REVIEW

Strategies to Regulate Myopia Progression With Contact Lenses: A Review

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Purpose: Higher myopic refractive errors are associated with serious ocular complications that can put visual function at risk. There is respective interest in slowing and if possible stopping myopia progression before it reaches a level associated with increased risk of secondary pathology. The purpose of this report was to review our understanding of the rationale(s) and success of contact lenses (CLs) used to reduce myopia progression.

Methods: A review commenced by searching the PubMed database. The inclusion criteria stipulated publications of clinical trials evaluating the efficacy of CLs in regulating myopia progression based on the primary endpoint of changes in axial length measurements and published in peer-reviewed journals. Other publications from conference proceedings or patents were exceptionally considered when no peer-review articles were available.

Results: The mechanisms that presently support myopia regulation with CLs are based on the change of relative peripheral defocus and changing the foveal image quality signal to potentially interfere with the accommodative system. Ten clinical trials addressing myopia regulation with CLs were reviewed, including corneal refractive therapy (orthokeratology), peripheral gradient lenses, and bifocal (dual-focus) and multifocal lenses.

Conclusions: CLs were reported to be well accepted, consistent, and safe methods to address myopia regulation in children. Corneal refractive therapy (orthokeratology) is so far the method with the largest demonstrated efficacy in myopia regulation across different ethnic groups. However, factors such as patient convenience, the degree of initial myopia, and non-CL treatments may also be considered. The combination of different strategies (i.e., central defocus, peripheral defocus, spectral filters, pharmaceutical delivery, and active lens-borne illumination) in a single device will present further testable hypotheses exploring how different mechanisms can reinforce or compete with each other to improve or reduce myopia regulation with CLs.

Key Words: Myopia progression—Contact lens—Peripheral defocus—Accommodation—Spectral filter—Refractive error regulation—Refractive therapy—Orthokeratology.

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There is increasing interest in actively interfering with the progression of myopia rather than simply compensating for the refractive deficit associated with the condition. Refractive therapeutic intervention addresses myopia not only as a refractive anomaly that can be optically compensated but also a condition that can be treated (or at least managed), as Rubin and Milder suggested in 1976.[1] However, those authors still advocated for conservative (compensatory) treatments based on the lack of evidence to support other treatments portending to address myopia progression.

An interesting report from Kelly et al.[2] in 1975 compared the myopia progression in several cohorts of patients using spectacles alone (control), spectacles plus atropine, contact lenses (CLs) alone, and CLs plus atropine. They concluded that CLs alone were the least effective method to regulate myopia progression. The first reports on the potential beneficial role of CLs as treatments to reduce myopia progression were published in the early 70s. However, little information is available from studies by German researchers Küster[3] and Volckmar.[4] Later reports in the 80s by Kerns,[5] Drobec,[6] Andreo,[7] and Goldschmidt[8] reported the potential of CL to reduce myopia progression. Although pharmacological and spectacle-based optical treatments were the object of extensive review works,[9–12] no updated information is available in the CL field, despite the numerous advances in the last half of that decade.[13]

In the 90s, Singaporean researchers Heng and Khoo published a review article with a suggestive title, "Can contact lenses control the progression of myopia?" in which they discussed the potential role of strategies such as regular wearing of rigid gas-permeable lenses and orthokeratology lenses to regulate myopia progression. The authors concluded that more research in the Asian eye was necessary, as most of the evidence reported early in the 70s had been with Caucasian eyes.[14] Since then, a great deal of new scientific knowledge and clinical evidence has been presented and will be discussed in this review. The question today may be rephrased as "Which contact lenses are more effective to regulate the progression of myopia?" Thus, the aim of this review is to present a summary of the evidence published in peer-reviewed journals related to CL strategies to regulate myopia progression. Other treatments not involving CL wear are out of the scope of this report.

The authors of this report choose the terms "refractive therapy" and "refractive error regulation" as the most accurate terms for the future therapeutic management of refractive errors. The animal studies to date support the ability to influence scleral growth in

either direction; hence, the terminology will apply in the event there is interest or need beyond the present discussion of myopia to regulate hyperopia and astigmatism toward emmetropization. The refractive therapy efforts described here are only a part of the overall research in regulating myopia. The following discussion is limited to CL refractive therapy in contrast to pharmaceutical refractive therapy. Heretofore, the term myopia control has been used by some. The authors prefer the term regulate instead of control consistent with other medical therapeutic interventions.

Socioeconomic Burden and Risks of Myopia Progression

The increase in the prevalence of myopia and the complications associated with the condition have a large socioeconomic impact. Costs associated with myopia can be classified as direct costs, related to spending on eyeglasses, ophthalmic lenses, CLs, and health care office visits, or indirect costs, associated with surgical interventions and treatment of retinal detachment, glaucoma, or lack of productivity derived from visual impairment or blindness.[15,16] A study conducted in Singapore with 301 subjects between the ages of 12 and 17 years revealed that the mean annual direct cost of myopia for each subject in Singapore dollars was \$221.7±313.7 (US \$148±\$209.1). Based on age-specific prevalence of myopia, the authors estimated that costs of \$37.5 million would be required to correct myopia for only Singaporean teenagers.[17] In 2006, Vitale et al.[18] conducted a study for the National Health and Nutrition Examination Survey (NHANES) in the United States and estimated the annual direct cost of correcting myopia to be between \$3.9 and \$7.2 billion.

Ocular diseases such as cataract, glaucoma, maculopathy, and retinal detachment are often associated with high myopia increasing the risk of blindness. These sequelae establish myopia as a major public health problem in some countries in East Asia and in certain ethnic groups such as the Chinese.[19–23] The definition of pathological myopia is not clear in the literature, and a single definition is complicated because patients with lower myopia also exhibit pathological ocular findings.[24] However, it is accepted that the higher the myopia, the greater is the risk of pathological changes. In the Blue Mountains Eye Study, the risk for myopic maculopathy increased from ×2.2 for myopia below 3.00 diopter (D) to ×41 for myopia between −5.00 and −7.00 D and to ×350 for myopia over −9.00 D.[25] The risk for retinal detachment shifts from ×5 to ×10 for myopia under −3.00 D to myopia over −3.00 D, according to a Japanese study.[26] Table 1 exemplifies the average myopia progression per year in different studies for periods ranging from 4 to 8 years. Most of these studies evaluated the general population; of course, the rates of progression are expected to be faster in the becoming myopic or myopic population.

