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Childhood Myopia A Global Challenge to Vision; Consensus Guidelines on Prevention and Management

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Message from President, SSI/SPOSI 2022-23

MYOPIA; PREVENTION & RETARDATION OF PROGRESSION: SPOSI-ENTOD GUIDELINES; 2023.

Myopia, a common form of refractive error, is increasingly prevalent but can be predicted and prevented to some extent. Myopia is the leading cause of visual impairment, visual disability, and the second major cause of avoidable blindness worldwide.

Based on my 51 years of experience, apart from the simple solution of using regular diluted atropineeye drops, physical fitness achieved through maintaining a protein-rich balanced diet, addressing multifactorial deficiencies, increasing the duration of outdoor games, preferably using contact lenses to improve quality of vision by correctingminor astigmatic errors , field of vision and might help in arresting myopia progress to some extent along spectacle free visually related quality of life . Be alert, no screen time to babies below the age of two years and limiting screen time to no more than 30 minutes at a time, with necessary breaks in between, may help slow down the progression of myopia.

On behalf of all members of the Strabismology and Pediatric Ophthalmological Society of India, I, Dr. Pradeep Deshpande, as the President, and Dr. Pramod Pandey, as the Secretary, are pleased to release this essential booklet in collaboration with multinational company Entod Pharma Ltd.

Dr. Pramod Pandey, our society's dedicated and knowledgeable Secretary, has worked diligently for the past year to contribute to and compile this valuable and conclusive information booklet on myopia. He deserves special appreciation for his efforts.

This booklet represents the culmination of continuous research by experts in the field of child eye care, providing prevention strategies, simple solutions to slow down the progression of myopia, and novel treatment modalities to minimize the blinding complications resulting from progressive myopia. It serves as a boon to myopic children, their parents, and especially concerned parents, offering the hope of a more comfortable and visually fulfilling quality of life.

We extend our gratitude to the pioneers and visionaries in the field of specialty pharmaceuticals, Mr. Kishore Masurkar , Mr. Nikhil K Masurkar (CEO), Mr. Raman Marke, (Senior VP of Marketing), and the entire field-based sales team of Entod Pharma, a multinational pharmaceutical company.

Their contributions, including arranging physical and online discussions on "myopia guidelines" at the SPOSI conferences in Chandigarh and Aurangabad, have facilitated the publication of this booklet for the betterment of our new generation and the benefit of mankind.

Pradeep G Deshpande

MBBS, D.O, M.C.P.S.,and M.S.
Recipient of 'Distinguished Scientist' Dr P Siwa Reddy endowment
award by A. P .Academy of Medical Sciences Hyderabad.

Message from the Secretary, SSI/SPOSI

Myopia has been the topic of intense scientific inquiry since the work of Johannes Kepler in early 17th century, who using principles of refraction of light proposed that an inverted image of the object is formed on the retina rather an erect image on the anterior surface of the lens, a popular belief held till then. Kepler, the German astronomer, and mathematician, who came up with the modern idea of lenses that correct nearsightedness. believed his own myopia was due to his intense study of astronomical tables. Kepler's landmark discovery on refraction through the eye made it possible to explain central visual acuity, visual fields, dark adaptation, and errors of refraction. Myopia has intrigued man and has been a topic of philosophical discussion since the time of Aristotle (350 BC). Over the millennia, myopia has been conceptualized in extremely variegated ways be it's etiology, clinical presentation, age of onset, progression pattern, pathological myopia, high myopia and serious structural complications that can be the cause for irreversible visual loss and morbidity. The prevalence and incidence of myopia has seen an unprecedented spurt in recent couple of decades and it is projected that by 2050 almost half of the world population is likely to be affected, the prevalence of high myopia is also expected to see a monumental surge and is projected to constitute 10 % of myopes from present 1-2 %. This has serious individual, societal and economic implications in many a covert and overt ways. The reasons for this phenomenal surge are poorly understood but environmental, genetic, and epigenetic factors have all been blamed including decreased time spent outdoors, increased near workloads, use of mobiles, tablets and laptops but clarity still eludes us. The more we unearth, more questions are raised than addressed.

Strategies are therefore required on war footing to stem the onset of myopia and retard it's progression. The challenge is far more formidable in developing countries like India, steeped in poverty, lack of resources and many a misconception about the disease entity. The incidence of myopic strabismus, especially intermittent divergent strabismus is also seeing a surge with it's attendant epiphenomena. Other than preventive environmental factors and lifestyle modulations, many therapeutic modalities including pharmacological agents and optical devices have been tried with variable results with their own baggage of side effects and adverse events riding piggyback. There is no single best treatment and therapeutic responses vary from person to person, place to place depending upon many known and unknown variables. Low dose atropine eye drops seem to provide the most optimum responses, but many issues need to be settled. Same is true with other preventive strategies like optical devices.To tackle the mammoth problem effectively, public, government agencies and other service providers need to be made aware of the complexities of this abstruse, rather esoteric situation. Parents and patients also need to be educated about the cause and effect and the ways to mitigate it. Till irrefutable level 1 evidence is gathered from RCTs, it is imperative to evolve effective and robust practice patterns incorporating sound strategies and guidelines to tackle this public health menace of great import.

The Strabismological society of India and Entod Pharmaceuticals have come together to frame the current practice patterns and evolve guidelines (SPOSI- ENTOD) for effective management of this emerging myopia epidemic in India. It is hoped that these guidelines and body of evidence presented will enable practicing ophthalmologists, public health planners and providers and other stake holders to draw a roadmap to contain the scourge effectively.

On behalf of the Society, I would like to put on record my deep sense of gratitude to all distinguished executive committee members and all other SSI members who have made valuable contributions to this endeavor for the public good. I would like to place on record the sterling contribution of our Learned President, Dr. P. Deshpande ji since the very inception of this initiative. I would also like to acknowledge the whole -hearted unwavering support, cooperation, and commitment we have received from the entire Entod Team since the very inception of this initiative.

Looking forward to continued support, cooperation, and lasting partnership for the cause of childhood blindness and strabismus in India.
'All I know is that I know nothing'- Plato's account of the Greek Philosopher, Socrates.

Warm Regards.
Dr. P. K. Pandey,
Secretary, Strabismological Society of India
Dated- 21. 6. 23

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MYOPIA; PREVENTION & RETARDATION OF PROGRESSION: SPOSI- ENTOD GUIDELINES, 2023

Aristotle is credited with having introduced the term and concept of myopia around 350 BC (muein- to close and ops the eye). Aristotle connected bulging eyes, frequent blinking, squeezing of the eye lids and close reading. He believed that bulging eyes could not collect well the ether movements coming from distant objects. Our understanding of myopia has enhanced tremendously since, but many pieces of the jigsaw remain to be fixed.

