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REVIEW ARTICLE

High myopia: Reviews of myopia control strategies and myopia complications

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Abstract

Background: Myopia and especially high myopia are recognised as major public health concerns. Although the prevalence of high myopia in young children is low, 10–20% of high school children in Asia have high myopia, with many still progressing, and one in three patients with high myopia develop visual impairment with age. Most participants in myopia control studies have low and moderate myopia; relatively little is known about myopia control in high myopia.

Method: Literature searches were undertaken in MEDLINE and EMBASE to identify publications in English, investigating (Aim 1) the efficacy of myopia control strategies (environmental, pharmacological and optical) in high myopia (≤−6.00 D) and (Aim 2) the complications of high myopia using keywords. Outcomes included change in spherical equivalent refractive error (SE) and/or axial length (AL) to evaluate progression in high myopia.

Results: Aim 1: Twelve studies were identified that reported the efficacy of optical and pharmacological (none on environmental) interventions on AL and SE for high myopia control. A statistically significant reduction in progression of SE and AL in high myopes was reported with 1% and 0.5% atropine. Defocus Incorporated Multiple Segment spectacle lenses had lower efficacy in slowing high myopia progression compared to moderate and low myopia. Ortho-K lenses were equally effective in reducing myopia progression in low, moderate and high myopia. Aim 2: Myopic patients have an increased risk of myopic macular degeneration, retinal detachment, cataract and glaucoma, with the risk increasing with the level of myopia.

Conclusions: High myopia has significant effects on quality of life, risk of pathological complications and vision impairment. Young children, excluding those with some syndromic associations, who are fast progressing moderate and high myopes require early intervention and close monitoring. Further research investigating the efficacy of myopia control strategies in highly myopic patients, both independently and through combination treatments, are necessary.

KEYWORDS
complications, high myopia, myopia, myopia control, myopia management

BACKGROUND

Introduction

Myopia is defined as a condition in which the spherical equivalent refractive error (SER) of an eye is ≤−0.50 D and high myopia where the spherical equivalent is ≤−5.00 D[1] or ≤−6.00 D[2] when ocular accommodation is relaxed.[2] It is noteworthy that one threshold for high myopia was chosen because uncorrected myopia of −5.00 D results in vision impairment that meets the threshold for blindness.[1] Some reports define high myopia as an SER of

≤−6.00 D and an axial length (AL) ≥ 26 mm.[3] The terms pathologic myopia and high myopia are sometimes used interchangeably although it is important to distinguish the two. High myopia by definition is where there is a high degree of myopia (SER or SER and AL), whereas pathologic myopia is characterised by the presence of myopia-related pathology (e.g., myopic lesions on the fundus). In this paper, the term *myopia control* is used to refer to specific products that have been evaluated for their potential to slow myopia progression and associated axial elongation.[4]

Prevalences of high myopia were reported to be 0.03–0.2% in children <7 years of age in China,[5,6] 0.2% in children <6 years of age in Singapore,[7] 0.5% in US children aged between 5 and 7 years[8] whereas no cases of high myopia were found in a sample of 346 children aged 6–7 years in Ireland in 2019.[9] These figures change considerably with increasing age. Children who develop myopia at a young age (e.g., during primary school) tend to have a faster rate of progression and axial elongation,[10] and therefore are at a higher risk of high myopia later in life. Higher levels of myopia are also associated with an increased risk of progression.[11,12] The prevalence of myopia in Singapore, China, Japan, South Korea and Taiwan is noted to be the highest in the world, reaching 80–90% in high school children in parts of southeast Asia[13] of whom 10–20% are suffering from high myopia.[14-16] The prevalence of high myopia in Europe has risen from 1.0% to 5.3% and this increase in prevalence is expected to continue.[17]

With the increasing global prevalence of myopia and high myopia, the condition has been recognised as a major public health concern[18] because of the significant increase in the risk of vision impairment from associated pathological conditions, especially with high myopia. In addition to the risk of myopia-associated pathology, this refractive error impacts the quality of life[19] in other ways. For example, the quality of life, although improved by refraction, may not be restored to the level of emmetropes.[20-22] Spectacle wearers may have concerns about their cosmetic appearance and the inconveniences of having to look after their spectacles,[23] contact lens wearers may have concerns about possible complications, while those who have undergone refractive surgery may have to live with glare and dry eye-related symptoms. If interventions to slow myopia progression are not adopted, it is predicted that myopia and high myopia will affect nearly 50% and 10% of the entire world's population, respectively, by 2050.[24] This equates to more than a doubling in myopia prevalence (from 22% in 2000) and a fivefold increase (from 2% in 2000) in the prevalence of high myopia.

Key points

- Most participants in myopia control studies have low and moderate myopia with an emphasis on early intervention to prevent high myopia—relatively little is known about myopia control in high myopia.
- It is important to understand the efficacy of myopia control strategies for individuals with high and progressive myopia as eye care practitioners often encounter these patient groups in the course of their clinical practice.
- Longitudinal studies investigating the efficacy of available myopia control strategies as standalone treatments and as combination treatments in participants with high and progressive myopia are needed.

METHODS

This literature search was performed with two aims. First, to review papers evaluating the efficacy of myopia control strategies (environmental, pharmacological and optical) in highly myopic patients. Literature on human participants, published in English and reporting the effect of the interventions on AL and SE were included (Figure 1). Exclusions included letters and commentaries, conference abstracts unless sufficiently detailed for inclusion and literature on general myopia control and adult high myopia. Literature pertaining to the myopia control of low and moderate myopia was only included if data relating to these two groups were reported as part of a study evaluating efficacy of control strategies in high myopia. This led to the exclusion of a few studies that included some participants with high myopia but did not report separate analyses of these participants.[25-29] The second aim of the review was to report on the structural and pathological complications of eyes as a result of high myopia.

The following searches of Embase and MEDLINE databases were completed on 15 September 2023 and updated on 20 May 2024:

Search terms relating to first aim:

('high myopia') AND ('myopia control' OR 'myopia management').

('high myopia') AND (spectacle) AND ('myopia control' OR 'myopia management').