This risk differential highlights the relevance of treatments directed to keeping myopia at lower levels. Therapeutic intervention is even more relevant considering the evidence that points to higher prevalence of myopia in the younger populations, even in western countries, as has been reported in the U.S. NHANES.[33,34]

Contact Lenses and Pathways to Reduce Myopia Progression

It is very important for clinicians to be aware of the rationale that supports the application of optical treatments to regulate myopic progression. We will discuss the role of peripheral myopic defocus, the role of near add power to compensate for the higher accommodative demand, the role of accommodative lag, and very briefly will comment on the recently proposed role of modulation of the activity of different visual pathways by means of spectral filters.

Relative Peripheral Defocus

Results from several animal species including young chickens[35] and monkeys[36] have demonstrated that their eyes are capable of responding to myopic or hyperopic defocus by altering their posterior chamber shape. Asymmetrical ocular elongation results when defocus is only imposed in one half of the retina or when different sign defocus is imposed in both hemifields.[37] Troilo and Wallman were able to demonstrate that the supposed visually guided eye growth mechanism in chickens tends to recognize defocus and adjust axial growth according to its signal even with a sectioned optic nerve. The authors concluded that the mechanism behind the defocus sign recognition and eye growth modulation must be located within the eye and be somehow independent from central neural system, while brain activity must be maintained for emmetropia to succeed.[38]

When infant rhesus monkeys were raised with central opening diffusers that deprived the animal's peripheral vision allowing only clear foveal vision, an accelerated axial elongation resulted.[39] The monkeys were then submitted to another experience where their

TABLE 1. *Summary of Studies Evaluating the Annual Progression of Myopia Derived With Cycloplegic Refraction and/or Axial Length Elongation in Children Aged 6 to 12 Years From Different Ethnicities*

Author (Year)	Sample (n, Eyes)	Ethnicity	Age	Methods	D/year	Elongation (mm/year)
Pointer (2001)[27]	60 (41)	Caucasian	7–13	Static dry retinoscopy+Sx	−0.09 D/yr (stable from 11 to 13)	NR
Xiang et al. (2012)[28]	607	Chinese (twins)	7–15	Cycloplegic autorefraction	−0.7 D/yr	0.21 mm/yr
Fan et al. (2004)[29]	255	Chinese	2–6	Cycloplegic autorefraction/ ultrasound biometry	−0.24 D/yr	0.34 mm/yr
Zhao et al. (2002)[30]	4662 myopes	Chinese	5–13	Cycloplegic autorefraction	−0.18 D/yr (−0.37)	NR
Anderson et al. (2011)[31]	114 myopes	8 Asians, 19 blacks, 29 whites, 51 Hispanics, and 7 individuals of mixed ethnicity	7–13	Noncycloplegic autorefraction	−0.23 D/yr	NR
Shih et al. 2010[32]	Aggregate from different studies	Urban Chinese population	7–12	Different methods	Boys: −0.20; girls: −0.27	NR

NR, not reported.

central vision was deprived by foveal ablation and only clear peripheral vision was allowed. The authors concluded that foveal vision is not essential for the emmetropization to occur in primates and that peripheral retina visual experience may be responsible for the regulation of ocular growth.

A recent study reported by Liu and Wildsoet concluded that myopic peripheral defocus with refractive-corrected central vision (concentric multifocal CLs) results in an inhibitory effect on axial eye growth in young chickens, but the contrary effect occurred when myopic defocus was restricted only to central vision with a focused peripheral area.[40]

Whether by design or default, most of the currently available treatments for myopia regulation with CL can be viewed as owing their success to their propensity to change the relative peripheral defocus. Several patents have been issued for this purpose. Commercially available and investigational devices falling in this category will be discussed further in the Discussion section.

Accommodative Lag and Phoria at Near

Different studies have linked myopia onset and myopia progression with increased levels of near-vision work,[41] and a link to the activity of the accommodative system has been established.[42,43] Eyes after the onset of myopia are observed to have greater accommodative lag (under-accommodation for a given target distance) compared with emmetropic eyes.[44] The same study suggests that higher accommodative lag seems to be a consequence instead of a cause of myopia. Considering the higher lag, myopic eyes are exposed to hyperopic defocus and respective poor image quality[45,46] during near-work, and these optical effects may have a role in the myopia progression mechanism. Weizhong et al.[47] could not demonstrate a higher myopia progression in myopic eyes having higher accommodative lag. This contradiction leads to some controversy regarding the role of accommodative lag alone in myopia progression.

The use of bifocals or progressive addition ophthalmic lenses for slowing the progression of myopia has been reported to result in small therapeutic regulation of myopia. Myopia showed 0.15 to 0.50 D slower progression in the treatment groups when compared with control groups over a period of 1.5 to 3 years.[48–50] Despite the positive effect of the intervention with bifocal and progressive addition lenses, the low annual regulation may not be clinically relevant for the general population of patients with myopia.

Other studies showed a greater effectiveness with bifocal and progressive addition ophthalmic lenses in children with esophoria and high accommodative lag.[51] Moreover, some authors have reported that high myopia is related to higher esophoria.[52] The link between esophoria and accommodative lag might provide a working hypothesis based on the relationship between the accommodative and convergence systems.[53] A hypothesis in patients with esophoria suggests that the accommodative lag is higher to prevent the increase of the esophoria at near. Thus, providing a near add will warrant that the visual effects in the form of hyperopic defocus at near associated with a higher lag will be minimized.

Concentric bifocal CLs might also provide myopia regulation by imposing some degree of peripheral myopic defocus. This has been postulated by Smith[54] and suggests a synergistic effect by interfering simultaneously with the foveal vision partially compensating the negative effects of accommodative lag and simultaneously inducing peripheral myopic defocus. However, our evaluations using an open-field autorefractometer failed to detect any significant effect on peripheral refraction or relative peripheral defocus by concentric annular multifocal CLs.[55] The autorefractometer measures covered an area of 2.3 mm in diameter. The measurement zone might be too large to detect the power differences between 6 concentric rings of alternating near and distance power. Aberrometric evaluation for smaller pupil sizes may bring more detailed information on the sign of the local peripheral defocus with concentric bifocal CLs. Even so, measurement of such lenses may not be accurate with Hartmann-Shack sensors because of the overlapping and duplication of the microarray spots formed by light passing through the distance and near power rings.

