Review Articles

Clinical methods for myopia control

Introduction

Myopia, also known as short-sightedness, is a common refractive problem. Prevalence of the condition is alarmingly high in places such as Hong Kong[1], Taiwan[2] and Singapore.[3] In Hong Kong, sufferers are increasingly of a lower age, with children as young as five or six, and up to 80% of teenagers, becoming myopic.[1]

Although myopia can be corrected with either refractive surgery or optical aids such as contact lenses and spectacles, high myopes have an increased risk of suffering from sight-threatening diseases such as maculopathy,[4] retinal degeneration, retinal detachment [5-6] and glaucoma.[7] The long term care and rehabilitation of these myopia-related eye diseases will have significant impact on the economy and the cost of public health.[8] Myopia is an imminent public health issue, and effective control of the condition would help to alleviate such concerns.

A number of clinical methods are currently used for slowing myopia progression in children. However, none of them have been definitively proved to cease the development or progression of myopia, and all have different limitations. The clinical methods of myopia control can be mainly summarized into two categories: pharmaceutical agents and optical lenses. In order to be considered clinically meaningful, a therapy should slow the progression of myopia by 50% or above.[50-52]

1. Pharmaceutical agents

Atropine is the most popular drug used for myopia control, especially in Asian countries.

Table 1 summarizes the clinical trial of myopia control using atropine and pirenzepine. Regular (1%) atropine eye drops were the most effective in slowing myopia progression,[9-11] but they are rarely used for myopia control in the United States due to side effects of photophobia (sensitivity to light) and near blur. Recent clinical trials showed that low concentration (0.5% to 0.01%)[12-18] atropine also yielded significant treatment effect with minimal side effects (0.01%).[14,15] However, the safety of long-term use of atropine is still uncertain and needs to be further investigated.

Table 1. Effects of atropine and pirenzepine on myopia progression compared to controls in the clinical trials.

Table 1. Effects of atropine and pirenzepine on myopia progression compared to controls in the clinical trials.

References and years	Study design	Study duration (years)	Treatment methods	Control	Mean change in myopia progression (D)		Treatment effect, D
					Treatment	Control	Mean difference (%)
Yen et al (1989)[9]	Randomized clinical trial	1	1% atropine, 1% cyclopentolate	Saline	Atropine: -0.22 Cyclopentolate: -0.58	-0.91	Atropine: 0.7 (77%) Cyclopentolate: 0.33 (36%)
Shih et al. (1999)[12]	Randomized clinical trial	2	0.5%, 0.25%, 0.1% atropine	0.5% tropicamide	0.5%: -0.04 0.25%:-0.45 0.1%: -0.47	-1.06	0.5%: 1.02 (96%) 0.25%: 0.61 (58%) 0.1%: 0.59 (56%)
Chau et al. (ATOM1)(2006)[10]	Randomized clinical trial	2	1% atropine	Placebo	+0.38	-1.20	1.58 (132%)
Fan et al. (2007)[11]	Interventiona control	1	1% atropine	No treatment	+0.06	-1.19	1.25 (105%)
Wu et al. (2011)[13]	Retrospective case–control	3	0.1% atropine	No treatment	-0.31	-0.90	0.59 (66%)
Chia et al. (ATOM2)(2012)[14]	Randomized clinical trial	2	0.5%, 0.1%, 0.01% atropine	placebo in ATOM1	0.5%: -0.30 0.1%: -0.38 0.01%: -0.49	-1.20	0.5%: 0.9 (75%) 0.1%: 0.82 (68%) 0.01%:0.71 (59%)
Clark et al. (2015)[15]	Retrospective case-control study	1	0.01% atropine	No treatment	0.0%: -0.10	-0.60	0.5 (83%)

Polling et al. (2016)[16]	Prospective and clinical-based study	1	0.5% atropine	Pre-treatment	0.5%: -0.10	-1.00	0.9 (90%)
Lee et al. (2016)[17]	Prospective	1	0.25%, 0.125% atropine	No treatment	0.25%: 0.00 0.125%: -0.05	-1.05	0.25%: 100% 0.125%: 95%
Wang et al. (2017)[18]	Randomized clinical trial	1	0.5% atropine	Placebo	0.5%: -0.80	-2.00	1.2 (60%)
Tan et al. (2005)[19]	Randomized double-masked	1	2% pirenzepine gel	placebo	Pirenzepine -0.26	-0.53	0.27 (51%)
Siatkowski et al. (2008)[20]	Randomized double-masked	2	2% pirenzepine gel	placebo	Pirenzepine -0.58	-0.99	0.41 (41%)

ATOM1: Atropine for the Treatment of Myopia phase 1, ATOM2: Atropine for the Treatment of Myopia phase 2

Pirenzepine, like atropine, is a muscarinic antagonist, but it is less likely to induce pupil dilation and cycloplegia. Studies in the United States and Singapore showed that pirenzepine slowed myopia progression by 51% and 77% respectively[19,20]. Although pirenzepine provides effective myopia control with few side effects of photophobia and near blur, it is not approved by the US Food and Drug Administration (FDA) for myopia control, nor is it commercially available.

2. Optical lenses

2.1 Under-correction

Based on the hypothesis that it will reduce accommodative demand during viewing at near task in the same way as prescribing bifocal or multifocal spectacles, under-correction has been considered as a solution for myopia control. However, two clinical trial studies,[21,22] showed that under-correction by 0.50D to 0.75D did nothing to slow myopia progression.

In a randomized study, children were asked to wear spectacle lenses that were under-corrected to achieve distance visual acuity of 6/12. The under-correction was in the range of 0.50 to 0.75D.[21] Children in the control group were given full corrections.

After two years, the under-corrected group had a greater myopia progression of -1.00D, compared to the control group of -0.77D.

Another 18-month study, retrospectively investigating the clinical data from a private optometric practice, also found that under-correction resulted in greater myopia progression[22].

2.2 Spectacle lenses

2.2.1 Bifocal or Multifocal Spectacle Lenses

Numerous researchers have assessed the effect of bifocal or multifocal (Progressive Addition Lens (PAL)) spectacles on myopia progression. Bifocal and multifocal spectacle lenses are thought to reduce accommodative effort at near and are therefore able to lessen myopia progression.

The effect of PALs on slowing the myopic progression rate is insignificant (less than 0.2D per year) (**Table 2**) overall.[23-28] Some myopic children with esophoria and accommodative lag may benefit from PAL[26,27] but the result is not clinically meaningful.

