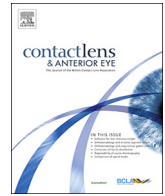




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## Contact Lens and Anterior Eye

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## Overnight orthokeratology

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## ABSTRACT

Overnight orthokeratology lenses are approved in countries all over the world for the temporary reduction in myopia, and recently, one lens design has received regulatory approval for myopia control in Europe. The modern orthokeratology lens has a substantial history from its origins of attempting to flatten the corneal curvature with a spherical rigid contact lens to sophisticated gas permeable lenses, designed to reshape the cornea. These lenses are predominantly prescribed for children to slow myopia progression and limit axial elongation of the eye. This article reviews the peer-reviewed literature on the efficacy of orthokeratology for myopia control, sustainability after treatment is discontinued, and the safety concerns of overnight contact lens wear. Future avenues of research are discussed.

## 1. History

The wearing of rigid gas permeable contact lenses can produce changes in corneal curvature. [1]. Orthokeratology (Ortho-K) may be defined as the planned, temporary reduction in myopia by the wearing of flat-fitting rigid contact lenses [2]. The first deliberate application of this approach was reported in the early 1960's when the "orthofocus" technique was described [3]. Orthokeratology is referred to as Vision Shaping Treatment (VST) by Bausch + Lomb and Corneal Refractive Therapy (CRT) by Paragon Vision Sciences.

The first evaluation of orthokeratology was conducted in the 1970s by Kerns, who compared a group wearing flat-fitting rigid contact lenses during the day to both spectacle wearers and conventional rigid lens wearers [4,5]. Orthokeratology contact lenses were fit 0.25 to 0.50 D flatter than the flattest corneal meridian. Although a reduction in myopia (mean change =  $+0.77 \pm 0.91$  D) was observed after 300 days of orthokeratology lens wear [4], Kerns still concluded that the procedure was unpredictable and uncontrollable as changes in refractive error ranged from a 2.62 D decrease to a 1.00 D increase in myopia along with induced astigmatism from lens decentration [6]. Binder et al. compared subjects wearing flat-fitting PMMA contact lenses on a daily basis to conventional fitting PMMA lens wearing patients [7]. Their orthokeratology lenses were fit between 0.50 D and 2.75 D flatter than the flattest corneal meridian. Like Kerns, Binder et al. felt that the procedure resulted in inconsistent and unpredictable reductions in myopia. In the early 1980s, Polse et al. conducted The Berkeley Orthokeratology Study [8–10], a randomized clinical trial comparing a

group wearing flat-fitting contact lenses daily to a control group wearing conventionally fit lenses [8]. The mean reduction of myopia in the orthokeratology group was  $+1.01 \pm 0.87$  D as compared to  $+0.54 \pm 0.58$  D in the control group [9]. Polse et al. again regarded these reductions to be variable and unpredictable as indicated by the relatively large standard deviations.

There then followed a decade of no peer-reviewed research on orthokeratology (Fig. 1). This changed in the 1990s due to a convergence of three technologies: reverse geometry contact lenses, higher oxygen transmissibility and corneal topography instruments.

The original flat-fitting approach using conventional rigid contact lenses led to problems with centration of the lens on the cornea and accompanying poor and variable outcomes. Rigid gas permeable contact lenses for orthokeratology evolved into a new generation of designs, termed reverse geometry contact lenses [11–13]. Wlodyga and Stoyan collaborated to develop a series of lenses wherein the base curve radius was designed to be flatter than the central corneal curvature, and the secondary curve steeper than the base curve radius. This created a reverse geometry lens. At the secondary curve junction, the lens and cornea formed a tear reservoir exhibiting a band of mid-peripheral fluorescein pooling. This design improves the centration and stability of the lens and led to more predictable and consistent reductions in myopia [14].

Advances in oxygen transmissibility of rigid gas permeable materials further changed the practice of orthokeratology. The previously-described research used PMMA lenses. Materials have been developed that, in theory, should limit corneal oedema to levels normally

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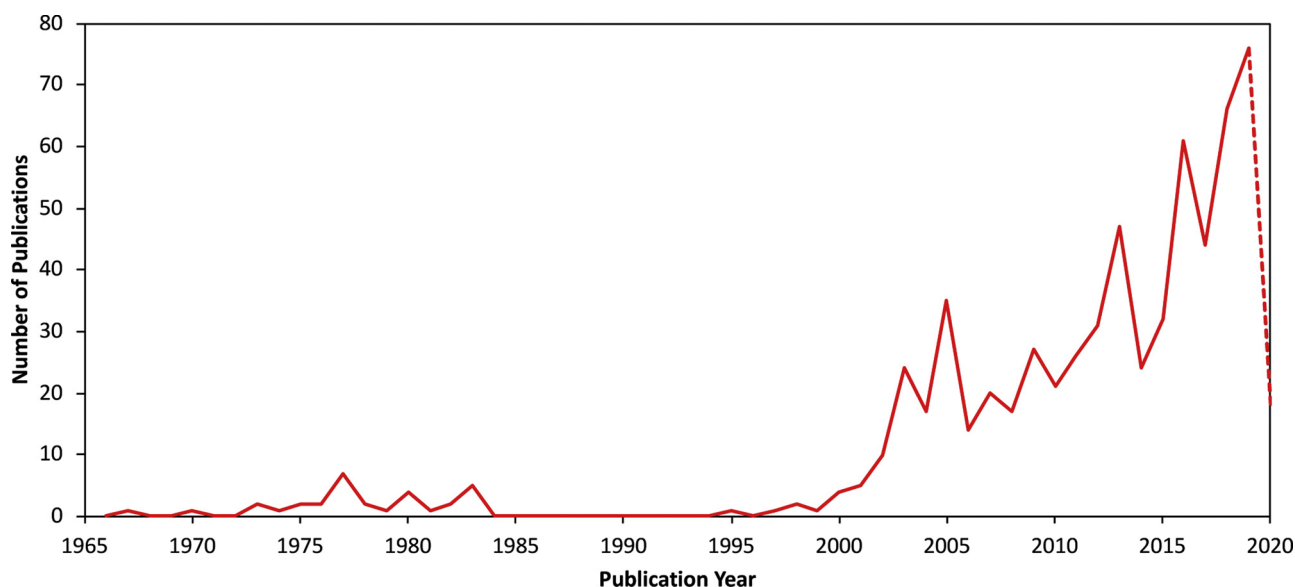