Instead of solely compensating for accommodative lag using a positive add at near, another alternative is to improve the accommodative response in the myopic eye. Allen et al.[56] reported a reduction in accommodative lag of myopic eyes by fitting soft CLs to induce -0.1 μm of fourth-order spherical aberration at a pupil diameter of 5.0 mm. For the average eye with positive spherical aberration,[57] this intervention will push the best image focus backwards and the eye will need to accommodate more efficiently to bring it forward to the retinal plane.

Contact lens devices falling in this kind of intervention include the use of refractive and diffractive bifocal CLs, near-center multifocal CLs, and single vision lenses with induced negative spherical aberration to improve accommodative function[56] without the purpose of multifocal vision. CLs with negative spherical aberration will induce relative peripheral hyperopic defocus.[58] This is in opposition to the desired myopic peripheral defocus previously described. Both mechanisms within the same device could interact in an antagonistic way. Commercially available and investigational devices falling in this category will be discussed further in the Discussion section.

METHODS

A search was performed in PubMed (www.pubmed.com) using the following combination of keywords "myopia progression contact lens" by June 2014; this was the combination that produced the most sensitive and specific outcome. The primary outcome of interest in this search was to find the peer-reviewed publications addressing the potential effect of CLs on myopia progression, with particular interest in clinical trials conducted in the field. Selection criteria were original articles or case reports published in peer-reviewed journals from 2004 to 2014 reporting clinical and biometric data of eye growth and myopia progression with CLs; no conference abstracts nor review articles were considered. A total of 107 citations were retrieved. Of them, 49 were related to generic topics and not directly related to the use of CL in myopia research, 19 were review articles, 9 were investigating the effect of CL on peripheral refraction, and 4 were related to animal studies. Of the remaining 26 articles reporting clinical trials, 9 were related to single vision contact lenses (SVCL), 8 to orthokeratology or corneal refractive therapy, 2 to non-orthokeratology gas-permeable CLs, 3 to bifocal soft CLs, 1 to multifocal dominant design CL, and 1 to peripheral gradient CLs. There was one case report related to the use of orthokeratology and one related to bifocal CLs. For the purpose of this review, the results of the last eight studies with orthokeratology/corneal refractive therapy, six studies describing

the use of other CLs, one study reporting the results of a dominant design multifocal CL for presbyopia, and two studies on the effect of SVCL have been tabulated and subjective to more detailed analysis and discussion.

RESULTS

The main characteristics of the CL designed with the primary purpose of regulating myopia progression and their reported effectiveness are discussed here. Other CLs that have been reported in isolated case reports or in systematic clinical trials with their respective effectiveness as myopia regulation treatments are included. Table 2 presents a summarized overview of the main outcomes of the clinical case reports and clinical trials. Considering the strong body of literature arising in the recent years for orthokeratology/corneal refractive therapy treatments, Table 3 addresses specifically the outcomes of these studies. A graphical overview of these interventions is shown in Figure 1 for an approximate simulated pupil size of 6 mm.

DISCUSSION

Refractive Bifocal and Multifocal CLs

Goldschmidt,[8] in a review article published in 1990, described the results of a Danish study conducted in the 80s, which was reported to show evidence of the beneficial effect of bifocal CLs on myopia progression. To our knowledge, this is one of the first results reported in the peer-reviewed literature (although indirectly) on the potential effect of CL in preventing myopia progression.

Bifocal and Dual-focus Contact Lenses

Bifocal lenses used with the purpose of reduction of myopia progression included ACUVUE Bifocal lens (Johnson & Johnson, Jacksonville, FL) made of etafilcon A (ionic, 58% water content) with a total diameter of 14.0 mm and a base curve radius of 8.5 mm. The optical design of the lens comprises a central distance zone with a diameter of 2 mm surrounded by a 0.6 width near addition ring, a 0.6 mm width distance ring, a 0.35 near addition ring, and a fifth 1.45-mm wide distance ring (approximate design shown in Fig. 1C).

The use of bifocal CLs to prevent myopia progression with modern CLs was initiated by Aller and Wildsoet who reported on the case of two identical twin sisters in a cross-over clinical fitting during 2 years. They found that bifocal CLs were able to reduce the ocular growth in the twin sisters alternatively fitted with ACUVUE Bifocal.[59] Furthermore, the authors reported in 2006 on a 1-year clinical trial testing the efficacy of ACUVUE Bifocal CL in myopic endophoric patients. They reported a 71% reduction in refractive change as measured with cycloplegic autorefraction and a 79% reduction in axial length with the bifocal CL.[60]

The only human randomized controlled clinical trial with this category of lenses was conducted by Anstice and Phillips[66] with refractive bifocal (dual-focus) CLs in the Dual-focus Inhibition of Myopia Evaluation in New Zealand study. Dual-focus CLs consist of a hydrophilic soft CL made of hioxifilcon A, nonionic 49% water content material (Benz Research and Development, Sarasota, FL), with a total diameter of 14.2 mm and a base curve of 8.5 mm. The optical design consists of a series of concentric areas starting with a 3.36-mm central distance area, surrounding by a 0.71-mm width treatment zone (near zone), a 0.99 distance zone ring, and a 0.78 with second treatment zone. A graphical representation of the lens design is shown in Figure 1G over a 6-mm diameter. In this study, either eye of 40 young children between 11 and 14 years of age was randomly fitted with a dual-focus lens or with a single vision lens and replaced bimonthly.

After a period of 10 months with the first prescription, the treatments were switched between right and left eyes. In this clinical trial, right eye lenses were blue-tinted to avoid confusion. At the end of the study, data from the 2 parts of the study (up to a total of 20 months) were combined to obtain the progression effect during dual-focus and single vision lens wearing. The spherical equivalent refraction increased by -0.44 ± 0.33 D in the dual-focus group and -0.69 ± 0.38 D in the single vision lens group ($P<0.001$). Axial length increased by 0.11 ± 0.09 mm for the eyes during the dual-focus lens wearing and 0.22 ± 0.10 mm during the single vision lens wearing ($P<0.001$).

Another recent approach to regulate myopia progression with CL is represented by the defocus incorporated soft contact lens (DISC). This is a refractive concentric bifocal soft CL comprising 10 to 12 rings of alternating power over the optic zone. A graphical representation of the lens design is shown in Figure 1H. In the lens description presented by the authors in the animal studies conducted with pigmented guinea pigs, the authors describe the lenses as Fresnel lenses designed to minimize spherical aberration.[77] The 2-year clinical trial in humans was completed by 65 children wearing the DISC lenses bilaterally and 63 children wearing single vision CLs.[67] The clinical group using the DISC lenses showed a 31% lower axial elongation compared with the SVCL group over the 2-year period. Apparently, the retention effect was positively correlated with the number of hours of lens wear, varying from 25% for the subjects wearing the lenses for shorter periods during the day to 60% for those wearing the lenses 8 or more hours. However, the authors only provided this analysis in terms of spherical equivalent refraction rather than axial elongation, so blur adaptation in those wearing the lenses for longer periods might confound this analysis. Additionally, the authors do not report the average age of subjects in each group of wearing time, which might also be a confounding factor, as older children tend to progress at a slower rate than younger children.