The global prevalence of axial myopia especially in the younger generation has seen an exponential increase over last 3 decades. East and Southeast Asia have been particularly affected by this epidemic and are a cause for concern. The prevalence of myopia varies greatly with geography. For example, in sub- Saharan African countries it may be just 3 % to about 80 to 90 % in senior high school children in east and south east Asia. The reasons are not fully understood but may have multifactorial aetiology. It is projected that by 2050 about half of global population is going to turn myopic and the incidence of high myopia is also going to rise manyfold to about 10 5 from current about 2 %. This poses an enormous burden on health care delivery systems and has tremendous economic and quality of life issues. Early onset of myopia may also mean higher prevalence of myopia with it's attendant consequences. Myopic maculopathy and high myopia associated optic neuropathy are the most frequent causes of irreversible visual loss and blindness in East Asia. Besides axial elongation may continue unabatedly even beyond 5th decade of life. The attendant thinning of choroid and sclera is most marked at the posterior pole. There could be superadded enlargement and misalignment of the optic nerve head, associated elongation and thinning of lamina cribrosa, shifting and enlargement of the Bruch's membrane opening manifesting as peripapillary gamma zone and delta zone, rotation of the optic disc, glaucoma like non glaucomatous optic nerve damage, formation of lacquer cracks and secondary Bruch's membrane defects in the macular region. Scleral staphyloma, myopic macular choroidal neovascularization with subsequent scar formation can also occur (Fuch's spots). Older age and female gender are an additional risk factor for development of myopic pathology.

In view of the foregoing, there is a compelling need to study the impact of myopia on individuals and the wider society, both from the monetary perspective and also in terms of emotional well-being and quality of life. The benefits of myopia control could be far reaching and diverse, some are enumerated below:

1. Short-term benefits of better vision and cosmesis (primary impact)

A child with lesser myopia is more functional in the mornings and can cope a little better without them rather than being disabled without them. A lower prescription is easier to manage and handle by the child. Lesser power also gives a better quality of vision. Power less than 4 D typically reduces the chances of amblyopia and increases the chances of better vision in adulthood and shifting to therapies like contact lenses and making the child spectacle free. Also, if the patient decides to have refractive surgery to correct their myopia in adulthood, a lower prescription means more likelihood of them being suitable, and

better visual outcomes after surgery. Lower myopia is also better for sports and other outdoor activities. Lower myopia is also beneficial for office workers as it delays the onset of presbyopia and makes them free for leisure activities as well. Patient usually dislike wearing thick spectacle lenses which are felt to be unsightly and a social handicap.

2. Long-term benefits (secondary impact)

A child with myopia has an increased risk for developing vision threatening eye diseases in the future, such as Glaucoma, Cataracts, Retinal detachment and Myopic macular degeneration. In this regard, the Rotterdam Eye Study pointed out in a population-based cohort study the presence of bilateral visual impairment in high myopic eyes, with 39% of the patients affected by myopic maculopathy, 17% by open-angle glaucoma and 5% by cataracts. In addition, it has been demonstrated that an early onset of myopia, is more dramatically related to a more severe degree of the disease during the adult age, which can lead to blindness. Pathologic myopia causes more vision impairment or blindness in Asians (0.2–1.4%) than in Caucasians (0.1–0.5%). Overall vision impairment due to pathologic myopia occurs in 5–10 Asian people per 100,000 annually.

3. **Economic benefits**

The annual direct cost of myopia correction for Asian adults has been estimated at US $328 billion/annum. With greater myopic progression, the cost of care is also likely to increase significantly and will be exacerbated by an even greater increase in the prevalence of high myopia, from 2.8% (190 million people) to 9.7% (924 million people) by 2050, representing a 4.9-fold increase in high myopia. High myopes have greater risk of developing several vision-threatening conditions including myopic macular degeneration, retinal detachment, glaucoma, and cataract. Those affected individuals incur costs for specialist eye care, or specialist optical aids for patients with visual impairment. These costs are in the region of US $250 billion/annum.

4. Quality of life

The impact of myopia is not only financial; it also affects quality of life and personal development. A study of Singaporean adolescents found that those with vision impairment, measured in terms of presenting vision (i.e. wearing their habitual correction), had statistically significantly lower scores for total quality of life ($P = 0.03$), psychosocial functioning ($P = 0.03$) and school functioning ($P = 0.02$). The Quality-of-Life Impact of Refractive Correction (QIRC) is useful to detect differences in quality-of-life impact from various refractive corrections (spectacles, contact lenses, and refractive surgery). Pesudovs et al. reported that QIRC score was highest in refractive surgery patients (mean QIRC score of 50.2 ± 6.3), followed by contact lens wearers (mean QIRC score 46.7 ± 5.5), and spectacle wears (mean QIRC score 44.1 ± 5.9). Visual impairment and blindness associated with myopic macular degeneration will increase significantly, hence affecting the quality of life and causing socioeconomic impact

Myopic progression impacts mobility, convenience, ocular-comfort symptoms, general symptoms, emotional well-being, and increases social issues. Myopia may impair many aspects of life including educational and occupational activities. Myopes, especially high myopes, tend to have reduced quality of life due to adverse influences from psychological, cosmetic, practical and financial factors. Hence, affecting productivity, mobility, and activities of daily living. Myopia progression in fastest in younger children, so starting myopia control as soon as possible will give the best overall results and decrease the burden of social and economic issues, increasing overall quality of life in these patients.

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Strategies are therefore warranted on an urgent basis to stem this tide of myopia / high myopia and pathological myopia and to reduce the burden of avoidable blindness and its attendant morbidities.

The strategies that can be adopted to prevent or delay development of myopia and retard its progression are of utmost import and fall under 3 broad categories-

1. **Public health Interventions; encouraging primeval well lit terrestrial environment. (Increased outdoor activities / less near work etc.)**
2. **In the efferent arm of Emmetropization- Pharmacologic approach primarily to decrease the axial length elongation with medications like low does Atropine eye drops**
3. **In the afferent arm of Emmetropization- To create a myopic defocus in the fundus mid periphery- Various optical measures in the form of spectacles and contact lenses**

EVOLUTIONARY UNDERPINNINGS

The underpins of myopia lay in the ocean. Animal life originated in the ocean and then spilled over to terrestrial and arboreal life. With subtle difference in the refractive indices of the water and the cornea, in order to focus the rays light on the retina, the dioptric power of the cornea and crystalline lens in marine life is exponentially high. As the animal navigates deeper and deeper, the illumination drops, range of vision decreases, smaller wavelengths (UV at blue end of the spectrum are diffracted, leaving red end of the electromagnetic radiation for refraction. A hypermetropic defocus results, serving as stimulus to either increase the dioptric power of the eye (cornea and lens power) or to increase the axial length.