Fig. 1. Peer-reviewed publications on orthokeratology over the past 55 years (source: Web of Science, 2020 Clarivate Analytics).

occurring during sleep (i.e. 3–4% swelling) along with minimizing other ocular changes [15,16]. It should be noted, however, that these data are based largely on soft contact lens wear, whereas rigid lenses, including orthokeratology lenses, are smaller in diameter, but are also thicker. New materials provided oxygen transmissibility values that minimize, and perhaps eliminate, hypoxic stress and corneal oedema when worn on an overnight basis. Thus, overnight orthokeratology, also referred to as overnight corneal reshaping, became feasible, although overnight corneal swelling greater than lens-free values still occurs, particularly in the peripheral cornea, but may diminish in magnitude during weeks of overnight wear [17,18]. The potential advantage of this approach is that lenses are worn, the cornea is reshaped, and the level of myopia is reduced as the patient sleeps. Lenses are removed upon waking and good vision is obtained without correction through the day—an attractive feature for those with an active lifestyle. However, this myopia reduction is temporary, meaning contact lenses must be worn on a nightly basis to continue the effect.

Finally, corneal topographers had been developed, largely in response to the boom in refractive surgery. This allowed the orthokeratology practitioner to monitor the change in corneal curvature induced by the lens, the zone of the cornea flattened and its centration—reflecting the centration of the lens. Prior to this technology, the clinician had to rely on the less quantitative interpretation of fluorescein patterns and keratometry. Some contact lens manufacturers/laboratories will design an orthokeratology lens based on the topography and a few other parameters.

In 1997 Mountford published the first report of orthokeratology of patients wearing reverse geometry contact lenses on an overnight basis [14]. Unlike the earlier evaluations of orthokeratology, Mountford reported more predictable and sustained reductions in myopia (pre-treatment mean =  $-2.19 \pm 0.79$  D; post-treatment mean =  $0.00 \pm 0.68$  D; mean change =  $+2.19 \pm 0.57$  D). In a follow-up study, Mountford evaluated the retention and regression of the orthokeratology effect over a period of 8–9 h after contact lens removal [19]. Most of the refractive changes occurred within the first month of lens wear. Furthermore, Mountford found the amount of regression of the orthokeratology effect to be between 0.50 and 0.75 D during the day. While not explicit, greater regression would be expected in higher corrections. Modern designs incorporate a compression factor—an additional flattening of the base curve—to account for this regression.

Nichols et al. extended these findings, further quantifying the course of visual and refractive changes, the changes in corneal topography and

thickness, and the extent to which these refractive and topographical changes are sustained throughout the course of the day [20]. Ten myopic adults were fit with reverse geometry rigid contact lenses and examined at several times throughout the 60 days after commencing wear. Eight subjects completed the study and all visual, refractive, and topographic outcomes were sustained over the course of an 8-h day. Mean uncorrected visual acuity improved from  $+0.52 \pm 0.23$  logMAR (6/20) to  $-0.04 \pm 0.12$  logMAR (6/5.5) by day 14. Mean manifest refraction was significantly reduced from baseline at day 60 (mean change =  $+1.83 \pm 1.23$  D) and was accompanied by significant central corneal flattening (mean change in apical radius =  $+0.20 \pm 0.09$  mm) and thinning (mean change =  $-12 \pm 11$   $\mu$ m). Beyond 7 nights of wear, visual acuity was constant for 8 h following lens removal.

These and other studies established that overnight orthokeratology using rigid gas permeable contact lenses is effective in temporarily reducing myopia, providing good vision over the course of the day in myopes up to  $-4$  D [14,20–22]. Subsequent studies have demonstrated the partial or complete efficacy of orthokeratology in patients with myopia up to  $-10$  D [23,24]. The corneal changes that accompany orthokeratology occur much more rapidly than those noted in earlier studies, a finding likely due to reverse geometry orthokeratology lens designs and, possibly, overnight wear of the lenses. Most of the change in visual and refractive outcome variables occurred in the first seven nights of contact lens wear and asymptote around day 30. The visual and refractive changes that occur during overnight orthokeratology are well sustained through the course of an eight-hour day, but if lens wear is discontinued, refractive error will regress towards baseline. Around half of the myopia reduction will be lost after 24 h and 90 % within 72 h [25,26].

## 2. Regulatory history

In 1994, the United States Food and Drug Administration (FDA) granted the first daily wear approval for a lens indicated for orthokeratology for the Contex OK-Lens. In 2002, Paragon Corneal Refractive Therapy (CRT) lenses, manufactured by Paragon Vision Sciences, were granted FDA approval for overnight wear, with other lens designs and materials covered by the original approval. In 2003, Paragon received CE marking for their family of CRT lenses in the European Union. In 2004, Bausch + Lomb received approval for overnight wear of the Boston Vision Shaping Treatment (VST) lens. These contact lenses are marketed as a range of branded designs falling under the VST approval

such as Contex OK E-system, Euclid Emerald, DreamLens and BE Retainer lens. In January 2017, the China Food and Drug Administration granted approval and commercial availability for Paragon CRT Contact Lenses in China. Like the US, Paragon's China approval does not include any indication for myopia control, just temporary myopia reduction. In May 2019, Menicon received the first and only CE-mark approved orthokeratology lens for myopia control: Menicon Bloom.

### 3. Contact lens market penetration by orthokeratology

Cope et al. conducted a population-based survey to estimate the number of contact lens wearers aged 18 years or older in the United States [27]. The authors estimate that there are 40.9 million contact lens wearers aged 18 years or older of whom approximately 6.5 % are RGP lens wearers (2.7 million). The authors did not survey children nor did they ask specifically about orthokeratology.

For five years, Efron et al. asked practitioners in 38 countries to document their first 10 contact lens fits (new or refits) after receiving the questionnaire [28]. Patients under 18 years old accounted for 13.2 %, but the proportion varied among countries, ranging between 25 % in Iceland to 1 % in China. Orthokeratology fits represented 28 % of all rigid contact lenses prescribed to minors, including 47 % among 6–12 year-olds. The authors reasoned this proportion was due to the popularity of myopia control. These data represent the proportions of contact lens fits rather than the wearers and may thus overestimate the proportion of children in the total population of wearers, although the mean age for new fits did increase from 28 years in 2002 to 32 years in 2014. Also, the response rate was 13 % and leaving the potential for respondent bias.