('high myopia') AND (atropine) AND ('myopia control' OR 'myopia management').

('high myopia') AND ('contact lens') AND ('myopia control' OR 'myopia management').

('high myopia') AND ('outdoor') AND ('myopia control' OR 'myopia management').

Search terms relating to second aim:

('high myopia') AND ('complications').

RESULTS

This search yielded 544 results which were screened for relevance. Initially titles were reviewed, and papers

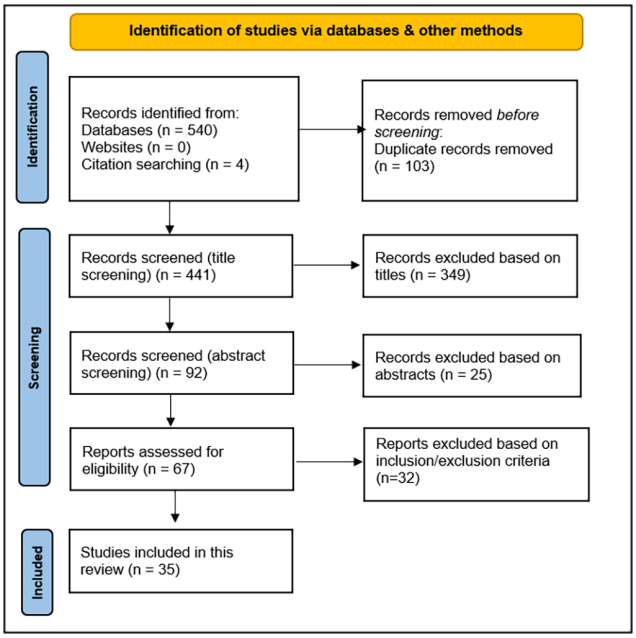

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram presenting the process of study identification, screening and selection of relevant published papers.

on topics not relevant to the scope of this review were excluded, leaving 92 titles deemed to be potentially relevant. Abstracts for these titles were reviewed to confirm applicability to the overarching aim of the literature review. After exclusion of ineligible abstracts, duplicate articles and secondary resources including other literature reviews, 67 papers were reviewed for inclusion. In total, 35 papers met the inclusion criteria (Figure 1). The findings are compared with other relevant reviews in the Discussion section.

Atropine

Atropine is the most commonly used topical pharmacological intervention for myopia control, although the exact mechanism is not fully understood.[30] Atropine has been widely used in clinical trials in concentrations ranging from 0.01% to 1.00%. Higher concentrations of atropine have been shown to be effective in slowing axial length growth in children albeit with a higher incidence of side effects. These side effects include pupil dilation and reduced accommodation, resulting in blurred near vision and photophobia. A rebound effect (increases in myopia on stopping treatment) has been observed with higher concentrations of atropine.[31,32] Recent studies have evaluated the efficacy of lower concentrations of atropine and reported conclusively that over 5 years, low-dose atropine (0.01%) has fewer side effects than high-dose (0.5 and 1%) atropine[33,34] with virtually no rebound effect after stopping but with minimal[31,35,36] or no[37] reduction in axial elongation.[31,35,36]

In 1997, Chou et al.[38] investigated the effectiveness of 0.5% atropine in controlling high myopia in children. Twenty highly myopic children with refractive error of ≤−6.00 D were treated with 0.5% atropine once/night. The mean myopic progression was −0.01 ± 0.04 D/M (Dioptre/Month) which was significantly lower than during a period of tropicamide treatment (−0.12 ± 0.09 D/M) ($p < 0.05$). Chou et al.'s conversion of myopia progression over 'up to 5 years' into rates of dioptres per month is questionable, as this infers an unreasonable assumption of linearity.

Fan et al.[39] investigated the safety and efficacy of topical 1% atropine eye ointment in retarding myopic progression in children with moderate and severe myopia. Twenty-three children 5–10 years of age with myopia ≤−3 D were treated with 1% atropine once a day for a year. A control group of 23 children were matched with the study subjects with respect to age, sex and SER. The initial refractive errors were −5.18 ± 2.05 D and −5.12 ± 2.33 D in the atropine and the control groups, respectively ($p = 0.94$). Myopic progression was significantly less in the atropine group compared with the control group (+0.06 ± 0.79 D vs. −1.19 ± 2.48 D, $p = 0.005$). Axial elongation was also significantly smaller in the atropine group compared to the control group (0.09 ± 0.19 mm vs. 0.70 ± 0.63 mm, $p = 0.004$). Although approximately half (52.2%) of the participants reported temporary photophobia and there were complaints of near vision problems, progressive addition spectacles were well tolerated and no major ocular or systemic adverse effects were noted.

Polling et al.[40] reported 1-year results on the clinical effectiveness of 0.5% atropine in European children with progressive myopia (cycloplegic SER ≤−3.00 D and SER progressing ≥1.00 D/year). Seventy-seven children with progressive myopia completed the first 12-month follow-up. Although this was not specifically a study of myopia control in highly myopic children, half (50.6%) of the children were already highly myopic (SE <−6.00 D, ranging from −6.13 D to −18.63 D). At baseline, mean refractive error was −6.63 D (±3.31). Of the 77 children, 60 (78%) adhered to therapy for the complete follow-up period of 1 year. This study found that 0.5% atropine was an effective treatment in progressive myopia with an annual progression rate of −0.10 D ± 0.7 for the children who maintained therapy versus −0.50 D ± 0.6/year for the children who discontinued therapy ($p = 0.03$). An interesting finding was that age modified the treatment effect significantly ($p = 0.01$) with children below 9 years of age having the lowest treatment effect (annual progression rate −0.49 D, CI: −0.90 to −0.08) and older children (>12-year-old) the highest treatment effect (annual progression rate 0.02 D, CI: −0.27 to +0.3). Similar to other published studies with higher doses of atropine, this study reported a relatively high occurrence of adverse events.[40]

Polling et al.[41] later reported results from a 3-year study of atropine treatment for progressive myopia in European children. In this prospective clinical effectiveness study, 124 children, aged 5–16 years, with progressive myopia