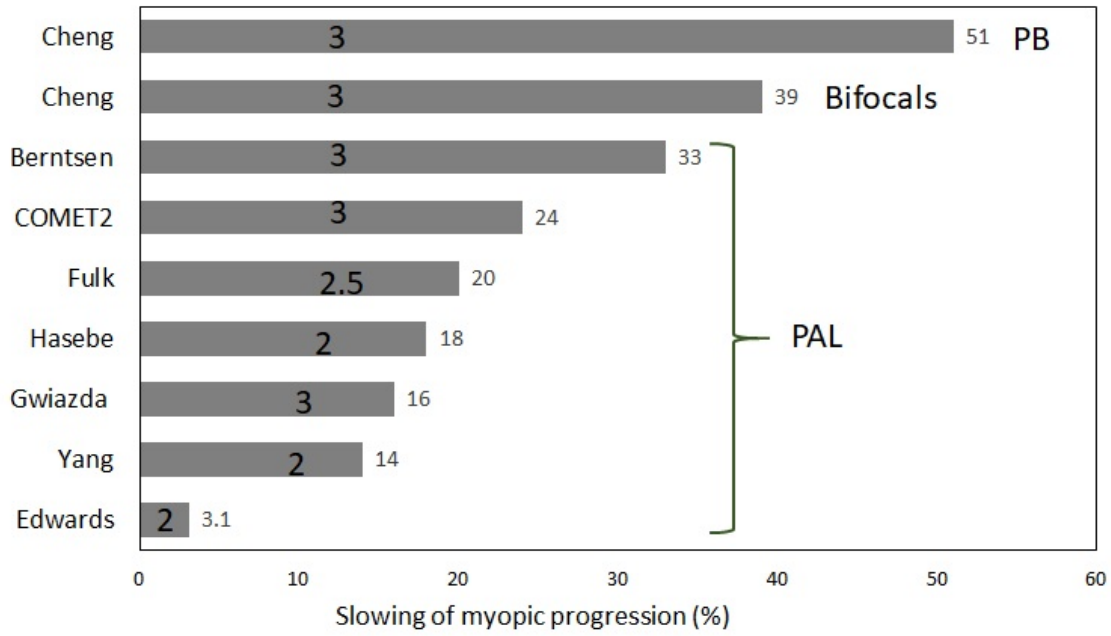
However, a clinical trial by Cheng et al.[29] has shown that in a selected group of fast-progressing myopic children, executive top bifocals both without and with 3Δbase-in prism (Myopilux®) did have meaningful effects when compared with single vision spectacles.

The myopia progression rate can be slowed down by about 40%-50% over 3 years, and the efficacy is more obvious in those with low accommodation lag.[29]

Inclusion of base-in prism in the experiment lenses was an attempt to reduce demand of fusional vergence to enhance the treatment effects of bifocals. A positive effect on the myopia was exhibited by changes in spherical equivalent refraction. However, the effects of the bifocals, assessed by measuring changes in axial length, showed the same results without and with base-in prism. Therefore, the potential benefits of base-in prism are not clear-cut.

Also, this option may not be preferable for some children due to the poor appearance of the lenses. **Figure 1** compares the slowing of myopia progression using PALs, bifocals and prismatic bifocals.[23-29]

Figure 1. The percentage of slowing of myopia progression reported by various controlled studies using bifocal or multifocal spectacles. The length (years) of the trial is indicated in the bar. [PAL (progressive addition lenses); PB (prismatic bifocals)]



Another proposed hypothesis is that correction or reduction in relative peripheral hyperopia may slow myopia progression.[30,31] Sankaridurg et al.[30] performed the clinical trial to test this hypothesis using three specially designed spectacle lenses (MyoVision™) that reduced peripheral hyperopic defocus while maintaining clear central vision.

After 12 months, no significant reduction in myopia progression was found between the treatment groups and the control group. Only one of the treatment lenses showed a 30% reduction of myopia progression in a subgroup of children whose parents were myopes. A similar trial applied on soft contact lens[31] exhibited more meaningful effects and will be mentioned in a later section on soft multifocal contact lenses.

2.2.2 Novel Spectacle Lenses

More recently, a novel spectacle lens called Defocus Incorporated Multiple Segments (DIMS), and also Multi-Segment of Myopic Defocus (MSMD), has been used for myopia control in a randomized trial by Lam et al.[32]

The results showed that children wearing DIMS lenses had less myopia progression and axial elongation by about 60% when compared with children wearing single vision spectacle lenses.

The DIMS lens controls myopia by applying the principle of simultaneous vision with myopia defocus. It comprises a central optical zone for correcting refractive error with multiple segments of constant myopic defocus (+3.50D) surrounding the central zone. It also provides clear vision and myopic defocus simultaneously for the wearer at all viewing distances.[32]

2.3 Contact lenses

2.3.1 Orthokeratology

Orthokeratology (Ortho-K) lenses are rigid gas permeable contact lenses. Worn overnight, they reshape the cornea - temporarily correcting low to moderate myopia. This has become a far more popular mode of controlling myopia in children in recent decades. In addition to the enhanced unaided vision at daytime, Ortho-K is also able to control myopic progression. The working principle is that the lenses slow progression by keeping light in the periphery visual field to be focused in front of the retina.[33]

Table 3 summarizes the recent myopic control studies of Ortho-K.[34-40] The studies

show significant slowing of axial elongation in myopic children by 31-63%.[34-40] The overall treatment effect is around 50% and might possibly be due to reduced relative hyperopic refraction at peripheral retina after corneal reshaping.[41,42] Children need to sleep with lenses overnight to maintain appropriate corneal curvature for clear vision at daytime. Also, safety issues remain a major concern.

Table 2. Myopia control studies using PAL, bifocal and multifocal spectacles.

Authors and years	Study duration (years)	Design	Age(years), ethnicity	Inclusion Criteria of Rx (D)	Interventions and sample size (n)	Treatment effect in retarding myopia progression	
						Study period in D (%)	Per year in D
Edward et al. (2002)[23]	2	Randomized, double masked	7-10.5, Chinese	-1.25 to -4.5	- SV, n = 132 - PAL (1.5D Add), n = 121	0.14 (11%)	0.07
Gwiazda et al.(2003)[24]	3	Randomized, masked	6-11, diverse ethnicity	-1.25 to -4.5	- SV, n = 233; - PAL (2D Add), n= 229	0.20 (14%)	0.07
Yang et al.(2009)[25]	2	Randomized, masked	7-13, Chinese	-0.5 to -3	- SV, n=75 - PAL (1.5D Add), n=74	0.26 (17%)	0.13
COMET2 and PEDIG (2011)[26]	3	Randomized, masked, multi-centres	8 to12	-0.75 to -2.50	- SV, n =58 - PAL (2D Add), n= 52	0.28 (24%)	0.09
Berntsen et al.(2012)[27]	1	Randomized, masked, all worn SV in 2nd year	6 to11	-0.75 to -4.50	- SV, n =42 - PAL (2D Add), n= 41	0.18 (35%)	0.18

Hasbe et al.(2014)[28]	1.5	Randomized, masked, cross-over	6-12, Japanese	-1.25 to -6.	- SV, n=44; - PAL (1.5D Add), n= 42	1st period: 0.31 (18%) 2nd period: 0.02 (2%)	1st period: 0.2 2ndperiod: 0.01
Cheng et al.(2014)[29]	3	Randomized, masked	8-13, Chinese	-1 to -5.5	- SV, n=41; - BF (1.5D Add), n=48; - PBF (1.5D Add, 3ΔBI), n=46	BF: 0.81 (39%) PBF: 1.05 (51%)	BF: 0.27 PBF: 0.35
Sankaridurg et al.(2011)[30]	1	Randomized	6-16, Chinese	-0.75 to -3.50	-type I, III lenses, SV, n = 50 each group -Type II, n =60	Type III lens: 0.29 (30% only in subgroup of children with myopic parents)	0.29 for subgroup of subjects
Lam et al. (2017)[32]	2	Randomized, masked	8-13, Chinese	-1.00 to -5.00	-SV = 90 -DIMS = 93	0.55 (59%)	0.28

COMET2 and PEDIG = Correction of Myopia Evaluation Trial 2 Study Group and the Pediatric Eye Disease Investigator Group, SV = single vision spectacle lens, PAL = progressive addition lens, BF = bifocal spectacle lens, PBF = prismatic bifocal lens, DIMS = Defocus Incorporated Multiple Segments spectacle lens

2.3.2 Soft bifocal and multifocal contact lenses

Soft bifocal contact lenses (called dual power lenses in some studies) with a centre-distance design have also been found to reduce myopia progression by incorporating myopic defocus in the periphery[43]. This utilizes myopic defocus as natural optical signals to inhibit refractive eye growth and to control myopia through different optical designs. These lenses are worn during daytime and fitted more commonly than orthokeratology lenses.

