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CURRENT STRATEGIES IN ADDRESSING MYOPIA

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Abstract

Myopia is a current worldwide problem, due to a marked increase in its prevalence, all the more important in the age of monitors and working predominantly indoors. This impacts in particular on visual acuity and thus on quality of life, individual performance, with consequences for the labour market and economic implications for public health services. Consequently, much research is focused on modifying the factors that determine the onset and especially the progression of myopia, using various methods, such as the use of anticholinergic agents, the use of progressive lenses (aerial or contact), orthokeratology, refractive surgery techniques, each of which has varying degrees of effectiveness.

The aim of this paper is to highlight the association between myopia progression and environmental and occupational factors, and to review currently available strategies for reducing myopia progression.

Keywords: myopia, environmental factors, axial elongation, atropine, orthokeratology, progressive contact lenses.

Myopia can be considered a public health problem due to its high incidence and disabling potential, with approximately 1/5 of low vision worldwide due to this refractive error. It is estimated that in 2020, 30% of the world's population was affected by this refractive error and this percentage is estimated to increase to 50% by 2050 [1].

Myopia is the most common refractive error, and is caused by an increase in the axial length of the eyeball, so that the image of a distant object will form anterior to the retinal plane and be perceived as blurred. IMI (International Myopia Institute) proposes standardised definitions, terminology and criteria for myopia. Thus, the threshold value for myopia is considered to be that spherical equivalent value exceeding -0.5 dioptres, high myopia has a spherical equivalent value above -6 dioptres, and pathological myopia is a term defining the occurrence of structural complications associated with refractive error. [2].

Uncorrected myopia causes a considerable loss of vision, impairs quality of life, school performance, and work ability. But even when corrected, myopia can be accompanied by complications such as posterior scleral staphyloma, glaucoma, early cataract, retinal breaks, retinal detachment, choroidal neovascularisation, the risk of which is proportional to the dioptric value of the ametropia; this

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justifies the concern for limiting the progression and treatment of myopia. [3].

In order to halt the deterioration of visual acuity, the use of anticholinergic substances, the correction of refractive errors, the use of multifocal air lenses or contact lenses, orthokeratology as well as the practice of refractive surgery have been studied. The increased interest in understanding the mechanisms of myopia onset and progression stems from the desire to stop or at least slow its progression by using new strategies or therapies. It is important to evaluate the general condition of the patient with myopia, as well as the living and working conditions[4-20].

Myopia can be a refractive error in its own right (non-syndromic myopia) or can be found in more complex syndromes such as Marfan syndrome or congenital stationary night blindness (syndromic myopia).

The increase in overall prevalence is linked to both genetic factors, which play a determining role, and environmental and behavioural factors, which are increasingly influential [3]. In support of the inherited myopia theory, numerous studies find a higher risk of developing myopia for children with myopic parents. The Northern Ireland Childhood Errors of Refraction (NICER) study shows that a child's risk of myopia increases 2.91-fold and 7.79-fold respectively when they have one or both myopic parents [4]. In another study, conducted in Australia, the authors report a risk of developing childhood myopia of 7.6%, 14.9% or 43.6% when neither, one or both parents are myopic [5]. CREAM (The Consortium for Refractive Error and Myopia) conducted the largest international meta-analysis of eyeball axial length in myopia, which included over 14,000 Caucasians and over 8000 Asians in 18 cohorts in Europe, Australia and Asia. The studies measured axial length by both laser interferometry and A-mode ultrasonic biometry, refraction was measured objectively with automated refractometers and verified subjectively, and the working tool was the spherical equivalent, calculated as the sum of the sphere value and half the cylinder value. All subjects included in the study were genotyped using Illumina or Affymetrix platforms. This genome-wide association study identified a total of 6 loci influencing eye axial length, 4 of which were newly discovered, and proved their effect on spherical equivalent and ocular refraction as well as significantly increasing the risk of myopia [22].

The role of environmental factors in the development of non-syndromic forms of myopia is also unquestionable. The theory of genetic determinism does not explain the increase in myopia prevalence from one generation to the next, the existence of a small number of myopes in societies with low levels of schooling, the directly proportional relationship between the number of years of education and the risk of myopia onset and progression; countries with higher educational attainment are affected by true myopia "epidemics", the onset and progression of myopia being associated with higher levels of education [21]. The common elements of these groups are the increased use of near vision, through a range of activities such as reading, use of computers, TVs, video games; spending time in enclosed spaces, therefore prolonged use of accommodation.

