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Optical treatment strategies to slow myopia progression: Effects of the visual extent of the optical treatment zone

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ABSTRACT

In order to develop effective optical treatment strategies for myopia, it is important to understand how visual experience influences refractive development. Beginning with the discovery of the phenomenon of form deprivation myopia, research involving many animal species has demonstrated that refractive development is regulated by visual feedback. In particular, animal studies have shown that optically imposed myopic defocus slows axial elongation, that the effects of vision are dominated by local retinal mechanisms, and that peripheral vision can dominate central refractive development. In this review, the results obtained from clinical trials of traditional optical treatment strategies employed in efforts to slow myopia progression in children are interpreted in light of the results from animal studies and are compared to the emerging results from preliminary clinical studies of optical treatment strategies that manipulate the effective focus of the peripheral retina. Overall, the results suggest that imposed myopic defocus can slow myopia progression in children and that the effectiveness of an optical treatment strategy in reducing myopia progression is influenced by the extent of the visual field that is manipulated.

Myopia is a significant public health issue. In East Asia, where the prevalence of myopia has reached epidemic proportions (Lin et al., 1999; Saw et al., 1996), the ocular morbidity associated with the exaggerated axial growth that produces the most common forms of myopia is a leading cause of permanent vision disability (Liu et al., 2001; Saw et al., 2005). Unfortunately, the prevalence of myopia, and particularly high degrees of myopia, are continuing to increase in the urban areas of Asia (Lin et al., 2004) and recent evidence indicates that a similar trend is occurring in the USA (The Framingham Offspring Eye Study Group, 1996; Vitale et al., 2008) and other non-Asian countries (Bar Dayan et al., 2005; Rose et al., 2001).

Myopia usually manifests in childhood (most often between the ages of 7–10 years in the USA; Hirsch, 1952; Young et al., 1954) and the degree of myopia typically continues to increase in magnitude over a period of years (Goss and Winkler, 1983). Because the personal and societal burdens of myopia increase with the degree of myopia (Saw et al., 2005), treatment strategies that can eliminate or reduce the progression of myopia would have significant benefits. As a consequence, substantial effort has been devoted to developing treatment regimens that are effective in reducing myopia progression (for a recent review see Walline et al., 2011b).

To date, pharmaceutical strategies that employ muscarinic cholinergic receptor blockers have been the most effective treatment strategies for childhood myopia. Specifically, topically applied atropine, a powerful muscarinic antagonist, has been shown to reduce myopia progression in children by more than 70% over a two-year treatment period (Chua et al., 2006; Shih et al., 1999). It is clinically significant that these reductions in myopia progression were due to reduced axial elongation rates. Although atropine and other muscarinic agents (e.g., pirenzephine) can slow myopia progression, concerns about post-treatment rebound effects (Tong et al., 2009) and the short- (Chua et al., 2006; Shih et al., 1999) and long-term side effects (Smith et al., 1984) associated with prolonged treatment courses have discouraged the widespread use of these drugs. However, recent studies have shown that very low doses of atropine (e.g., 0.01% versus the more typical concentrations of 0.5% or 1.0%) can also produce meaningful reductions in myopia progression (Chia et al., 2011), which may mitigate some of these concerns.

Regardless, it would be advantageous to develop a variety of treatment options to reduce myopia progression, particularly optical strategies that can be readily incorporated into the spectacles

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and contact lenses that are normally employed in children to correct the optical consequences of myopia on distance vision. With respect to optical treatment strategies, three observations in laboratory animals provide a rationale for potential optical treatment strategies. First, animal studies have demonstrated that refractive development and axial growth are regulated by visual feedback associated with the eye's effective refractive status, in essence optical defocus. In particular, lens compensation experiments have shown that optically imposed myopic defocus can slow axial growth (Howlett and McFadden, 2009; Hung et al., 1995; Schaeffel et al., 1988; Siegwart and Norton, 2010; Smith and Hung, 1999; Whatham and Judge, 2001). Second, the dominant effects of vision on refractive development are mediated by local retinal mechanisms that operate in a regionally selective manner (Smith et al., 2009a; Smith et al., 2010; Wallman et al., 1987). As a consequence, visual signals in the periphery can influence ocular shape and axial length in a manner that is independent of central vision. The fact that it is possible to alter vitreous chamber elongation and refractive error in a localized manner also rules out many of the global mechanisms that have historically been hypothesized to influence myopia progression (e.g., the act of accommodation). And third, although it is logical to expect visual signals from the fovea to dominate visually guided refractive development (Stone and Flitcroft, 2004), peripheral vision and the peripheral retina can, probably as a result of areal summation effects (Wallman and Winawer, 2004), have a substantial influence on overall ocular growth and central refractive development (Liu and Wildsoet, 2011, 2012; Smith et al., 2009b; Smith et al., 2005). Although the manner in which signals are integrated across the retina, i.e., across local retinal mechanisms, is largely unknown, optical treatment strategies that take into account the periphery are more likely to be successful than those that ignore the optical state of the periphery.

Traditional optical treatment strategies, which have been designed to primarily manipulate central vision, have been shown to significantly alter ocular growth and refractive development in children. However, with most of these strategies the reductions in myopia progression have been modest and in one case the intervention actually appears to have increased myopia progression. In this review, the results for these traditional strategies are 1) interpreted in light of the results from animal studies and 2) compared to the results reported in recent, but largely preliminary studies that have investigated the efficacy of optical treatment regimens that manipulate retinal imagery over a relatively large proportion of the retina. The trend across studies suggests that imposed myopic defocus can slow myopia progression and that the effectiveness of an optical treatment strategy in reducing myopia progression is influenced by the extent of the visual field that is manipulated.

1. Undercorrection versus full-correction spectacles

The finding that optically imposed myopic defocus slows axial growth in animals suggests that myopia in children should be self-limiting. If the refractive error is left uncorrected, progression should not occur. Similarly, at first glance, the results from animal studies imply that undercorrecting myopic eyes, i.e., prescribing spectacles for distance vision that do not fully correct the manifest myopic refraction, should slow myopia progression. Interestingly, the two recent studies that have examined the effects of undercorrection versus full-correction spectacles report that undercorrection may actually increase myopia progression. Fig. 1 illustrates the relative myopia progression in subjects who wore full corrections versus individuals who were undercorrected by either 0.50 (Adler and Millodot, 2006) or 0.75 D (Chung et al., 2002). At the end of the first year of treatment, the 72 subjects in the undercorrected groups had, on average, progressed 0.17 D more than the 70 subjects in the full-correction groups. The Chung et al. study was halted at 2 years because myopia progression was significantly higher in the undercorrected subjects than in the control subjects (0.23 D) and the 30% higher progression rates were associated with faster axial elongations rates.