Migration to terrestrial life was likely an accident that posed formidable challenges on the visual plant. As compared to water, the air- cornea interface produced far more refraction necessitating decrements in the dioptric power of the cornea and the crystalline lens, both got flatter and the anterior chamber depth increased. To cater to enhanced range of vision and field of vision, the axial length had to increase 3- fold. Together these 2 events are the cornerstone that determine the dioptric power of the eye and are known as the process of emmetropizatiom

Enhanced illumination also entailed better resolution of images and more of shorter wavelengths were able to reach the eye. Mammoth number of photoreceptors had to be housed and closely packed for better resolution and field of vision entailing increase in axial length of the eye.

These evolutionary underpins strongly influence the tight rope walk of emmeropization from a hypermetropic state to a myopic state and as and when this process goes haywire, refractive errors, pre myopia and myopia bubble up to surface. Such insights help us unravel how change in life style due to massive urbanisation, universal education, enhanced load on near work and less outdoor activities in school age children are shaping the contours of the present myopia epidemic. This together with robust experimental evidence on emmetropization and axial length growth enable us to draw the roadmap for preventive and therapeutic approach to the evolving myopia epidemic further driving research on myopia and potential therapeutic interventions in future

EMMETROPIZATION:

In neonate human eye, cornea and crystalline lens have a dioptric power of 52 and 38 D respectively that slides down to about 42 D and 18 D by 2 years of age. The axial length grows from about 16.5 mm to about 23 mm by 2 years of age. The process of emmeropization sets in at rapid pace and lasts upto 6 years and at a slower pace thereafter. How this happens leaves many pieces of the jigsaw to be fixed.

Visual signals relating to retinal defocus both myopic and hypermetropic regulate eye growth and axial length. Identifying afferent and efferent are of this arc may offer novel therapeutic options. The afferent arm is in the mid- peripheral retina, the efferent arm is poorly understood. Refractive strategies to create a myopic defocus through optical devices work at the afferent arm located in the mid- peripheral retina. In the efferent are dopamine, retinoic acid and nitric oxide likely involved. Atropine affects eye growth through antimuscarinic and non-. muscarinic mechanisms. Dopamine plays an important role in these processes. As part of diurnal rhythm, light inhibits melatonin secretion and dopamine secretion is augmented. Retina has 2 of the 5 Dopamine receptors (D1 and D2). As we shall see, host of anti- myopia strategies are programmed to exploit open spaces and increase in background illumination.

Dopamine, important neurotransmitter in the retina modulates neurogenesis/ visual signalling / Emmetropization

Close relationship between light exposure & Dopamine release

Inverse relationship between outdoor activities and Myopia

Retina has high levels of Dopamine / D1/ D 2 receptors.

Atropine increments dopamine levels.

Modulation of these processes by environmental, Transgenic & pharmacologic pathways may hold the key to taming of myopia.

Recommendations:

1 - Cycloplegic refraction and fundus evaluation should be carried out on all normal children by 3 year of age and in cases of suspected poor vision strabismus, prematurity, low birth weight, retinopathy of prematurity at an earlier age, 6 months onwards as appropriate.

2 - Glasses prescribed as per recommendations for the age and presence or absence of strabismus, anisometropia and astigmatism. The guidelines for prescription of glasses already exist.

3 - Refraction should be repeated at 5 years of age to detect new additions to pre myopes and myopes and to deploy appropriate management strategies.

International Myopia Institute and definitions of pre- myopia and myopia:

The International myopia institute (IMI) took shape following WHO- Brien Holden Vision Institute meeting on myopia and high myopia in 2015 at Sydney to address the rising levels of myopia and high myopia globally that can lead to potentially sight threatening complications for the person and mammoth global burden of avoidable blindness. Blindness. The IMI are a global group of experts who have come together to make available latest evidence-based recommendations on various aspects of myopia in the form of white papers. One of missions of IMI is to disseminate information about myopia to all corners of the world to help future vision impairment and blindness linked to higher incidence and prevalence of myopia and to involve practitioners, governments, policy makers, educators and general public at large in this gigantic task.

The International Myopia Institute definations:

Qualitative Definitions:

Myopia-A refractive error in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina when ocular accommodation is relaxed. This usually results from the eyeball being too long from front to back but can be caused by an overly curved cornea and or a lens with increased optical power It also is called near-sightedness.

Axial myopia, Refractive myopia, Secondary myopia.

Quantitative Definitions:

Pre-myopia: Refractive state of the eye between + 0.75 D and -0.50 D in children where a combination of baseline refraction, age and other quantifiable risk factors provide a sufficient likelihood of the future development of myopia to merit preventive interventions.

Myopia: A condition in which the spherical equivalent refractive error of an eye is <- -0.50D when ocular accommodation is relaxed.

Low Myopia: A condition in which the spherical equivalent refractive error of an eye is < - 0.05 and <-6 D when ocular accommodation is relaxed.

High Myopia: A condition in which the spherical equivalent refractive error of an eye is <- 6 D when ocular accommodation is relaxed.

Pathological myopia: Excessive axial elongation associated with myopia that leads to structural changes in the posterior segment of the eye (including posterior staphyloma, myopic maculopathy and high myopia aso glaucoma like associated optic neuropathy) and that can lead to loss of best corrected visual acuity.

Myopic Macular degeneration- (MMD): A vision threatening condition occurring in people with myopia, usually high myopia that comprises diffuse or patchy macular atrophy with or without lacquer cracks, macular Bruch's membrane defects, CNV and Fuchs's spots. MMD is further sub divided into myopic maculopathy, presumed myopic macular degeneration, myopic tractional maculopathy, myopia associated glaucoma like optic neuropathy.