Morgan et al. recently reported 14 years of data from contact lens fitters, each reporting on at least 500 contact lens fits in 45 countries creating a database of 295,044 contact lens fits [29]. Overall, orthokeratology lens fits represented 1.2 % of all contact lens fittings with a range of 0 % in some countries to 6 % in the Netherlands. The overall extent of orthokeratology contact lens fitting has risen slowly each year through the 14 year survey period, increasing from 0.5 % in 2004 to 1.3 % in 2017. Compared to non-orthokeratology lenses, orthokeratology lenses were also fit to a younger population ( $25 \pm 13$  years vs.  $40 \pm 15$  years). The overall increase in prescribing orthokeratology and the younger age population likely reflects its increased use for myopia control.

Wolffsohn et al. reported on 971 respondents for a self-administered, internet-based questionnaire distributed globally [30]. Orthokeratology was perceived to be the most effective method of myopia control, followed by increased time outdoors and pharmaceutical approaches. Among effective myopia therapies, orthokeratology was the most frequently prescribed myopia correction option for progressing, young myopes in all regions with frequencies around 20 % in Australasia and Europe but only 10 % in Asia and the Americas. While the authors assert that the survey was “completed both by people cynical and enthusiastic to the issue,” the extent to which the findings can be generalized is uncertain. The survey results have recently been updated [31].

### 4. Mechanisms underlying refractive changes

The prevailing wisdom was that orthokeratology flattened the cornea by bowing of the cornea, but limitations in instrumentation prevented testing this or alternative hypotheses. Swarbrick et al. provided the first insight into the anatomical changes due to orthokeratology [32]. They found significant central corneal epithelial thinning, accompanied by thickening of the total mid-peripheral corneal thickness. Nichols et al. confirmed the central thinning of the cornea but were unable to show significant changes in the mid-peripheral thickness of the cornea [20].

Overnight in the absence of contact lens wear, the cornea swells by 3–4 %, and this oedema is increased by overnight wear of most lenses. Haque et al. evaluated both corneal and epithelial thickness changes after 4 weeks of overnight CRT in 23 subjects using optical coherence tomography [33]. After the first night of wear, the central and para-central cornea swelled significantly by 4.9 % and 6.2 %, respectively. The central epithelium thinned by 7.3 %, and the mid-peripheral epithelium thickened by 13 %. Corneal swelling recovered within the first 3 h after lens removal. Maximal overnight central epithelial thinning was 13.5 % and attained after four nights of wear. Three days after lens wear was discontinued, both corneal and epithelial thickness returned to baseline values.

Reinstein et al. reported a single case measuring a patient's epithelial, stromal, and corneal thickness using high-frequency digital ultrasound, before and during orthokeratology treatment [34]. The central epithelium thinned by 18  $\mu\text{m}$  and the mid-peripheral epithelium thickened by up to 16  $\mu\text{m}$ . They concluded that refractive changes were mainly induced by alterations in epithelial thickness and, while stromal changes may occur, their contribution is limited.

Qian et al. evaluated topographical changes in epithelial thickness using Fourier-domain optical coherence tomography (OCT) in 60 children fitted with myopic orthokeratology lenses and 44 control children [35]. Epithelial thickness of the central 2 mm was significantly thinner in the orthokeratology group. Superior and inferior mid-peripheral corneal epithelium were thickest in patients with more than 14 days of orthokeratology wear.

Recently, Lau et al. fit orthokeratology lenses of different compression factors (0.75 vs 1.75 D) in 28 children (aged 7–11 years) and measured ocular components weekly for one month of lens wear and for three weeks after discontinuing wear [36]. Again, central corneal thickness decreased by 9  $\mu\text{m}$  at week 1 and stabilized for the remaining period of lens wear. Interestingly, anterior chamber depth decreased by 41  $\mu\text{m}$  after one week of wear and was stable thereafter. Anterior chamber depth rebounded in the first week after cessation of wear. Corneal bowing or other posterior surface changes could contribute to these anterior chamber depth changes, although the authors believe them to be associated with accommodative changes.

There is some additional evidence, albeit equivocal, that the posterior cornea undergoes some changes as a result of overnight orthokeratology. Owens et al. fitted 19 young myopes with orthokeratology lenses that were worn nightly for a month [37]. Central and mid-peripheral corneal thickness, topography and posterior corneal radii were evaluated within two hours of waking on four occasions. Significant anterior corneal flattening was observed after one night and beyond, along with significant posterior corneal flattening after one week. In contrast, Yoon and Swarbrick found no change in posterior corneal radius, although they did observe a more oblate shape, while acknowledging that their posterior geometry was calculated rather than measured [38].

Chen et al. reported changes in, and recovery of, posterior corneal curvature after 6 months of overnight orthokeratology in 28 young adults [39]. Posterior corneal curvature was evaluated using rotating Scheimpflug imaging. The posterior cornea significantly steepened after the first overnight lens wear, but these changes were not observed at subsequent visits. The posterior cornea was steepest immediately following lens removal and significantly flattened two hours later.

Finally, Gonzalez-Mesa et al. evaluated the effect of overnight orthokeratology on anterior chamber depth and posterior corneal curvature over one year [40]. A significant reduction in anterior chamber depth and a flattening posterior corneal curvature was observed over the year.

In summary, the refractive changes that accompany orthokeratology are due to local changes in corneal epithelial thickness—central thinning and mid-peripheral thickening—thereby flattening the central cornea.

5. Efficacy of overnight orthokeratology for myopia control

Practitioners began discussing the viability of orthokeratology for myopia control around the beginning of the millennium [41,42]. The first peer-reviewed report of its efficacy was published in 2005 [43]. Cho et al. enrolled 43 children fitted by eight private practitioners, of whom 35 completed two years of follow up. A historical control group of 35 children wearing single-vision spectacles from an earlier study was used as a comparison. The increase in axial length was  $0.29 \pm 0.27$  mm and  $0.54 \pm 0.27$  mm in the orthokeratology and control groups, respectively. Note that because of the change in transient corneal curvature and refractive error induced by orthokeratology, nearly all studies present effectiveness in terms of axial elongation. Axial elongation is the underlying cause of myopia progression and the two are highly correlated. For reference, a 0.1 mm difference is equivalent to around 0.25 D [44,45].

The results were confirmed by Walline et al. who used a historical comparison group of 28 soft lens wearing children [46]. Forty subjects, 8–11 years old, were fitted with overnight orthokeratology contact lenses and followed for two years, with 28 completing the study. In spite of being conducted on an ethnically different population, the study showed results remarkably consistent with those of Cho et al. [43]. The increase in axial length was  $0.25 \pm 0.22$  mm and  $0.57 \pm 0.51$  mm in the orthokeratology and control groups, respectively.