Table 4 summarizes recent clinical trials using soft bifocal contact lenses for myopia control.[31, 44-48] Overall, soft bifocal contact lenses slow the progression of myopia in children by about 50% - a similar success rate to that of orthokeratology contact lenses.

The study by Aller et al.[47] showed the most promising results, reporting myopic slowing of 70%. Lam et al.[45] also suggested that the use of DISC (Defocused Incorporated Soft Contact) lenses for at least six hours a day could result in more effective myopia control, reaching 50 to 60%.

A recent study has indicated that MiSight® Dual-Focus Myopia Control 1-Day Soft Contact Lens also slowed myopic progression and axial elongation in children by 59% and 52% respectively over 3 years.[49]

Table 3. Myopia control clinical trials of orthokeratology.

Authors and years	Study design	Study duration (years)	Control group	Mean change in AL (mm)		Treatment effect in retarding AL elongation
				Orthokeratology	Control	Mean difference (%)
Walline et al.(2009)[34]	prospective, historical controls	2	SVCL	0.25	0.57	0.32 (56%)
Kakita et al.(2011)[35]	self-selected retrospective	2	SV	0.39	0.61	0.22 (36%)
Cho et al. (2012)[36]	randomized clinical trial	2	SV	0.36	0.63	0.27 (43%)
Hiraoka et al.(2012)[37]	self-selected retrospective	5	SV	0.99	1.41	0.42 (30%)
Santodomingo-Rubido et al.(2012)[38]	self-selected prospective	2	SV	0.47	0.69	0.22 (32%)
Charm and Cho (2013)[39]	randomized clinical trial	2	SV	0.19	0.51	0.32 (63%)
Chen et al. (2013)[40]	self-selected prospective	2	SV	0.31	0.64	0.33 (52%)

SV = single vision spectacle lens, SVCL = single vision soft contact lens

Table 4. Clinical studies of myopia control using soft bifocal and multifocal contact lenses.

Authors and years	Study duration (months)	Study Design	Age (years old), ethnicity	Criteria of Rx (D)	Interventions and sample size (n)	Treatment effect in retarding myopia progression	
						Study period in D (%)	Per year in D
Anstice and Phillips (2011)[44]	10	Randomized, paired-eye control, cross-over	11-14, diverse ethnicity	-1.25 to -4.5	DF (Add+2D), n=40 SVCL, n=40	1st period: 0.25 (37%) 2nd period: 0.2 (54%)	1st period: 0.3 2nd period: 0.24
Sankaridurg et al. (2011)[31]	12	Randomized	7-14, Chinese	-0.75 to -3.5	RPH CL, n= 45 SV, n=40	0.29 (34%)	0.29
Lam et al.(2014)[45]	24	Randomized, masked	8-13, Chinese	-1 to -5	DISC (Add+2.5D), n=65 SVCL, n =63	0.21 (25%) 0.44 (50%) >6 hours 0.54 (58%) >7 hours 0.53 (60%) >8 hours	0.11

Paune et al.(2015)[46]	24	Prospective, non-randomized	9 to 16, Caucasian	-0.75 to -7	SRRG, n = 30 OK, n= 29 SV, n = 41	0.42 (43%)	0.21
Aller et al. (2016)[47]	12	Randomized, masked	8-18,	-0.50 to -6	BFSCL, n=39 SVCL, n=-40	0.57 (72%)	0.57
Cheng et al. (2016)[48]	24 (only 12-month data)	Randomized, masked	8-11	-0.75 to -4	+SA, n= 64 SVCL, n=63	6-month: 0.21 (56%) 12-month: 0.12 (20%)	0.16

DF = dual focus contact lens, SVCL = single vision contact lens, RPH CL = contact lens designed to reduce relative peripheral hyperopia, SV = single vision spectacle lens, DISC = Defocus Incorporated Soft Contact (DISC) lens, SRRG = soft radial refractive gradient contact lens, OK = orthokeratology, BFSCL = bifocal soft contact lens, +SA = soft contact lens with positive special aberration

3. Other methods for myopia prevention and slowing myopic progression

3.1 Outdoor activities

Recent epidemiological studies have found that children who spend more time outdoors during daytime are less likely to become myopic or have less myopia progression, regardless of their level of near work or their parental history of myopia.[53-58] Some evidence of this relationship has also been shown in young adults.[59]

A longitudinal study conducted in Taiwan encouraged children at a primary school to go outside during recess (outdoor group), while children in other schools continued their normal recess routine (the control group).[60]

The rate of myopia onset after a year was significantly higher in the control group (18%) than in the intervention group (8%, $p<0.001$). Refractive error also showed a greater myopic shift in the children who continued their normal recess routine (-0.38 D/year) than in the group encouraged to participate in outdoor recess activities (-0.25 D/year).

However, there was no significant difference in myopia progression between the two groups of children, suggesting that outdoor time seems to reduce the onset of myopia, but it does not reduce progression in myopic children.

The mechanism by which outdoor activity could protect against myopia development is still unknown. However, there are a number of proposed theories, such as relaxed accommodation for viewing distance receiving more myopic defocus in an outdoor environment.

Another potential factor is the distinct difference in light intensity between outdoor and indoor environments.[61] Sunlight provides much higher illumination than most indoor lighting. Alternatively, it may be that constriction of the pupil in high outdoor-light levels results in less retinal image blur, thus reducing any signal to growth triggered from the

retinal blur.

Animal studies of myopia also suggest that it is the greater intensity of light experienced outdoors which is the possible influencing factor.[61,62] Natural daylight is known to stimulate the release of retinal dopamine, which is an important neurotransmitter in the control of eye growth. In fact, myopia is usually caused by increased axial growth at an earlier age. The animal studies show that dopamine agonists inhibit myopia development, whereas dopamine antagonists block the ability of brief periods of normal vision to prevent form-deprivation myopia.[63]

Besides the light intensity, the spectral composition of sunlight may also play a role in myopia control. Sunlight is characterized by abundant short-wavelength visible light such as blue rather than red.[64] Animal studies have demonstrated that blue light had a suppressive effect against myopia.[65,66] Recently, Torri et al.[67] proposed that violet light (VL), which is not present in indoor environments, may play a role in the inhibition of myopia development and progression. They have demonstrated that exposure to VL inhibited myopic shift and axial elongation in the chick model.

On this basis, a clinical trial has been conducted with myopic children. Groups were assigned to wear VL-blocking eyeglasses, partial-VL-blocking contact lenses, or VL-transmitting contact lenses. Changes in axial lengths were compared after one year. The results showed that children who wore VL transmitting contact lenses had significantly less axial length elongation compared with those assigned the other types of lenses. This data provides evidence that VL may contribute to protecting us from myopia progression.

3.2 Effectiveness of myopia control

Several studies have conducted meta-analysis on the outcomes of myopia control using various treatment and methodologies.[50-52, 68]
A review of nine randomized controlled trials comparing the effects of multi-focal and single-vision spectacle lenses showed that multifocal, with powers ranging from +1.50

to +2.00D, were associated with a statistically significant decrease in myopia progression in school-aged children[68].

This effect is more prominent in children with a higher degree of myopia at baseline and is sustained for a period of 24 months or more. Asian children were found to have greater benefit from the intervention when compared with white children.

A meta-analysis of six clinical trials on the effectiveness of atropine on myopia control showed the drug slowed myopia progression by 0.773D/year when compared to placebo treatments.[69] The analysis also suggested a dose-response relationship between atropine and myopia progression, concluding that 0.5% and 1% was found to be effective in children. However, there are adverse reactions associated with this dose, such as photophobia, glare and allergic blepharitis.