Although this fact might not be relevant, some recent developments supporting the use of blue-tinted lenses to provide myopic regulation effect might bring a possible additional source of variability in myopia regulation effect, although this observation is merely speculative.[76]

Multifocal Center-Distance Contact Lenses

Center-distance multifocal CLs are used for presbyopia correction. Their optical design has been proposed as a viable way to induce myopic peripheral defocus,[79] which may be inhibitory for axial elongation similar to the refractive effect created with corneal refractive therapy.

Center-distance multifocal CLs used in myopia progression studies were Proclear (CooperVision, Pleasanton, CA) dominant "D" design lens made of omafilcon A (nonionic, 62% water content), with an overall diameter of 14.2 mm and a base curve radius of 8.6 mm. The optical design consists of a spherical central zone of 2.3 mm in diameter dedicated to distance vision, surrounded by an annular aspheric zone of 5.0 mm (1.35-mm width) of increasing addition power and a spherical annular zone of 8.5 mm (1.50 mm

TABLE 2. *Summary of Studies Evaluating the Myopia Regulation Effect With Single Vision, Multifocal, Dual-Focus, Gradient Power*

Author (Year)	Ethnicity (Age)	Study Design (Duration[a])	Test Group (n Eyes) (Rx Range)	Control Group (n Eyes) (Rx Range)
Aller and Wildsoet (2008)[59]	Caucasian	Case report	ACUVUE Bifocal (n=2)	SV SCL (n=2)
Aller and Wildsoet (2006)[60]	Various (8–18)	Randomized (12 months)	ACUVUE Bifocal (n=38)	SV SCL (n=40)
Sankaridurg (2011)[61]	Chinese (7–14)	Parallel, controlled, randomized (6 months)	Peripheral gradient (45) (−2.24±0.79)	Spectacles (40) (−1.99±0.62)
		Parallel, controlled, randomized (12 months)	Peripheral gradient (43) (−0.75, −3.50)	Spectacles (39) (−0.75, −3.50)
Walline and McVey 2010[62]	NR (10–11)	24 months	Multifocal CL (n=14) (–2.31±1.05)	SV SCL (14) (–2.22±0.97)
Horner et al. (1999)[63]	NR (11–14)	3 years	SV SCL (n=62) (−3.01±0.22)	Spectacles (68) (−3.10±0.21)
Walline et al. (2008)[64]	47.1% white, 21.5% black, 21.5% Hispanic, 6.6% Asian or Pacific Islander (8–11)	3 years	SV SCL (237) (−2.38±0.98)	Spectacles (247) (−2.43±1.10)
Marsh-Tootle et al. (2009)[65]	Ethnically diverse (5–6)	2 years	Spectacles (106) (−4.32±1.40)	SV SCL (77) (−4.25±1.52)
Antice and Phillips (2010)[66]	Various (11–14)	Cross-over, controlled, randomized (20 months)	Dual-focus (n=35) (−1.25, −4.00)	SV SCL (n=35) (−1.25, −4.00)
Lam et al. (2014)[67]	Chinese (8–13)	Controlled, randomized, (24 months)	DISC (n=65) (−2.90±1.05)	S (n=63) (−2.80±1.03)

Author (Year)	Refraction Method	Biometric Method	Dioptric Progression in Test Group vs. Control (Regulation Effect, %)	Axial Growth in Test Group vs. Control (Regulation Effect, %)
Aller and Wildsoet (2008)[59]	Noncycloplegic refraction	IOLMaster	0.00 vs. −1.25 (100%)	NR (at baseline)
Aller and Wildsoet (2006)[60]	Cycloplegic autorefraction	IOLMaster	−0.22 vs. −0.78 (71.8%)	0.05 vs. 0.24; 0.19 mm (79.2%)
Sankaridurg (2011)[61]	Cycloplegic open-field autorefraction		−0.28 vs. −0.57 (50.9%)	0.09 vs. 0.26; 0.17 mm (65.4%)
			−0.54 vs. −0.84 (37.5%)	0.24 vs. 0.39; 0.15 mm (38.5%)
Walline and McVey 2010[62]	Cycloplegic open-field autorefraction	A-scan ultrasonography	−0.55 vs. −1.10 (50.0%)	0.32 vs. 0.47; 0.15 mm (31.9%)
Horner et al. (1999)[63]	Noncycloplegic subjective examination	NR	14.7%	NR
Walline et al. (2008)[64]	Cycloplegic autorefraction	A-scan ultrasonography	−1.30 vs. −1.12 (−16.1%)	0.62 vs. 0.59; −0.03 mm (−5.1%)
Marsh-Tootle et al. (2009)[65]	Cycloplegic autorefraction	A-scan ultrasonography	47.1%	11.1
Antice and Phillips (2010)[66]	Cycloplegic autorefraction	IOLMaster	−0.17 vs. −0.38 (55.3%)	0.03 vs. 0.15; 0.15 mm (80.0%)
Lam et al. (2014)[67]	Cycloplegic autorefraction	IOLMaster	−0.59 vs. −0.80 (26%)	0.25 vs. 0.36 (31%)

SV SCL, single vision soft contact lenses; NR, not reported; DISC, defocus incorporated soft contact lenses.

[a]Report from interim results before study completion.

width) reaching the maximum add power. This design is presently available also in the Biofinity multifocal (comfilcon A, 48% water content silicone hydrogel material).