A number of subsequent studies were published, generally showing similar results. These are summarized in the comprehensive tables below (Table 1 and 2) [23,24,43,46–53]. Only studies with a control group and axial length data are listed. The first randomized clinical trial randomized 102 children, 6–10 years old, to either orthokeratology or spectacles [47]. For the 78 patients completing the two-year study, the mean axial elongation was  $0.36 \pm 0.24$  and  $0.63 \pm 0.26$  mm in the orthokeratology and control groups, respectively.

6. Summary of effectiveness

Inspection of the Tables on the previous page shows a range of treatment effects. The highest is from a study of partial myopia reduction in high myopia and the lowest in a case report of a pair of twins. In 2015–2016, there were four meta-analyses published summarizing the effects of orthokeratology on myopia progression [54–57]. As expected, and as can be seen from Table 2, the studies included in each meta-analysis are very similar (with two identical). Six studies are common to all four analyses and the maximum included is nine. Likewise, the treatment effect for each meta-analysis are very similar (Table 3):

Li et al. showed that the treatment effect in the randomized clinical trials ( $-0.28$  mm, 95 %CI,  $-0.35$  to  $-0.20$  mm) was no different from that in cohort studies ( $-0.27$  mm, 95 %CI,  $-0.32$  to  $-0.22$  mm) [57].

Although only two-year data are shown in Table 2, Hiraoka et al. reported five year data [48]. Of the original 59 enrolled subjects, 43 (22 orthokeratology and 21 control) completed the 5-year study. The increase in axial length was  $0.99 \pm 0.47$  mm and  $1.41 \pm 0.68$  mm for the orthokeratology and control groups, respectively. Santodomingo et al. recently reported seven-year follow up data on their subjects [58]. Fourteen of the 29 orthokeratology subjects who had completed the two-year trial were examined five years later along with 16 of the 24 control subjects of whom four still wore spectacles and 12 had switched to soft contact lenses after the initial two-year trial. The axial elongation in the orthokeratology group was 0.44 mm lower than the control group following 7 years of lens wear. Interestingly, the axial length increases over the first two years were similar to those found in the subsequent five years for both the orthokeratology ( $0.42 \pm 0.05$  and  $0.39 \pm 0.04$  mm, respectively) and control ( $0.71 \pm 0.10$  and  $0.65 \pm 0.11$  mm, respectively) groups. At seven years, the subjects were all between 17 and 19 years old and the majority of their myopia would have stabilized regardless of treatment [59].

Table 1 Design and baseline data of 11 peer-reviewed studies of the efficacy of orthokeratology for myopia control.

Study (year)	Country	Design	Ortho-K Lens	Control	Duration (yrs)	Age (yrs)	N (complete/enrol)		Baseline Refraction (D)		Axial Length Measure
							Ortho-K	Control	Ortho-K	Control	
Cho (2005)	HK	Cohort	4/5 curve Boston XO or HDS 100	Specs	2	7–12	35/43	35	-2.27 ± 1.09	-2.55 ± 0.98	Ultrasound
Walline (2009)	US	Cohort	Paragon CRT HDS-100	SCL	2	8–11	28/40	28	—	—	Ultrasound
Kakita (2011)	Japan	Cohort	Euclid Emerald	Specs	2	8–16	42/45	50/60	-2.55 ± 1.82	-2.59 ± 1.66	IOLMaster
Hiraoka (2012)	Japan	Cohort	Euclid Emerald	Specs	5	8–12	22/29	21/30	-1.89 ± 1.06	-1.83 ± 1.06	IOLMaster
Santodomingo (2012)	Spain	Cohort	Menicon Z Night	Specs	2	6–12	29/31	24/30	-2.20 ± 1.09	-2.35 ± 1.17	IOLMaster
Cho (2012)	HK	RCT	Menicon Z Night	Specs	2	6–10	37/51	41/51	-2.05 ± 0.72	-2.23 ± 0.84	IOLMaster
Charm (2013)	HK	RCT	Procornea Dreamlite Boston XO	Specs	2	8–11	12/26	16/26	-6.38	-6.00	IOLMaster
Chen (2013)	HK	Cohort	Menicon Z Night Toric	Specs	2	6–12	35/43	23/37	-2.46 ± 1.32	-2.04 ± 1.09	IOLMaster
Chan (2014)	HK	Twins	Menicon Z Night	Specs	2	8	1/1	1/1	-2.76	-2.39	IOLMaster
Zhu (2014)	China	Retro	Euclid	Specs	2	7–14	65	63	-4.29 ± 2.04	-4.24 ± 2.38	IOLMaster
Pauné (2015)	Spain	Cohort	Precilens DRL	Specs	2	9–16	18/29	21/41	-3.44 ± 2.18	-3.11 ± 1.53	Ultrasound

**Table 2**  
Results of 11 peer-reviewed studies of the efficacy of orthokeratology for myopia control.

Study (year)	Drop Out (%)		Axial Increase (mm)		Treatment Effect (mm)	Included in Meta-Analysis?			
	Ortho-K	Control	Ortho-K	Control		Si (2015)	Sun (2015)	Wen (2015)	Li (2016)
Cho (2005)	17	NA	0.29 ± 0.27	0.54 ± 0.27	0.25	*	*	*	*
Walline (2009)	30	NA	0.25 ± 0.22	0.57 ± 0.51	0.32	*	*	*	*
Kakita (2011)	7	17	0.39 ± 0.27	0.61 ± 0.24	0.22	*	*	*	*
Hiraoka (2012)	24	30	0.45 ± 0.29	0.71 ± 0.35	0.36	*	*	*	*
Santodomingo (2012)	6	20	0.47 ± 0.18	0.69 ± 0.33	0.22	*	*	*	*
Cho (2012)	27	20	0.36 ± 0.24	0.63 ± 0.26	0.27	*	*	*	*
Charm (2013)	54	38	0.19 ± 0.21	0.51 ± 0.32	0.32	*	*	*	*
Chen (2013)	19	38	0.31 ± 0.27	0.64 ± 0.31	0.33	*	*	*	*
Chan (2014)	—	—	0.61	0.80	0.19				*
Zhu (2014)	NA	NA	0.34 ± 0.29	0.70 ± 0.35	0.36				*
Pauné (2015)	38	49	0.32 ± 0.20	0.52 ± 0.22	0.20				