A study comparing the treatment effect of atropine, soft bifocal and orthokeratology contact lenses indicated that both atropine and orthokeratology lenses showed treatment effect reaching over 75% while soft bifocals were about 48%. **Figure 2** shows the comparison of treatment effect of the different treatment modalities.[50]

Another recent study compared the efficacy of 16 pharmaceutical and optical interventions for myopia control in children. It concluded that atropine, pirenzepine, orthokeratology, soft contact lenses with myopia control features and progressive addition spectacle lenses were effective and produced a statistically significant reduction of myopia progression in terms of refraction or axial length.

The pharmaceutical treatments delivered an average treatment effect of around 50%. For spectacle treatments, the effects range from minimal in the PAL trials [25-27] to moderately effective in a study on executive bifocals.[29] The investigators also performed a random effects network meta-analysis combining the direct and indirect evidence to compare different interventions with single vision spectacle lenses/placebo.[52] Atropine as a myopia treatment method was found to be the most effective, retarding myopia progression at around 0.5 to 0.6D per year.

Figure 2. Comparison of treatment effects of atropine, soft bifocal contact lenses and orthokeratology contact lenses in myopia control (extracted from Smith MJ, Walline JJ. Controlling myopia progression in children and adolescents. Adolesc Health Med Ther. 2015 Aug 13; 6:133-40.)

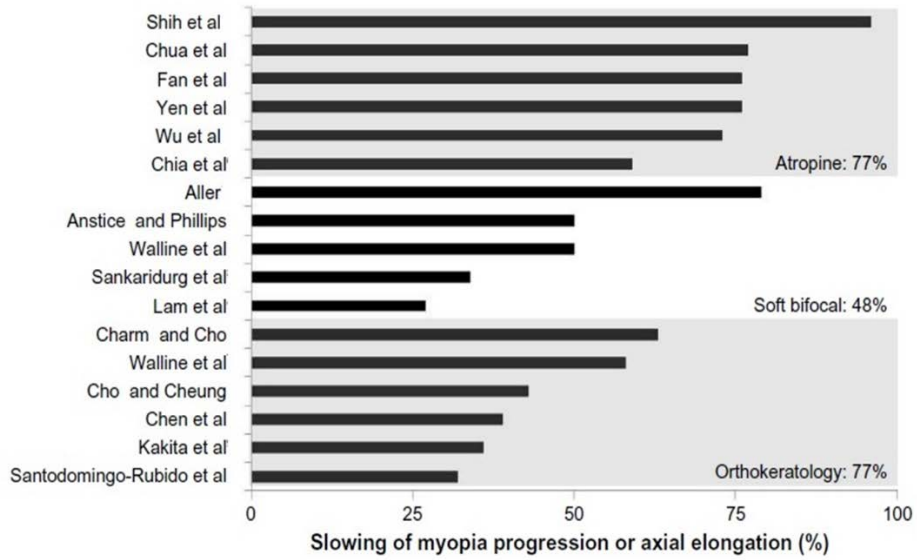


Figure 3. The mean difference in refraction and axial length changes for the different intervention studies. (extracted from: Huang J, Wen D, Wang Q, et al. Efficacy Comparison of 16 Interventions for Myopia Control in Children: A Network Meta-analysis. Ophthalmology. 2016; 123:697-708.)

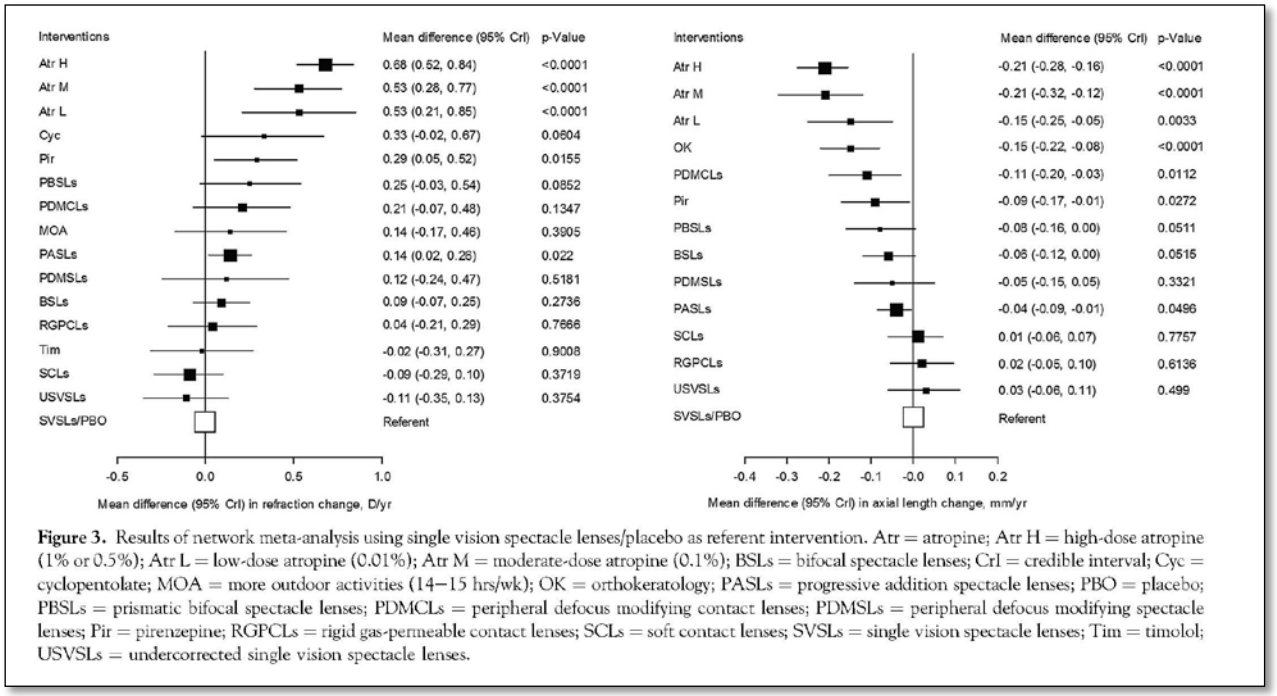


Figure 3. Results of network meta-analysis using single vision spectacle lenses/placebo as referent intervention. Atr = atropine; Atr H = high-dose atropine (1% or 0.5%); Atr L = low-dose atropine (0.01%); Atr M = moderate-dose atropine (0.1%); BSLs = bifocal spectacle lenses; CrI = credible interval; Cyc = cyclopentolate; MOA = more outdoor activities (14–15 hrs/wk); OK = orthokeratology; PASLs = progressive addition spectacle lenses; PBO = placebo; PBSLs = prismatic bifocal spectacle lenses; PDMCLs = peripheral defocus modifying contact lenses; PDMSLs = peripheral defocus modifying spectacle lenses; Pir = pirenzepine; RGPCLs = rigid gas-permeable contact lenses; SCLs = soft contact lenses; SVSLs = single vision spectacle lenses; Tim = timolol; USVSLs = undercorrected single vision spectacle lenses.

Conclusions

In summary, pharmacological treatment using atropine is relatively more effective (over 70%) than optical intervention with contact lenses or spectacle lenses. However, the side effects of atropine, such as sensitivity to light and near blur, hinder its clinical application. Low concentration atropine may provide promising myopia control with minimized side effects.