≥1.00 D/year or myopia ≤−2.50 D were prescribed atropine 0.5%. While this study did not investigate the efficacy of atropine in high myopes, children presented either with a high degree of myopia or a high progression rate. The median SER at baseline was −5.03 D and high myopia (SER ≤−6.00 D) was present in 46 (37.1%) children (range: −6.13 to −17.06 D).[41] The median annual progression of SER and AL for children who completed the 3-year follow-up was −0.25 D (IQR: 0.44) and 0.11 mm (IQR: 0.18), respectively, with no rebound of axial elongation.[41] Polling et al. managed side effects by prescribing photochromic progressive addition lens spectacles at the start of the study and reduced the risk of rebound growth by tapering the dose of atropine in children who had stable SER and AL. Tapering prevented rebound increases in AL and SER. A total of 72% of the children in this study continued therapy for 3 years despite the side effects. The data indicated that high-dose atropine was a treatment option for rapidly progressing myopia even in children with fair skin and blue eyes.[41]

Agarwal et al. investigated 0.01% atropine in highly myopic children in India in a non-randomised, parallel-group, longitudinal intervention study. Children with high myopia (≤−5.00 D), aged 6–16 years were included. In year 1, neither group received treatment. In years 2 and 3, the intervention arm received 0.01% atropine at bedtime while the control arm had no treatment but underwent routine clinical examination and monitoring. The mean baseline spherical equivalent of the full sample was −8.9 ± 2.7 D (range: −5.00 to −16.50 D) with no significant differences between the intervention (37 eyes) and control arms (23 eyes). The progression of myopia in children with high myopia receiving the daily topical dose of 0.01% atropine was significantly less (Table 1) when compared to children not receiving treatment.[42] One-year treatment with 0.01% atropine achieved a 54% reduction and 2-year treatment resulted in a 78% reduction in mean progression. Although this study was not a randomised-controlled trial, it was the first study to investigate the role of low-dose atropine in a group of highly myopic children. As families could opt for treatment, it is likely that families who were more concerned about myopia progression opted for the intervention group, thereby introducing bias.

Spectacle interventions

When considering spectacle lenses for myopia control, the last few years have seen the launch of several novel lens designs. The Defocus Incorporated Multiple Segment (DIMS) lens has a central clear zone for correcting the distance refractive error surrounded by an annular peripheral zone consisting of multiple lenslets approximately 1 mm in diameter, each providing +3.50 D of defocus.[51] Another lens design with a central clear zone, spherical front surface with 11 concentric rings formed by contiguous aspherical lenslets 1.1 mm in diameter was tested by Bao et al.[52] some 2 years later. Two variants of this lens design were studied, namely highly aspherical lenslets (HAL) and slightly aspherical lenslets (SAL). The DIMS spectacle lens design and the highly aspherical lenslet target (H.A.L.T.) are both available in many countries in the same power range (0.00 to −10.00 D) with cylindrical correction from (0.00 to −4.00 D). More recently, another design that uses cylindrical annular refractive elements (C.A.R.E®) with a single vision power in the central zone (7 mm or 9 mm) and alternating zones of correction and defocus (+3.80 D/+4.60 D) in a ring-like pattern expanding to the lens periphery has become available.[53] Diffusion Optics Technology (DOT™) spectacle lenses integrate thousands of light scattering elements called dots that modulate the retinal contrast.[54] This has been reported to slow myopia progression by reducing contrast signalling in the retina. Additionally, perifocal designs are also available.[55]

Liu et al.[49] evaluated the effectiveness of DIMS spectacle lenses using retrospective data collected from a clinical setting involving 3639 patients using DIMS lenses and 6838 patients wearing single vision spectacle lenses. The patients were 6–16 years of age (11.02 ± 2.53 years). The baseline SER was between 0.00 and −10.00 D (−2.78 ± 1.74 D). A total of 2102 low myopes (0 to−2.875 D), 1282 moderate myopes (−3.00 to −5.875 D) and 255 high myopes (<−5.875 D) wore DIMS spectacle lenses. The specific treatment efficacy for these different sub-datasets was −0.27 ± 0.02 D, −0.35 ± 0.04 D and −0.35 ± 0.06 D, respectively.

Long et al. investigated DIMS spectacle lenses in a retrospective report on 1-year data for children aged 6–15 years. Ninety children with SER −0.50 to −7.75 D (−3.82 ± 1.57 D), fitted with DIMS spectacle lenses were matched (for age, sex, refractive error and progression of myopia in the previous year) to a control group of 90 children fitted with single-vision spectacle lenses. Twenty-seven low myopes (SER <−0.50 and ≥−3.00 D), 53 moderate myopes (SER <−3.00 and ≥−6.00 D) and 10 high myopes (SER <−6.00 D) wore DIMS spectacle lenses.[50] There were 31, 50 and 9 participants in the corresponding subgroups with single vision lenses, respectively. Children wearing DIMS spectacle lenses had less myopia progression during the first year compared with children wearing single-vision spectacle lenses (−0.51 ± 0.50 vs. −0.85 ± 0.51 D, respectively). When comparing the annual change in SER for DIMS and SV subgroups, the differences were significant for low myopes ($p = 0.002$) and moderate myopes ($p = 0.02$) but non-significant for high myopes (see Discussion section).

Contact lenses

Orthokeratology (Ortho-K) involves the use of special rigid gas permeable contact lenses that are worn overnight. Ortho-K lenses temporarily change the corneal topography (flattening the central cornea) to correct the myopic refractive error and alleviate peripheral hyperopic defocus. The reduction in refractive error required in high myopia is too great to be fully corrected by Ortho-K lenses because excessive pressure from the Ortho-K lens could compromise

TABLE 1 Summary of studies evaluating the efficacy of myopia control strategies in children with high myopia.

