the mAChRs results in the proliferation of human and mouse scleral fibroblasts present in the scleral collagenous matrix, thereby promoting scleral remodeling. Atropine receptor blockage theoretically halts scleral fibroblast proliferation and consequential axial elongation of the eye; however, the hypothesis is currently under evaluation. Additional studies using Real-time PCR have determined that M_1 , M_3 , and M_4 gene expression levels were upregulated, while M_2 and M_5 gene expression showed little change, in experimental mouse eyes following atropine treatment. The understanding of the mechanism of atropine on gene expression level provides future gateway to the exploration at the molecular and protein level.¹³²

The Atropine in the Treatment of Myopia study (ATOM) was a randomized, double-masked, placebo-controlled trial conducted from 1999 to 2004 involving 400 Singapore children aged between 6 and 12 years old, where 1% atropine was instilled nightly for 2 years. The study had a 2-year treatment phase followed by a 1-year washout phase. The two-year results demonstrated a 77% reduction in progression of myopia with an unchanged axial length, in comparison to the control group.^{133,134} Although successful at the end of two-year treatment phase, the 1-year washout phase displayed significant rebound phenomenon in both the refraction and the axial length. The topical instillation of atropine was overall well tolerated but contained both short term and long-term side effects. Short-term side effects include red eyes, photophobia, blurred near vision, allergic dermatitis, increased intraocular pressure and angle closure glaucoma. Rarer long-term side effects are ocular diseases such as retinal vascular disease, and cataract.^{133,134}

The ATOM1 study was followed by a 5-year clinical trial entitled ATOM2, which examines the efficacy of lower doses of atropine on reducing the myopic progression, while simultaneously decreasing the side effects of the drug. Participants were randomly assigned to receive 0.5%, 0.1% or 0.01% concentration of atropine for 24 months, followed by a 1-year washout phase. The third phase consisted of restarting the treatment with the optimal concentration from Phase 1 on children showing progressive myopia. The ATOM2 study concludes that while all

three concentrations of atropine remain effective in reducing progression of myopia when compared to placebo group, 0.01% is a viable concentration for reducing myopic with minimal side effects thereby increasing safety profile.^{135,136} Shih et al have compared the effects of multifocal lens wearers treated with 0.5% atropine with placebo control groups, and have found that myopic control was greater with a reduced elongation length in the atropine treated group than the placebo.¹³⁷

Studies also reveal a dose dependent rebound effect after cessation, which was more common in eyes treated with 1.0% (ATOM1), 0.5% and 0.1% (ATOM2) atropine. A recent study conducted by Yam et al states that 0.05%, 0.025% and 0.01% atropine eye drops reduce myopia progression and exert a concentration-dependent reaction, of which 0.05% atropine was the most effective in controlling progression of spherical equivalent and axial elongation.¹³⁸ It is evident that atropine plays a significant role in controlling myopia progression either alone or in combination with another therapeutic regimen. Table 2 displays the role of atropine in the treatment of myopia progression over the years. Currently, the prescription of atropine eye drops has not yet been adopted as standard practice in Western countries; but it is commonly used in Asian countries including Singapore and Taiwan.

Pirenzepine

Pirenzepine has been used as an alternative to atropine treatment for pediatric myopia. Pirenzepine is a selective M_1 muscarinic receptor antagonist with actions similar to atropine in arresting myopia progression and axial elongation. Pirenzepine is known to have reduced mydriatic and cycloplegic effects compared to atropine and is prone to fewer side effects in patients.

A study conducted by Siatkowski et al formulated a 2% ophthalmic gel, with an acceptable safety profile, instilled twice daily for one year on children aged 8 to 12 years old, with a spherical equivalent of -0.75 D to -4.00 D with astigmatism of 1.00 D or less. The study demonstrated the efficacy of pirenzepine for anti-myopia treatment, as the mean increase of myopia was 0.26 D in the pirenzepine group versus 0.54 D in the placebo group. In addition, the average axial length increase at 1 year was 0.19 mm for patient in the pirenzepine group and 0.23 in the placebo group; however, this was considered statistically insignificant.

Adverse events were mild to moderate in severity, with the most frequent events being mydriasis, erythema of eyelids and ocular itching.^{125,139,140} In general, the study