For optical interventions, PALs and multifocal spectacles do not yield any clinically meaningful effects on slowing myopia progression. Only one single study using prismatic bifocals on progressing myopic children showed moderate treatment effect. However, Ortho-K contact lenses, soft bifocal contact lenses and the very recent DIMS spectacle lenses showed clinically significant treatment effects (~50% to 60%). These methods confirmed that myopic defocus can inhibit refractive eye growth and control myopia through the different optical designs.

Although various clinical methods exist for controlling myopia in children, effects vary, and none have been proved to definitively cease its development or progression. The most suitable choice of treatment should be determined by the eye care professional

and based on age, parental history, myopic progression rate, corneal health and lifestyle of the child.

Of course, the preferred solution for dealing with myopia in children is to prevent it altogether. Large studies have reported that the prevalence of myopia in children who spend time engaged in outdoor activities is significantly lower than in those who do not. Although the underlying mechanism of this effect is not known, at least one of the simplest strategies for preventing myopia is to provide children with substantial hours of outdoor activity during their study schedules.

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Review Articles

Optical modulations of refractive development in animal models of myopia: a mini review

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Introduction

During development, our body parts actively regulate their size and shape. The eye, as the most important sensory organ, experiences a fundamental regulatory challenge that it must matches its axial length to the combined optical power of its refractory components. Intriguingly, the eye is not only the first organ responsible for forming vision perception; the eye itself is also being shaped by vision.

The present literature review first describes how the use of animal models has contributed to understanding of the role of visual environment in controlling ocular growth. Secondly, it discusses the various scientific evidences for the existence of an active feedback mechanism that constantly align the position of retina to the focal plane of the eye. Lastly, the review specifically examines the experiments which collectively suggested that visual experience can be manipulated for inhibiting excessive eye growth by introducing defocused optical image anterior to the retina through the use of dual-power lenses. Such optics, named “myopic defocus”, provides a basis for the subsequent development of contact lenses and spectacle lenses designed for the purpose of controlling myopia progression in children and teenagers.

Earlier Literatures on The Induction of Refractive Error

In more than 150 years ago, *Cohn* stated that “myopia is a result of too much close work”[1]. However, there was no scientific evidence to prove myopia is a result of controllable environmental conditions. Therefore, for many years, the consensus was that myopia was by-and-large genetically determined.

The earliest experimental evidence about the influence of visual environment on myopia development can be traced back to the 1960s. *Young* reported that monkey raised in restricted visual space developed myopia[2]. In late 1970s, scientists designed experiments to assess the consequences of visual form deprivation on the cellular receptive-field properties in the central

visual pathway[3,4]. Originated from unintended findings, chicks[5], cats[6], tree shrews[4], and rhesus monkeys[7] were subsequently developed as experimental models of myopia (fig. 1). Such visual form deprivation was mostly carried out by suture of eye lids, or placement of translucent diffusers over eyes (fig. 2). Chicken, for example, developed over 20 dioptres of myopia within two weeks with ocular elongation of >2mm following form deprivation. A-scan ultrasonography revealed that elongation of the vitreous chamber is the common major structural change among the animal models. Similar to myopia in humans, thinning of the choroid and fibrous sclera were also observed[8-11]. The key lesson from the experimental myopia following visual form deprivation is that visual exposure during the early stage of development provides critical information for the eye to reach their normal near-emmetropic state.

Emmetropization: The Active Regulatory Mechanism

Generally speaking, naturally occurring refractive errors are scarce and small in magnitude among both wild and domesticated animals including pigeon[12], chick[13], tree shrew[14], rhesus monkey[15], fish[16], marmoset[17], and guinea pig[18]. The early natural refractive development in most animal models happens to be similar to human refractive development in terms of refractive distribution. Refractive error generally showed a board distribution at birth in monkeys, at eye opening in tree shrews, and at hatching in chicks. But with time, their refractive errors approaches emmetropia from hyperopia with a reduced variability between animals[19,20]. This findings were similar to the narrowing of dispersion of refractive errors (fig. 3) with age in children[21,22]. Such phenomenon coined the term “emmetropization”, which implies that axial elongation and/or the optical components are regulated to match the focal plan with the retina. Initially, it was controversial whether emmetropization was a passive result of development or was a result of actively feedback mechanism. The increasing number of studies using animal models have provided the definitive evidences that the process is active, and that a visual feedback mechanism regulates the axial dimension primarily through modulating the vitreous chamber depth.

Compensation for hyperopic and myopic defocuses

Interventions that move the image plane behind the retina (hyperopic defocus) promote axial elongation. In contrast, interventions that shift the image plane in front of the retina (myopic defocus) cause inhibition of axial eye growth. These indicated that the eye has the capability to detect the relative positions of image plane, and accordingly alter its rate of axial growth to re-approach the state of emmetropia. The fact that compensations can be quite accurate over a range of induced defocus[23-25] strongly suggests the existence of an active and precise regulation of the axial dimensions by visual inputs.

When a negative lens is fitted over a developing eye (fig. 4), the eye responds and compensate

rapidly with an accelerated rate of growth until the imposed defocus is being neutralized[23,26]. In other words, the experimented eye approached emmetropia under the lens and became intrinsically myopic after removal of the lens. Therefore, it is commonly known as lens-induced myopia (LIM). Conversely, when a positive lens is fitted over a developing eye, the eye responds by compensating with an inhibited rate of axial growth until the imposed defocus is being neutralized. The experimented eye developed relative emmetropia under the lens but became intrinsically hyperopic after removal of the lens. This manipulation is therefore called lens-induced hyperopia (LIH). Both LIM and LIH are closed loop system as the processes terminate when the adjusted rates of growth have fully compensated for the imposed lens power. It is generally accepted that the compensatory growth responses are stimulated by the sign or the magnitude of defocus, which is detected by the retina, although the exact underlying mechanisms are not completely clear.

The compensation for lower powered positive lenses (LIH) was found to be qualitatively consistent across animal species. It slowed axial elongation in chicks[27], tree shrews[28] and macaque monkeys[25]. When the power of the positive lenses was higher, different species demonstrates different responses. For lens powers of +10D to +15D, chick eyes still underwent hyperopic growth[27]. Rhesus monkeys showed insignificant refractive changes when exposed to binocular treatment of high powered positive lens[15]. Tree shrews, however, developed relative myopia when exposed to high powered positive lens as if they were under visual form deprivation[28]. Further experiment has shown that monkey[15] was also capable to compensate for stronger lenses when the power was increased stepwise. These results suggested that different species have different operative range of emmetropization towards imposed myopic defocus[29]. Apparently, chicken has a wider range. It may be due to their smaller body size, shorter viewing distance or the presence of a stronger choroidal compensatory mechanism.

The range of operation towards imposed hyperopic defocus (LIM) in higher primate is not so limited in comparison, because the eye are usually fitted with lenses with powers within their accommodative capacity of the eye. And that the animals may exert accommodation to partly neutralize the imposed hyperopic defocus to produce focused images at least for part of the time.

Role of Accommodation

Based mainly on clinical observations, one of the earlier hypotheses for the cause of myopia was that myopia is caused by increased accommodation during protracted near work[30]. Such notion was supported by the finding that atropine (one of the common cycloplegics) inhibited myopia in monkeys[31]. Nevertheless, subsequent animal studies showed that atropine also

blocked experimental myopia in an avian model in which it cannot block accommodation[32], suggesting that the effect of atropine was mediated via a non-accommodative mechanism. Furthermore, compensation to imposed defocus has been shown to persist when accommodation is surgically or pharmacologically eliminated[33-35]. These evidences strongly suggest that accommodation is not crucial for emmetropization. However, the accuracy (lead/lag) of accommodation may still indirectly influence the development of myopia as it determines the magnitude and amplitude of defocus imposed on the retina.