The amount of relative peripheral refractive error is correlated with the add power chosen from +1 to +3 D.[78,79] Figure 1D represents the in vitro power profile for a −2.00 D distance powered with +2.00 D add Proclear D lens; Figure 1E,F represent the on-eye corneal topography power map over a plano lens at distance with add power of +3 and +4 D. Walline and McVey reported on the potential benefit of using Proclear multifocal dominant "D" design as a method to regulate myopia progression in children. The Bifocal Lens Inhibition of Myopia Progression study was a 2-year study comparing the progression of myopia between children wearing single vision CLs and age-matched children wearing multifocal dominant design lenses. Two-year outcome reported was a regulation effect in axial length growth of 29% in the children who used Proclear D (add power +2.00 D) when compared with the cohort wearing conventional single vision CLs. The authors claimed a 50% regulation effect in the progression of refractive error. A statistically significant, though weak correlation existed between baseline myopia and axial length regulation.[80]

Peripheral Gradient Lenses

Similar to center-distance multifocal lenses, custom rigid gas permeable and soft CLs can be designed to compensate for central myopic errors, and at the same time, they impose peripheral positive defocus.[81] A special soft CL with these features was used in a clinical trial to assess its effectiveness in myopia regulation.[61] The treatment CLs made of a silicone hydrogel lens material (8.6-mm base curve, 14.2-mm diameter, lotrafilcon B; CIBA Vision, Duluth, GA) had a clear central zone that corrected for the eye's central refractive error (1.5-mm semichord and 1.5 mm within a relative plus of +0.25 D). Outside the central zone, the refracting power of the lens increased progressively in relative positive power to reach a relative positive power of +1.00 D at 2 mm semichord and +2.00 D at a semichord of 4.5 mm. Approximate design is shown in Figure 1I.

Sankaridurg et al. performed a randomized and controlled clinical trial in China with a cohort of 43 Chinese children aged from 7 to 14 years, with baseline spherical refractive error ranging between −0.75 and −3.50 D and −1.00 D or less of astigmatism, and who were treated with the special design CLs for a period of 12 months. The control group consisted of 39 Chinese children with similar baseline ocular characteristics and age range who were treated with single vision spectacle lenses during the same period.

At the end of the 12 months, the eyes treated with the special contact lens showed a 33% slower axial elongation compared to the control group treated with single vision lenses. Although the regulation effect of myopia progression is still below the expected, it demonstrates the effectiveness of this category of CL for the regulation of myopia.

TABLE 3. *Summary of Studies Evaluating Myopia Regulation Effect With Corneal Refractive Therapy (Orthokeratology)*

Author (Year)	Cheung et al. (2004)[68]	Cho et al. (2005)[69]	Walline et al. (2009)[70]	Kakita et al. (2011)[71]	Santodomingo-Rubido et al. (2012)[72]
Test group (n eyes, M/F) (average SER)	Ortho-k (n=1 eye, male) (−2.50-0.50×170)	Ortho-k (n=34, 16/19) (−2.27±1.09)	CRT (n=28, 16/19)[a]	Ortho-k (n=28, 21/21) (−2.55±1.82)	Ortho-k (n=31, 15/16) (−2.35)
Ethnicity	Chinese	Chinese	Caucasian	Japanese	Caucasian
Age range	13	7–12	8–11	8–16	6–12
Mean age (years)	—	9.6	10.5	12.0	9.7
Range SER, D	−2.50	−0.25 to −4.00	−0.75 to −4.00	−0.50 to −10.00	−0.75 to −4.00
Max. cylinder, D	−0.50	−2.00	−1.00	−1.50	−1.00
Refraction baseline	Noncycloplegic refraction	Noncycloplegic refraction	Cycloplegic autorefraction	Noncycloplegic autorefraction	Cycloplegic autorefraction
Duration of study, years	3	2	2	2	2
Randomization	Case report	Nonrandomized	Historic data	Nonrandomized	Nonrandomized
Control group (n eyes, M/F) (average Rx)	Emmetrope (n=1 eye) (−0.25-0.75×168)	SVSL (n=34, 16/19) (−2.55±0.98)	SVSL	SVSL (n=50, 22/28) (−2.59±1.66)	SVSL (n=30, 15/15) (−2.53)
Refraction	Noncycloplegic refraction	Cycloplegic refraction, retinoscopy	Cycloplegic autorefraction	Noncycloplegic autorefraction	Cycloplegic autorefraction
Biometry (outcome measures)	US A-Scan (VCD, AL)	US A-scan 5500, (VCD, AL)	US A-scan (ACD, LT, VCD, AL)	PCI (AL)	PCI (AL)
Dioptric regulation (D) effect, %	+3.25 vs. −0.75, −118% vs. 150%	+2.09±1.34 vs. −1.20±0.61, −92% vs. 47%	[a]	+1.87±1.34 vs. −1.24±1.71, −73% vs. 48%	+1.86 vs. −1.27, −80% vs. 50%
Increase AL treated vs. control, mm	0.13 vs. 0.34	0.29±0.27 vs. 0.54±0.27	0.25±0.72 vs. 0.57±0.74	0.39±0.27 vs. 0.61±0.24	0.47 vs. 0.69
Mean growth regulation effect per year (%)	−0.11 mm (62%)	−0.12 mm (46%)	−0.16 mm (56%)	−0.11 mm (36%)	−0.11 mm (32%)
Contact lens	WAVE lens	Boston XO/Paragon	Paragon CRT	Emerald	Menicon Z Night
Material	NR	HDS	Paragon HDS 100	Boston XO	Tisilfocon A
Dk[c]	NR	100×10^{-11}	100×10^{-11}	100×10^{-11}	163×10^{-11}
Central thickness	0.22 mm	NR	NR	NR	NR
Overall diameter	10.6 mm	NR	NR	NR	NR
Optic zone diameter	6.0 mm	NR	NR	NR	NR