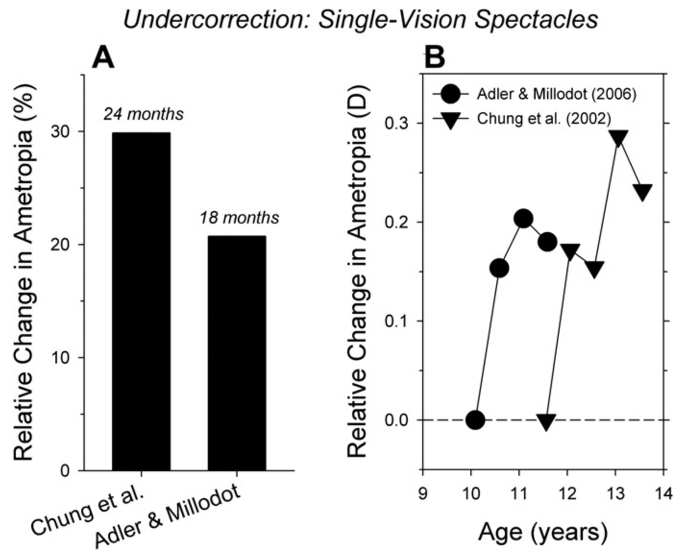

Fig. 1. A. Average relative changes in refractive error obtained at the end of the treatment period in undercorrected myopic subjects and control subjects prescribed traditional full myopic corrections (percentage: treated − control/control). Positive values indicate that the treated, undercorrected subjects exhibited larger myopic shifts than the controls subjects. B. Average differences in refractive error (diopters: control group − treated group) plotted as a function of time from the onset of treatment. The first symbol for each study reflects the average age of the subjects in the treated group. All of the subjects wore single vision lenses. The data were replotted from Adler and Millodot (2006) and Chung et al. (2002).

It has been argued that the pattern of results obtained with undercorrection strategies cast doubt on whether the results of animal studies can be applied to children (e.g., Adler and Millodot, 2006). However, it is important to recognize that the conditions created by undercorrecting myopic children are not necessarily the same as those produced by optically imposed myopic defocus in normal infant animals. When similar optical conditions are produced in children and animals, the effects of the visual manipulations on refractive development have been consistent. For example, conditions like form deprivation that eliminate meaningful visual feedback consistently result in unregulated/un-dampened axial growth and relative myopic shifts in refractive error in both children (Rabin et al., 1981) and animals (Smith et al., 1987; Wiesel and Raviola, 1977). More importantly, optically imposed defocus produces similar compensating alterations in the refractive errors of children and animals. For instance, monovision correction strategies that impose myopic anisometropia that is very consistent over time produce compensating anisometropic changes in children (Phillips, 2005) that are qualitatively similar to those produced by optically imposed anisometropia in monkeys (Smith and Hung, 1999). One reason that the similarities between humans and animals are more obvious with these anisometropic rearing regimens is that regardless of the viewing distance the imposed anisometropia is always present and the viewing conditions in animals and humans are very similar.

Why does undercorrection fail to slow myopia progression? It has been suggested that the vision-dependent mechanisms that regulate refractive development in myopic children may not be able to accurately detect the sign of defocus, i.e., the mechanisms that mediate emmetropization are not functioning properly (Chung et al., 2002). In this respect, it has recently been reported that in the periphery myopes exhibit asymmetric sensitivities to myopic and hyperopic defocus (Rosen et al., 2012). However, prior to the onset of myopia, the emmetropization process appears to operate normally in children who eventually develop myopia. With respect to the apparent discrepancy between the results from children and animals, there are several distinct differences between the optical consequences of undercorrecting myopic eyes and those produced by optically imposed myopic defocus in young animals. In infant monkeys, because refractive error is essentially constant across a very large part of the visual field (essentially the central 90°; Hung et al., 2008), positive lenses, particularly of the magnitude typically employed in animal experiments (Smith and Hung, 1999), impose myopic defocus across a large extent of the retina. On the other hand, the myopic eyes of children and adults often exhibit large amounts of relative hyperopia in the near periphery (Millodot and Lamont, 1974; Mutti et al., 2000). As a consequence, when myopic eyes are undercorrected by 0.50–0.75 D only a small part of the retina will experience myopic defocus and only during distance fixation. For fixation distances inside 1 m, it is likely that the foveal image will be in good focus and the eye will experience peripheral hyperopia. Even if the eye does not exhibit relative peripheral hyperopia, the low degree of optically imposed myopic defocus may not exceed the depth of field of vision-dependent mechanisms in the periphery, in essence restricting the effects of undercorrection to the fovea. It seems reasonable to propose that undercorrection fails to stop myopia progression because this strategy produces a small degree of myopic defocus over a small part of the retina and primarily only when the eye is fixating distant targets.

It is not known why there is a tendency for undercorrected eyes to progress faster than normal. As indicated above, undercorrected eyes will typically experience relative peripheral hyperopia. Although imposed peripheral hyperopia can produce central axial myopia in animals, it is not clear, as discussed below, if and to what extent that the amounts of relative peripheral hyperopia that are commonly found in myopic eyes contribute to myopia progression. However, the defocus produced by peripheral hyperopia is relatively constant over time, which increases the likelihood that its presence can promote myopia (Kee et al., 2007). It is possible that undercorrection alters the fixation and viewing behaviors of children. Perhaps to avoid blurred vision, undercorrected children spend more time viewing near objects, and/or possibly less time outdoors, which has been shown to be a risk factor for myopia onset (Jones et al., 2007; Rose et al., 2008). In other words, deliberately blurring distance vision may encourage children to engage in activities that promote myopia. Regardless, undercorrection is clearly not an effective treatment strategy for myopia progression in children. Moreover, the available data suggests that the refractive corrections of progressing myopes should be updated regularly to ensure that they are not undercorrected.

2. Multifocal spectacles versus single-vision spectacles

As documented in previous reviews, multifocal spectacles have for a variety of reasons been prescribed to children in efforts to reduce myopia progression (Cheng et al., 2010b; Grosvenor, 1998). However, most recent studies have been motivated by the observation that optically induced hyperopic defocus consistently produces axial myopia in animals, both young (Smith and Hung, 1999) and old (Zhong et al., 2004). Specifically, it has been hypothesized that children who consistently under-accommodate during near work activities experience hyperopic defocus and are at risk of developing myopia and/or of myopia progression. This idea is supported by observations that myopes typically exhibit larger accommodative lags than emmetropes (Gwiazda et al., 1993; McBrien and Millodot, 1986). However, it has not been resolved as to whether these elevated accommodative lags exist prior to the onset of myopia (Gwiazda et al., 2005; Mutti et al., 2006) or whether there is an association between the degree of accommodative lag and the rate of myopia progression (Allen and O'Leary, 2006; Rosenfield et al., 2002; Weizhong et al., 2008). Regardless, the results of recent clinical trials indicate that multifocal spectacles can reduce myopia by a small, but statistically significant amount.