Dimensional changes in ocular structures

Sclera forms the outer coat of the eye, defining its shape and size. In vertebrates, sclera generally comprises an inner cartilaginous layer and an outer fibrous layer. In primates, only the outer fibrous layer is present. It composed primarily of collagen fibrils, elastin fibrils and associated proteoglycans. In experimental myopia, there is an upregulation of degradative process, downregulation of synthesis process and consequently a loss of material in the fibrous sclera[9, 36-40]. As a result of the active remodelling of the sclera, the fibrous sclera becomes thinner[9-11,41] and more extensible[42], rendering it more readily expanded by the physiological intraocular pressure.

Choroid is the vascular layer of structure that metabolically support the sensory retina from behind. Animal studies showed that the choroid expands and thickens in volume in response to myopic defocus, pushing the photoreceptor layer forward towards the image plane. It also thins and shrinks in volume in response to hyperopic defocus, pulling the photoreceptor layer posteriorly towards the image plane. In chicks, choroidal thickness is much more obvious than the choroidal thinning percentage-wise[8]. Similar dimensional changes of choroid, but much less marked, have also been found in other species such as guinea pigs[43], marmosets[17], tree shrews[44] and rhesus monkeys[45]. With the recent advance in optical coherence tomography, similar changes have been observed in human as well[46].

One unique feature of dimensional choroidal changes is that it compensates the imposed defocus in a relatively short amount of time, by moving the retina towards the focal plane in minutes to hours following the introduction of defocus[47]. In large mammalian species with a relatively thin choroid, dimensional changes in choroid have a smaller optical effect compared to that of smaller animals. E.g. chicks.

Local Control and Spatial Localization

One of the most interesting aspects of emmetropization is that the feedback loop is independent of the central nervous system but is entirely within the eye. Compensation to diffuser and lens induced defocuses still occurred (with some quantitative differences) when the optic nerve had been surgically sectioned or when the action potential of ganglion cell had been pharmacologically blocked[48-51].

Another important aspect is that emmetropization is spatially localized so that a region of the posterior globe may elongate independently. Studies have found that naturally occurring lower field myopia existed among several species including pigeon[52], toad and chicken[53]. It was proposed that this is an adaptive feature to the visual environment, allowing the animals to see various objects below and above the horizon simultaneously with little accommodative effort. Experimental study supported this notion by showing that upper field myopia was induced from housing chicks in enclosure having a low ceiling[54]. Similarly, it has been shown that compensatory changes took place in hemifields of the eye where visual form deprivation was induced through diffusers covering the corresponding halves of visual field in chicken[55], guinea pigs[56], tree shrews[57] and rhesus monkey[58]. Further evidence comes from the findings that ocular growth was retarded or accelerated regionally on the posterior eye where myopic defocus or hyperopic defocus were respectively applied using powered lenses in the conjugate visual field (fig. 5). This localized feedback has been shown in chicken[59] and tree shrews[28] and rhesus monkey[60,61]

These localized aspects of emmetropization indicate that the major underlying signaling pathways for regulating ocular growth and myopia development lie within the eye, spanning from the retina to choroid and sclera. A detailed review of literature on the signaling pathways may be found in a previous paper[62].

Spatial-temporal integration of emmetropization

From animal studies, it is now clear that the retina is able to detect the sign of defocus and elicit compensatory mechanical changes in choroid and sclera. It is also clear that myopic defocus is a major optical STOP signals while hyperopic defocus is a major optical GO signals. Because the natural visual environment usually comprises a combination of optical signals that changes from one occasion to another occasion (fig. 6), studying the sign of defocus experienced by the retina and their spatial-temporal interactions are critical in understanding refractive development.

In general, effects of the GO and STOP optical signals increase with the duration of the stimulation. The GO signal requires essentially constant stimulation to be effective, while the STOP signal is effective even when imposed as short periods of stimulation. Visual form deprivation was decreased by interruptions as short as 15min in chicks[63] and 1hr in monkeys[64]. Normal vision was less effective in reducing hyperopia induced by myopic defocus than reducing myopia induced by hyperopic defocus[65]. In chicks, myopic defocus tended to dominate hyperopic defocus when the eye experienced alternating defocuses of opposite directions[66].

Animal studies has shown that emmetropization was modulated by the ratio of myopic and hyperopic defocus present in the visual space. Interestingly, myopic defocus was also found to be more potent[67,68]. Myopic defocus occupying percentages of 25% and 33% of the tested visual field were able to substantially inhibit myopia and produced hyperopia, respectively. The potential influence of the interplay of defocuses in space on myopia development was extensively discussed in a previous review[69].

Using myopic defocus against myopia development

Although the exact mechanisms of emmetropization remains elusive, evidences from animal studies have accumulated with time and increasingly suggested that myopic eye growth could be inhibited by manipulating myopic defocus. Unlike animal experiments, it is impractical to imposed myopic defocus simply through positive lenses or by under-correcting pre-existing myopia. To translate the use of myopic defocus for controlling myopia clinically, one must satisfy the need to simultaneously provide good vision through correcting existing refractive errors. The situation becomes even more complicated as human often exert a lag of accommodation during near work, and that the STOP effect of any imposed myopic defocus would only materialize if the eye can differentiate it from the hyperopic defocus resulted from lag of accommodation.

This question was tested in our experimental animal models using concentric dual-powers lenses having multiple annuli of alternating powers, which refract incoming rays into two longitudinally distinct image shells (fig. 7). Our first trial using chicks as model has shown that refractive development of the animals was determined by the positions of both image shells in a dose-dependent manner[67]. The eye apparently can integrate information of the competing defocus stimuli and use them to modulate its growth. For example, chicks fitted with a +10D/-10D dual-power lens (with 50:50 area ratio) developed an intermediate refractive set-point slightly biased towards hyperopia. The resultant set-points were found to change with the powers of the applied competing defocuses but were always intermediates with respect to the

elementary lens powers. In our second trial using guinea pigs as model, it was found that incorporating a plano (-5D/0D) or positive power (-5D/+5D) in a similar dual-power lens design induced an inhibited ocular growth and a smaller amount of myopia compare with animals that wore single vision lens (-5D) having the same negative power[70].

In a different study on marmosets, dual-power multi-zone contact lenses of alternating powers (-5/+5D, 50:50 area) produced relative hyperopia in the treated eyes equivalent to that produced by a +5D single vision contact lenses[71]. In a recent trial on infant rhesus monkeys, the effects of dual-power spectacle lenses with alternating powers of +3D and plano (+3D/pl) or -3D and plano (-3D/pl) were tested. The +3D/pl lens induced relative hyperopia similar to that produced by a +3D single vision lens. Moreover, the -3D/pl lens induced a refractive status more hyperopic than that resulted from wearing a -3D lens[72]. To summarize, myopic defocus imposed under a dual image shell paradigm appeared to be effective in slowing axial eye growth.

Conclusion

The eye is not only the first organ for forming visual perception, the eye itself is also being shaped by vision. The present manuscript reviewed the key scientific discoveries about the optical regulation of refractive eye growth since 1960s. Many animal studies have provided solid evidences for the existence of an active feedback mechanism that constantly align the position of retina to the focal plane of the eye. Such process is now commonly known as emmetropization. The major GO optical signal of emmetropization is hyperopic defocus which is the result when optical image is formed posterior to the photoreceptor layer. The major STOP optical signal is myopic defocus, which is the result when optical image is formed anterior to the photoreceptor layer. Experiments using dual-power lens on chicks, guinea pig, marmosets and rhesus monkeys collectively suggested that myopic eye growth can be inhibited by incorporating myopic defocus on ophthalmic lenses. This forms the scientific basis for controlling myopia progression in children through incorporation of myopic defocus into corrective lenses.