Table 2 Studies on Atropine-Induced Control of Myopic Progression

Authors	Year	Study Ethnicity	Study Design
Brodstein et al ¹⁹⁵	1984	United States	Prospective, Atropine 1% vs controls
Yen et al ¹⁹⁶	1989	Taiwan	RCT, Atropine 1% vs cyclopentolate 1% vs controls
Chou et al ¹⁹⁷	1997	Taiwan	Cohort, Atropine 0.5% in myopia ≥ -6.0 D
Shih et al ¹⁹⁸	1999	Taiwan	RCT, Atropine 0.5% vs 0.25% vs 0.1% in 6-13-year-old children
Kennedy et al ¹⁹⁹	2000	United States	Cohort, Post-treatment effects of atropine (median 3.5 years)
Hsiao et al ²⁰⁰	2000	Taiwan	Myopia Intervention Trial (MIT), Single Vision Lenses vs Multifocal Lenses vs Atropine 0.5% with Multifocal Lenses
Lee et al ²⁰¹	2006	Taiwan	Cohort, Atropine 0.5% in myopic school-age children
Fan et al ²⁰²	2007	Hong Kong	Cohort, Atropine 1.0% ointment
Liang et al ²⁰³	2008	Taiwan	RCT, Atropine 0.25% with stimulation of auricular acupoints
Fang et al ²⁰⁴	2010	Taiwan	Cohort, Atropine 0.025% role in pre-myopic children
Wu et al ²⁰⁵	2011	Taiwan	Cohort, low concentration Atropine (0.05% -0.1%)
Lin et al ²⁰⁶	2013	China	Cohort, Atropine 1.0% in myopic anisometropia.
Chia et al ²⁰⁷	2013	Singapore	Full-field electroretinogram findings in ATOM2 study
Cooper et al ²⁰⁸	2013	United States	3+3 study design, to determine highest atropine concentration without clinical symptoms
Lin et al ²⁰⁹	2014	Taiwan	Cohort, Atropine 0.125% vs Orthokeratology Lenses
Cheng et al ²¹⁰	2014	Taiwan	RCT, Atropine 0.125% vs Atropine 0.125% with auricular acupoint stimulation.
Li et al ²¹¹	2014	China	Meta-analysis, Effects of atropine in Asian vs White Children.
Chia et al ²¹²	2014	Singapore	RCT, double-masked, ocular parameters in 1 year after atropine withdrawal
Kumaran et al ²¹³	2015	Singapore	RCT, biometric changes in eyes of Atropine 1% vs Placebo
Yi et al ²¹⁴	2015	China	RCT, Atropine 1.0% effects in myopic eyes
Clark et al ²¹⁵	2015	United States	Cohort, Atropine 0.01% in ethnically diverse, broad-ranged myopic population.
Polling et al ²¹⁶	2016	Europe	Effectiveness study, Atropine 0.5%
Loughman et al ²¹⁷	2016	United States	Acceptability and tolerance of Atropine 0.1%
Kothari et al ²¹⁸	2017	Indian	Cohort, Atropine 1.0% safety and efficacy
Wan et al ²¹⁹	2018	Taiwan	Retrospective, Effects of orthokeratology and Atropine (0.125% & 0.025%)

has proven the efficacy and safety of pirenzepine used for anti-myopia treatment. Further exploration comparing atropine versus pirenzepine will provide an accurate depiction of its efficacy and safety profile.

Anti-Hypoxia Drugs

Drugs such as salidroside and formononetin have been known to exhibit anti-hypoxic effects in cardiac myocytes, which may hold great potential to treat scleral hypoxia in myopia.^{141,142} Salidroside has a protective effect for hypoxia-induced cardiac apoptosis and pulmonary hypertension.^{143,144} In cardiac myocytes, the extrinsic apoptotic pathway occurs through the binding of the death receptor Fas and FasL, which initiates a pathway of cytosolic death through aggregation of Fas-Associated Death Domain (FADD) adaptor protein and activation of caspase 8.^{143,145} The activity of the Fas receptor dependent apoptotic pathway in cardiac tissue of mice with chronic intermittent hypoxia decreased after treatment with salidroside. It was reported that salidroside treatment resulted in the decrease in Fas ligand, Fas receptor, FADD, activated caspase-8 and activated caspase-3.¹⁴³ The same mechanism is

thought to occur in the case of scleral hypoxia-induced myopia, for which treatment with salidroside can exert anti-hypoxic effects to minimize scleral remodeling.

Formononetin has shown to have protective effects in hypoxia-induced retinal neovascularization by decreasing the expression of HIF-1 α , Vascular Endothelial Growth Factor (VEGF) and Prolyl Hydroxylase Domain-2 (PHD-2).¹⁴² Both drugs have shown to antagonize chloride-induced hypoxic effects.^{146,147}

In experimentally induced myopic animal models, Wu et al documented that the anti-hypoxic drugs down-regulated HIF-1 α expression and the phosphorylation levels of eIF2 α and mTOR to inhibit the development of form deprivation myopia, without affecting the normal ocular growth in guinea pigs.³⁰ The suppression of myopia in the animal models suggests the potential of these agents in the treatment of myopia in human eyes. The role of scleral hypoxia induced scleral ECM remodeling in the pathogenesis of myopia bears further investigation. This may lead to future clinical approaches in the prevention of myopia development and treatment of myopia progression.

Surgical Management

High myopia is characterized by progressive axial elongation as well as progressive thinning and weakening of the posterior sclera. Surgical intervention to halt the progression of myopic axial elongation and scleral weakening has sparked the interest of many vitreoretinal surgeons. One such surgical management is the macular buckle surgery.