Fig. 2 illustrates the relative reduction in myopia progression in myopic children produced by multifocal spectacles in comparison

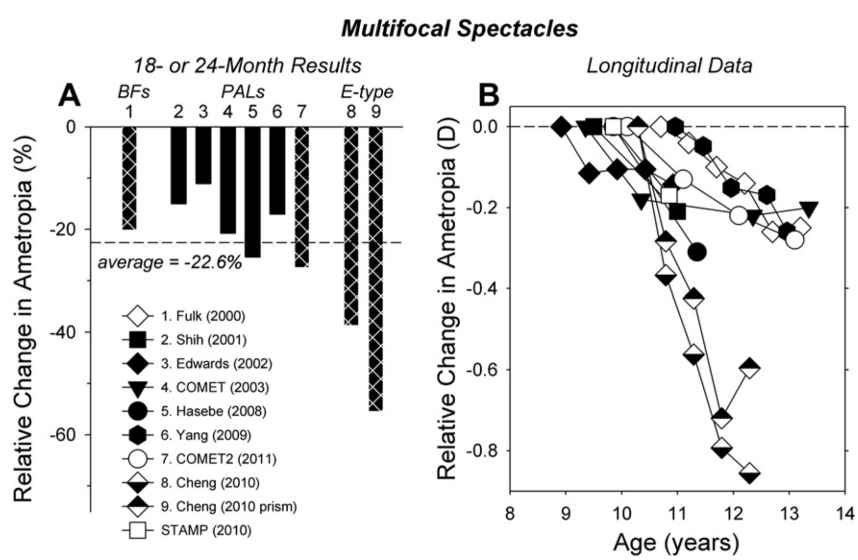

Fig. 2. A. Average relative changes in refractive error obtained over 18- or 24-month treatment periods in control subjects wearing single-vision spectacles and treated subjects wearing multifocal spectacle lenses (percentage: treated – control/control). Negative values indicate that myopia progression was lower in the treated subjects wearing the multifocal lenses. BFs = D-segment bifocals; PALs = progressive addition lenses; E-type = executive or franklin bifocals. B. Average differences in refractive error (diopters: control group – treated group) plotted as a function of time from the onset of treatment. The first symbol for each study reflects the average age of the subjects in the treated group. The cross-hatched bars in panel A and the open and half open symbols in panel B indicate studies that employed inclusion criteria related to the near heterophoria (studies 1 & 7), the magnitude of the accommodative lag at near (studies 7 & STAMP), or the rate of myopia progression prior to the onset of treatment (studies 8 & 9). The data were replotted from Berntsen et al. (2012b), Cheng et al. (2010a), Edwards et al. (2002), Fulk et al. (2000), Gwiazda et al. (2011), Gwiazda et al. (2003), Hasebe et al. (2008), Shih et al. (2001), and Yang et al. (2009).

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to single-vision lenses (SVLs). Panel A shows the reduction in progression obtained after either 18 or 24 months of treatment expressed as a percentage of the degree of progression observed in control subjects. The study results have been grouped according to the form of the multifocal lens (BFs = D-segment bifocals; PALs = progressive addition lenses; E-type = executive or franklin bifocals); the add powers were either +1.50 (studies 1, 3, 5, 6, 8, 9), +2.00 D (studies 4 & 7), or unspecified (study 2). The cross-hatched bars represent studies in which the subjects were selected because they manifest either esophoria (study 1) and/or a high lag of accommodation at near (study 7), or exhibited high myopia progression rates the year prior to the experimental intervention (studies 8 and 9). In aggregate, the results in Fig. 2A reflect data from an ethnically diverse subject population of 756 multifocal wearers and 726 control subjects who were corrected with SVLs.

Qualitatively, the results are very consistent between studies. Although the differences between multifocals and SVLs did not reach statistical significance in some studies (Edwards et al., 2002; Shih et al., 2001), every study reported that multifocal lenses reduced myopia progression. The magnitude of the treatment effect in most studies was, however, modest. The weighted average across all studies indicated that multifocals reduced the rate of myopia progression by −22.6% over an 18- to 24-month treatment period. Although it has been concluded that the overall results are not clinically significant, from a scientific perspective the results, particularly those from the larger studies (e.g., Gwiazda et al., 2003), provide strong evidence that the form of a correcting lens can influence the rate of myopia progression.

Several features of the data set are of interest. First, several studies restricted enrollment to subjects with esophoria at near (Fulk et al., 2000) and/or high accommodative lags (Berntsen et al., 2012b; Gwiazda et al., 2011). The rationale for the restrictive inclusion criteria was that children with esophoria would be good candidates for lenses with near adds because esophoric myopes show larger accommodative lags than non-esophores (Cheng et al., 2010b) and near adds would effectively reduce the near esophoria. Moreover, retrospective analyses of clinical data suggested that multifocal lenses have a more beneficial effect on myopia progression in esophoric children (e.g., Goss, 1986) and a subgroup analysis in the COMET study found that esophoric children with high lags exhibited stronger treatment effects (Gwiazda et al., 2004). However, as illustrated in Fig. 2A and B, the magnitude of the treatment effects in studies that specifically targeted children with esophoria (Fulk et al., 2000) and/or high accommodative lags (Berntsen et al., 2012b; Gwiazda et al., 2011) are not obviously different from those obtained in studies that did not employ these restricted inclusion criteria.

Fig. 2B shows relative progression rates (multifocal vs SVLs) plotted as a function of time from the onset of treatment (first symbol) for different studies. A second key feature found in several studies is that the beneficial treatment effects are not maintained beyond the early treatment period, i.e., the treatment effects plateau or saturate. For example, in the COMET (Gwiazda et al., 2003) and Edwards et al. (2002) studies, PALs produced a relative reduction in the rate of myopia progression over the first 6–12 months of lens wear with no further beneficial effects with longer treatment periods. On the other hand, in the studies by Fulk et al. (2000), the COMET2 group (Gwiazda et al., 2011), Yang et al. (2009) and Chen et al. (2010) the beneficial effects generally continued to accumulate as the treatment was continued beyond one year.

Third, there is a suggestion that the form of the treatment lens may influence the treatment effect. In particular, the results obtained using executive bifocals were larger than those obtained using conventional BFs or PALs. However, it should be noted that in the only study to employ executive bifocals, Chen et al. (2010) restricted their study to subjects who exhibited relatively fast myopia progression rates the year before the onset of the experimental trial. In this respect, Leung and Brown (1999), in an early pilot study of PALs found treatment effects similar in magnitude to those reported by Chen et al. (2010). As illustrated in Fig. 2A, there is also an indication that including base-in prism in the experimental lenses in order to reduce fusional vergence demands enhanced the beneficial effects of executive bifocals, at least as determined by changes in the spherical equivalent refractive error. However, when the treatment effects of executive bifocals were assessed using changes in axial length, the results obtained with executive bifocal with and without base-in prism were identical. Thus, the potential beneficial effects of base-in prism are not clear cut.

How do multifocal lenses influence refractive development? As stated above, the premise has been that multifocal lenses, by reducing the accommodative demand associated with near viewing tasks, would eliminate the lag of accommodation and the resultant hyperopic defocus at the fovea. In this respect, it is disappointing that none of these multifocal lens studies actually assessed the effects of the actual treatment lenses on the accommodative postures of their subjects. Although near adds are very effective in eliminating accommodative lags in adults (Jiang et al., 2007; Shapiro et al., 2005), in myopic children with high accommodative lags, near adds only appear to reduce the accommodative lag by about 25% of the add power (Berntsen et al., 2010a). In other words, myopic children tended to reduce their accommodative efforts when viewing through a near add and, as a consequence, near adds may not eliminate the lag of accommodation, particularly in children with high accommodative lags. This pattern of results casts doubt on the idea that the beneficial effects obtained with multifocals come about as a result of a small reduction in accommodative lag, particularly since the magnitude of the accommodative lag is not obviously related to the rate of myopia progression (Berntsen et al., 2012b).