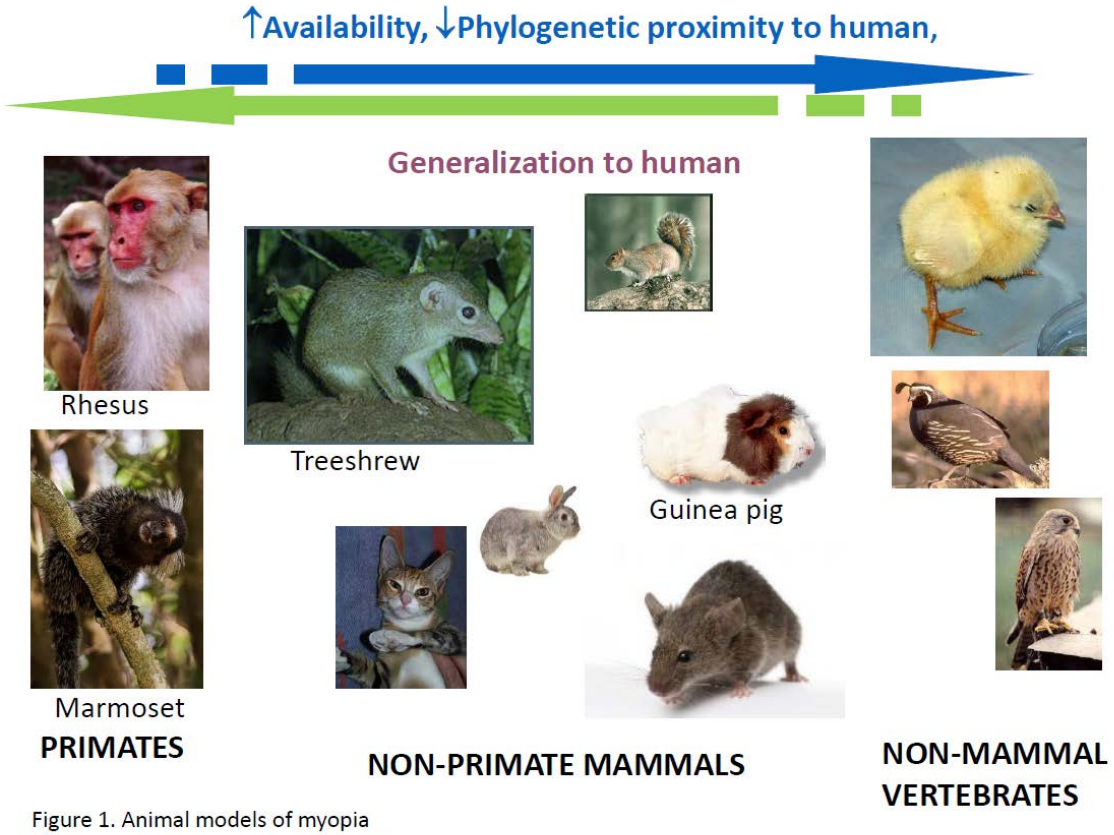

Figure 1. Animal models of myopia
(Photos collected from the internet)

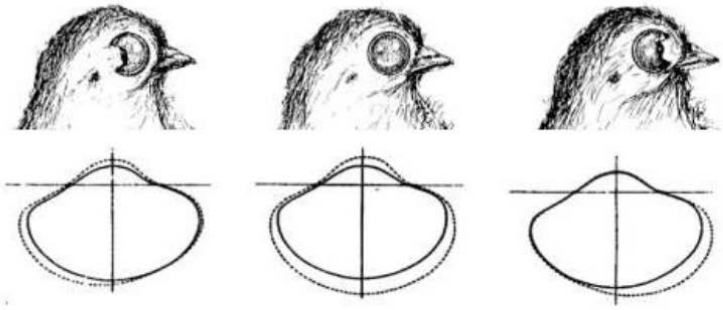

Figure 2. Visual form deprivation of chicks eyes. When chicks were raised with white translucent occluders covering their eyes so that either the nasal half, the temporal half, or all of the retina was visually deprived, the resulting ocular enlargement was limited to the deprived part of the retina, regardless of which half of the retina was visually deprived; the nondeprived part remained nearly emmetropic.

(Taken from Wallman, J, et al, *Science, 1987.* ***237(4810): p. 73-7.)***

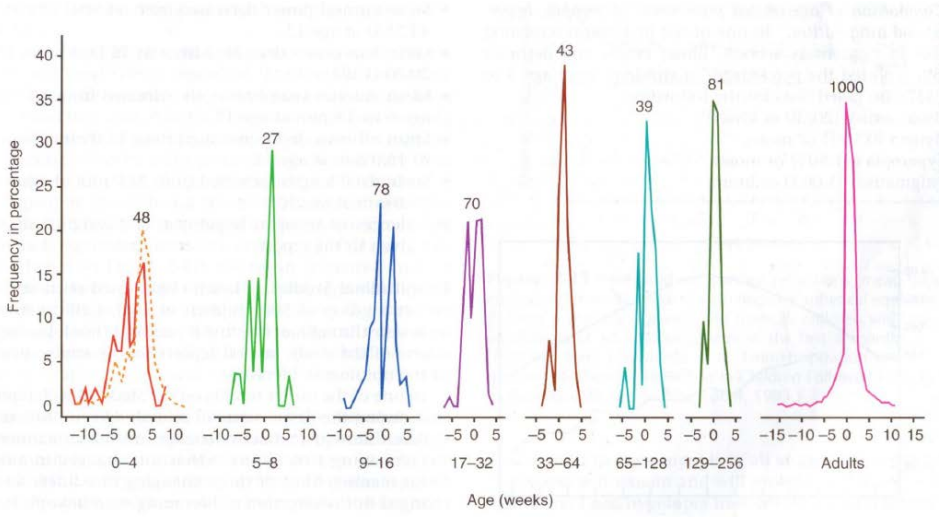

Figure 3. Narrowing of distribution of refraction during the first 5 years of life

(Taken from Grosvenor T, Chapter 2 in Primary Care Optometry 5th edition. Butterworth-Heinemann St. Louis)

Lens-induced refractive compensations

(Evidences for active emmetropization)