Myopia control strategy	References	Sample size/age/SER	Study type	Spherical error	Axial length	Key findings
Atropine (0.5%)	Chou et al.[38]	20 myopic children; ≤−6.00 D in either eye	Prospective clinical effectiveness study	Less progression in atropine group vs. control group (−0.01 ± 0.04 D/M vs. −0.12 ± 0.09 D/M, $p < 0.05$)[a]		0.5% atropine was effective for slowing myopia progression in highly myopic children
Atropine (1%)	Fan et al.[39]	23 children with moderate and severe myopia	Prospective clinical effectiveness study	Less progression in atropine group vs. control group (+0.06 ± 0.79 D vs. −1.19 ± 2.48 D, $p = 0.005$)	Less ALE in atropine group vs. control group (0.09 ± 0.19 mm vs. 0.70 ± 0.63 mm, $p = 0.004$)	1% atropine was effective in retarding myopia progression in moderate and severe myopia
Atropine (0.5%)	Polling et al.[40] (1 y results)	77 children; No lower age limit stated, up to 16 years; ≤−3 D and progression rate ≥ 1 D/Y	Prospective clinical effectiveness study	Less progression in atropine group vs. discontinued group (−0.1/Y vs. 0.5 D/Y, $p = 0.03$)	No difference between treatment (−0.11/year) vs. children who discontinued (−0.12 D/Y) ($p = 0.73$)	0.5% atropine can be effective with sustained treatment effect on progressive high myopia, but with adverse events
	Polling et al.[41] (3 y results)	124 children; 6–16 y; <−2.5 D in children <10 y or ≤−5 D in children >11 y & progression rate ≥ 1 D/Y		Median progression reduced to 0.00 D in Y1, −0.41 and −0.38 D in Y2 & Y3 (all $p < 0.01$)	Annual AL progression: 0.04 mm Y1, 0.16 & 0.14 mm Y2 & Y3	0.5% was associated with decreased progression in European children with or at risk of high myopia
Atropine (0.01%)	Agarwal et al.[42]	60 children (37 eyes intervention arm, 23 eyes control arm); 6–16 y; ≤−5.00 in either eye	Prospective non-randomised parallel group study	Y1: 0.15 ± 0.9 D in 0.01% atropine group vs. 1.1 ± 1 D in control group ($p = 0.001$). After 2 y of treatment, 0.3 ± 1.1 D in 0.01% atropine group vs. 1.4 ± 1.1 D in control group ($p \leq 0.001$).	Mean ALE Y1 to Y2 for control group 0.33 ± 0.4 mm vs. 0.11 ± 0.29 mm ($p = 0.01$) atropine group. Mean ALE Y1 to Y3 for control group 0.44 ± 0.4 mm vs. 0.18 ± 0.45 mm ($p = 0.01$) for atropine group	Compared to no treatment, 0.01% atropine treatment had a marked effect on myopia progression in highly myopic children
Ortho-K	Charm & Cho[43,44]	28 participants; 8–11 y; SER <−5.75 D, myopia <−5.00 D	Prospective study		ALE greater in control vs. PR Ortho-K group at 2 y (0.51 ± 0.32 mm vs. 0.19 ± 0.21 mm, $p = 0.005$)	PR Ortho-K slowed myopic progression in high myopia with 63% slower ALE in PR Ortho-K group compared to control group
Partial treatment (Ortho-K and SV Spectacles vs. SV Spectacles)	Zhu et al.[45]	65 children; 7–14 y; Low myopia (−3.00 D < SER < −0.50 D), moderate- (−6.00 D < SER ≤ −3.00 D) & high myopia (SER ≤ −6.00 D)	Retrospective study		ALE greater in control vs. Ortho-K group at 1 y (0.39 ± 0.21 mm vs. 0.16 ± 0.17 mm, $p < 0.001$) & 2 y (0.70 ± 0.35 mm vs. 0.34 ± 0.29 mm, $p < 0.001$)	Ortho-K effective for reducing myopia progression in children with low, moderate and high myopia
Ortho-K	Yu et al.[46]	65 children; 7–15 y; Moderate myopia in one eye (≤−3.00 D, but >−6.00 D), high myopia in the other eye (≤−6.00 D)	Retrospective study		ALE by 0.14 ± 0.13 mm and 0.13 ± 0.16 mm in moderate and high myopic groups, respectively ($p = 0.78$). ALE in 7–10 y children with moderate and high myopia 0.24 ± 0.14 and 0.21 ± 0.15 mm, respectively. In 11–12 and 13–15 y children, ALE was 0.12 and 0.09 mm, respectively, in both myopic groups	Ortho-K equally effective in reducing myopia progression in moderately myopic and fellow highly myopic eyes. ALE decreased at the same rate with increasing age irrespective of baseline myopic SER

(Continues)

TABLE 1 (Continued)

Myopia control strategy	References	Sample size/age/SER	Study type	Spherical error	Axial length	Key findings
Ortho-K (partial reduction targeting 6.00 D and 4.00 D)	Lyu et al.[47]	102 myopic children; not stated; −6.00 D to −8.75 D, ≥−1.50 DC	Prospective study	Significant increase in RE SER (0.57 ± 0.31 D) and AL (0.29 ± 0.14 mm) in control group compared to Ortho-K–treated groups ($p < 0.05$). No significant differences between Ortho-K groups 1 (target 6.00 D, (0.10 ± 0.18 mm) and 2 (target 4.00 D, 0.12 ± 0.19 mm) ($p > 0.05$). Higher rate of fluorescein staining in group 1 vs. group 2 (29% vs. 13%, $p = 0.05$)		Both regimens (target reduction 6.00 D and 4.00 D) had similar effect in controlling AL and SER in highly myopic children. For safety, Ortho-K lenses with a target reduction of 4.00 D recommended for high-myopia and any residual SER corrected with spectacles
Multifocal rigid gas permeable (mRGP) contact lenses and single vision spectacles	Yu et al.[48]	77 children; 5–17 y; ≤−6.00 D or baseline AL ≥26.50 mm with >−12.00 D	Prospective study		ALE 0.21 ± 0.15 and 0.37 ± 0.27 mm, after 1 and 2 y, respectively, in mRGP group, and by 0.24 ± 0.13 and 0.43 ± 0.23 mm, respectively, in control group	AL increased at a similar rate in both control and mRGP groups. mRGP did not high myopia progression
Spectacle lenses	Liu et al.[49]	10,477 children (3639 DIMS, 6838 SV); 6–16 y; Low myopia (0 to −2.875 D), moderate myopia (−3.00 to −5.875 D), and high myopia (>−5.875 D)	Retrospective analysis of records from diverse clinical settings	Treatment effect of −0.32 ± 0.02 D for low myopia vs. −0.07 ± 0.04 D for high myopia at 1 and 2 y		DIMS lenses have greater efficacy in younger patients with lower levels of myopia
Spectacle lenses	Long et al.[50]	180 children (90 DIMS and 90 SV); 6–15 y; −0.50 D to −8.00 D, ≥−1.50 DC	Retrospective study of 1 y longitudinal data	Significant differences in SER progression for low myopes ($p = 0.002$) and moderate myopes ($p = 0.02$) but non-significant for high myopes		DIMS lens reduced myopia progression in Y1 and efficacy increased with age. DIMS lenses show greater myopic retardation in low myopia. DIMS lenses alone are not sufficient to manage myopia progression in high myopia