Author (Year)	Hiraoka et al. (2012)[73]	Chen et al. (2012)[74]	Cho et al. (2012)[75]	Charm and Cho (2012)[76]
Test group (n eyes, M/F) (average SER)	Ortho-k (n=22, 10/12) (−1.89±0.82)	Ortho-k (n=25, —/—) (−2.64±0.82)	Ortho-k (n=37, 19/18) (−2.16±0.77)	Ortho-k (n=12, —/—) (−6.38)
Ethnicity	Japanese	Chinese	Chinese	Chinese
Age range	8–12	9–14	7–10	8–11
Mean age (years)	10.0	11.2	9.0	10.0
Range SER, D	−0.50 to −5.00	−1.00 to −4.50	−0.50 to −4.50	−5.00 to −8.30
Max. cylinder, D	−1.50	−1.50	−1.50	−1.50
Refraction baseline	Noncycloplegic refraction	Noncycloplegic refraction	Noncycloplegic refraction	Cycloplegic refraction
Duration of study, years	5	2	2	2
Randomization	Nonrandomized	Nonrandomized	Randomized	Randomized, single-masked
Control group (n eyes, M/F) (average Rx)	SVSL (n=21, 8/13) (−1.83±1.06)	SVSL (n=22, NR/NR) (−2.40±0.86)	SVSL (n=41, 22/19) (−2.36±0.86)	SVSL (n=16, —/—) −(6.00)
Refraction	Noncycloplegic autorefraction	NR	Cycloplegic refraction	Cycloplegic autorefraction
Biometry (outcome measures)	PCI (AL)	PCI (AL)	PCI (AL)	AL
Dioptric regulation (D) effect, %	+1.19 vs. −3.20, −63% vs. 175%	NR	NR	−0.13 vs. −1.00, 0.87 D (87.0%)
Increase AL treated vs. control, mm	0.99±0.47 vs. 1.41±0.68	0.55 vs. 0.50[b]	0.36±0.24 vs. 0.63±0.26	0.19 vs. 0.51
Mean growth regulation effect per year (%)	−0.13 mm, 37% (2 years); −0.08 mm, 30% (5 years)	+0.05 mm, −10%[b]	−0.14 mm (43%)	NR
Contact lens	Emerald	Hiline	Menicon Z Night	Procornea
Material	Boston XO	Boston XO	Tisilfocon A	Boston XO
Dk[c]	100×10^{-11}	100×10^{-11}	163×10^{-11}	100×10^{-11}
Central thickness	0.22 mm	NR	NR	0.22 mm
Overall diameter	10.6 mm	10.6–10.8 mm	NR	10.5 mm
Optic zone diameter	NR	6.0 mm	NR	6.0 mm

Positive values of dioptric regulation effect and negative values of axial growth regulation effect mean a lower ocular elongation in the orthokeratology group.

[a]Refractive error and corneal curvature are temporarily altered by orthokeratology, so they are not compared in this investigation.

[b]Authors do not report the increment in AL for the whole sample in the orthokeratology group or SVL group, so an average of the data presented by the authors for their different subgroups is displayed in the table.

[c]Barrer (cm^2/s) ($mL \cdot O_2/mL \times mm\ Hg$).

AL, axial length; Average Rx, average Rx at baseline; NR, not reported; PCI: partial coherence interferometry (IOLMaster, Carl Zeiss, Dublin, CA); SVCL, single vision contact lenses; SVSL, single vision spectacle lenses; US, ultrasound; VCD, vitreous chamber depth.

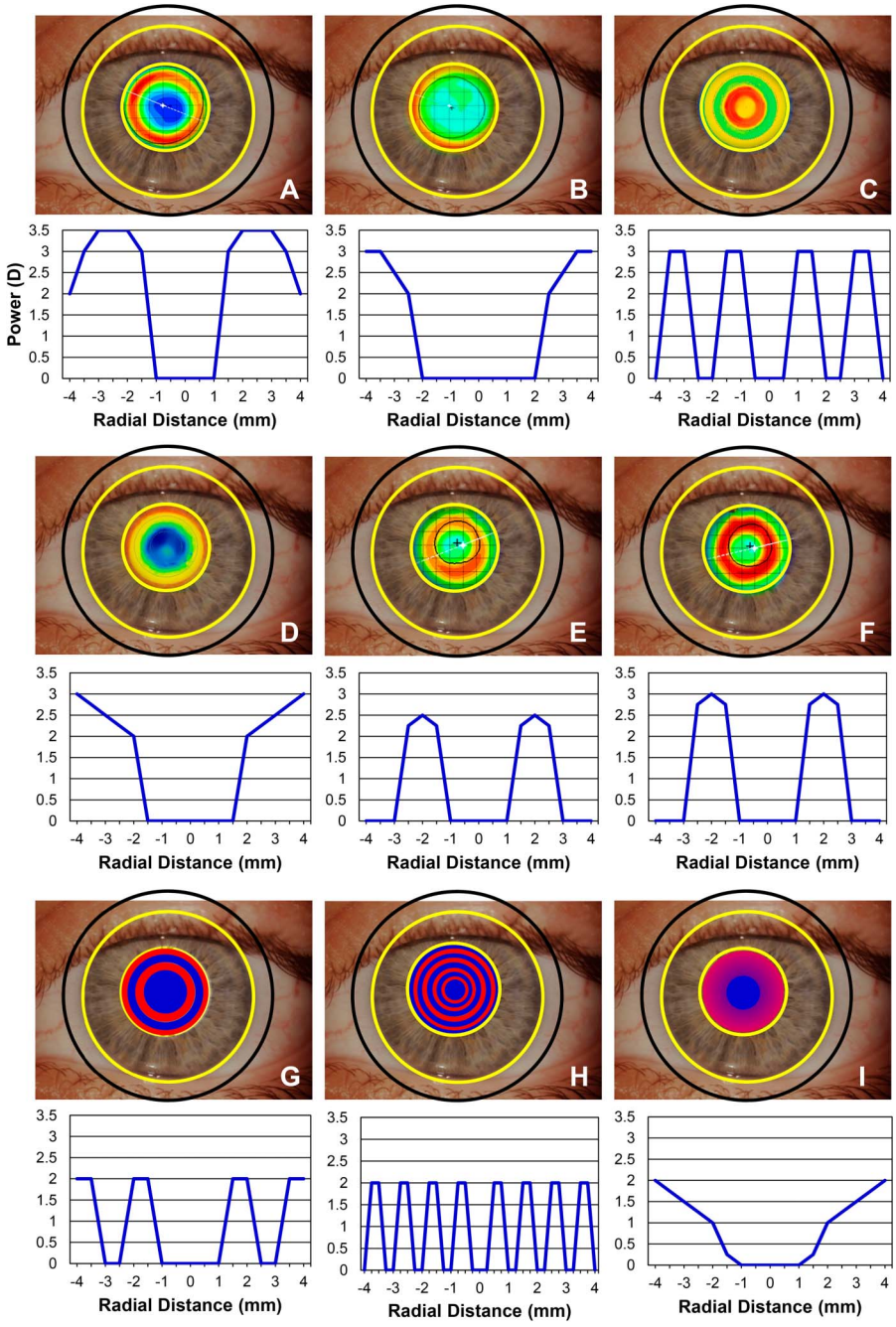

FIG. 1. Representation of the optical design of different contact lenses with potential to retain myopia progression over the 6 mm of the pupil and graphs representing the approximate power profile over the central 8 mm: (A) corneal refractive therapy for an axial myopia of −3.5 D; (B) corneal refractive therapy for axial myopia of +1.5 D; (C) bifocal annular design; (D) power profile of a multifocal center-distance soft contact lens as measured in vitro; (E) and (F) power profile of a multifocal center-distance soft contact lens on-eye with +3.00 and +4.00 D of addition for near, respectively, as measured with a corneal topographer; (G) dual-focus as described by Anstice and Phillips[66]; (H) defocus incorporated special contact lens (DISC)[67]; and (I) peripheral gradient design as described by Sankaridurg et al.[61] Note: Drawings might not be a true representation of the lens design; some lens designs might be different for different patients depending on their pupil size, refractive error, or other clinical parameters. Graphs do not represent the actual profiles reflected in the maps. Red areas represent maximum positive power, whereas blue or green areas represent distance refractive correction (plano for the purpose of this comparison). All graphs are drawn to represent a maximum power addition of 3 D over a base of plano power except for A (+3.50), B (+1.50), F (+4.00), and G (+2.00).

