

# Contact Lens Update

CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

## Controlling the progression of myopia: A public workshop

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*Workshop summaries provided by Alisa Sivak, Marc Schulze, Doerte Luensmann, Hiba Mannan and Karen Walsh at the Centre for Contact Lens Research, University of Waterloo. The ideas presented in this summary solely reflect the information provided by workshop presenters. References identified in the presentations are listed throughout the summary.*

A September 30, 2016 workshop on myopia control, presented by the United States Federal Drug Administration (FDA), was designed to provide an overview of the increasing prevalence of myopia in addition to obtaining “consensus for clinical trial design attributes when contact lenses or other medical devices are studied for controlling the progression of myopia.” According to opening remarks from William Maisel, Deputy Center Director for Science and Chief Scientist with the Center for Devices and Radiological Health branch of the FDA, the purpose of bringing the sponsoring organizations\* together was to come up with a complete picture of the future of myopia control to determine the best path for developing this technology. This process will include a patient-centered approach to clinical trials, a thorough evaluation of the benefits and risks involved, and evaluation of the evidence and collaboration between those working in this field of research and practice.

### Demographics and natural history of myopia in the United States

Has the prevalence of myopia increased in the United States over the past few decades? To address this question, Donald Mutti (The Ohio State University College of Optometry) looked at various studies over the past century.

A 1983 study by Sperduto et al.<sup>1</sup> reported the prevalence of myopia in United States for the age group of 12-54 years to be 25% between 1971 and 1972. This number was later revised by Vitale et al.,<sup>2,3</sup> who examined the prevalence of myopia from 1999 to 2004. Her study concluded 33.1% of adults over the age of 20 had myopia  $\geq -1.00D$  spherical equivalent. If we compare the estimates from Vitale’s more recent study to a study by Angle and Wissmann,<sup>4</sup> who reported the frequency of myopia to be 32% between 1966 and 1970, there has not been a significant increase in prevalence over this 30-year period.

The United States has undergone significant changes in ethnic diversity over the past few decades. A 1928 study in Washington<sup>5</sup> estimated that 3.8% of the population between the ages of 6 and 14 years was myopic. This was predominantly a Caucasian population with a European ancestry. The CLEERE study by Kleinstein et al.<sup>6</sup> reported a 9.2% prevalence of myopia. However, if we compare the prevalence of myopia by ethnicities, only 4.4% of the Caucasians were myopic. In comparison, the prevalence of myopia in African-Americans, Asian and Hispanics was 6.6%, 18.5% and 13.2%, respectively. So, overall the 9.2% prevalence of myopia reported by Kleinstein et al.<sup>7</sup> appears to be merely a product of including a greater diversity of ethnic groups.

Even though the prevalence of myopia varies among ethnicities, the process of myopia development is the same, with the axial length being too long for the focal length of the eye. One of the factors that does differ with ethnicity is the rate of progression. Asian Americans have the greatest progression rates and reach the highest levels of myopia compared to other ethnic groups.

Another interesting way to examine prevalence of myopia is to look at the same community over different time periods. One example is a study conducted in Orinda, California in 1959<sup>8</sup> and then again in the 1990s.<sup>9</sup> The 1959 study estimated the prevalence of myopia to be 15%, whereas the later study found that the prevalence of myopia

increased to 20%. This suggests there is some evidence of increase in myopia prevalence, as both studies were done in the same community, with the same ethnic make-up and age groups.

Apart from ethnic differences, what are the sources of the changes across America that can lead to increase in myopia? One of the most important factors is time spent outdoors. A study by Jones et al.<sup>10</sup> reported that 14 hours/week was an important factor to reduce the risk of developing myopia. This was also true when compared across numbers of myopic parents. So, time outdoors can reduce the risk of becoming myopic. However, it may not impact the magnitude of myopia once the child is already myopic.

In conclusion, Mutti suggested the best estimate for prevalence of myopia in United States currently is 33%. There is some evidence of a higher prevalence of myopia over recent decades among all ethnic groups, which is mostly likely due to environmental factors such as spending less time outdoors. Although 33% is a significant number, it is not necessarily indicative of a “myopia epidemic” in the United States.

### **Demographics and natural history of myopia outside of the United States**

Ian Morgan (Australian National University) provided insights on changes in the prevalence of myopia worldwide. He suggested it is important to examine the East Asian countries to understand what can happen if efforts to prevent myopia progression is not realized in the United States.