Note: The spherical equivalent refraction (SER) and axial length (AL) figures quoted in the table are mean ± standard deviation (SD) unless otherwise specified.

Abbreviations: ALE, axial length elongation; D, dioptre; DIMS, Defocus Incorporated Multiple Segment Lenses; M, month; Ortho-K, orthokeratology; PR-Ortho-K, partial reduction orthokeratology; RE, refractive error; SV, single vision; Y, year; y, years.

[a]See Results section.

corneal health. Ortho-K may still be considered as a partial correction and for its potential to slow future myopia progression.

Charm and Cho investigated the myopic progression associated with Ortho-K lenses in children with myopia of 6.00 D or greater using a single masked, randomised pilot study. Fifty-two subjects were randomly assigned to a partial reduction (PR) Ortho-K group ($n = 26$) or a spectacle-wearing control group ($n = 26$).[43] At the end of a 2-year single masked randomised study, the median increase in non-cycloplegic residual myopia for the control group ($n = 16$) and PR Ortho-K ($n = 12$) participants was 1.00 D and 0.13 D, respectively. The mean ± SD increases in axial length were 0.51 ± 0.32 mm and 0.19 ± 0.21 mm in the control and PR ortho-K groups, respectively (unpaired *t*-test, $p = 0.005$).[44]

In a retrospective study, Zhu et al. compared axial elongation in children with low (SER −3.00 D to −0.50 D), moderate (SER −6.00 D to −3.00 D) and high myopia (SER ≤ −6.00 D) undergoing Ortho-K treatment, combined with spectacles when PR was required. The control group (63 subjects) exhibited significantly greater axial elongation than the Ortho-K group (65 subjects) at both 12 months (0.39 ± 0.21 mm vs. 0.16 ± 0.17 mm, $p < 0.001$) and 24 months (0.70 ± 0.35 mm vs. 0.34 ± 0.29 mm, $p < 0.001$).[45] When comparing the Ortho-K and spectacle control groups with high myopia, the difference in axial elongation was significant during the first year (0.34 ± 0.22 mm vs. 0.16 ± 0.18 mm, $p = 0.004$), but not during the second year (0.27 ± 0.21 mm vs. 0.18 ± 0.15 mm, $p = 0.11$). At the end of the 2-year study, significant differences in total axial elongation were found between the Ortho-K and control groups for all degrees of myopia.[45]

Lyu et al. compared two Ortho-K lens designs with a target reduction of 6.00 D and 4.00 D and evaluated the changes in refractive error and axial length. One hundred and two participants were randomly allocated to three groups, all of whom had similar mean SER (~−6.50 D): (1) Ortho-K group 1 who wore lenses designed for target myopia reduction of 6.00 D; (2) Ortho-K group 2, with lenses having a target myopia reduction of 4.00 D and (3) the control group who used single-vision spectacles. As expected, the control group had a significantly greater increase in refractive error (0.57 ± 0.31 D) and axial length (0.29 ± 0.14 mm) when compared with the Ortho-K groups ($p < 0.05$). No significant differences between the changes in refractive error and axial length were noted between the Ortho-K groups 1 (0.10 ± 0.18 mm) and 2 (0.12 ± 0.19 mm) at 12 months ($p > 0.05$). There was a higher rate of corneal fluorescein staining when the Ortho-K target reduction of 6.00 D was used compared to the Ortho-K target reduction of 4.00 D (29% vs. 13%, $p < 0.05$).[47] The study concluded that due to concerns about corneal health, the management of high myopia with Ortho-K should use lenses with a target reduction no greater than 4.00 D.[47]

A retrospective study by Yu et al. investigated Ortho-K in 65 children of Chinese ethnicity with moderate (SER ≤−3.00 D, >−6.00 D) and highly myopic eyes (SER error −7.75 D to −6.00 D). The highly myopic eyes were fully corrected with lenses specifically designed to correct high myopia (correction up to −8.00 D) with no differences noted among the age groups ($p = 0.06$). Three age groups were included: 7–10 years ($n = 18$), 11–12 years ($n = 21$) and 13–15 years ($n = 26$).[46] From baseline to one-year, axial length increased by 0.14 ± 0.13 mm and 0.13 ± 0.16 mm in the moderate and high myopia groups, respectively ($p = 0.78$). Axial elongation in 7- to 10-year-old children with moderate and highly myopic eyes was 0.24 ± 0.14 mm and 0.21 ± 0.15 mm, respectively. The axial elongation for both moderate and highly myopic groups was 0.12 mm for 11- to 12-year-old children and 0.09 mm in 13- to 15-year-old children. In moderately myopic eyes, axial elongation in the youngest group was greater than the other two age groups ($p < 0.01$).[46] The authors concluded that Ortho-K achieved a similar level of effectiveness in controlling axial length elongation in the moderate and contralateral highly myopic eyes.[46]