**Table 3**  
Summary of four published meta-analyses summarizing the effects of orthokeratology on myopia progression.

Si et al. [54]:	−0.26 mm (95 % CI: −0.31 to −0.21 mm)
Sun et al. [55]:	−0.27 mm (95 % CI: −0.32 to −0.22 mm)
Wen [56]:	−0.25 mm (95 % CI: −0.30 to −0.21 mm)
Li [57]:	−0.27 mm (95 % CI: −0.32 to −0.23 mm)

A few other studies not listed in Tables 1 and 2 are worthy of mention in spite of not having a robust control group. Downie and Lowe reported a retrospective study of 26 myopic children wearing orthokeratology lenses and 30 spectacle-wearing controls [60]. Children were younger than 16 years at baseline and had been followed for a minimum of two years. No axial length data were reported and the manifest refraction over the orthokeratology lens was recorded. Also, the spectacle-wearing subjects included single-vision distance lenses only ( $n = 12$ ), multifocal lenses only ( $n = 5$ ), and a combination ( $n = 9$ ). The mean rate of myopic refractive change in control eyes over the first 2 years of treatment was  $-0.46 \pm 0.06$  D/year. Data for the orthokeratology patients are not given, but the figures show the mean change is less than  $-0.05$  D/year. The authors state that 64 % of orthokeratology eyes demonstrated an “apparent total arrest of manifest myopic refractive change.”

Turnbull et al. reported a comparative case series of 110 patients, aged 4–33 years, who attended a myopia control clinic between 2010 and 2014 [61]. They included 56 prescribed orthokeratology and 22 who received advice only. Mean follow-up time for the orthokeratology was  $1.3 \pm 0.9$  years and the annualized myopia progression and axial elongation were  $-0.09 \pm 0.17$  D/year and  $0.08 \pm 0.31$  mm/year, respectively in the orthokeratology patients. The control group is not useful as they were older ( $14.0 \pm 7.3$  vs.  $11.7 \pm 2.6$  years).

## 7. Mechanism of myopia control with orthokeratology and soft multifocal lenses

Overnight orthokeratology most likely does not slow myopia by mechanical means, in part because conventional-fitting rigid gas permeable lenses have no effect on myopia progression [62,63]. Rather, orthokeratology flattens the central area of the cornea thereby providing a clear image on the central retina, while the mid-peripheral cornea is steeper, imposing myopic defocus on the peripheral retina.

There is compelling evidence that peripheral refractive error is important in the incidence and progression of myopia [64–66]. While myopic eyes have excessive axial length, they also have a more prolate shape as the eyes have grown longer axially than equatorially [67]. As a result, myopic eyes tend to have more hyperopic peripheral refractions, compared with their foveal refractive error [68,69].

Queiros et al. measured peripheral refraction in 28 myopic subjects before and after one month of orthokeratology and found an

elimination of uncorrected myopia within the central 20 degrees of retinal eccentricity, no change in spherical equivalent at 25 degrees eccentricity, and a myopic shift beyond 25 degrees [70]. They also found an association between greater amounts of treated myopia higher myopic shifts in peripheral refractive error beyond 20 degrees eccentricity. Several subsequent studies have confirmed that reshaping of the cornea with orthokeratology converts relative peripheral hyperopic defocus before treatment to relative peripheral myopic defocus after orthokeratology [71–75].

A number of different lens designs have been used by researchers (Table 1) including Menicon Z Night (3), Euclid Emerald (2 or 3), Paragon CRT HDS-100, Precilens DRL, and Procornea Dreamlite. In spite of the variety of manufacturers, there are similarities in lens design. The back optic zone diameter (BOZD) of all of the above lens designs was between 6.0 and 6.2 mm. Alterations in BZOD can influence the treatment zone and thus have the potential to impact peripheral refraction [73,76,77]. Kang and Swarbrick compared three different lenses—Capricornia BE, Paragon CRT, and Contex—and found that, while central corneal curvature changes varied among lenses, there was little variation in the induced changes in peripheral refraction [73]. Recently, Gifford et al. systematically reduced the BZOD by 0.5 mm, resulting a 0.8 mm smaller treatment zone [76]. Again, there was no significant difference in the resultant changes in peripheral refraction. In summary, BZOD size has little effect on peripheral refraction, but other parameters need to be evaluated along with their long-term impact on rates of myopia progression.

Soft contact lenses with a central distance zone and increased positive power in the periphery can slow myopia to a similar degree as overnight orthokeratology [44]. It is a very important observation, therefore, that these multifocal soft lenses produce very similar changes in peripheral refractive error to that observed in eyes treated with overnight orthokeratology. Lopes-Ferreira et al. evaluated the influence of the Proclear Multifocal—the same lenses shown to slow myopia progression by Walline et al. [46]—on peripheral refractive error in 28 myopic patients [78]. Baseline relative peripheral refractive error was  $-0.69 \pm 1.14$  D spherical equivalent at 35 degrees in the nasal visual field. Two add powers, +2 and +3 D, increased the relative peripheral myopic defocus by  $-0.82 \pm 1.23$  D and  $-1.42 \pm 1.45$  D, respectively. Similarly, Paune et al. evaluated the effect of an experimental soft lens on peripheral refraction in 10 subjects [79]. The lens significantly increased the relative peripheral myopic defocus by around  $-0.50$  D at 30 degrees eccentricity.

Thus, a strong case can be made for overnight orthokeratology and multifocal soft contact lenses possessing the same underlying mechanism for myopia control. This hypothesis is further supported by a compelling body of studies of myopia development in animal models [80,81].

## 8. Is the effectiveness sustained after treatment is discontinued?

An important question with any myopia control modality is whether the benefits are retained once the intervention is discontinued. The Atropine for the Treatment of Myopia (ATOM) study followed 158 subjects for 12 months after stopping 1% atropine after 2 years of treatment [82]. The mean one-year progression in the previously atropine-treated group was  $-1.14 \pm 0.80$  D compared with progression of  $-0.38 \pm 0.39$  D in the placebo-treated eyes, with corresponding changes in axial elongation. In other words, those eyes treated with 1% atropine accelerated dramatically once treatment was discontinued.