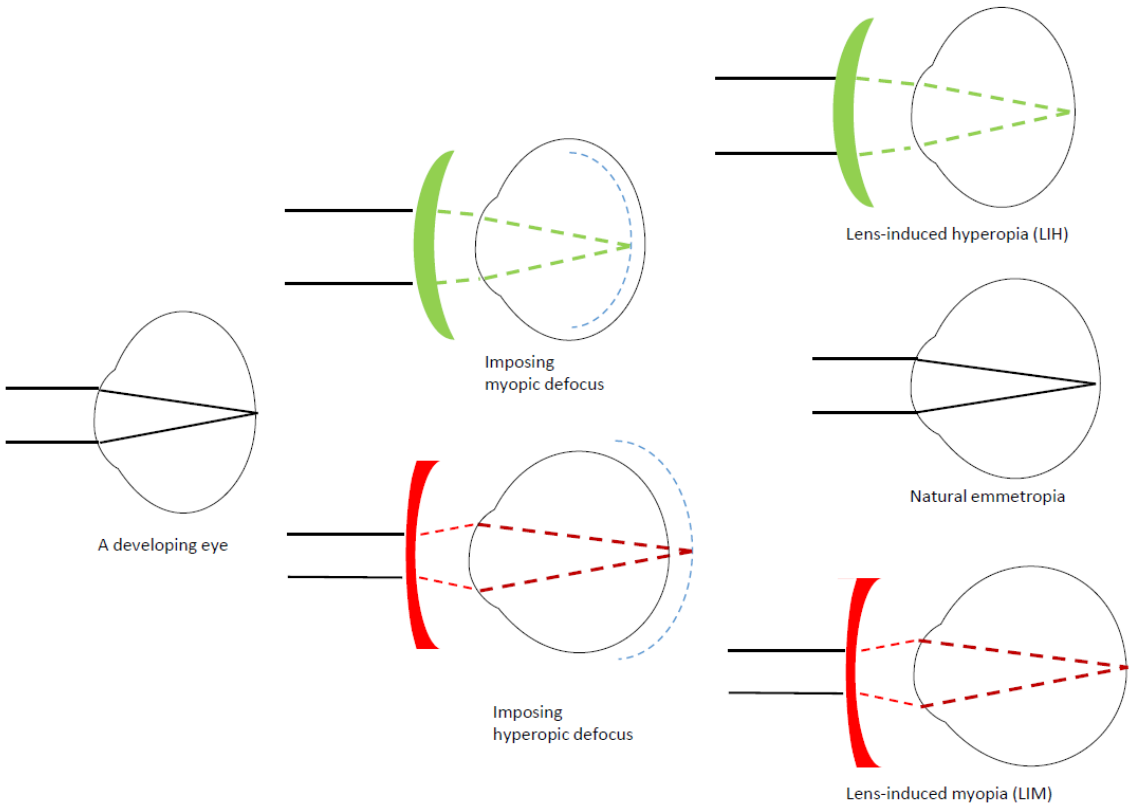

Figure 4. Schematic diagrams of lens-induced compensations (Figures drawn by Dennis Tse)

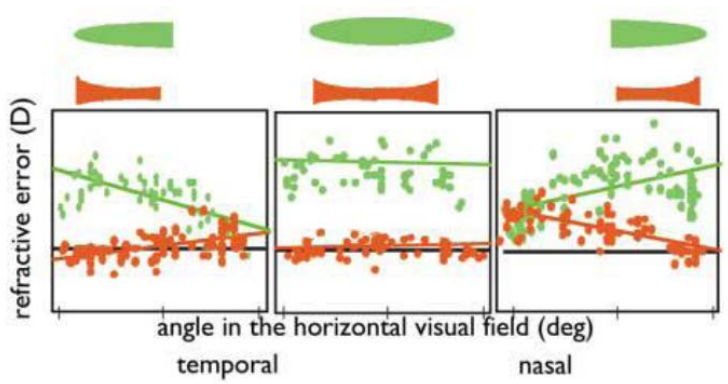

Figure 5. Refractions measured across the horizontal visual field of chicks following application of full-field negative lenses (middle) or lens segments (left and right panel). Compensatory refractive changes were localized to the defocused half of visual field.

(Taken from Diether, S and Schaeffel F, *Vision Res, 1997.* ***37(6): p. 659-68)***

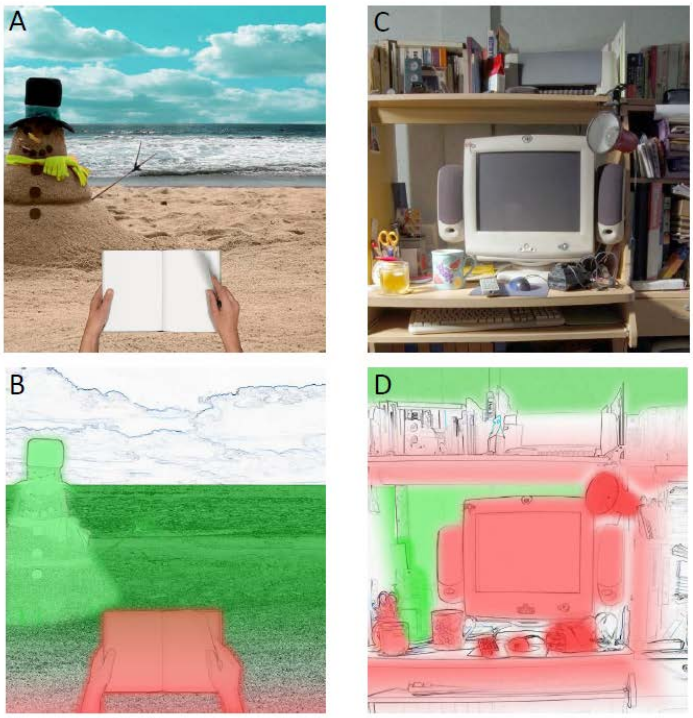

Figure 6. Examples of visual environments characterizing different profiles of simultaneous defocus. (A) A spacious outdoor reading environment . The subject adopts a frontal reading posture. (B) Map of optical defocus distribution for (A). Saturation of the colors represents relative strength of defocus. (C) Example of a confined indoor working environment . (D) Map of optical defocus distribution for (C). Saturation of the colors represents relative strength of defocus. (B, D) Green: myopic defocus ; Pink: hyperopic defocus.

(Taken from Tse DY, Lam CS et al. IOVS, *2007.* ***48(12): p.5352-9)***

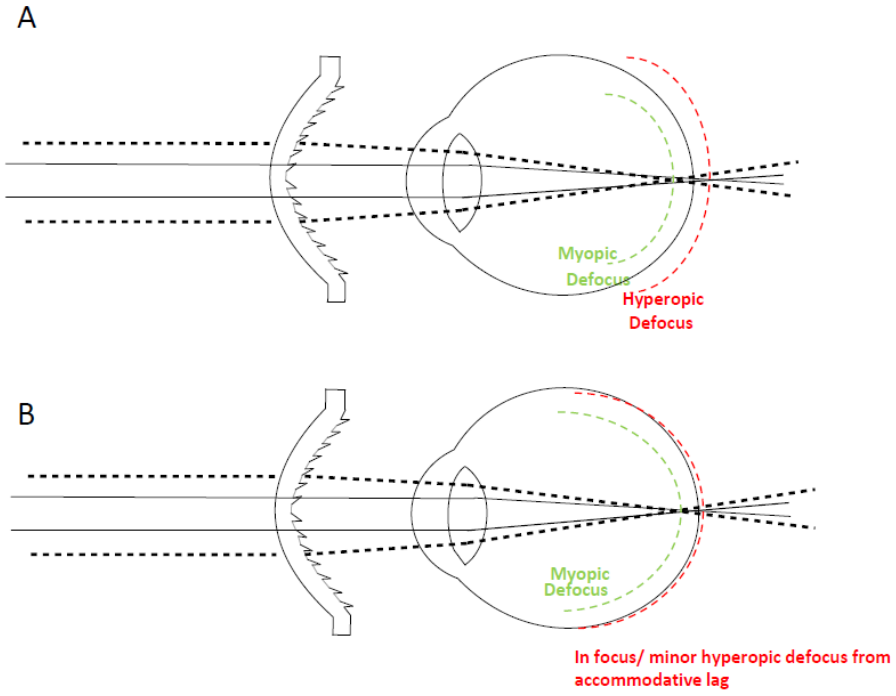

Figure 7. The optic powers of concentric dual-power lens produce two distinct image shells. A) A dual-power lens configurated to simultaneously impose myopic defocus and hyperopic defocus in animal models. B) A dual-lens lens configurated to correct existing refractive error and impose myopic defocus simultaneously for myopia control.

(Figures drawn by Dennis Tse)

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