Yu et al. evaluated a novel multifocal RGP (mRGP) contact lens designed to control high myopia by comparing the efficacy of this lens to single vision spectacles for myopia control in 77 children and adolescents ($n = 38$ mRGP group, $n = 39$ control group) who completed the 1-year follow-up and 41 participants ($n = 17$ mRGP group, $n = 24$ control group) who completed the 2-year follow-up.[48] Among the 77 children who completed the 1-year follow-up, there were no significant differences ($p = 0.84$) in mean axial elongation between the mRGP (0.20 ± 0.17 mm) and control groups (0.21 ± 0.14 mm). Of the 41 children who completed 2 years of follow-up, the mean axial elongation values in the mRGP and control groups were 0.21 ± 0.15 mm and 0.24 ± 0.13 mm, respectively, at the 1-year follow-up, and 0.37 ± 0.27 mm and 0.43 ± 0.23 mm, respectively, at the 2-year follow-up, without significant between-group differences at either time point ($p = 0.22$).[48]

DISCUSSION

The literature review addressing the first aim identified 12 studies evaluating the efficacy of optical and pharmacological interventions at slowing axial elongation and myopia progression for high myopia. Five clinical effectiveness studies investigated the role of atropine in high myopia and progressive myopia, one using 1% atropine, three studies using 0.5% atropine and one using 0.01% atropine. The findings of all four studies using higher dose atropine (0.5% and 1%) found a substantial treatment effect at slowing myopia progression in highly myopic participants. However, the higher incidence of side effects and rebound effect upon discontinuing therapy[33] has limited the use of these higher doses.[33] The effect on reducing myopia progression when using low-dose atropine is notably smaller[33] but when compared with no treatment, 0.01% atropine showed an effect at slowing myopic progression in highly

myopic children,[42] with the added benefit of reduced side effects and reduced likelihood of a rebound effect.[56]

Two studies evaluated the efficacy of DIMS lenses in managing myopia progression in highly myopic subjects. Both studies reported decreasing efficacy of DIMS spectacle lenses with increasing levels of myopia.[49,50] Liu et al. reported a decrease in the efficacy with increasing level of baseline myopia, an adjusted treatment effect of −0.32 ± 0.02 D for participants with low baseline myopia compared with −0.07 ± 0.04 D for those with high baseline myopia. Similar results were found with the 2-year data set. Long et al.[50] reported significant myopia control effects of DIMS spectacle lenses for low and moderate myopes but not for high myopes.[36] This could be partly explained by the increase in relative hyperopic peripheral defocus with increasing level of central myopia. This is illustrated in Figure 2, reproduced from Zheng et al.[57]

Although the introduction of peripheral myopic defocus has been well evidenced to decrease myopia progression, the required amount and location of myopic defocus remains unknown. Some clinical trials have indicated that the efficacy of myopic defocus is dose dependent within a certain myopic prescription range.[58,59] If this is correct, then it is possible that the +3.50 D myopic defocus exerted by the DIMS lenses was insufficient on its own for the control of myopia progression in highly myopic patients.[50] The initial age and level of baseline myopia in the DIMS group positively influenced the benefits of DIMS over single vision lenses, with a greater observable benefit in younger individuals and a lesser effect on myopia progression in those with high myopia.[49,50]

Both studies investigating the efficacy of DIMS spectacle lenses were retrospective.[49,50] Data on axial length were not available as it was not a routine measurement in the clinical sites. Information about compliance and wearing times were also unavailable, which may be significant contributing factors to the efficacy of the DIMS spectacle lenses in myopia control. Additionally, it is noteworthy that the proportion of high myopes in both studies

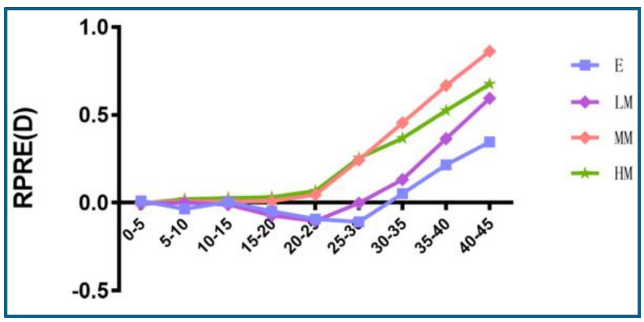

FIGURE 2 Trend of relative peripheral refractive errors (RPRE) in different eccentricities (*x*-axis) of four refractive groups.[57] E, emmetropes; HM, high myopia; LM, low myopia; MM, moderate myopia. Reproduced from relationship between peripheral refraction in different retinal regions and myopia development of young Chinese people by Zheng et al.[57] under the Creative Commons Attribution Licence (CC BY).

(participants wearing both DIMS and SV lenses) was much smaller (~6–11%) when compared to the proportion of low and moderate myopes.

Long et al. recommended a combination of interventions combining topical low-dose atropine or more time outdoors with DIMS spectacle lens wear to slow myopia progression in highly myopic children. Time outdoors has been found to have a protective effect against myopia but its role in reducing the progression of myopia following onset is limited.[60] A recent study by Nucci et al.[61] reported DIMS spectacle lenses and atropine (0.01%) were each effective in reducing myopia progression and axial elongation in a European population of low myopes, but most successful at reducing progression when used in combination.

Myopia control spectacle lenses in young children have been reported to be safe with minimal stated side effects, good adaptability[51,52,53,62] and no rebound effect.[63] Further research evaluating the efficacy of combination treatment with different strengths of low-dose atropine and spectacle lenses for myopia control is warranted in individuals with moderate and high myopia. The possibility of adding other interventions that are believed to have a different mechanism, such as diffusion optics, should also be further explored.[55] Although repeated low-level red-light (RLRL) treatment has been advocated[64] as a myopia control intervention that has an additive effect with optical treatments,[65] recent serious concerns about the safety of RLRL[66,67] means that the present authors do not endorse this treatment or consider it further in this review.

Four studies investigated the effect of Ortho-K on axial elongation in highly myopic patients. One of the studies used Ortho-K lenses only,[46] two studies used single vision spectacles to correct any residual refractive error[44,47] and the fourth study compared Ortho-K combined with spectacles and spectacles alone.45 In all four studies, Ortho-K lenses had a similar effect in slowing axial elongation at 1 year although there were reports of higher rates of corneal fluorescein staining in cases where lenses used more extreme treatment zones to target a higher target myopia reduction. In two studies, Ortho-K appeared to have a similar effectiveness in slowing axial elongation with full correction and in cases where there was partial correction.[45,46] Based on the best available evidence, topical antimuscarinic agents and orthokeratology appear to be the most effective interventions in slowing childhood myopia progression in high myopia.[38,39,40,41,44,45,46,47] Further work is necessary regarding Ortho-K as a myopia control option in young children (age 5–9 years) with moderate or high myopia independently or as a combination treatment with atropine or myopia control spectacle lenses.