PREMYOPIA
(Prevention of onset)

Pre myopia essentially entails a non- myopic refraction that entails high risk of progression to myopia. Studies like Collaborative longitudinal evaluation of ethnicity and Refractive error (CLEERE) have demonstrated that eyes programmed to turn myopic show an accelerated pattern of axial elongation several years before the onset of myopia[2]. Additional risk factors that are likely to add to the risk score may include number of myopic parents, parental education, environmental risk factors such as time spent indoors / outdoors, rate of change of axial length, rate of change of refraction, and genomic risk scores[3,4,5]

Preventive Aspects:

Outdoors Activities

Classroom lighting Levels

Less near Work

Parental Myopia a risk factor

AC/ A ratio/ Axial Length / Peripheral refraction- poor markers

Robust experimental & clinical evidence regarding effect of Dopamine / Apomorphine on axial length of the eye

ATOM 3 study underway to address role of weak Atropine eye drops, 0.01 % in Pre-myopia

Devices employing myopic defocus not very apt in Pre- myopia as these children are spectacle free

Future Questions for guidelines

Pigeonholing pre- myopia

What to treat.

When and how to treat; age, options, optimum dosage Frequency and time of applications, mechanism of action of antimuscarinic drugs like Atropine

Duration of treatment

Potential rebound phenomena

Age at which therapy can be stopped

RECOMMENDATION:

Preventive and prophylactic options like increased outdoor activities, less near work and Treatment with low concentration of atropine drops 0.01 % are the strategies to be entertained. Treatment can be undertaken from 5 to 12--16 years. Non responders / poor responders / poor responders who convert to myopia need to be treated as appropriate. In a recent study published in 2023, repeated low level red light has been shown to prevent conversion of pre myopes to myopes[6]. RLRL therapy was given twice a day, 5 days a week with each session lasting 3 minutes. The 12-month incidence of myopia was decreased by 33.4%. RLRL intervention requires dedicated devices and investment in time, nevertheless. Mechanism of action is speculated to be that RLRL therapy may increase the blood flow and prevent scleral hypoxia

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THERAPEUTIC MODALITIES FOR RETARDATION OF MYOPIA PROGRESSION:

ROLE OF OUTDOOR ACTIVITES IN MYOPIA

The light that falls on the retina has a big effect on the growth of the eye ball. The quantity and the spectrum of light has an impact (2). It has been suggested that there is release of dopamine from retina in response to bright light and this inhibits axial elongation of eyeball. This hypothesis was supported by an investigation done in chickens in which it was found that D2-dopamine antagonist partially reduced the protective effect of bright sunlight. Brighter light potentially reduces the development of myopia by pupil constriction, resulting in less visual blur (2 &3). Outdoor activities at least 2 hours a day shown to decrease the development of myopia in children at risk (3 to 9 years) (4). Using LED lamps was associated with more myopic refractive error and longer axial length (5) Different wavelengths of light has different effect on the growth of the eye ball. Fish raised in short wavelength (485nm) developed eyes significantly shorter than those raised in blue light (623nm), subsequently recovery occurred when the fish were returned to white light (1).

What is the role of light?

Sunlight is 10000 to 20000 Lux, which stimulates dopamine release that promotes normal development. But Indoor light is only around 5000 Lux, so that may affect light-dopamine pathway and hamper normal development (6). The reason of outdoor time's positive effect on myopia control might be that the radiant intensity of sunlight peaks at a wavelength of about 550 nm, corresponding precisely to the peak in the sensitivity of the average human observer. Indoor illumination peaks at longer wavelengths, thus most of the received light beams focus behind the retina and cause a situation similar to that of negative lenses in front of the eye, which has been proven to stimulate the globe growth and the subsequent myopia (7)

Outdoor activities prevent progression of myopia because of the beneficial effects of Spectral composition and intensity of lighting (UV & blue light), Strengthened circadian rhythm, Less Dioptric demand due to Small pupil and Increased vit D (A number of studies have reported lower levels of serum vitamin D in myopes compared with non-myopes) (8)

Studies conducted in Singapore incorporating outdoor activities at least 45 minutes to 1 hour in school reported fall in incidence of school myopia by 5%. Studies conducted in China incorporated outdoor activities in their curriculum and were able to significantly reduce incidence of myopia in their population. Outdoor activities are said to be an independent protective factor (not related to near work) against development (and progression?) of myopia (10 & 11)

Jin et al (2015) (12) reported increasing outdoor activities prevented myopia onset and development (in young children <14 years), as well as axial growth and elevated IOP in children. Shuyu Xiong (2017) et al (13) reviewed 51 articles with relevant data and 25 were included in the meta-analysis. The purpose was to evaluate the evidence for the association between time outdoors and risk of onset of myopia (incident/prevalent myopia), risk of a myopic shift in refractive error and risk of progression in myopes only. They concluded that that Increased time outdoors is effective in preventing the

onset of myopia as well as in slowing the myopic shift in refractive error. But paradoxically, outdoor time was not effective in slowing progression in eyes that were already myopic. Kai Cao et al (2019) (14) in their review article concluded, for myopic children, outdoor time helps slow down the speed of change in refractive error and axial length; for non-myopic children, outdoor time helps reduce the risk of developing myopia. Gupta et al (2021) (15) in their hospital based prospective longitudinal study found negative directional relationship between outdoor activities and myopia progression. Each hour increase in outdoor activities per day had a protective effect in the progression of myopia (children between 7-14 years). On the other hand, other studies from China and the United States have found no association between hours spent in outdoor activity and the progression of myopia (16&17)

There is thus irrefutable evidence that more outdoor activities provide protection against myopia development in the human eye. Evidence linking time outdoors to the prevention of myopia is stronger than that linking it to slowing the progression of existing myopia. Based on available evidence, the answer is clear that outdoor time helps prevent myopia

RECOMMENDATIONS:

A minimum of 8-15 hrs. of outdoor activity per week is recommended for school age children to achieve protection from myogenic stimuli

Individuals who are at risk of developing myopia should maximize natural light exposure.

Outdoor time can be adjusted by adding recess time during school hours and by encouraging parents and children to go outside on weekends. Besides, adding outdoor time does not cause external burden to children, parents, school, or society. Therefore, outdoor activity should be considered an effective and feasible option for myopia control. external burden to children, parents, school, or society. Therefore, outdoor activity should be considered an effective and feasible option for myopia control.

There is thus robust evidence to support the contention that increased outdoor time does prevent the onset of myopia in pre myopes. However it is not established whether increased outdoor time is useful in retarding myopia progression. There are studies that support both contentions. Studies on children aged 8 to 12 years confined indoors during lockdown during Covid pandemic showed significant myopia progression. It is therefore recommended that if a child does not have myopia and one parent has myopia, 2-hour daily exposure to sunlight will help prevent onset of myopia. Even in children with myopia, a 2 hour of daylight exposure / day may have a preventive role and should be encouraged.