The fact that optically imposed peripheral myopic defocus slows axial growth and produces relative hyperopic shifts in the refractive errors of animals provides the foundation for an alternative hypothesis (Guthrie et al., 2011; Liu and Wildsoet, 2011, 2012; Tepelus et al., 2012). Specifically, it has been proposed that the beneficial effects of multifocal lenses come about because when children are not doing near work, the near addition components of multifocal lenses produce myopic defocus in the peripheral retina (Berntsen et al., 2010b; Cheng et al., 2010b). In agreement with this idea, refractive error measurements obtained while subjects were wearing PALs show that relative to SVLs, PALs produced significant amounts of peripheral myopia in the superior retina and they reduced peripheral hyperopia along the horizontal meridian (Berntsen et al., 2010b). Moreover, the degree of peripheral myopic defocus measured in the superior retina was associated with slower myopia progression (Berntsen et al., 2012a). In other words, more myopic defocus in the peripheral retinal areas corresponding to the locations where PALs have their greatest relative positive power is negatively correlated with central myopia progression. This hypothesis also provides a potential explanation for the greater beneficial effects observed with executive-type bifocals. It is reasonable to propose that executive bifocals have a greater treatment effect on myopia progression, because the near segments of executive bifocals cover a larger part of the visual field than the near adds of traditional D-segment bifocals and PALs (Cheng et al., 2010b). In this respect, it would be interesting to know whether bifocals produce asymmetries in eye shape in young children similar to those produced by optically induced hemi-field defocus in animals (Diether and Schaeffel, 1997; Smith et al., 2010).

If the beneficial effects of multifocals are mediated by the peripheral retina, it is possible that the plateau effects observed with PALs in some studies come about because, as the children become more myopic, the eyes become more prolate, and the effective peripheral myopic defocus produced by PALs decreases below a critical threshold. Moreover, if the effects of multifocals are mediated primarily by the periphery, these beneficial effects would also be largely independent of the degree of accommodative lag and/or the near heterophoria, which is in general agreement with the results shown in Fig. 2. However, because multifocal lenses affect the accommodative and vergence demands at near, esophoric individuals and individuals with high lags may benefit more from wearing multifocals than other individuals because they are more comfortable viewing near targets through plus adds. A more beneficial treatment effect in this population could come about because lens wearing compliance is higher in this subgroup of individuals, i.e., esophores and individuals with large lags benefit from wearing multifocals in ways that other individuals do not and, therefore, they wear the multifocals more consistently.

3. Peripheral optical treatment strategies

3.1. Spectacles and contact lenses

The majority of optical treatment strategies for reducing myopia progression have been designed to influence the retinal image at the fovea. However, recent attempts to develop more effective optical treatment regimens have included optical designs/procedures that selectively influence the effective focus of the peripheral retina or impose optical effects over a very large part of the retina. These recent attempts have been motivated by observations in humans that suggest that the pattern of peripheral refractive errors may promote the development and/or progression of central myopia. For example, the pattern of peripheral refraction varies with the central refraction (Chen et al., 2010; Ehsaei et al., 2011; Millodot, 1981). Although there is substantial intersubject variability (Tabernero et al., 2011), on average, in individuals with axial myopia, the degree of myopia decreases with eccentricity in the horizontal meridian, i.e., the average myopic eye exhibits relative peripheral hyperopia. On the other hand, hyperopic eyes typically manifest relative peripheral myopia and emmetropic eyes tend to have relatively constant and near emmetropic refractive errors over the central 40–50° of the retina. Because hyperopic defocus is a recognized stimulus for axial growth and the presence of relative peripheral hyperopia has been observed prior to the onset of central myopia in both children (Mutti et al., 2007) and adults (Hoogerheide et al., 1971), it has been argued that peripheral hyperopia may play a causal role in the genesis of axial myopia.

The relationship between peripheral hyperopia and central myopia in humans is, however, complex. For example, the pattern of peripheral refraction in myopic eyes often varies from relative peripheral hyperopia in the horizontal meridian to relative peripheral myopia in the vertical meridian (Atchison et al., 2006). Although peripheral hyperopia has been reported to be present prior to the onset of axial myopia (Hoogerheide et al., 1971; Mutti et al., 2007) and although a more prolate ocular shape, the primary cause of relative peripheral hyperopia, has been correlated with subsequent central myopic shifts (Schmid, 2011), a number of studies have failed to show that peripheral hyperopia, at least along the horizontal meridian, is a risk factor for the development or progression of axial myopia (Mutti et al., 2011; Sng et al., 2011). However, the relationship between the degree of hyperopia and the rate of myopia progression may be non-linear. Vision-dependent eye growth may reflect a threshold-dependent all-or-none response (Tran et al., 2005). In which case, large individual differences in the susceptibility to myopiagenic conditions and large variations in inherent ocular growth rates similar to those observed in animals may mask the relationship between the degree of peripheral hyperopia and myopia progression (Smith, 2011). Even some of the strongest human data supporting a causal relationship is not clear cut. For example, the study by Hoogerheide et al. (1971) of the pattern of peripheral refractions in young adults undergoing intense pilot training is often cited as evidence for a role for peripheral hyperopia in the genesis of myopia. Specifically, they reported that young adults with relative peripheral hyperopia were more likely to develop axial myopia during pilot training than individuals with relative peripheral myopia. However, given that the subjects in the Hoogerheide et al. study were adults, it is likely that the observed relative peripheral hyperopia in the at-risk group was present for a long time before the onset of myopia and that the refractive errors in these adult subjects were stable prior to starting pilot training, i.e., by itself the peripheral hyperopia was not sufficient to produce myopia. Instead, the results suggest that there was something associated with the onset of pilot training that, in combination with the existing peripheral hyperopia, increased the risk for the development of central myopia.

Studies of form deprivation myopia in monkeys provide the clearest evidence that the association between peripheral hyperopia and central myopia is not always causal in nature. During the development of form-deprivation myopia, the eyes of infant monkeys become more prolate in shape and develop relative peripheral hyperopia (Huang et al., 2009). Because the strong diffuser lenses employed in this study virtually eliminated sign of defocus information, the presence of peripheral hyperopia could not have influenced refractive development. Therefore, these results indicate that in some cases relative peripheral hyperopia is a consequence of axial myopia, not a cause. On the other hand, animals experiments also clearly show that optically imposed peripheral hyperopia can cause central axial myopia (Liu and Wildsoet, 2011; Smith et al., 2009b). More importantly, optically imposed peripheral myopia can reduce axial growth and produce central hyperopia (Guthrie et al., 2011; Liu and Wildsoet, 2012; Tepelus et al., 2012). These results imply that treatment regimens that take into account peripheral image quality are more likely to be successful than those that do not. In this respect, a comparison of the results in Figs. 2 and 3 suggests that treatment regimens that effectively reduced the degree of peripheral hyperopia and/or produced relatively peripheral myopia across a large part of the retina are generally more effective than traditional multifocal spectacles in reducing myopia progression.