Single Vision Contact Lenses

Conventional single vision soft CLs are largely used to correct refractive errors. It has been described recently that undercorrection, full correction, and overcorrection with single vision soft CL causes hyperopic shifts in the peripheral visual field.[82] In another study, Shen et al.,[83] using commercially available spherical CLs, reported the ability to decrease the amount of relative peripheral hyperopia. This seems to be more effective in high myopia (manifest spherical equivalent=−8.31±2.10 D), where central refractive correction with spherical CLs can result in significant absolute myopic peripheral defocus.[85]

Other studies performed to evaluate myopia progression reported that single vision CLs do not produce an effect on the change of refractive development in a test group when compared with a control group wearing spectacle lenses.[63,64] When children switched from spectacle lenses to CLs, Marsh-Tootle et al.[65] found a significant but clinically irrelevant increase in myopia. Fulk et al.[85] reported an increase in the amount of myopia three times faster in children who switched to single vision CLs than those who remained in spectacles (mean difference, −0.74 D; $P<0.001$). Nevertheless, no differences were observed in the vitreous chamber depth, and the refractive change between both groups was related with the change

verified in corneal curvature (mean difference, 0.189 D, P=0.007), probably related with molding effects or slight edema.

An additional form of single vision intervention in myopia progression has been tested in the context of the Cambridge Anti-myopia Study (CAMS). Allen et al.[67] used CLs to induce negative spherical aberration to improve the accommodative function and reduce the accommodation lag in myopic eyes. The CAMS evaluated the role of accommodative visual therapy and negative spherical aberration CL, alone or combined in myopia progression, in adolescents and young adults from 14 to 22 years of age in a 2-year randomized controlled clinical trial. The results of the CAMS clinical trial were recently published and concluded that there was no effect of improving accommodative function either through vision training alone, negative spherical aberration lenses alone, or the combination of both on myopia progression. It is necessary to consider that these CLs will probably induce relative peripheral hyperopia as a result of their aspheric design as has been observed in multifocal CLs using center-near designs.[58] Thus, there is a possibility that the potential benefit of improving the accommodative function could be somewhat counterbalanced by the negative effect of induced hyperopic peripheral defocus.

Corneal Refractive Therapy and Orthokeratology

In the last decade, several clinical studies evaluated the effect of overnight corneal reshaping for the temporary correction of myopia in the regulation of myopia progression. Cheung et al. reported the case of an 11-year-old child treated with orthokeratology in one eye with full undercorrection in the contralateral eye. This case showed a reduction in myopia progression of 62% compared with the contralateral eye not wearing an orthokeratology lens.[68]

Between 2005 and 2012, the results of 6 different clinical trials have been reported in 7 peer-reviewed publications. All of them agreed that treatment with overnight corneal reshaping lenses demonstrated regulation of myopia progression by 30% to 50% in children of different ethnicities aged 8 to 12 years.

Lenses used in these studies were tetracurve and pentacurve reverse geometry lenses and proximity control lenses made of paflufocon D (Paragon HDS 100), hexafocon A (Boston XO), and tisilfocon A (Menicon Z). A graphical representation of the power profile of the cornea over a 6-mm pupil diameter after overnight corneal reshaping for a moderate (−3.5 D) and low (−1.5 D) myopic correction is presented in Figure 1A and 1B, respectively. Four of the most recently published studies report on East Asian populations,[69,71] one report results from the United States,[70] and the second reports on Caucasian patients living in Spain.[72] A summary of these and other studies and their characteristics and outcomes are reported in Table 3. Only studies including vitreous chamber or axial length measurement as a primary outcome were included in this analysis. With the exception of the U.S. study, all studies included a control population of spectacle wearers. The U.S. study included a control population of soft CL wearers. The follow-up time was 2 years with the exception of the Japanese study presented by Hiraoka et al.[73] Hiraoka et al. reported on the 5-year outcomes showing an average myopia regulation effect of 30% over the 5 years compared with the 37% regulation effect presented previously by Kakita et al.[71] in the same population. This might suggest that the therapeutic regulation effect of orthokeratology might decline over time. The apparent decline might also be related to a slower myopia progression in the control population, as the children became older. Santodomingo-Rubido et al. in 2012 reported a regulation effect of 32% over 2 years in children aged 6 to 12 years.

More recently, the results of the only randomized clinical trial (Retardation of Myopia in Orthokeratology study) conducted in Hong Kong confirmed the results of previous studies with an average axial growth regulation effect of 43% at a consistent rate of −0.14 mm per year in children wearing orthokeratology lenses compared with spectacle wearers who experienced an average growth of 0.63 mm per year.[75]

Considering the consolidated evidence of the role of corneal refractive therapy on regulating myopia progression, there is a growing interest in evaluating the potential factors associated with a higher or lower efficacy of the treatment. Baseline myopia was considered as a potential candidate to predict the efficacy of the treatment, considering the linear relationship between baseline myopia and the relative peripheral refractive error induced by the corneal refractive therapy treatment. However, only Cho et al. in the LORIC study have been able to demonstrate a moderate and statistically significant direct correlation between the amount of baseline myopia and the effect on myopia regulation.[69] More recently, Chen et al. demonstrated that pupil size might have a significant impact on myopia regulation. In their study, larger pupils were associated with a greater efficacy of the treatment, whereas smaller pupil size was related to no regulation effect[74] as Figure 1A,B illustrate. Previous studies using orthokeratology for myopia regulation did not report on the potential effect of pupil size on the degree of myopia regulation.

Despite the apparent susceptibility of East Asian ethnic groups to suffer myopia, corneal refractive therapy has shown to be effective in all ethnic groups including Asian, Caucasian, and African ethnic groups.