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Near Work and Myopia

From the ocean we imbibed the physics of light, that as the objects come closer, more dioptric power is required to bring rays of light to a sharp focus and for better resolution more densely packed rods and cones are required, accordingly axial length / dioptric power of the eye has to increase. This happens as the rays of light turn more divergent as the object comes closer. Vision at close range / near work have thus served myogenic stimulus for the eye down the line of convergent / divergent evolution.

The supporting evidence is voluminous, higher myopia prevalence rates in Eskimo children1 after introduction of schooling, higher prevalence in orthodox Jewish boys with far more intense schooling as compared to boys and girls in general schools or in the case of Chinese fishermen who reported reading in childhood[2,3]

Induced hyperopic defocus has been on trial since more divergent rays demand more refractive power for the dioptric system of the eye. Myopes are known to display more accommodative lag induced by objects at closer range. That brings us to the role of accommodation in induction of myopia ref 4. The evidence is nevertheless tenuous of a relationship between extent of accommodative lag and subsequent migration to myopia. Accommodative lag and accommodative retention are known to be higher in myopes than hypermetropes5. What needs to be established is whether greater accommodative lag is seen before onset of myopia in children that subsequently slide down to myopia. The evidence from the experimental studies suggests that eye growth regulatory processes can operate in the absence of accommodation[6].

Some circumstantial evidence in support of accommodation as modulating factor does emanate from effect of atropine in blocking myopia progression7 Experimental studies in animals suggest that most eye growth control processes operate by skirting / absence of accommodation8 atropine in blocking the eye growth in man and experimental animals. However on close scrutiny this sounds untenable. Lower vertebrates have alternative modes of accommodation like a retractor like lentis muscle (originating from the persistent embryonic fissure) shifting the circular crystalline lens forward and backward for changing the dioptric power of the eye. The cornea has very little dioptric power as most of the refraction takes place at the level of crystalline lens. Avian species like chicks also have a different mode of accommodation as they lack zonules and ciliary muscle acts directly on the crystalline lens. Both Atropine and Pirenzepine , the muscarinic antagonists inhibited myopia in chicks that lack muscarinic receptors in their ciliary muscle.9. Over and above myopia could be is species that had no functional accommodative mechanism. The primate mode of accommodation is a later evolutionary event and can not linked to axial growth through accommodation and effect of Atropine through Accommodative pathway. It is vision at close range rather near work and accommodation that seems to be the primeval driving force for axial growth. Detailed comprehensive studies in which time -based parameters and adjustments with other confounding need to be undertaken before deriving any conclusive inferences. The robust evidence of coupling of accommodation and myopia led to shift away and exploring alternative avenues in the retina, choroid and sclera, most mammalian species have muscarinic receptors (M1- M5) present in these tissues. As we shall see later

The intensity of near work has been another area of debate, both the viewing distance but also the time spent. Total weekly use of 3 to 4 hours is known to increase odds of myopia, Such modest time- lines can easily be breached in a day by most children in present times. Time spent outdoors may likely alleviate this effect. Near work has consistently blamed as environmental risk factor for myopia onset and progression. The detailed studies in which time- based measures were used or with adjustment for other contributing factors, the evidence is nevertheless tenuous in support of this precept[11]

Recommendation

Children take break every 30 minutes to be outdoors as continuous time spent at near work may have cumulative effect. Continuous close work > 45 minutes should be discouraged Near work rule- After 20 minutes of near work look 20 feet away for 20 seconds should be encouraged. Changing reading habits can make a phenomenal difference to the child's propensity for developing myopia and it's progression.

Other factors like lighting conditions and break time from near work can be compounding factors. A working distance of more than 20 cm is recommended. Near work in dim light should be discouraged. Smart phones and tablets as compared to television and projection screens as educational devices likely are more myogenic and should be discouraged. Time spent on near work may add up to about 14 % enhanced likely hood of myopia. For every one dioptre hour more of near work per week, the odds of myopia increased by 2 %

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OPTICAL MEASURES

As opposed to efferent arm of emmetropization in pharmacological treatment of myopia, optical devices exploit the afferent arm of the emmetropization by creating a myopic defocus in the retinal mid periphery, retro equatorial region. Initial strategies employing under correction of myopic refractive errors and use of conventional bifocal spectacles did not produce tangible results. Progressive addition lenses (PAL) as compared to single vision lenses suggested an advantage of an imposed peripheral myopic defocus inhibited and an imposed hyperopic defocus accelerated globe enlargement in experimental animals like guinea pigs, chicken and marmoset and rhesus monkey. Although how much globe enlargement takes place with particular amount of defocus seems to be a matter of conjecture.

The optical measures include defocus incorporated multiple segments spectacle lenses (DIMS), highly aspheric lenslet target (H.A.L.T.) spectacle lenses and concentric zone dual focus soft contact lenses or the use of OK contact lenses.

Multifocal Spectacle Lenses:

Initial aspheric spectacle lens designs created to reduce peripheral hyperopic defocus did not lead to a decrease in the rate of myopia progression. Development of DIMS lenses did give rise to significant retardation of myopia progression as well as axial elongation and were well tolerated. DIMS lenses are custom made plastic lenses with an optical zone diameter of 9 mm for use to correct distant refractive error and with a peripheral annular zone with multiple round segments about 1 mm in diameter of +3.5 D of add power for impinging a peripheral myopic defocus. In a randomised trial on Chinese children aged 8 to 13 years, the average myopic progression has been shown to be cut to half in children wearing DIMS lenses over 2 years. The mean axial elongation was also cut by almost half. Other spectacle lens designs on the same principle like Zeiss, Myovision showed less efficacy.

Recent advancements in spectacle lens myopia control is the development of H.A.L.T. technology (Highly Aspheric Lenslet Target) spectacle lenses along with DIMS technology (Defocus Incorporated Multiple Segment) spectacle lenses.

What are H.A.L.T and DIMS technology spectacle lenses?