There are also studies that have reported no statistically significant associations between myopia progression

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and near activities in children [23,24].

The work from short eye distance associated with prolonged crystalline accommodation has long been held responsible for increased axial eyeball length. An argument in favour of this hypothesis has been provided by atropine, a muscarinic agent with an accommodation-blocking effect that reduces myopia progression. Other studies do not find a strong association between accommodation and myopia and postulate the hypothesis that hyperopic defocus is a significant stimulus for increased globe length and thus myopia.[25].

Natural light and spending time outdoors may have a protective effect in children at risk of developing and progressing myopia. In 2020, Eppenberger and Sturm published the results of an analysis of two cross-sectional studies, 7 prospective cohort studies and 3 interventional studies published between October 2008 and January 2019, totalling 32381 participants aged 6 to 18 years. Most studies reported an inverse proportional relationship between myopia incidence/prevalence and time spent outside the home [26]. Dirani and Sun emphasized the protective effect of hours spent outdoors against the development of myopia [27,28]. Dirani examined 1249 adolescents in the SCORM (Singapore Cohort study Of Risk factors for Myopia) and reported that the total number of hours spent outdoors was associated with myopic refraction and shorter ocular axial lengths; also, the negative association was found for playing sports outdoors but not for indoor sports [29]. Similar results are reported by Sun et al. in a study of risk factors for schoolchildren's myopia conducted on 4890 participants in the economic and technological development area of Qingdao, East China. They find that the number of instructional classes, both myopic parents, and continuous close work without even a 5-minute break are associated with increased myopia prevalence [30].

The protective effect of outdoor activities is, however, not very pronounced. In 2017, a systematic review of literature data, followed by meta-analyses and systematic dose-response analyses of relevant literature data, looked at the association between time spent outdoors and the risk of myopia onset and progression of already established refractive error. The findings showed a protective effect on the onset of myopia, but the effect was inconsistent in eyes in which myopia had previously started [31].

Various hypotheses attempt to explain the mechanism by which time spent outdoors may have induced a decrease in the incidence of myopia. On the one hand, sunlight reaches the threshold level of stimulation at a wavelength of 550 nm, which coincides with the sensitivity threshold of the human eye. Indoor light peaks at a longer wavelength. Thus, most of the light rays received by the eye are focused behind the retinal plane and could cause an overall increase in myopia [32]. Another hypothesis would be related to the stimulation of dopamine release in the retina by bright light, but the mechanisms of the producer require further studies [33].

Therapeutic Strategies

The use of atropine. Atropine is a non-selective antimuscarinic agent with proven efficacy in controlling myopia, but the mechanism by which it acts is not yet

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fully understood. What we do know is that this mechanism is not related to accommodation; animal studies have shown that the effect of atropine is mediated through non-accommodative mechanisms [34]. Atropine has affinity for all 5 subtypes of acetylcholine receptors present in various ocular tissues and scleral fibroblasts [35], and studies in mice have shown that antagonists of these receptors inhibit scleral proliferation and thus axial elongation of the globe [36]. Some studies have shown that atropine instillation causes an increase in retinal dopamine release and postulated that dopamine may stimulate nitric oxide release as part of the signalling chain [37]. Additionally, pupil widening by atropine increases the area of retina exposed to myopic defocus, increases high-order aberrations and exposure to violet light, and these radiations control scleral growth through collagen cross-linking [38]. However, tropicamide instillation does not produce the same effect of controlling myopia progression.

As expected, atropine 1% instillation is not without side effects, such as blurred vision, photophobia, difficulties with near vision. The ATOM (The Atropine in the Treatment of Myopia) study, a randomised, double-masked trial conducted in Singapore on 400 children aged 6 to 12 years, examined the efficacy on myopia progression and adverse effects of lower concentrations of atropine (0.5%, 0.1% and 0. 01%), and the results showed a direct concentration-effect relationship, with a greater effect induced by higher concentrations [39], but also a rebound effect when the medication is stopped in the first year, and this effect is also greater at higher concentrations. The same concentration-effect relationship was also reported by a more recent study, in which Yam et al. compared the consequences on myopic progression induced following instillation of collyria with low concentrations of atropine (0.05%, 0.025% and 0.01%). Atropine 0.05% was effective in controlling both spherical equivalent and ocular axis elongation [40].