There is a cluster of areas with a high prevalence of myopia in East Asia, with Seoul, South Korea being the highest, with >90% of the population being myopic. Morgan suggested that the high prevalence in these regions may be due to variations in environmental exposure rather than genetic background. This can be seen in Singapore, where the population consists of three ethnic groups: Chinese, Malay and Indians, with similar environmental exposures. The prevalence of myopia in Singapore Chinese, Singapore Indians and Singapore Malays is 85%, 75% and 70% respectively. The minor differences in the level of myopia among the three ethnic groups can potentially be explained by differences in time spent outdoors, as well as different patterns of educational success. The Singapore education statistics report higher school performance in Chinese than in Indians and Malays, while epidemiological studies suggest that Malay children spend more time outdoors than their Chinese and Indian counterparts. Additionally, Singapore Indians have a much higher prevalence of myopia than Indians from India, suggesting that environmental factors play a greater role than genetics in the development of myopia.

The Refractive Error Study in Children (RESC) has further investigated the impact of formal schooling.<sup>11</sup> Nepal has a low prevalence of myopia at 1-2% in children between the ages of 5 and 15 years, which is likely due to limited access to formal schooling. This suggests that children do not become more myopic as they get older, but rather children become myopic when they go to school. This factor is difficult to compare to the United States and other Western countries, where schooling starts at an early age. However, RESC data are consistent with other epidemiological studies that demonstrate lower rates of myopia in societies with lower rates of school attendance.

The effects of formal education systems are also seen in East Asian countries over the past century. The prevalence of myopia increased in Hong Kong, Singapore and South Korea after World War II, a pattern that parallels an increased focus on education. The same pattern has been noted in China, where the trigger point was the end of the Cultural Revolution in 1974. As educational pressures increased, the prevalence of myopia also increased, with a 10% increase in prevalence over just one decade, with the current prevalence about 80%.

Other parts of the world, including Australia,<sup>12</sup> Europe,<sup>13</sup> Germany<sup>14</sup> and Israel<sup>15</sup> have seen smaller increases in the prevalence of myopia. For example, in Australia, the prevalence has increased from 17% to 30%, but that is largely due to an increase in the East Asian population.

In addition to higher rates of myopia of all levels, there has been a substantial increase in the prevalence of high myopia ( $-6D$  or more), which affects more than 15% of the 18-year olds in some Asian countries.<sup>16</sup> This represents a new form of myopia, compared to older cohorts, where the high myopia was predominantly of genetic aetiology. This also shows an association with education. Whether acquired high myopia will have the same pathological effects as genetic high myopia is still unknown; Morgan suggested that the pathological effects will be less severe, but still significant.

There are several important components in development of myopia prevention plans. One of the most important factors is to promote the importance of time spent outdoors through parental, maternity and child-care education. Systematic time outdoors should also be implemented in preschools and schools. Furthermore, restriction of homework, especially in preschools and primary schools, should be considered. Finally, a referral system for immediate correction, optical and pharmaceutical interventions should be employed.

There are two existing models of myopia prevention that could be considered. Singapore currently uses an education program on increasing time outdoors through parent education, but there is no evidence that this program is effective. In comparison, Taiwan has mandated that students must spend at least two hours per day outdoors as part of the school curriculum. Taiwan also has a systematic screening and referral program for atropine. Since the introduction of the program in 2011, age specific visual acuity has started to improve after declining for 40 years, which illustrates the success of the program. Other East Asian countries such as China and Singapore are looking into following Taiwan's model.

### Contact lens use in a pediatric population: behaviors and hygiene

Between 2005 and 2009, 14% of new contact lens fits were with teenagers and 3% with children.<sup>17</sup> According to Robin Chalmers (independent clinical trials consultant and founding member of the Contact Lens Assessment in Youth study group), these figures correspond to an increased interest in the wear and hygiene patterns associated with this population, but epidemiological research is sparse, and little remains known on this topic.

Bullimore<sup>18</sup> determined the risk of microbial keratitis (MK) with overnight corneal reshaping lenses and included 677 children and 640 adults. The incidence rate of MK in children was 13.9 per 10,000 patient-years, while there were no reports for adults. Over a lens wear period of at least three months a total of two cases of MK were reported, both in children.

The CLAY (Contact Lens Assessment in Youth) group conducted a retrospective chart review to determine whether children and youth (ages 8-33) are at increased risk of contact lens complications (including both major and minor risks that interrupt wear). The study<sup>19</sup> included 3,549 participants for a total of 14,305 visits; 1,139 participants were under the age of 18. Results showed a total of 502 events, of which 187 cases were corneal infiltrative and inflammatory events (CIEs). The youngest wearers (age 8-12 years) had a lower number of inflammatory events compared to the other age groups, and the risk of CIE was highest between 15 and 25 years of age, with an increased risk with overnight wear (younger wearers are less likely to wear their lenses overnight compared to teenagers and young adults). Daily disposable lenses were the largest protective factor, presenting a 12.5 x lower risk (if not worn overnight) compared to frequent replacement lenses. Not having to use a lens case or lens care solution may further contribute to the reduced rates of MK in daily disposable wearers.