These spectacle lenses are based on animal studies which showed that myopic defocus leads to inhibition of eye growth and hyperopic defocus leads to enhancement of eye growth. The Essilor Stellest lens is designed with (H.A.L.T.) technology. These special type of polycarbonate lenses have a spherical front surface with 11 concentric rings which are formed by contiguous 1021 aspherical lenslets of diameter 1.12 mm centred on a 9 mm-diameter clear central zone. The area of the lens devoid of lenslets provides correction for distance. These aspherical lenslets are of same geometry in a single ring but have a different geometry in each ring thus creating a VoMD (volume of Myopia Defocus) in front of the retina eccentrically which serves to control myopia progression2. Defocus Incorporated Multiple Segments (DIMS) spectacle lens are marketed from Hoya under the trade name “MiYOSMART”. These spectacle lenses uses a central 9 mm optical zone (clear vision zone) for distant vision and a peripheral annulus comprising many circular ring segments (treatment zone), each segments having ~1mm

(treatment zone), each segments having ~1mm diameter and power of 3.50D. This lens provides clear central vision while inducing myopic defocus in the peripheral retina3.

H.A.L.T. (Highly Aspheric Lenslet Target) spectacle lenses and myopic progression

There have been some clinical trials which have evaluated the efficacy and visual outcomes of these special spectacle lenses. A study conducted by Bao et al. evaluated the 1-year efficacy of two different myopia control spectacle lenses that had lenslets of different asphericity. This study included 170 school children of age between 8–13 years having myopia of −0.75 D to −4.75 D. They were randomised into three groups of spectacle lenses with highly aspherical lenslets (HAL), spectacle lenses with slightly aspherical lenslets (SAL), or single-vision spectacle lenses (SVL). The parameters that were measured were Cycloplegic autorefraction (spherical equivalent refraction (SER)), axial length (AL) and best-corrected visual acuity (BCVA) at baseline and 6 months. The results depicted that both the HAL and SAL groups experienced less SER progression by 0.53 D and 0.33 respectively than the SVL group. AL elongation was reduced by 0.23 mm in the HAL group and 0.11 mm in the SAL group. Furthermore, 20% of children in the HAL group, 4% in the SAL group and 0% in the SVL group were observed to experience a hyperopic shift, while 8% in the HAL group, 7% in the SAL group and 2% in the SVL group showed no change in myopia progression. Myopic shift was experienced by 72% of participants in the HAL group, 89% in the SAL group and 98% in the SVL group. This 1-year study concluded that HAL and SAL were effective at controlling the progression of myopia and HAL than SAL2.

Further Bao et al. reported the 2-year findings in this cohort, which lend further credence to the provisional 1-year findings. After two years, myopia progression was slowed by 0.80 D in the HAL group and by 0.42D in the SAL group when compared with SVL group while the increment in axial length over 2 years was 0.34 mm, 0.51 mm, and 0.69 mm in the HAL, SAL, and SVL groups, respectively. During the second year, HAL still slowed the progression of myopia when compared with SVL but no difference was observed in myopia progression and axial length change between the SAL and SVL groups during the second year. Thus, myopia progression was slowed in SAL group mainly during the first year when compared with SVL. The SER progression was similar for full-time wearers and parttime wearers in the SAL and SVL groups but was lower for full-time wearers in the HAL group. Axial length elongation was similar among full time and part-time wearers in the SAL and SVL groups but was lower for full-time wearers in the HAL group. Hence, a positive dose-response relationship was confirmed between efficacy of myopia control and asphericity of lenslet4.

DIMS (Defocus Incorporated Multiple Segment) spectacle lenses:

The effect of DIMS lenses on myopia progression in 183 Chinese children was studied in a recent study by Lam et al3. It was a two year, double-masked randomized controlled clinical trial conducted in Chinese children of age 8–13 years, with myopia between −1.00 and −5.00 D and astigmatism less than 1.50 D. Children who wore DIMS spectacle lens were compared to those who wore single vision (SV)spectacle lenses. They inferred that the myopia progression was reduced by 52% in the children in DIMS group when compared with the children in SV group. This study also revealed that the DIMS even stopped myopia progression in some children. 21.5% of children in the DIMS group in comparison to 7.4% in the control group had no myopia progression over these 2 years. Similarly, DIMS group showed 62% lower axial length elongation when compared to the SV group3. The effect of DIMS was more in older children and the myopia progression was higher in younger children.

However, Lam et al. continued this study to the third year of follow up to determine the progression of myopia in children who continued to wear the DIMS lenses or children who switched from control- to-DIMS group for a 1-year period following a 2-year randomized control trial. Total 128 children participated in this study. Historical control group was obtained by reviewing the clinical records to compare the third-year changes. The study claimed that the children after switching from SV to DIMS lenses showed significant reductions in myopia progression and axial elongation and their changes in (spherical equivalent refraction) SER and AL in the third year were comparable to the first-year changes in the DIMS group, even though these subjects were 2 years older. In the third year, more than 80% of the children in Control-DIMS had myopia progression of less than 0.5D, and about 70% showed progression less than 0.25D which suggested that the myopia control effect was achieved even though the subjects began to wear DIMS lenses at a later age. No statistically significant differences were obtained in myopia progression and axial elongation between the Control-to DIMS group and the DIMS group in the third year. Only 5% in the DIMS and 2% in Control-to-DIMS groups had shown myopia progression of more than 1D and axial elongation was less than 0.1 mm in 52% in the DIMS group and 58% in Control-to-DIMS group. They concluded that good myopia control effect was shown in the children when they changed from SV to DIMS spectacle lenses5.

In order to study the long-term myopia control effect and safety in children wearing Defocus Incorporated Multiple Segments (DIMS) spectacle lenses Lam et al. conducted the study for total of 6 years where children who completed the 2-year RCT were followed for a total of 6 years. Cycloplegic refractions and axial length were measured. Group 1wore DIMS spectacles for 6 years; Group 2 wore DIMS spectacle lens for the initial 3.5 years and then afterwards SV spectacles; Group 3 wore SV spectacles in the initial 2 years and then switched to DIMS; Group 4 wore SV spectacles in the first 2 years then switched to DIMS for 1.5 years and then SV spectacles again. Myopia progression and axial elongation showed no significant difference between the first and the later 3 years. In the last 2.5 years, DIMS lens groups (Groups 1 and 3) had less myopia progression and axial elongation when compared with the single vision groups (Groups 2 and 4). No evidence of rebound after stoppage of the treatment was found. Visual functions were normal in all the groups. The results showed that DIMS lenses provide sustained myopia control over 6 years without adverse effects6.