To the best knowledge of the present authors, there have been no previous reviews of myopia control for high myopia. Therefore, it is not possible to compare the findings of the present review with any previous reviews.

High myopia in infants and very young (pre-school) children often has a different aetiology compared to

older children. The priority following the initial diagnosis of high myopia in childhood is to exclude a medical diagnosis (indicating secondary myopia) that could be of greater overall importance to the child's health.[68] The recommended diagnostic tests and decision-making stages for determining which cases require referral from community eye care practitioners were recently summarised in an International Myopia Institute (IMI) publication by Flitcroft et al.[68] whose figure is reproduced below (Figure 3).

There is a lack of evidence of efficacy when using interventions for reducing myopic progression in childhood high myopia with variable responses likely due to the heterogeneous nature of high myopia in young children.[68] Typically, studies of myopia control in high myopia do not include selection criteria to exclude secondary or syndromic myopia, and certainly do not follow the detailed process recently recommended by the IMI.[68] It would be advisable for future research on myopia control in cases of high myopia to follow the process outlined in Figure 3.[68]

Although age and baseline myopia are key factors when considering progression, treatment and myopia control strategies, it is perhaps more imperative that practitioners identify key risk factors (such as age, parental myopia and environmental factors) and consider the risk of pathologic complications with increasing refractive error. All myopic children are at risk of progression though it is well evidenced that younger myopes show faster progression than older children. It is these younger children who are most likely to benefit from early intervention and treatment to slow myopia progression because any reduction in progression is beneficial and reduces the risks of pathological complications and the associated population-based burden in later life.

In performing a review of literature on the control of high myopia, it has become evident that there are very few available myopia control strategies for individuals with high myopia and only one 'on-label' soft contact lens option for very high refractive errors. 'Off-label' options (e.g., centre-distance multifocal soft contact lenses) are available but clinicians may be reluctant to use 'off-label' products.

The need for effective myopia control interventions in high myopia, or children whose early onset and/or rapid progression predict subsequent high myopia, leads to the consideration of two strategies. The first approach is to increase the dose of atropine.[68] An analogous approach may also, hypothetically, be possible with optical interventions. If the degree of peripheral myopic defocus that is required is greater than that provided by current interventions, would there be an additive effect if two such interventions were combined? For example, a progressing high myope of −6.00 D might be fitted with Ortho-K to correct 4.00 D of the myopia and wear DIMS spectacle lenses to correct the residual −2.00 D and thus provide peripheral myopic defocus from the DIMS technology lenslets in addition to that from the Ortho-K. The present authors do not advocate this approach, that to the best of their knowledge is unresearched, but raise this as a topic for consideration in future studies. This hypothesised approach assumes that the mechanism for so-called optical interventions is indeed optical. Radhakrishnan et al.[69] noted that an alternative mechanism could be from the loss of contrast in the far image on the retinal periphery, caused by the out-of-focus image formed by the lenslets. This aspect was emphasised by the designers of Diffusion Optics Technology (DOT™) spectacle lenses.[55]

A second, or possibly complementary approach, is to combine myopia control interventions that are believed to have

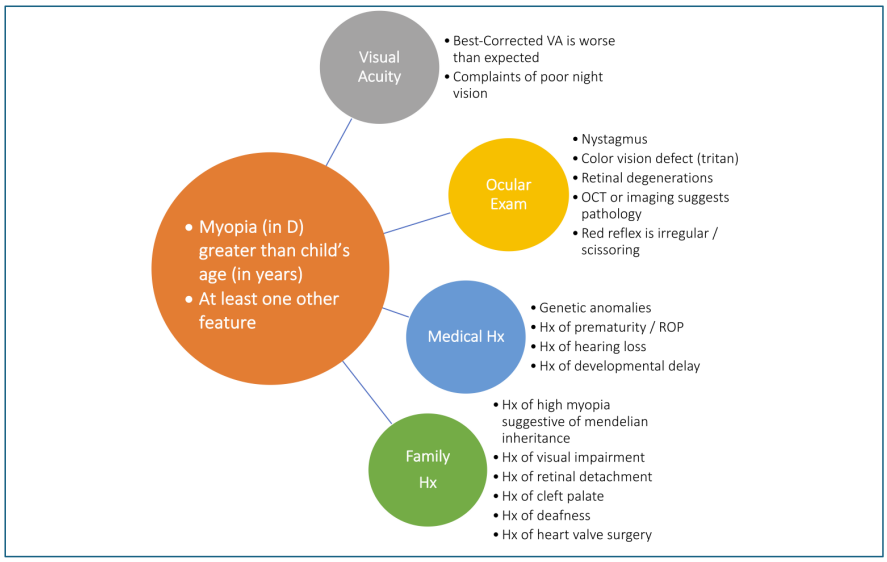

FIGURE 3 Guide for identification of cases that may represent secondary or syndromic myopia in a primary eye care setting and hence merit referral.[68] Reproduced from IMI-management and investigation of high myopia in infants and young Children by Flitcroft et al.[68] under the Creative Commons Attribution Licence (CC BY). Hx, history; OCT, optical coherence tomography; ROP, retinopathy of prematurity; VA, visual acuity.

different mechanisms. This approach is already followed by some clinicians who commence myopia control with atropine or an optical intervention and then, if the myopia or axial elongation continues to progress, proceed to add the other approach. There is considerable scope for developing this further with some of the emerging interventions.