Macular buckle or posterior scleral reinforcement (PSR) surgery uses a scleral buckle to apply direct mechanical force onto the posterior pole. It was first proposed by Shevelev in 1930,¹⁴⁸ and later modified by Thompson in 1978.¹⁴⁹ The surgery is believed to slow the axial elongation as the reinforcement buckle band surrounds and applies direct mechanical force onto the posterior pole, and causes scleral remodeling from the non-specific inflammatory reaction between the posterior sclera and the reinforcement band. Shen et al documented significantly higher Best-Corrected Visual Acuity (BCVA) and lower refractive error in the PSR surgery group of pre-school children compared to the control group. The study proposed that PSR surgery combined with patching therapy is a reliable method for arresting the progression of myopia.¹⁵⁰ Patients who underwent PSR surgery have shorter mean axial length and lower mean refractive error in comparison to the control group.^{151,152}

In accordance with studies, newer buckle shapes, buckle materials, techniques and modifications have emerged for treatment of pathological myopia and its complications.^{153–155} Studies have evaluated the anatomic and functional perspective of macular buckling surgery in myopic macular hole with retinal detachment and posterior staphyloma, which reported high reattachment rates and improved visual acuity.^{156,157} These published results, however, are often limited by study size and non-standardized materials and surgical techniques to limit its broad adoption, to date.

Implications for Future Research

The world is currently experiencing myopia epidemic making it imperative to develop viable treatment options for adequate correction and decreased disease progression. For the past decades the environment and surroundings that children are exposed to have drastically changed, which could explain the relatively recent rapid rise in the myopic population.

In addition, children are participating in more near work activities, which has interestingly made the pediatric population more near-sighted. For example, the leisurely habit of

watching TV at moderate distance of 10 feet has now evolved into using computers, tablets and cell phone at arm's length or closer, which requires more accommodation of their eyes. With the increasing pace, technologically advanced and the competitive society, children are seldom involved in outdoor activities on a regular basis. When such factors are considered, it warrants a more efficient and successful method to treat myopia and halt its progression in young children.

To date, atropine has been the most effective and widely accepted pharmaceutical treatment for adequate control of myopic progression, but it has not yet been utilized to its greatest potential. Single-vision lenses, unlike atropine, do not prevent continued myopia progression. Atropine, on the other hand, reduces the progression of myopia and more importantly, axial elongation.

Although many theories have been postulated for understanding the mechanism of action of atropine, it remains undetermined thereby creating hesitation for its use in pediatric eyes. However, several studies have been conducted worldwide, and it has shown promising results.^{158,159} Overall, topical atropine has been proven to be quite effective and safe for use in most children. Despite atropine's global success, unwanted side effects and the undetermined mechanism of action have kept society skeptical for its use in myopic correction in children.

As this and previous studies have reported, there are numerous unconventional treatment options proven to be effective for the treatment of pediatric myopia. Although none of these interventions have FDA approval, an appropriate treatment plan with informed consent must be instituted in ophthalmology clinics at once.

While many hypotheses are being generated by modern studies, there are additional areas requiring further research. First, the proposed alternative therapies will be more attractive with a thorough understanding of their mechanism of action, and the precise mechanism of the process of accommodation and emmetropization. This is achieved through additional human and animal studies.

Interventional focus must be directed towards the prevention of the myopia onset rather than the slowing of its progression. To achieve this, it is vital to educate society on the various modifiable risk factors that have been proven to be a cause of pediatric myopia. Children should be encouraged to spend more time engaging in outdoor activities, and parents, schools and policymakers should be informed of the potential benefits of outdoor activities. Furthermore, researchers must focus on investigating the

alterations in the current lifestyle of children that could have been the leading cause in the recent myopia boom.

It is evident that identification of an effective and acceptable treatment to slow myopia progression has the potential for a global public health impact on children and families. This will be vital to reduce the risk of future myopia-induced ocular complications, retain the ability of myopes to remain candidates for refractive surgery in adulthood, and improve the quality of life of this expanding group of patients.

Conclusion

Myopia is a major public health concern, for which the advent of potential treatments methods for adequate correction of refractive error and decrease in disease progression is essential. Understanding the role of environmental and genetic factors in myopia onset and progression will allow for the development of more successful treatments and lifestyle modifications. Although numerous studies remain unconventional in the treatment of pediatric myopia, atropine has been widely accepted worldwide in reducing myopia progression and axial elongation. Alternative myopia treatments, including other pharmacological, optical and surgical modalities, have shown promise, but require additional studies to validate its significance. Further research will be necessary to derive a conventional treatment modality capable of reducing personal and societal burden and arresting the progression of myopic disease including worsening refraction, axial elongation and retinal degeneration.

Disclosure

Dr Balamurali Ambati reports a pending patent PCT/US2019/012501. The authors report no other conflicts of interest in this work.

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