RECOMMENDATION:

Spectacle lenses are a simple, non-invasive and easy to use modality compared with pharmacological or contact lens treatments. Daily wear of these lenses significantly slowed down the progression of myopia and axial elongation. Mid peripheral blurred vision was the main visual complaint that was noted once or twice a day. The high costs could be dampening factor in a poor country like India. Future work needs to be done to showcase their role in the Indian context. In a meta- analysis of literature, pharmacologic treatment with low dose atropine drops has been shown to be more efficacious.

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CONTACT LENSES

There are broadly 2 types of contact lens interventions, the soft multifocal contact lenses and orthokeratology.

Dual focus and multi-focus soft contact lenses:

These have a centre- distance design in the form of lenses of concentric rings as distinct zones of relative plus power and lenses with a gradient design with increasing relative plus power towards the lens periphery. Soft multifocal contact lenses have been shown a reduction in myopia progression of an average of36.4 % and a decrease in axial elongation by37.9 %. MiSight soft contact lenses (clear centre for distance and concentric rings of relative plus power, there was a 59 and 52 % reduction in the progression in the spherical equivalent refractive error and axial length respectively over 3 year period as compared to control group The US FDA approved the commercially available daily wear single use multifocal contact lenses for retardation of progression of myopia in 2019. The relative peripheral hyperopia at 30 degrees and 40 degrees nasal to fovea and 40 degrees temporal to fovea was significantly corelated to with a proportional reduction in the progression of refractive component and axial elongation.

RECOMMENDATION:

- The optimum evaluation of the refractive power in different zones for maximum myopia control with no deterioration of functional vision remains to be established.
- Lack of sufficient literature to support their efficacy.
- High cost.
- Compliance.
- Risk and benefit ratio of contact lens wear in the paediatric age group.

In conclusion, the efforts are directed to slow myopia progression by optical correction, however, the risk-benefit ratio combined with the low compliance of the patients has not given favourable strong evidence. We need to conduct more RCTs all over the world in multi-ethnic populations to reach an unequivocal conclusion.

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ORTHOKERATOLOGY:

Control of myopia progression has become of greater interest as rates of myopia and high myopia continue to increase, particularly in developed countries.The concept of orthokeratology was introduced as spectacle blur, a phenomenon describing corneal reshaping after wearing hard contact lenses. Ortho-k induces peripheral myopic defocus along the horizontal and vertical meridians. This increased myopic defocus along with reduced peripheral hyperopic blur leads to a decreased stimulus for eye growth, thus halting myopia progression.It is a Non-surgical, topographical approach. It is a process of planned corneal reshaping, thereby temporarily reducing myopia and improving unaided visual acuity of patient. Modern Ortho-K lenses employs reverse geometry lenses. They have secondary peripheral radii of curvature that are steeper than the back optic zone radius. Also known as 4 zone design. Lens is supported by peripheral curve.

MECHANISM

The flatter central fitting relationship results in a positive pressure for applanating force on the cornea induces possible compression or thinning of corneal epithelial cells resulting in decrease in number of cell layers at the center and Epithelial thickening at mid periphery.

INDICATION

- Rx -0.50 to -4.00 Ds.
- Less than -1.50 Dc of WTR corneal astigmatism.
- Central Kflat reading ≥ 42.00 D with relatively high eccentricities (≥0.50).
- <6 mm pupil size in dim illumination.
- HVID >11 mm.
- Normal anterior eye.
- Sporting person.
- Corneas that steepen in the periphery.

CONTRAINDICATION

- Previous failures with GP CL wear.
- Disease of cornea, conjunctiva, dry eye, keratoconus.
- Older patients where cornea is less likely to respond well.
- Against the rule astigmatism with cylinder >0.75 Dc.
- Low sphere power with high cylinder.

- When cornea is spherical.
- Deep set eyes.
- Very steep or very flat K value.

Wearing ortho K lenses over long term can improve accommodation amplitude, change wavefront aberration, and correct peripheral refractive errors. These combined slow the axial length elongation

SOFT OK (ARTMOST) Disposable lenses

- Lens size: 14.4mm, 2mm >HVID.
- To achieve centralized fitting with minimum movement (0-0.5mm).
- Tear reservoir underneath the lens to get best BVS near vision result.

Two randomized controlled trials, the retardation of myopia in orthokeratology (ROMO) study by Cho and associates and HM study by Charm and Cho showed a reduction in axial elongation by 43 to 63%. The reduction was more pronounced in younger age children aged 7-8 years and slower in older children1,2. In another study, the median increase in myopia after 2 years was 0.13 D in the study group and 1 D in control group using spectacles3. In a recent meta analysis effect of OK was described to be modestly beneficial4. A Cochrane review and meta-analysis has affirmed that OK contact lenses are beneficial for slowing axial elongation[5,6].

Microbial keratitis, fibrillary ring formation and altered corneal nerve patterns (fibrillary lines) are known to occur7, 8. Higher incidence of microbial keratitis may a cause for concern and warrants careful monitoring

RESEARCH EVIDENCE:

Orthokeratology may be effective in slowing myopic progression for children and adolescents, with a potentially greater effect when initiated at an early age (6–8 years).

Ortho-k has been shown to reduce myopia progression by slowing axial length elongation by slightly less than 50%; ranging from 41-45% in most meta-analyses1 . When treating patients for myopia control with ortho-k, axial length measurements at baseline and throughout the treatment process are critical

slightly less than 50%; ranging from 41-45% in most meta-analyses1 . When treating patients for myopia control with ortho-k, axial length measurements at baseline and throughout the treatment process are critical.

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A combined treatment is more effective than monotherapy in slowing down myopia progression. Three randomized clinical trials showed a greater efficacy range of about 56% to 100% in controlling axial elongation in the group treated with the combination of OrthoK with 0.01% atropine than the OrthoK alone2

Patients with rapid progression – i.e. all patients whose myopia onset occurred before the age of 10 – whose myopia was more severe at the beginning (>-2.00 D) or who have large pupils (>5 mm) will benefit from orthokeratology lenses3

For smaller pupils, the effect of orthokeratology lenses can be enhanced by combining this strategy with low doses (0.025%) of atropine. This medication causes a slight dilation of the pupils (1 mm to 2 mm), which allows for greater exposure to the convex powers generated by orthokeratology lens3

There is also higher rebound increase in myopia progression after cessation of lens wear4 These lenses are of limited availability in India.

RECOMMENDATION:

OK is more effective in slowing myopia progression in younger rapidly progressing myopic children and in high myopia as partial OK. Toric Ok is also effective in slowing moderate to high corneal astigmatism. These lenses are of limited value in India due to restricted availability.