Fig. 3 illustrates the relative myopic progression obtained from recent studies employing spectacles and contact lenses that, as a consequence of their optical design, imposed relative myopic defocus over a large part of the retina. It is important to note that overall the results shown in Fig. 3 are preliminary in nature. In some cases, these studies employed small subject numbers (e.g., $n = 27$; study 5) or restricted inclusion criteria (e.g., esophoria at near, study 7). In other cases, the data represent a sub-group analysis from a larger study (e.g., younger subjects with at least one myopic parent, study 2), or the data are available only in abstract form (studies 5–7). And only two studies had treatment durations that exceeded 1 year (e.g., studies 5 & 6). Nevertheless, the available results are promising.

The smallest reductions in myopia progression were obtained with spectacles lenses. Sankaridurg et al. (2010) examined the effects of three different experimental spectacle designs. In each case, the effective power of the lenses became less negative/more positive with distance from the optical center. Two of the lenses

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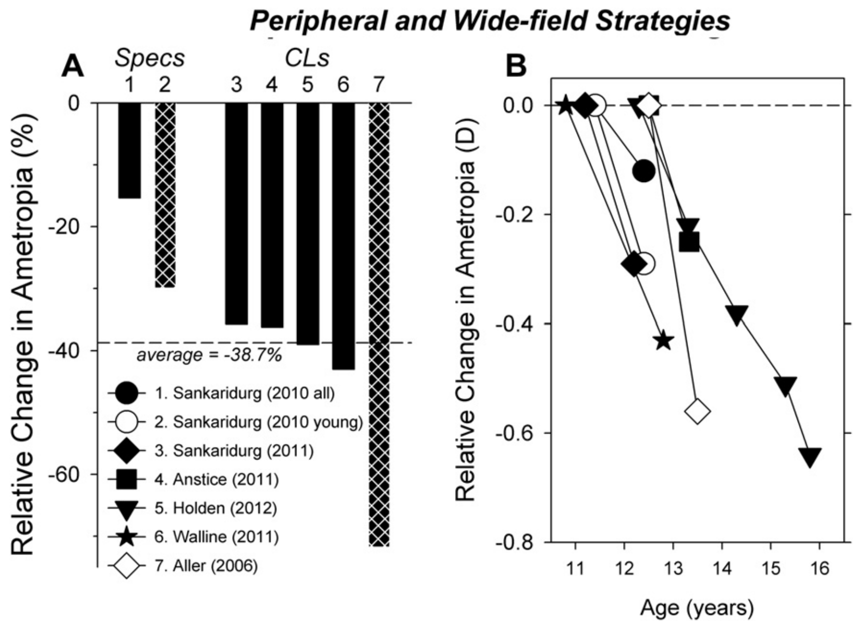

Fig. 3. A. Average relative changes in refractive error obtained at the end of the treatment period in control subjects (wearing either single-vision spectacles or single-vision soft contact lenses) and treated subjects wearing treatment lenses that induced relative myopic defocus selectively in the periphery or over a large part of the central and peripheral retina (percentage: treated − control/control). Negative values indicate that myopia progression was lower in the treated subjects wearing the peripheral and wide-field treatment lenses. Specs = spectacle lenses; CLs = contact lenses. B. Average differences in refractive error (diopters: control group − treated group) plotted as a function of time from the onset of treatment. The first symbol for each study reflects the average age of the subjects in the treated group. The cross-hatched bars in panel A and the open and half open symbols in panel B indicate studies that employed inclusion criteria related to the near heterophoria (study 7) or subject age and parental myopia status (study 2). The data were replotted from Aller et al. (2006), Anstice and Phillips (2011), Holden et al. (2012), Sankaridurg et al. (2010), Sankaridurg et al. (2011), and Walline et al. (2011a). Note that the results from Sankaridurg et al. (2010) refer only to the type III spectacle lenses.

had rotationally symmetric power profiles and had central zones for distance vision that were 20 (type I) or 14 mm in diameter (type II); the relative positive powers of these lenses ramped up from the distance segment to reach maximum relative peripheral powers of +1.0 D (type I) and +2.0 D (type II) 25 mm from the optical center. For a typical subject, these lenses created a distance viewing segment that encompassed the central 50°–60° of the visual field. The type I lens had no measurable effects on the pattern of peripheral refractions within the central 80° of the field of view. The type II lenses produced modest reductions in the degree of relative peripheral hyperopia at 30° and 40° eccentricities. Neither the type I nor the type II lenses produced significant amounts of relative peripheral myopia and neither lens altered the rate of myopia progression (data not shown in Fig. 3). The third treatment lens had an asymmetric profile that had a central distance vision segment that extended 10 mm from the optical center in the nasal, temporal and inferior directions. In the superior segment the positive power ramp began only 5 mm from the lens center (i.e., the central distance zone was elongated in the horizontal meridian); in all segments the power ramped up to a maximum relative positive power of +1.9 D at an eccentricity of 25 mm. The type III did not alter the measured pattern of peripheral refractions in the horizontal meridian. Although the peripheral refractive errors were not measured in the vertical meridian, it is likely that the type III lenses produced relative myopic shifts in the inferior field. As illustrated in Fig. 3, the type III lenses (study 1) reduced the rate of myopia progression by −15.4% in comparison to standard SVLs. Although this difference was not statistically significant, when the analysis was restricted to younger subjects with at least one myopic parent, the type III lens produced a significant reduction in progression in this relatively fast progressing subgroup (−29.9%; Fig. 3, study 2).

Incorporating peripheral treatment designs into spectacle lenses is difficult for a number of reasons (e.g., the required power profiles can produce substantial variations in spectacle magnification across the plane of the lens), many of which can be minimized with contact lenses. In particular, moving the principal planes of the correcting lens closer to the eye's principal plane and having a lens that moves with the eye are distinct advantages. Specifically, it is possible to incorporate more aggressive optical treatment profiles into contact lenses (e.g., more relative positive power in the near periphery) and as the preliminary results illustrated in Fig. 3 show, contact lenses can produce larger reductions in myopia progression than most multifocal spectacle lenses. The contact lens designs employed in the studies included in Fig. 3 were either commercially available bifocals (e.g. studies 6 & 7; typically +2.0 D adds), similarly designed "dual-focus" lenses that also imposed simultaneous myopic defocus over the fovea and a large part of the periphery (study 4; +2.0 D treatment zones), or lenses specifically designed to reduce relative peripheral hyperopia while maintaining uncompromised foveal vision (studies 3 & 5; maximum peripheral powers = +1.5 or +2.0 D). Measurements obtained during lens wear showed that the contact lenses specifically designed to reduce peripheral hyperopia were able to impose relative peripheral myopia over much of the nasal field and to reduce the degree of peripheral hyperopia in the temporal field (Sankaridurg et al., 2011). An interesting and potentially key factor in the success of the simultaneous bifocal designs (i.e., in essence dual focus lenses) is that children appear to accommodate normally for near objects; they do not appear to use the relative positive powered portions of these treatment lenses as near adds (Anstice and Phillips, 2011). As a consequence, these treatment-lens designs simultaneously imposed absolute myopic defocus over much of the peripheral retina for both distance and near viewing distance. For moderately myopic eyes, these lenses would probably produce absolute myopic defocus from the fovea out to eccentricities of about 30°–40°.