According to Chalmers, to minimize risks with lens wear:

- Children should wear daily disposables from the beginning, so that they never learn bad habits;
- Eye care practitioners should emphasize training at each follow-up visit (no re-use, no extended wear, no storage case) and provide an easily accessible supply of lenses;
- Parents should be involved in the care and supply of contact lenses.

More studies are needed to fully understand the risk of MK in children wearing soft contact lenses.

### **Complications of contact lens use**

Jodhbir Singh Mehta (Singapore National Eye Centre) provided an overview of the complications associated with contact lens use. Clinical events of different severity levels are known with contact lens wear and can relate to metabolic disorders, toxic hypersensitivity, abrasion and mechanical disorders, corneal infiltrates or – in severe cases – microbial keratitis (MK). In clinical studies, corneal infiltrates have been reported to be 5-10% per year with extended wear, while 2% have been reported with daily disposable wear. Better compliance with lens wear instructions and hygiene could lower the incidence rate. Eyelid complications such as MGD can further impact success with contact lens wear. The incidence rate of MK has been reported as 4.2 cases per 10,000/year, however vision loss of at least two lines is only estimated in 0.6 per 10,000/year.

The Asian cornea society infections keratitis study (ACSIKS) involves 13 study centers across Asia and has investigated the cause of infectious keratitis (IK) in 4154 cases. Overall, trauma has been reported as the primary risk factor and was associated with 53% of the IK cases, while contact lens wear was listed as the second highest risk factor with 18%. In developed Asian countries, however, contact lens wear is the primary risk factor (with a special reference to cosmetic contact lenses), while trauma is listed in second place.

Risk factors are 6-7 days/week lens wear, overnight lens wear, non-compliance with lens wear schedule and lens care products, poor hygiene, smoking and internet purchase. Use of daily disposable lenses is associated with a reduced risk. A delay of more than 12 hours from the onset of symptoms increases the chance of reduced best corrected vision after an event. It is important to seek advice early if a problem is suspected.

Where an organism can be cultured from a corneal scrape, more than half of the time the causative microbe is *Pseudomonas aeruginosa* (56%). Gram positive organisms are found 25% of the time.

It is important to rule out microbial keratitis in a contact lens complication. Where microbial keratitis is suspected, it is important to recognise the urgency of treatment, the likely causative organism and to then address the modifiable risk factors and lens replacement frequency (daily disposable) for the future.

### **Challenges in the design of clinical trials to prevent or halt progression of myopia**

Coming to agreement as to the qualities and standards of myopia control research is essential to develop meaningful clinical trials. Jeffrey Walline (The Ohio State University College of Optometry) outlined some of the factors that need consideration when developing new trials.

Developing and conducting a myopia control trial involves multiple components, including the significance of the research, optimization of recruitment, and selection of appropriate participant characteristics as well as deciding the most suitable study design and study outcomes. In addition, participant safety and retention over the course of study are also crucial.

Walline explained that recruitment of children as study participants is complex. Factors include the challenges faced through schools being less willing to allow for recruitment or the time commitment that is required for these (typically) longitudinal studies. The selection of study participants also involves multiple components, ranging from the age group to be included to the acceptable minimum and maximum levels of myopia at study start. According to Walline, the gold standard study design would be considered a randomized clinical trial, because of the reduced bias associated with these studies. However, due to their complexity, they are expensive and difficult to run. Further considerations in the planning of a myopia control clinical trial involve the selection of the appropriate

control group(s) and of the outcome variables (e.g. refractive error and/or axial length) to be studied, and on the magnitude at which differences between treatment groups may be considered clinically meaningful. Controlling and ensuring participant safety, particularly in this very young participant population, is another crucial component of designing a suitable and meaningful study.

Walline concluded that designing the “perfect” myopia control study was difficult, but suggested to aim for a study design that minimized bias while maximizing generalizability of the findings.

### **Research conducted on myopia control devices**

David Berntsen (University of Houston College of Optometry) provided an overview of the myopia control studies that have been conducted to date.