Cho and Cheung compared changes in axial elongation in subjects who discontinued and then resumed orthokeratology lens wear with those who continued to wear their lenses [83]. In the 15 subjects who discontinued wear for 6 months, axial length increased by  $0.15 \pm 0.08$  mm, compared with  $0.09 \pm 0.08$  mm in the 16 who continued wear. In a comparison group of 13 spectacle wearers, axial length increased by  $0.08 \pm 0.08$  mm. When subjects resumed orthokeratology wear, their elongation rate was similar to the continued wear group. This is a short-term study in a small number of subjects, but a couple of observations can be made. While the rate in the discontinued wearers is higher than in the continued wearers, it is similar to that of progression of control subjects wearing spectacles during initial myopia control studies [47,50]. Furthermore, the subjects chosen to discontinue were those who were progressing the least during treatment with orthokeratology, so their higher post-treatment elongation may simply be regression to the mean. Thus, these findings should probably not be viewed as a *post-treatment acceleration*. Likewise, a short-term contralateral study showed changes in axial length too small to make a compelling case for post-treatment acceleration [84]. Santodomingo et al. reported data for eight patients who completed two years of overnight orthokeratology and then wore soft lenses on a daily wear basis for five years [58]. Their mean axial elongation in the five years of soft lens wear was 0.80 mm; higher than the 0.65 mm in the control subjects. It is unclear, however, whether this is post-treatment acceleration as, during their two years of orthokeratology wear, they elongated by 0.57 mm compared to 0.42 mm in the other orthokeratology wearers, so it is possible that they were consistently faster progressors.

For comparison, Anstice and Phillips fitted 40 children with a Dual-Focus soft contact lens in one eye and a single vision soft contact lens in the other [85]. Children wore a Dual-Focus lens in one randomly assigned eye and a single vision lens in the fellow eye for 10 months. Lens assignment was then swapped between eyes, and lenses were worn for a further 10 months. Similar reductions in myopia progression and axial eye elongation were observed with Dual-Focus lenses in both phases. This finding that the treatment effect is equivalent in both phases of the study indicates that there is no post-treatment acceleration.

Finally, Cheng et al. randomized 127 myopic children to wear either soft contact lenses with positive spherical aberration or spherical control soft lenses [86]. After one year of treatment, subjects wearing test lenses increased in axial length by 0.14 mm less than eyes wearing control soft lenses (95 % CI: +0.10 to +0.19 mm). The difference in myopia progression was 0.14 D (95 % CI: -0.00 to +0.28 D). Subjects from the initial cohorts (N = 82) were then followed for an additional 1.5 years while wearing a standard spherical daily disposable contact lens. After ceasing treatment, the rate of axial elongation was not significantly different between the initial two cohorts. After one year, the difference was 0.00 mm. The refractive error data actually show a *continued treatment benefit* with a 0.12 D difference in favour of the test cohort throughout the post-treatment period. This benefit was significant at both 6 and 18 months, but not at 12 months.

In summary, treatment with 1% atropine is accompanied by a dramatic post-treatment acceleration [87], while other myopia control modalities less so. An alternative explanation is that post-treatment acceleration is smaller or negligible with less effective myopia control approaches and only occurs after treatments that produce a meaningful

slowing of axial elongation.

## 9. Safety—background and early concerns

Contact lens-related adverse events may be classified as serious—notably microbial keratitis—or non-serious. The latter category typically includes episodes of a painful red eye regarded not to be infectious or sight threatening, such as infiltrative keratitis. Some events may be allergic in origin and may not involve the cornea, so researchers often use the term *corneal infiltrative events* to indicate corneal involvement beyond mere staining. Corneal infiltrative events may be defined as a non-infectious infiltration of white blood cells into the corneal stroma, often with accompanying hyperemia [88]. Microbial keratitis is an infectious subset of this category, but usually accounts for around 5% of all corneal infiltrative events in soft lens wearers [89,90]. Microbial keratitis may be defined as one or more corneal stromal infiltrates greater than 1 mm in diameter with pain more than mild, and one or more of the following: anterior chamber reaction more than minimal, mucopurulent discharge, or positive corneal culture [91] although variations are common. The aforementioned non-serious events are characteristic of soft lens wear and extremely rare in overnight orthokeratology. In other words, a corneal infiltrate in an orthokeratology patient, has a much higher probability of being microbial keratitis than in a soft lens patient [92,93].

Beginning in 2001, there was a steady stream of case series and case reports of microbial keratitis associated with overnight orthokeratology, particularly in children, including five reports from three different continents that were published simultaneously in *Cornea* in 2005 [94–98]. Watt and Swarbrick summarized the first 50 published cases from the 16 peer-reviewed papers from 2001 to 2005 [99]. Most cases of microbial keratitis in orthokeratology were reported from East Asia (80 %) with most patients between 9 and 15 years (61 %). *Pseudomonas aeruginosa* (52 %) and *Acanthamoeba* infection (30 %) was the predominant organisms. Poor lens care procedures, noncompliance, and persisting in lens wear despite discomfort were identified as potential risk factors. A follow-up paper documented a total of 123 cases of microbial keratitis associated with orthokeratology [100].

In 2008, Van Meter et al. published an Ophthalmic Technology Assessment for the American Academy of Ophthalmology on the *Safety of Overnight Orthokeratology for Myopia* [101]. Based on searches of peer-reviewed literature in PubMed and the Cochrane Central Register of Controlled Trials for 2005, 2006, and 2007, the panel identified 75 articles deemed to be relevant to the assessment objective. The main source of reports of adverse events associated with overnight orthokeratology was 38 case reports or noncomparative case series, representing more than 100 cases of infectious keratitis

The report was unable to identify the incidence of complications associated with overnight orthokeratology nor the risk factors for various complications. The report concluded that

- well-designed cohort or randomized controlled trials were needed to quantify the risks of treatment and to identify risk factors for complications;
- overnight orthokeratology for slowing myopia progression in children also needs well-designed clinical trials to evaluate its efficacy; and
- because of variations in orthokeratology practice, a wide margin of safety should be built into overnight orthokeratology regimens.

## 10. Hospital-based case series of microbial keratitis in children

Serious corneal infections can occur in children wearing contact lenses, even if not being particularly prominent in well-conducted, large-scale, prospective epidemiological studies [102,103]. There are hospital-based case series from Taiwan and Hong Kong, describing the characteristics of children presenting with microbial keratitis, some of

which document cases overnight orthokeratology patients.