As illustrated in Fig. 3A, the experimental contact lenses reduced myopia progression relative to either traditional single-vision

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spectacles (study 3) or single-vision contact lenses (studies 4–7) by an average of −38.7%, with the study that restricted enrollment to esophoric subjects reporting the largest treatment effects (study 7). In each case, the reductions in myopia progression were associated with slower axial elongation rates. Little has been reported about the time course of the beneficial effects of these experimental contact lenses strategies. Holden et al. (2012) reported findings from multiple observations over a 43-month treatment period (filled triangles, Fig. 3B), which showed an accumulation of the beneficial effects over time. Although this study showed that there were no indications that the treatment effects plateaued after the first year, data are available for a relatively small number of subjects at the 36- (27 of 40) and 43-month measurement points (20 of 40).

3.2. Orthokeratology (Corneal Reshaping Therapy)

Orthokeratology (OK) or Corneal Reshaping Therapy (CRT) is a correction strategy that employs specially designed contact lenses to alter the shape of the cornea in order to temporarily compensate for an eye's refractive error. Typically, to correct myopia the OK lenses are worn overnight on a regular basis and are designed to flatten the central cornea. Upon removing the OK lenses in the morning, the resulting central corneal flattening reduces corneal power and, thus, reduces the degree of manifest myopia allowing good daytime vision without correcting lenses. With the recent development of new oxygen permeable lens materials and new lens designs that produce consistent and predictable changes in manifest refractive error, the use of OK is increasing, particularly in Asia (Swarbrick, 2006).

The interest in OK as a possible treatment strategy for myopia was stimulated primarily by anecdotal reports that suggested that OK strategies reduced myopia progression (Cheung et al., 2004; Reim et al., 2003). The results of subsequent studies on the efficacy of OK in reducing myopia progression are summarized in Fig. 4. Because the direct effects of OK can mask progressive myopic changes in refractive error, the treatment efficacy of OK is quantified by the relative differences in axial elongation between the control and experimental subjects. The earlier studies included historic (Cho et al., 2005; Walline et al., 2009) or self-selected control groups (Hiraoka et al., 2012; Kakita et al., 2011; Santodomingo-Rubido et al., 2012), which were treated with either single-vision spectacles or single-vision soft contact lenses. Only the most recent study, the ROMIO study (Cho and Cheung, 2012), included subject randomization. However, the results are relatively consistent across studies. All studies have reported that OK reduces myopia progression over a two-year treatment period by amounts ranging from 33% to 56% relative to controls; the weighted average reduction in axial elongation for the aggregate of 181 experimental and 189 control subjects included in Fig. 4 was −41.7%.

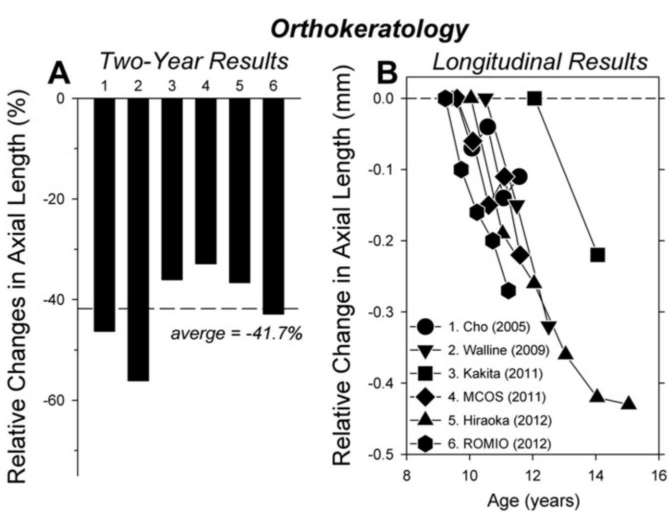

Fig. 4. Average relative changes in axial length obtained at the end of a two-year treatment period in control subjects (treated with either single vision spectacles or contact lenses) and treated subjects undergoing overnight orthokeratology to correct central myopia (percentage: treated − control/control). Negative values indicate that axial elongation was smaller in the treated subjects undergoing orthokeratology. B Average differences in axial length (mm: treated group − control group) plotted as a function of time from the onset of treatment. The first symbol for each study reflects the average age of the subjects in the treated group. The data were replotted from Cho and Cheung (2012), Cho et al. (2005), Hiraoka et al. (2012), Kakita et al. (2011), Santodomingo-Rubido et al. (2012), and Walline et al. (2009).

As illustrated in Fig. 4B, there were no indications that the beneficial effects of OK decreased over a two-year treatment period. In the longest study to date, OK produced significant reductions in relative axial elongation in each of the first three years (Hiraoka et al., 2012). OK continued to have small beneficial effects in the fourth and fifth years of the study, but these differences in the axial elongation rates between the experimental and control subjects were not significant. In part, the smaller treatment effects in the fourth and fifth years can probably be attributed to the normal age-related reduction in axial growth in the control and experimental groups, which included individuals who could have been as old as 17 years of age at the end of the 5-year treatment period.

Detailed studies of the corneal changes that take place during OK and their optical consequences suggest a possible mechanism for the beneficial effects of OK against myopia progression. The primary effect of the reverse geometry lenses currently employed to treat myopia is to alter the thickness of the corneal epithelium. These myopic OK lenses are fitted with a base curve that is flatter than the central cornea and steeper than normal peripheral curves that together produce a decrease in the thickness of the central epithelium layers (~10–15 μm) combined with an increase in epithelial layer thickness in a more peripheral annular zone (Alharbi and Swarbrick, 2003; Choo et al., 2008; Lu et al., 2008). The optical consequences of these lens-induced thickness changes are a reduction in refracting power in the central cornea and an increase in refracting power above baseline between 2 and 3 mm from the center of the treatment zone (Queirós et al., 2010b). The eccentricity dependent changes in corneal power have dramatic effects on the central manifest refraction and the pattern of peripheral refractive errors. In addition to correcting the manifest axial refractive error over about the central ±10° of the visual field, OK reverses the pattern of peripheral refraction, specifically converting the relative peripheral hyperopia typically observed in myopic eyes to relative peripheral myopia (Charman et al., 2006; Kang and Swarbrick, 2011; Queirós et al., 2010a). At eccentricities of about 30°–35°, the degree of relative peripheral myopia is directly proportional to the central manifest refraction at baseline, i.e., the degree of relative peripheral myopia increases with the magnitude of central myopia that is corrected by OK (Queirós et al., 2010a). Given that animal experiments show that relative peripheral myopia reduces axial growth and produces relative hyperopic shifts in central refractive error (Guthrie et al., 2011; Liu and Wildsoet, 2011, 2012; Tepelus et al., 2012), it seems reasonable to argue that the beneficial effects of OK on myopia progression come about as a consequence of the peripheral optical changes associated with the alterations in corneal shape (Charman et al., 2006; Kang and Swarbrick, 2011).