Pirenzepine, a selective muscarinic antagonist for M1 receptors, has also been found in clinical trials to be effective in controlling myopia progression in children with moderate adverse reactions; however, it is not used in current practice [41]. In experiments in mice, 7-methylxanthine, a non-selective adenosine antagonist, was found in oral administration to produce an increase in the diameter of fibrils in scleral collagen and cause scleral thickening [43].

Refractive surgery used to reduce amblyopia.

The most common cause of amblyopia is anisometropia. Myopic anisometropia greater than 2 dioptres has an increased risk of producing amblyopia, and when greater than 6 dioptres produces amblyopia in all patients [45]. Attempting to correct these children by using aerial lenses produces aniseikonia and loss of stereopsis, visual field narrowing and prismatic aberrations. Some of these shortcomings can be avoided by the use of contact lenses, but this is a more difficult option at younger ages due to the difficulty of handling them [44].

The use of refractive surgery to avoid or treat anisometropic amblyopia is theoretically an option in these cases. Among the procedures, photorefractive keratectomy (PRK), laser-assisted subepithelial keratectomy, (LASEK), laser-assisted in situ keratomileusis (LASIK), or implantation of phakic, anterior or posterior

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chamber intraocular lenses may be used. Excimer laser surgery is also an alternative for amblyopia caused by bilateral high myopia.

The reserved attitude towards the use of refractive surgery in children is due to a number of variables: changes in ocular parameters, such as axial globe length, lens thickness, biomechanical properties of the cornea, along with the growth process, may alter the long-term results of early surgery [49]. Another element that can alter the refractive outcome is myopia regression, more likely in the first year after surgery and with decreasing risk in the next 2-3 years [50]. Lack of paediatric nomograms, anaesthesia difficulties, instability of the refractive effect, susceptibility to trauma, and lack of accurate data on long-term prognosis and efficacy all leave refractive surgery second among therapeutic options in myopia [3].

Optical strategies.

In an attempt to halt the progression of myopia, various optical approaches have been proposed, including under- or over-correction, as well as reduction of hyperopic peripheral retinal defocus or induction of myopic retinal defocus.

The idea of under-correction was based on the principle that in under-corrected eyes the accommodative response for near vision is diminished [54]. Furthermore, in animal model experiments, myopic defocus with imaging in front of the retina reduced axial elongation and thus myopia progression [55]. Human studies, however, have reported widely differing results: some have found lower rates of progression associated with under-correction [56], others have observed similar results at one year in the under-corrected and fully corrected groups [37,38], but there have also been studies in which under-correction was associated with a higher rate of progression compared to full correction [39-42].

Current theories consider that an important stimulus for axial elongation of the eyeball is hyperopic peripheral retinal defocus [44,45]. This theory is also supported by studies in animal models, which have found that forcing hyperopic or myopic peripheral defocus influences eyeball growth, causing eyeball elongation or shortening, respectively. [46,47]. Therefore, research has focused on making optical devices that correct distance vision and simultaneously prevent hyperopic peripheral retinal defocus or even induce myopic retinal defocus. There are two arguments supporting the importance of achieving this goal: the evidence that visual impulses from the peripheral retina are stronger than those from the central retina [48] and the demonstrated fact that peripheral retinal defocus stimulates eye elongation and myopic defocus has the opposite effect [49,50].

This peripheral retinal defocus can be achieved with two types of aerial lenses: defocus incorporated multiple segment (DIMS) lenses and Apollo progressive addition lenses. DIMS includes a central optical zone of 9 mm diameter, which corrects for distance ametropia, and an annular zone, 33 mm diameter, which includes multiple concentric segments of 1.03 mm each, this peripheral zone having an addition of +3.5 dioptres. The effectiveness of this type of lens was the subject of a study conducted by Lam in 2020, enrolling 183 Chinese children

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between the ages of 8 and 13, to test the effect of DIMS type lenses on myopia progression. The results showed that myopia progressed 52% slower compared to the mono-focal lens group and axial elongation was 65% less than the control group, results that were maintained after 3 years of follow-up [51,52]. As an additional detail, Zhang et al. found that DIMS slowed myopia progression in children with initial hyperopic peripheral defocus, but not in those with initial myopic defocus, which could explain the variability of the effect of these lenses [53]. Apollo progressive addition lenses have asymmetric periphery with 3 different zones of myopic defocus: a superior zone with +2.5 dioptres full addition, and two zones, nasal and temporal, with 80% and 60% of addition, respectively. In 2020, Li and collaborators began a prospective, randomized, multicentre, 3-year, 600-school-age-child Chinese study that will compare the effectiveness of the two lens types, DIMS and Apollo, in controlling myopia progression [54].