The second aim of this paper was to review the complications of high myopia. Myopia can cause significant visual loss and is a risk factor for a range of ocular conditions including cataract.[3] The more serious, irreversible complications of myopia relate to structural changes in the posterior segment as a result of excessive axial elongation and the risk and severity of these changes increases with the degree of axial elongation. These changes involve the retina, retinal pigment epithelium, Bruch's membrane, choroid, optic nerve head, peripapillary area and sclera,[2] increasing the risk of optic neuropathy, glaucoma,[70] posterior staphyloma, retinal detachment (RD)[71] and myopic macular degeneration.[72] The risk of myopia-associated pathology increases with age, although some pathologies (e.g., retinal detachment) can occur at any age. One-in-three patients with high myopia (axial length ≥ 26 mm) develop visual impairment throughout their life and this occurs in 95% of those with axial length ≥ 30 mm.[73]

Myopic macular degeneration (MMD) is a vision-threatening condition occurring in people with myopia, usually high myopia. In communities with a high prevalence of myopia, MMD has been found to be the most frequent cause of irreversible blindness.[74] A meta-analysis of population studies reporting blindness and visual impairment due to myopic maculopathy,[75] estimated that approximately 10 million people had visual impairment MMD, of whom 3 million were blind in 2015. The prevalence of MMD in population-based studies was 0.2% in rural central India, 1.2% in Caucasian Australians and 4.0% in Singapore.[76-83] After stratification for the degree of myopia, the prevalence ranged from 13.3% to 65.4% in high myopes, 0.3–7.8% in moderate myopes and 0.1–7.0% in low myopes.[76-83] These data confirm that there are no safe levels of myopia. The risk of MMD increased by 60–70% per dioptre increase of myopic refractive error.[84] Low, moderate and high myopia were all associated with increased risks of MMD (OR 13.57, 95% confidence interval [CI] 6.18–29.79; OR 72.74, 95% CI 33.18–159.48; OR 845.08, 95% CI 230.05–3104.34, respectively).[12]

Common peripheral retinal lesions in high myopia include retinal detachment (RD), as well as pigmentary, lattice and paving-stone degeneration.[85,86] RD is a sight-threatening complication where fluid from the vitreous chamber enters the subretinal space via a full thickness retinal defect resulting in a separation of the neurosensory retina from the underlying retina. The annual incidence rates of RD ranged from 5.4 per 100,000 persons in Croatia (95% CI 4.1–6.4) to 16.5 per 100,000 persons in Japan (95% CI 15.0–18.1).[9] Pooled analyses by the same authors revealed an increased OR for any myopia (OR 3.45; 95% CI 1.08–11.00, no heterogeneity); low myopia (OR 3.15; 95% CI 1.92–5.17, no heterogeneity); moderate myopia (OR 8.74, 95% CI 7.28–10.50, no heterogeneity) and high myopia (OR 12.62; 95% CI 6.65–23.94, no heterogeneity).[9] These figures further highlight the increased risk of developing RD as the severity of myopia and axial length increase.

Several studies reported a positive association between posterior subcapsular cataract (PSC), nuclear cataract and myopia.[12] Regarding PSC, Haarman et al. in their review and meta-analysis reported a strong association for any myopia (OR 2.09; 95% CI 1.60–2.74, no heterogeneity), low myopia (OR 1.56; 95% CI 1.32–1.84, no heterogeneity), moderate myopia (OR 2.55; 95% CI 1.98–3.23, no heterogeneity) and high myopia (OR 4.55; 95% CI 2.67–7.75, no heterogeneity). Similarly for nuclear cataract, these same authors reported a significant association for any myopia (OR 2.51; 95% CI 1.53–4.13, no heterogeneity); low myopia (OR 1.79; 95% CI 1.08–2.97, no heterogeneity); moderate myopia (OR 2.39; 95% CI 1.03–5.55, no heterogeneity) and high myopia (OR 2.86; 95% CI 1.43–5.73, no heterogeneity).[12,86]

Glaucoma is the leading cause of irreversible blindness worldwide with Open Angle Glaucoma (OAG) being the most prevalent form of glaucoma.[77] Myopia is a well-known risk factor for OAG.[77,78] Ha et al. recently corroborated the dose–response relation between the degree of myopia and OAG and reported that individuals with myopia have an approximately doubled risk of developing OAG compared to those without myopia. They concluded that for each 1 D increase in myopia, the risk of glaucoma increases by approximately 20%.[87] The risk increases more steeply in high degrees of myopia (accelerating at −6.00 D and further acceleration at −8.00 D), representing a significant nonlinear relationship ($p = 0.03$).[87]

There is a lack of research on myopia control in adults. An IMI report by Bullimore et al.[88] on the onset and progression of myopia in adults noted that clinically meaningful myopia progression continues in early adulthood and may average 1.00 D between 20 and 30 years of age.[88] A large study in France with data from nearly 700 community optical practices found that myopia was still progressing in approximately 10% of myopes at 20 years of age, 5% at age 30 years and 4% at 40 and 50 years of age[89] Although progression is typically slower in adult high myopia than in children, the IMI report noted that a mean annual progression of 0.05 D/year between 20 and 40 years of age will add 1.00 D to an individual's refractive state and further increase their risk of eye disease and visual impairment later in life.[89] Bullimore et al. found no studies evaluating newer myopia control interventions in adults, and noted the challenges inherent in such trials that are nonetheless necessary. The present authors emphasise the need for studies to evaluate myopia control options in adults with high and still progressing myopia.

In conclusion, the limited research indicates that a significant reduction in the progression of refractive error and axial elongation in high myopia is likely when using 0.5% atropine. DIMS spectacle lenses appear to have lower efficacy in controlling high myopia progression compared with moderate and low myopes and Ortho-K lenses are

equally effective in reducing myopia progression in low, moderate and highly myopic patients. All myopic patients have an increased risk of myopic macular degeneration, retinal detachment, cataract and glaucoma, with high myopes bearing the greatest burden of risk.

AUTHOR CONTRIBUTIONS

Rakhee Shah: Conceptualization (lead); data curation (lead); formal analysis (lead); methodology (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Natalia Vlasak:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); methodology (supporting); resources (supporting); validation (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Bruce J. W. Evans:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); methodology (supporting); resources (equal); validation (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting).

CONFLICT OF INTEREST STATEMENT

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