As with contact lenses, OK benefits from the fact that the optical correction is relatively close to the eye's principal planes. In addition, the optical correction is absolutely fixed on the cornea so that even blinks and eye movements that can produce translational

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shifts in the position of a contact lens do not affect the OK-induced optical changes. OK does produce significant increases in optical aberrations in the periphery (Mathur and Atchison, 2009). However, probably because the visual system adapts very rapidly to visual effects that are constant over time, the peripheral optical consequences of OK on a patient's vision are minimized under ordinary viewing conditions. With respect to slowing myopia progression, the most important advantage of OK over either spectacles or contact lenses is that OK can induce very large optical treatment effects in moderate to high myopes (i.e., myopia between about −3 and −6 D). Whereas it is difficult to incorporate high amounts of relative positive power in the periphery (e.g., >+3.0 D) or over larger areas of the retina with traditional correction modalities, the degree of relative peripheral myopia induced by OK increases with the magnitude of the central correction that is attempted. This is potentially important because the degree of relative peripheral hyperopia generally increases with the degree of central myopia, at least in low and moderate myopes (Atchison et al., 2006). Thus, if the goal of a treatment strategy is to induce peripheral myopia, OK may be more effective in achieving that goal in moderate to high myopes than currently available spectacles or contact lenses.

In Fig. 5, the change in axial length (or vitreous chamber) obtained over a two-year OK treatment period is plotted as a function of the baseline refractive error for individual eyes from 3 studies. The open and filled symbols represent treated and control subjects, respectively. For the control eyes, there was no correlation between the baseline refractive error and the amount of axial elongation ($p = 0.94$). On the other hand, in the OK subjects, axial elongation was positively correlated with the baseline refractive error ($p = 0.0004$) suggesting that OK was more effective in reducing myopia progression in individuals with higher amounts of myopia. These results are in agreement with the idea that effectiveness of OK increases with the degree of induced peripheral myopia. Although this relationship could have been influenced by other factors, like age, simple inspection of the data indicates that relative to control subjects OK was effective in reducing myopia progression in individuals with moderate to high degrees of myopia.

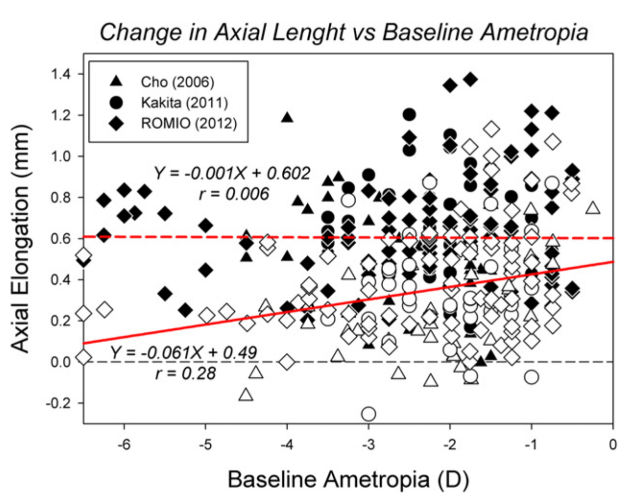

Fig. 5. Relative changes in axial length obtained over a two-year treatment period for individual control (filled symbols; single-vision spectacles) and treated eyes (open symbols; overnight orthokeratology for to correct central myopia) plotted as a function of the baseline ametropia. The dashed and solid red lines represent the regression functions for the control and treated subjects, respectively. The data were replotted from Cho and Cheung (2012), Cho et al. (2005), and Kakita et al. (2011). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Speculations and the need for future studies

The results summarized above and in previous reviews (Cheng et al., 2010b; Walline et al., 2011b) prove that various optical correction strategies can alter eye growth in children and, specifically, that it is possible to slow the progression of myopia relative to traditional correcting lenses. In particular, the available data from multifocal spectacle lens studies are robust and include the results from large, well-executed studies, the COMET study probably being the most noteworthy (Gwiazda et al., 2003). The studies of correction strategies that employed peripheral treatment effects, which have all been concluded recently, were limited in many cases by relatively small subject numbers and relatively short treatment periods. Nevertheless, the emerging results from these studies of peripheral optical treatment strategies are consistent and encouraging. Moreover, the most recent studies include many of the design features necessary to provide data the can support clinical practice (e.g., Cho and Cheung, 2012).

The key questions are which optical correction strategies are most efficacious and how effective will these strategies be in slowing myopia progression. Comparisons of the results between multifocal spectacle lens studies and between contact lens and spectacle lens trials suggest that treatment strategies that involve large areas of the retina will be more successful than those that do not. For example, executive bifocals, which produce relative myopic defocus over essentially half the visual field (Cheng et al., 2010a), appear to produce larger reductions in the rate of myopia progression than PALs (Gwiazda et al., 2003), which only produce significant degrees of myopic defocus in a limited part of the superior retina (Berntsen et al., 2012a). With respect to specifically designed peripheral treatment strategies, contact lenses (Sankaridurg et al., 2011) appear to produce a greater reduction in myopia progression than spectacle lenses (Sankaridurg et al., 2010), probably because the optical treatment zones of the contact lenses affected a larger part of the visual field than the peripheral treatment zones of the experimental spectacle lenses (see Fig. 3). In this respect, the relatively large and consistent reductions in myopia progression reported in investigations of orthokeratology may reflect the large portion of the near peripheral visual field affected by OK and perhaps the high degrees of relative myopic defocus that can be induced by OK. It is clear that more rigorous studies of these relatively new peripheral correction strategies need to be conducted. However, it is also clear that the available data strongly motivate these studies.

The emerging results from investigations of optical strategies that affect a relatively large part of the visual field suggest that current lens designs can reduce myopia progression by about 40%. This level of myopia control would be clinically significant if reductions of this magnitude can be maintained throughout the period of time when myopia is normally progressing. In particular, the number of individuals with very high degrees of myopia, i.e., individuals most at risk for the blinding conditions associated with myopia, would be significantly reduced. It is reasonable to expect that higher overall degrees of control are possible because aspects of the lens designs and the overall management strategies that have been investigated can be improved. For example, the contact lenses investigated by Sankaridurg et al. (2011) only produced relative myopic defocus in the nasal visual field, presumably because the lens was decentered from the visual axis. Designing a contact lens that produced myopic defocus in both the nasal and temporal visual fields is possible and could improve the efficacy of this general lens design. In almost every study of spectacles and contact lenses to date, only a single treatment-zone power has been investigated. In this respect, it will be important to determine whether the magnitude of imposed myopic defocus is a key factor. It seems likely that as we learn more about the exact nature of visual signals that slow axial

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growth, the power profiles of treatment lenses can be improved. It may also be that a combination of treatment strategies will be most effective. For instance, in low degrees of myopia, the optical treatment effects of OK are relatively small. It may be that the best overall strategy would be to employ spectacle or contact lenses that employ peripheral treatment strategies at the onset of myopia because it is possible to produce 2–3 D of myopic defocus over a large part of the visual field. However, as the degree of myopia increases, OK becomes a more attractive option because the degree of myopic defocus induced in the periphery increases with the degree of central correction, i.e., in high myopes it is possible to impose higher amounts of myopic defocus in the treatment zones than is now feasible with traditional spectacles and contact lenses.