Mono-focal, soft or rigid, gas-permeable contact lenses provide simple refractive correction and do not influence the progression of myopia [55]. Although their use has historically been thought to reduce globe elongation [56,57] and a more pronounced peripheral myopic defocus than spherical aerial lenses [58], most studies have found no difference between these two types of lenses in their effect of halting myopia growth, with contact lenses only temporarily flattening the corneal curvature, with no effect on globe elongation [59].

However, there are also contact lenses with promising results in preventing myopia progression: bifocal concentric lenses, peripheral gradient lenses and Extended Depth of Focus (EDOF) contact lenses. The first two include a central zone that corrects myopia; bifocal concentric lenses contain concentric zones in the periphery with positive addition that counteract the peripheral hyperopic defocus, and in peripheral gradient lenses, the transition to positive addition is constant from the edge of the central zone to the periphery [59,60]. EDOF lenses create a single elongated focal point to improve depth of focus, which also incorporates spherical aberrations, and overall retinal image quality has been optimized for points on the retina and anterior to the retina and degraded for points posterior to the retina, based on the assumption that poor image quality posterior to the retina prevents globe elongation [60]. These types of contact lenses provide very good distance vision, stabilization of both refraction and axial length by 30-50% [52,53], and better centration on the corneal surface [50]. MiSight lens technology is based on an optical zone formed by concentric rings, which produce two focal planes, allowing refractive error correction and producing simultaneous myopic defocus. A two-year randomized clinical trial [54] showed less progression and axial elongation in the MiSight group than in the mono-focal lens group. Numerous other studies have found that multifocal soft contact lenses provide a reduction, on average by 38%, in both myopia and ocular axis elongation .

Orthokeratology

Orthokeratology was defined by

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Kerns in 1976 as the reduction or elimination of a refractive error by the programmed application of contact lenses [55] and consists of the use of rigid, gas-permeable, reverse-geometry contact lenses worn overnight. These lenses induce temporary changes in corneal geometry, in the sense of flattening of the central corneal area with increased curvature of the mid-peripheral area and changes in corneal epithelial thickness. This effect is maintained throughout the following day, so that optical correction is no longer required. But, apart from corneal epithelial remodelling, these lenses create a myopic-type peripheral retinal defocus, probably due to the increase in the curvature of the mid-periphery of the cornea, thus becoming highly effective in controlling myopia progression by reducing the axial elongation of the globe [56].

Numerous studies have examined the efficacy and safety of orthokeratology lenses, and their results have shown a slowing of axial elongation ranging from 30% to 71% [57]. Other studies and meta-analyses have addressed the reduction in the rate of change of refractive error, which has been reported to be between 40% and 60% with orthokeratology lens wear compared to mono-focal aerial lenses. An interesting study examined the behaviour of highly myopic eyes with orthokeratology contact lenses compared to mono-focal aerial lenses. These eyes required the use of aerial lenses throughout the day to correct residual refractive error, but experienced an average of 63% less axial elongation of the eyeball than the control group.

Orthokeratology may also be a solution for myopic anisometropia [60] or for eyes with myopic astigmatism. Zhang and Chen reported, in a retrospective study of 62 eyes with myopic astigmatism compared with a group of 62 eyes with simple myopia, all treated with orthokeratology methods, that orthokeratology toric lenses provide better corneal centration and a 55% lower elongation rate in myopic children with medium or high astigmatic component [61].

The idea of combining these methods to control myopia has been explored in various studies. The combination of orthokeratology lenses with atropine led to improved control of myopia progression .

Orthokeratology results vary from individual to individual, depending on a number of factors, such as the size of the refractive error at the time of treatment initiation, the age of the child at the onset of myopia but also at the start of treatment, pupil diameter (which will influence the size of the peripheral retinal area accessed by the rays passing through the lens) .The ideal candidate for orthokeratological contact lens wear appears to be the 6–9-year-old child with rapid myopic progression, more than one dioptre per year or axial elongation greater than 0.2mm/7 months [60].

In conclusion, the rapid increase in the prevalence of myopia and its potentially disabling effects due to vision distortion and possible severe complications, are leading scientists to seek the most effective and safe solutions to correct and control its progression. Keeping these solutions up to date is the surest way to ensure optimal personalised management of each patient

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with myopia.

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