Hsiao et al. reviewed the medical records of 78 children, 16 years or younger, with microbial keratitis over a 4.5-year period in Taiwan between 1998 and 2002 [104]. Contact lens wear was a factor in 33 of cases (41 %), of which 8 were rigid gas permeable lenses worn overnight for orthokeratology and 25 were soft lenses. In a follow-up study at the same hospital, Lee et al. reviewed the medical records of 67 children aged 16 years or younger treated for microbial keratitis between 2008 and 2012 [105]. The leading risk factor was again contact lens use, accounting for a significantly higher proportion of cases (53 %) compared to the previous study. This was due to an increase in the number of cases attributed to orthokeratology, from 10 % to 19 %, likely reflecting higher numbers of orthokeratology wearers rather than any increase in the underlying risk. Young et al. reported 18 patients under 18 years of age with microbial keratitis who presented over ten years in Hong Kong [106]. Contact lens wear was the associated risk factor in 15 cases (83 %), with seven associated with orthokeratology lenses and eight associated with soft lens wear. Finally, Wong et al. [107] reviewed medical records of 138 consecutive patients aged 18 years or younger who had undergone corneal or conjunctival scraping over a 5-year-period in a tertiary ophthalmic centre. Of these, they classified 50 cases as microbial keratitis. Forty-one patients (82 %) had a history of contact lens wear, with 31 patients using soft contact lens, nine using overnight orthokeratology, and one wearing bandage contact lenses.

While the above studies document that microbial keratitis can occur in children wearing contact lenses in Asia, it is not possible to estimate the frequency or incidence of these serious events.

### 11. Acanthamoeba keratitis

Acanthamoeba keratitis (AK) is a severe infection of the eye with a significant risk of vision loss resulting from corneal ulceration and scarring. It is the most serious potential complication associated with overnight orthokeratology, so it deserves special mention. Most, but not all of the above case series report cases of Acanthamoeba keratitis. When reported, it is restricted to contact lens wearers.

Cope et al. reported a case-control study of RGP contact lens-wearing United States residents with a diagnosis of Acanthamoeba keratitis from 2005 through 2011 [108]. Patients were identified during two multistate Acanthamoeba keratitis outbreak investigations. Controls were RGP contact lens wearers with no history of Acanthamoeba keratitis, who were at least 12 years of age. Of the 37 Acanthamoeba keratitis patients in the two investigations, 8 (22 %) wore RGP lenses for orthokeratology; none of the 17 controls wore RGP lenses for orthokeratology. Significant risk factors for Acanthamoeba keratitis were wearing lenses for orthokeratology (OR, undefined;  $P = 0.02$ ), sleeping while wearing lenses (OR, 8.00;  $P = 0.04$ ), storing lenses in tap water (OR, 16.00;  $P = 0.001$ ), and topping off contact lens solution in the case (OR, 4.80;  $P = 0.01$ ). After stratifying by orthokeratology, storing lenses in tap water and topping off remained significant exposures. In summary, orthokeratology wearers appear to be overrepresented among these Acanthamoeba keratitis cases.

### 12. Summary of safety concerns

While the above reports highlight the importance of continued monitoring of complications associated with overnight orthokeratology, they do not allow comparison with overnight orthokeratology other contact lens modalities. Because relatively few patients wear overnight orthokeratology, large-scale studies usually identify no cases of microbial keratitis in these wearers [102,103].

Many of the cases of microbial keratitis associated with overnight orthokeratology that have been published have reported data from children, but that does not necessarily mean that children are at greater risk. Complications in children may be reported more often than in

adults due to a larger number of cumulative years that a young person may be exposed to risk or experience visual impairment. There may also be more children wearing overnight orthokeratology lenses than adults, due to the potential for myopia control. The risks of overnight orthokeratology in children cannot be compared to the risks in adults using only the above data.

Initially, there were insufficient data on the absolute frequency of microbial keratitis in overnight orthokeratology or on the risks compared to other types contact lenses [102,103]. Nonetheless, editorials and opinion pieces questioned the safety of corneal shaping lenses, particularly in children [101,109–112].

### 13. Safety—a comprehensive retrospective study

In 2006, the FDA mandated that both companies (Paragon Vision Sciences and Bausch + Lomb) with approval to market overnight orthokeratology in the US conduct post-market surveillance of their respective lenses to address concerns about the use of these lenses in children. Specifically, the companies were required to estimate “the relative risk of developing microbial keratitis in persons under the age of 18 as compared to adults” The two companies sponsored a retrospective cohort study of children and adult patients that is reported elsewhere, but summarized here [113].

Investigators were provided with a comprehensive database of all lens orders from 2005 and 2006, including practitioner, order date, and lens parameters, and 200 randomly selected practitioners, stratified by company and number of lens orders, were invited to participate. Participating practitioners were sent a customized form to complete, listing no more than 50 orthokeratology lens orders to minimize respondent burden and to avoid any single practice contributing a substantial proportion of the sample. Practitioners were asked for the fitting date, whether the patient continued to wear the lenses, and when the patient was last seen. Finally, the practitioner was asked to report and describe any episode of a painful red eye that required a visit to a doctor’s office on a separate event form. Patients with less than twelve months of documented follow-up were mailed a separate questionnaire by the practitioner.

For the 191 practitioners located and contacted, 119 agreed to participate, and 86 returned completed forms representing 1494 unique patients. Forty-eight patients who had not been followed for at least twelve months were contacted, and 22 of these returned the completed forms.

#### 13.1. Duration of lens wear

Only data on lens wear and cases of possible microbial keratitis from 2005 onwards were analysed, and exposure was calculated based on last patient contact with the practitioner. This resulted in a sample of 1317 patients: 640 adults (49 %) and 677 children (51 %) and 2599 patient-years of wear: 1164 in adults and 1435 in children. At the original fitting date, the mean age of the adults was  $38 \pm 11$  years, and the mean age of the children was  $12 \pm 3$  years. The mean follow-up for adults was  $1.8 \pm 1.0$  years, with 78 % having at least 12 months of follow-up. For children, the mean follow-up was  $2.1 \pm 0.8$  years, with 92 % having at least 12 months.

#### 13.2. Incidence of microbial keratitis

A total of 50 event forms were submitted from 27 practitioners, of which eight reported corneal infiltrates—six in children. A five-person expert panel, masked to patient age, reviewed all cases independently and determined by majority vote whether the event was definite microbial keratitis, probable microbial keratitis, probably not microbial keratitis, definitely not microbial keratitis, or microbial keratitis unrelated to contact lens wear using criteria for classification similar to a previous study [91]. Two cases were classified as definite microbial



Fig. 2. The evolution of orthokeratology.

keratitis by the panel. Neither resulted in any documented long-term loss of best-corrected visual acuity, and both occurred in children. The overall estimated incidence of microbial keratitis is 7.7 per 10,000 patient-years (95 % CI: 0.9–27.8). For children, the estimated incidence of microbial keratitis is 13.9 per 10,000 patient-years (95 % CI: 1.7–50.4). For adults, the estimated incidence of microbial keratitis is 0 per 10,000 patient-years (95 % CI: 0–31.7).