4.1. What part of the visual field should optical treatment strategies target?

The results from foveal ablation studies in animal experiments demonstrate that visual signals from the fovea are not essential for many aspects of vision-dependent ocular growth. Moreover, the fact that the myopic changes produced by form deprivation or lens-induced hyperopic defocus in intact retinas are similar to those observed in eyes with ablated foveas indicates that the overall contribution of the fovea to vision-dependent growth is minimal (for a review see Smith, 2011). The fact that the treatment effects obtained in the studies of contact lenses that employ peripheral treatment strategies are similar to those obtained in studies that employed contact lens designs that result in simultaneous myopic defocus in the fovea and near periphery also supports the idea that the overall contribution of the fovea is small. Similarly, the failure of undercorrection strategies, which as discussed above primarily affect foveal vision, demonstrates that treating the fovea alone is not sufficient. Because the contribution from the fovea is small and peripheral visual signals can dominate central refractive development (Liu and Wildsoet, 2011, 2012; Smith et al., 2009b, 2005), peripheral treatment strategies have the advantage of providing an effective signal to control central refractive development without compromising central vision. Moreover, peripheral treatment strategies, by eliminating the normally high degrees of peripheral hyperopia, may improve peripheral vision (Holden et al., 2011). Simultaneous bifocals or dual focus contact lenses, by the nature of their design, negatively impact foveal vision; their therapeutic benefit on myopia progression probably reflects the fact that these lenses produce peripheral myopic defocus.

It is unlikely that the periphery or any isolated part of the retina provides a unique cue to guide central refractive development. Instead, it seems reasonable to assume that central refractive development reflects the integration of signals from the fovea and the periphery with the near periphery contributing a stronger or more effective visual signal than the more peripheral parts of the retina. In other words, the relative weight of signals from a given local area of the retina to overall central refractive development probably decreases with eccentricity with these eccentricity-dependent effects being somewhat counterbalanced by areal summation effects that can increase with eccentricity (Wallman and Winawer, 2004). Knowledge of these relative weighting functions and whether there are regional differences in the weighting functions (e.g., are there difference between the horizontal and vertical retinal meridians) is critical for the development of the optimal peripheral or wide-field treatment strategy.

4.2. What is the optimal optical signal to slow ocular growth?

There are suggestions that inducing relative myopic defocus is beneficial. For example, the beneficial effects of PALs are significantly correlated with the degree of imposed myopic defocus in the superior retina (Berntsen et al., 2012a). Multifocal contact lenses that produced myopic defocus over a large part of the peripheral retina (e.g., Aller et al., 2006; Anstice and Phillips, 2011; Walline et al., 2011a) appear to produce larger reductions in myopia progression than PALs (e.g., Edwards et al., 2002; Gwiazda et al., 2011, 2003; Hasebe et al., 2008). The beneficial effects of contact lenses that are designed to reduce peripheral hyperopia are greater than those for spectacles with similar design goals, probably reflecting the fact that the experimental spectacles lenses produced only minimal reductions in relative peripheral hyperopia in the horizontal meridian (Sankaridurg et al., 2010), whereas the experimental contact lenses produced peripheral myopia in the nasal visual field (Sankaridurg et al., 2011). Thus, in agreement with the results from a large body of animal research, optically imposed myopic defocus appears to provide a strong signal for slowing growth.

However, in the periphery the through-focus point spread function is complex. The degree of radial astigmatism is often larger than the optical errors associated with the spherical-equivalent refractive error. Moreover, both convergent and divergent light are associated with both the tangential and sagittal image planes, at least in one meridian. This is important because when relatively high amounts of astigmatism are optically imposed on young monkeys, central refractive development appears to target the resulting line foci and not the circle of least confusion, i.e., not the spherical-equivalent refractive error (Kee et al., 2004). In this respect, the potential role of optical aberrations above the defocus term has largely been ignored in the periphery. Identifying the position within the through-focus point spread function that serves as the effective target of the emmetropization process is important. It has recently been reported that myopes exhibit differential sensitivity to myopic and hyperopic defocus in the periphery, which appears to be associated with specific combinations of high-order aberrations in the periphery (Rosen et al., 2012). It is not known if these sensitivity asymmetries are a cause or consequence of myopia progression, but the consequence of higher order aberrations in the periphery on the target for emmetropization are clearly worth investigating.

4.3. Do the beneficial effects of optical treatment strategies decrease with time?

The early investigations involving PALs reported that the beneficial effects of this optical correction strategy did not continue to accumulate after the first year of treatment (Edwards et al., 2002; Gwiazda et al., 2003). It is not clear why the treatment effects in these studies plateaued early in the treatment period. Studies of restricted subject populations involving other multifocal spectacle designs have observed beneficial therapeutic effects in the second year of treatment (Cheng et al., 2010a; Fulk et al., 2000) and subsequent PAL studies have reported continued accumulation of treatment effects in the second year of treatment (Gwiazda et al., 2011; Yang et al., 2009). In the only long-term investigation of contact lenses that employed a peripheral treatment strategy, the treatment effects continued to accumulate for over three years (Holden et al., 2012). Similarly, the beneficial effects of OK have been shown to continue through the second (Cho and Cheung, 2012; Cho et al., 2005; Kakita et al., 2011; Santodomingo-Rubido et al., 2012; Walline et al., 2009) and third years of treatment (Hiraoka et al., 2012). In the only OK study that reported data beyond 3 years of treatment, the accumulated beneficial effects were increasing at a slower rate in the fourth and fifth years of treatment, but the later treatment effects were not statistically significant. As pointed out above, the plateau effect observed in this

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last study may have been affected by the age-related slowing of myopia progression in the control group. Overall, it appears that the beneficial effects of optical treatment strategies are not limited to the first year of treatment. Moreover, preliminary results indicate that there is not a rebound effect once optical treatment strategies are discontinued (Fulk et al., 2002; Lee and Cho, 2010; Marsh-Tootle et al., 2009).

5. Conclusions

The novel lens designs and optical treatment strategies that have been studied and that are currently under investigation promise to produce not only statistically significant reductions in myopia progression, but also clinically significant reductions in the progression of myopia. Given that the investigations to date have largely ignored potentially important differences between subjects and have made little or no attempts to optimize optical treatment strategies for a given individual, it seems likely that beneficial effects can be increased. However, at the present time we still have much to learn about potentially significant lens design characteristics. Likewise, the impact of basic patient variables on the efficacy of optical treatment strategies is largely unknown. To optimize any optical treatment strategy the influence of key factors like age of onset of myopia and the age and degree of myopia at treatment onset need to be delineated. Moreover, to more fully appreciate the risk-benefit relationship of any optical treatment strategy, it would be highly desirable to be able to confidently predict who is at risk for developing high versus low degrees of myopia. Regardless, the emerging data from recent studies show that optical strategies that take into account the peripheral retina and influence imagery over a large part of the retina appear to produce larger reductions in myopia progression than those that do not.

Conflict of interest

The Author is a co-author on patents for lens designs to reduce myopia progression that involve manipulating peripheral refractive errors.

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