Berntsen noted that myopia control studies were typically based on two hypotheses: accommodative lag or peripheral defocus at the retina. Peripheral defocus at the retina occurs with standard single vision spectacle correction, and is based on the theory that the positioning of the image shell behind the retina (i.e. peripheral hyperopic defocus) contributes to myopia progression. To modify this, myopia control lens designs have been developed that aim to align the image shell closely with the retinal shape.

Berntsen reported that 24 out of 27 myopia control studies that used environmental or optical interventions resulted in a reduction in myopia progression over time, with studies using under-correction generally resulting in an increase in myopia progression.

All studies using pirenzepine or atropine eye drop treatments were found to have a positive treatment effect of at least 0.40D for studies ranging from ten months to two years. Treatment effects in spectacle studies were typically found to be around 0.25D in participants who wore some kind of bifocal or multifocal treatment, compared to a group of single vision lens wearers; in most cases, a large proportion of this effect was found in the first year of multi-year studies.

Treatment effects in orthokeratology (Ortho-K) studies were typically found to continue after the first year, with a cumulative treatment effect found after two years of wear. A comparison of studies evaluating the treatment effect of soft multifocal contact lenses and Ortho-K lenses showed, on average, a slowing of axial growth of 38% and 43%, respectively. Berntsen further explained that treatments causing myopic peripheral defocus were found to be associated with slower foveal myopic progression than if hyperopic peripheral defocus was present. From his review, Berntsen concluded that treatment effects of contact lenses, specifically Ortho-K and to a lesser degree soft bifocal/multifocal lenses, were larger than when using spectacle treatments, and suggested that treatments that exposed larger portions of the peripheral retina to myopic defocus to be more effective at controlling myopia progression.

### **Incorporating the patient perspective in the evaluation of medical devices**

The role of the patient has been evolving: traditionally, the therapeutic relationship was provider-led and one-sided, but in this “age of information” patients are both more empowered and sometimes more confused, requiring a move to shared decision-making. Katie O’Callaghan (FDA Centre for Devices and Radiological Health, (CDRH)) highlighted the importance of understanding patient needs, experiences and preferences, in the development of interventions for myopia control.

She outlined the vision of the CDRH: that patients in the United States have access to high-quality, safe, and effective medical devices of public health importance. She went on to explain the importance of partnering with patients, which promotes a culture of meaningful patient engagement and increases the use of patient input as

evidence in the decision making of the CDRH.

Through combining the ‘art of patient engagement’ and the ‘science of patient input’ it was felt that the result should be ‘patient-centric health care’. This should lead to improved patient health by understanding patient needs, experience and preferences.

She outlined where the patient perspective can help inform the development and evaluation of medical devices. This included patient-informed needs, patient preference benefit-risk information and patient-centred outcomes.

The science of patient input consisted of two areas: patient preference information and patient reported outcomes. By helping to understand what the patient perceives as a meaningful difference, patient preference information can provide information on the effect size in regulatory studies, the subgroups included, and labelling changes or expanded indications. Patient-reported outcomes help with defining the endpoints in studies, and the outcomes that need to be monitored post-market.

She mentioned that sponsors and stakeholders are encouraged to have early interactions with the FDA review division when considering submitting patient preference information. Her final point was that there are often multiple points of view when looking at data. It is often a judgment call, and the patient input can be invaluable in understanding what differences are meaningful and what risks are acceptable.

### Final thoughts

Historically, the clinical response to young myopic patients began and ended with prescribing corrective eyewear, but the overview presented in this collaborative workshop suggests that we need to make a significant shift in our treatment strategy. As Morgan suggested, while rates of prevalence of 30-40% in the United States, Australia, Europe, and Israel may not be indicative of an epidemic, increasing numbers of people with myopia—and particularly high myopia—suggest that it would be wise to pay attention to rising prevalence rates in East Asian countries, which has reached 80-90% in some cases. While it has been difficult to pinpoint a single cause of myopia, the patterns that appear to correlate with increasing focus on education and less time spent outdoors are compelling, particularly in the current climate of increased focus on digital devices and other visually demanding technology. As clinicians, we need to ensure that we understand all the options available to our pediatric patients with myopia. The kind of dialogue initiated by the FDA and its partners in presenting this workshop can only serve to enhance our understanding of those options.

*\*United States Food and Drug Administration (FDA), American Academy of Ophthalmology (AAO), American Academy of Optometry (AAOpt), American Association for Pediatric Ophthalmology and Strabismus (AAPOS), American Optometric Association (AOA), American Society of Cataract and Refractive Surgery (ASCRS), Contact Lens Association of Ophthalmologists, Inc. (CLAO)*

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