As discussed previously, the vast majority of previously published papers on microbial keratitis associated with overnight orthokeratology lenses are case reports and small case series, but there are other meaningful, though smaller, sources of safety data. Lipson retrospectively evaluated outcomes of overnight orthokeratology in 296 patients (507 patient-years) [114], of whom 52 % were 12 years old or younger. He reports three adverse events during the study, although none were microbial keratitis (Lipson, personal communication). There was no loss of best-corrected visual acuity, and all three patients were still wearing their lenses at the conclusion of the study.

Recently, Hiraoka et al. reported on ten years of overnight orthokeratology wear in 53 patients [115]. Eight cases of “corneal infiltration and keratitis” were observed, but no “serious complications such as infectious keratitis.” Of importance is that this was a retrospective study that searched records for patients with at least ten years of wear. Thus, it is possible that other patients experienced serious adverse events and discontinued wear.

#### 14. Comparison with soft lens wear

A large-scale prospective, 12-month, population-based study estimated the risk of contact lens-related microbial keratitis [116]. The authors identified 285 cases of contact lens-related microbial keratitis and recruited 1798 controls. The annualized incidence was 1.2 per 10,000 wearers (95 % CI: 1.1–1.5) for daily wear of rigid gas-permeable contact lenses. Consistent with earlier reports, the incidence for overnight wear of soft contact lenses was higher: 19.5 per 10,000 wearers (95 % CI: 14.6–29.5) for conventional hydrogels and 25.4 per 10,000 wearers (95 % CI: 21.2–31.5) for silicone hydrogels. No cases of microbial keratitis associated with overnight orthokeratology lenses were identified (Stapleton, personal communication). Thus, the incidence of microbial keratitis associated with overnight orthokeratology lenses estimated in the above retrospective study is substantially higher than that for daily rigid contact lens wear but similar to that for overnight wear of soft contact lenses [102,103,117–120].

Chalmers et al. reported the frequency of corneal infiltrative events, including microbial keratitis, associated with soft contact lens wear, including 1054 patients under the age of 18 years [90]. There were 187 corneal infiltrative events in 168 wearers, including 8 cases of microbial

keratitis. No cases of microbial keratitis occurred in the 8- to 12-year olds, and two occurred in the 13- to 17-year olds giving an incidence of microbial keratitis of 15 per 10,000 patient-years (95 % CI: 2–48) in the latter age group. The findings of this retrospective study were supported by a comprehensive review of nine prospective studies, mostly in patients 8–14 years old [92]. None of the studies reported any cases of microbial keratitis in collectively over 2000 patient years of lens wear. It could be inferred that younger patients receive greater parental oversight with regards to proper hygiene and care of contact lenses, whereas older children are left to their own device. This could be extended to the importance of reinforcing the proper care of contact lenses in all patients.

#### 15. Summary and future directions

Fig. 2 summarizes the evolution of orthokeratology from a daily regime of unpredictable, flat fitting lenses for temporary myopia reduction in adults to overnight wear of reverse geometry designs where the primary interest in the clinical community is myopia control in children.

The effectiveness of overnight orthokeratology for myopia control is well established, with a two-year slowing of axial elongation of around 0.25 mm. Questions remain as to whether these benefits are sustained and if discontinuation is associated with a post-treatment acceleration [83]. Furthermore, the benefits need to be weighed against the risks of serious infection. The incidence of microbial keratitis for overnight orthokeratology is similar to overnight wear of soft lenses [113] and while rare, higher than other myopia control options including daily wear multifocal soft lenses and atropine.

Future research should explore several potentially fruitful areas. First, the factors that influence myopia progression and axial elongation need further investigation, including baseline corneal shape [121] and peripheral refraction [122], as these might lead to more effective lens designs. Second, the mechanisms underlying the short- and long-term changes in axial length need further elucidation. Recently, Lau et al. fit orthokeratology lenses in 28 children and measured ocular components weekly for one month of lens wear and three weeks after cessation of wear [36]. Axial length decreased by  $26 \pm 41 \mu\text{m}$  at week 1, then gradually returned to its original length. This change was only partly explained by short-term choroidal thickening and central corneal thinning. A small but significant rebound in axial length occurred during the cessation period.

Atropine, a non-selective muscarinic antagonist, is effective at slowing myopia at high concentrations [87], but blurred near vision, photophobia, and the potential for post-treatment acceleration limit its widespread use [82]. Lower concentrations with fewer side effects and



rebound have been explored, although for 0.01 % the slowing of axial elongation is negligible [93,123,124]. On atropine, patients still require optical correction. Along with a desire for more robust myopia control, researchers are exploring combination therapy since atropine and optical treatments have different myopia control mechanisms. Early retrospective studies are inconclusive [125–127], although preliminary results from a randomized clinical trial suggest one-year axial elongation is significantly slower for orthokeratology and 0.01 % atropine combined than for orthokeratology alone:  $0.09 \pm 0.12$  vs.  $0.19 \pm 0.15$  mm [128]. Of course, this difference may be due, in part, to increased pupil size. Future work should also consider more potent concentrations of atropine, e.g., 0.05 % [124].

Finally, it is important to note that in the peer-reviewed literature, the maximum reported cumulative mean slowing of axial elongation for any myopia control modality is less than 0.50 mm, equivalent to little more than one dioptre, and this was with five years of treatment [129]. It should be emphasized that slowing myopia progression by one dioptre may still provide meaningful reductions in risk of myopia-associated disease [130]. Overnight orthokeratology, either alone or in combination with other therapies, will undoubtedly play a role in future efforts to obtain greater treatment magnitudes.

### Declaration of Competing Interest

Leah Johnson is an employee of Paragon Vision Sciences.

Mark Bullimore is a consultant for Alcon, CooperVision, Essilor of America, Eyeovia, Genentech, Johnson & Johnson Vision, Novartis, Paragon Vision Sciences and Tearfilm Innovations. He has ownership in Ridgevue Publishing, Ridgevue Technologies and Ridgevue Vision.

### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.clae.2020.03.018>.

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