A closer observation to information displayed in Table 3 shows that the lenses used in different studies are made of different materials and using different designs. Despite the differences in overall lens diameter and optical zone diameter, all studies are consistently showing similar myopia regulation of approximately 40%. Considering the recently observed relationship between pupil size and the myopia regulation effect, one might expect that the smaller treatment zones might be associated to higher myopia regulation. However, Kang et al. have recently reported that the peripheral refraction pattern was not significantly different between lenses with different treatment zones.[86]

It is presently accepted that the mechanism to explain lower myopia progression with corneal refractive therapy is the relative peripheral myopization optical effect resulting from flattening the central cornea and steepening the midperipheral cornea.[87–90] The effect of the treatment on foveal vision as a result of the higher order aberrations induced[91] may also have a therapeutic effect and is a worthwhile outcome to observe in future studies to evaluate if there is a synergistic effect between the manipulation of the peripheral refraction and the induction of bifocality/multifocality in the foveal region. The authors are aware of current developments in this field, but no current report is available in the peer-review literature so far.

The report of the effect of pupil size on treatment efficacy and the apparent role of the retinal area and location of the defocus raise issues for the role of the lens registration with regard to the center of the pupil or visual axis. Displacement of a multifocal CL or a corneal refractive therapy treatment induces on-axis coma while also shifting the peripheral defocus and generating an

asymmetric peripheral defocus circumferentially. Future studies might benefit from the inclusion of measurement of lens registration and evaluation of its impact on treatment efficacy.

Safety of Contact Lenses for Myopia Regulation

Refractive therapy in the form of CLs for the regulation of myopia is targeted to be prescribed for children and adolescents. Safety must be a primary goal. In the context of the present review, two different safety issues or risks are raised, as the two modalities of CL wearing raise their respective safety concerns. The first one is the safety of overnight wearing of corneal refractive therapy lenses, and the second is the safety of daily wearing of soft CLs with multifocal optics.

The safety of overnight corneal refractive therapy has been questioned, particularly after the cases of microbial keratitis presented mainly in Asian children in the early years of the past decade.[92] Most of these reports showed positive cultures for microorganisms that were potentially related to poor compliance. Indeed, the rate of reporting of adverse events in orthokeratology patients has decreased for the last 5 to 7 years, whereas the number of children fitted in this modality has increased as a consequence of the higher evidence of efficacy as a myopia regulation modality. Despite a significant part of contact lens–related corneal infections in children was related with corneal refractive therapy in a recent study in Hong Kong, those cases responded well to treatment and recovered without visual loss.[93] Recently, Bullimore et al. reported the rates of microbial keratitis in orthokeratology patients. A trend for higher indices of adverse events in children compared with adults was reported.[94] The reported risk was significantly lower than the numbers reported risk for overnight wear of soft CLs in extended or continuous modalities.[95] Overall, corneal refractive therapy is now considered an effective and safe alternative to correct and regulate myopia progression.[96]

Other less severe complications of overnight corneal refractive therapy are important to understand. Early work by Walline et al. in the context of the COOKI study showed that children wearing orthokeratology lenses for 6 months did not reported serious complications. The most frequent finding reported was central superficial punctate staining.[97] These findings have been confirmed by most of the subsequent longitudinal 2 to 5-year studies with orthokeratology presented in the next section. Santodomingo-Rubido et al.,[98] in the context of the Myopia Control with Orthokeratology in Spain study, reported the rate of adverse events and discontinuations in the orthokeratology clinical arm compared with the spectacles control arm. They reported 16 adverse events in children wearing orthokeratology, including 11 related with the CL (5 corneal erosions, 2 clinically significant corneal staining, 2 papillary conjunctivitis, 1 CL peripheral ulcer, and 1 dimple veiling). Most of the events occurred between the 6 and 12 months of treatment over the 2 years of the study, and none of them compromised visual function.

Studies were reviewed of daily wearing of soft CLs by children and adolescents. Jones-Jordan et al. in the context of the Adolescent and Child Health Initiative to Encourage Vision Empowerment (ACHIEVE) study reported that children are able to safely wear CLs.[99] Studies of the safety of daily disposable CLs are useful to estimate the risks.[66,100,101] Unfortunately, none of the studies reported, including soft CLs designed specifically for myopia regulation, had adequate statistical power for a safety analysis or provided information regarding the complications or adverse events.[61,66,80]

At present, there is no evidence that younger CL wearers are at a higher risk than adults for the occurrence of adverse events or even minor complications. Chalmers et al. have recently shown that age is a significant risk factor for infiltrative events in young CL wearers, this risk was the lowest for the age range from 8 to 15 years,[102] which is consistent with the age range for CL prescribing for myopia regulation as shown by the age profiles in the studies presented in this review.

CONCLUSIONS

Regulating myopia progression might provide substantial benefits in lowering the risks of several sight-threatening complications linked to moderate and high myopia. Contact lenses are convenient optical devices for the purpose of regulating myopia progression for several reasons: (1) they maintain near alignment with the optics of the eye, providing a more consistent effect than spectacle plane ophthalmic lenses; (2) they are well accepted esthetically, which is particularly important with children and teens; and (3) they have acceptable levels of safety[96,97] in terms of side effects.

Presently, different strategies are available that differ in their principle of action and also in their wearing modality. We are faced with the possibility and probability that the ethical/professional responsibility is to therapeutically intervene to regulate the rate of progression of the disease instead of following the traditional standard of prescribing a spectacle or CL refractive corrective.

From the clinical point of view, there are several conclusions that can be derived. First, CLs demonstrate greater efficacy over spectacles for eyes with higher myopia because of their inherent ability to reduce the peripheral hyperopic defocus induced by spectacle lenses.[83] Second, corneal refractive therapy (orthokeratology) is at present the modality with the largest volume of accumulated evidence relating to the efficacy to regulate myopia progression in children.[69,70,72,73] To date, the effect of treatment interruption and the presence or absence of subsequent myopia progression has not been adequately evaluated. Third, soft multifocal CLs are available and design refinements will become available to regulate myopia progression, and multifocal CLs have been reported to have promising preliminary results.[61,66] Long-term randomized controlled clinical trials with multifocal CLs with methods including pupil size measures, vitreous chamber depth increase, and peripheral refraction are needed. This could eventually elucidate the potential cumulative effect over time and the effect of treatment interruption.

In summary, CLs are ideal platforms for incorporating peripheral defocus, imposed foveal defocus, and specific aberration structures, independently or in combination with each other. The combination of several different utilities might potentially reinforce the effectiveness of the currently available approaches.

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