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PHARMACOLOGICAL CONTROL OF MYOPIA

Despite exhaustive work, both experimental and clinical on myopia pathogenesis, the cellular / molecular mechanisms underlying myopia development are poorly delineated stymieing the search for the most effective pharmacologic agents for myopia prevention and retardation / reversal of progression.

Myopia control using pharmacologic agents has been known to be most efficacious. Acetylcholine plays an important role in developing retina nad regulates the growth of the eye. Several drugs from parasympatholytic class have shown efficacy in slowing myopia progression however only atropine sulphate and pirenzepine have shown consistent results in this regard. Atropine is a non- selective broad muscarinic acetylcholine receptor antagonist and pirenzepine is an antagonist with selective MI Receptor subtype.

Atropine applications in concentrations of 1% once a day has shown significant reduction in cycloplegic refraction spherical equivalent (SE) and axial ,length elongation by as much as 80 to 95 % . Pirenzepine 2% twice a day has also shown promising results in upto 50 % of cases of slowing myopia progression. Because of regulatory and economic issues pirenzepine testing has been curtailed for further studies leaving only atropine as the sole anticholinergic agent in use with unquestionable efficacy, though many questions beg an answer. There is plethora of literature on this modality of therapy in different concentrations ranging from 1 to 0.01 %. Some of these studies will be visited later in this write up.

Atropine acts as reversible competitive antagonist with an affinity for all 5 types of Acetylcholine muscarinic receptors (MR1 to MR5) and acts primarily through MRs. The MRs belong to superfamily of G protein coupled receptors and have both neuronal and non- neuronal interaction in the eye. Muscarinic receptors are abundantly found in corneal, iris, ciliary body and ciliary muscles epithelium of crystalline lens, retinal pigment epithelium, amacrine cells, choroid, scleral fibroblasts.

Atropine was initially used for myopia control since it was hypothesized that excessive accommodation is the driving force for myopia and atropine acts by causing paralysis of accommodation. However later experimental studies showed that eyes unable to accommodate due to lesioning of Edinger Westphal nucleus and also those with sectioning of the optic nerve continues to respond to hyperopic defocus and ended up with myopia. Thus, atropine ought to work by non- accommodative mechanisms and focus has been on investigating such mechanisms. Several biological processes including role of RPE in relaying ocular growth regulatory signals from the retina to sclera through choroid, reduced choroidal thickness and decreased scleral thickness due to extracellular matrix remodelling have been investigated among a plethora of mechanisms. Atropine has been observed to modulate these biological mechanisms in a complex fashion by both muscarinic and non-muscarinic pathways, the truth is yet to reveal itself.

Atropine is linked to Dopamine, a neuro- transmitter in the CNS and retina. Dopamine is linked to Melatonin the neuro-transmitter regulating circadian rhythm through pineal gland and hypothalamus. Serotonin is also closely linked. Melatonin

and dopamine have an inverse relationship with mutually inhibitory effects. Dopamine facilitates inter neuron signalling and is crucial for ocular growth. Dopamine agonists such as apomorphine inhibit myopia progression in both animal models of form deprived and lens induced myopia.

Atropine could also act at the scleral site. By modulating glycosaminoglycan synthesis and many other proposed mechanisms. Pigment epithelium of the retina, Bruch's membrane, choroid have all been implicated through complex biochemical mechanisms to modulate axial growth. Both RPE and choroid secrete a variety of growth factors including transforming growth factor (TGF-beta) and basal fibroblast growth factor (bFGF)

In vitro, atropine has been shown to modulate expression and activity of these growth factors. There is robust evidence for the role of atropine eye drops in prevention and retardation of myopia progression, but mechanisms remain poorly delineated and elusive.

Clinical Application of Atropine for Myopia Prevention and Progression of Retardation:

Atropine is the only pharmaceutical agent that has consistently been demonstrated to slow myopic progression. The development and progression rate for myopia varies among many factors including ethnicity, geographical location, rural / urban, socio economic and many other factors .For example the rate of progression is about 1 D in east Asians and about -0.5 D in Caucasians. Several years on a significant proportion will breach the barriers and enter the confines of high myopia (> 5D). Early interventions for development and retardation of progression therefore are of quintessential importance. The high concentration of 1 % and 0.5 % atropine are effective in retardation of myopia progression but high rate of side effects has led to heavy drop out rates. (16- 58 %). Recently many publications from south Asia in particular portray efficacy of 0.01 % atropine in myopia control with much lower rates of side effects. Accordingly, there has been a renewed interest in exploring this exciting field of myopia pathogenesis and control measures.

First randomised placebo-controlled trial was undertaken by Yen and colleagues in 19891. The authors reported for the first time in 1989 that myopia progression was markedly less marked after use of atropine 1% eye drops for 1 year followed by the group with 1% cyclopentolate drops and control group with a placebo. Due to side effects of 1 % atropine like photophobia and near blur, the salutary effects of the study were not translated into clinical mould.

Ten years later in 1999, Shih and associates2 found in a randomised trial that progression of myopia after 2 years was least in 0.50 atropine eye drops followed by 0.25 and 0.01 %. Control group with Tropicamide 0.5 % had maximum increase by 1.06 +- group D / Year as compared to 0.5% atropine (-0.04+- 63 D / year. Limitations of this study were lack of biometry for axial length and lack of a placebo control group, the dye was nevertheless cast.

In 2006 Chua and colleagues3 in the atropine for the treatment of childhood myopia (ATOM1) mean progression of myopia in

In 2006 Chua and colleagues3 in the atropine for the treatment of childhood myopia (ATOM1) mean progression of myopia iwas -0.28 +-0.92 D / year and in eyes receiving placebo it was-1.20 +-0.69 D / year. Axial length remained broadly unchanged in treatment are (-0.02+-0.35 mm / 2 year) changing significantly with the control group (0.38 +-0.38 mm / 2 year implying a 77% reduction of myopia progression. However high concentration of atropine gave rise to marked rebound effect when treatment was stopped. It increased by -1.14 +-0.8 D / y in study group and by -0.38+-0.39 D / y in the control group. In other randomized trials atropine 0.5 and 1% was associated with far better efficacy and also a high rate of side effects mainly mydriasis and decrease in the amplitude of accommodation.

The ATOM 2 study4 published in 2012 revealed that 0.5, 0.1 and 0.01 % showed -0.30=- 0.60 , -0.38+-0.60, and -0.49+-0.63 D respectively 59 side effect of increase in pupil size was 3.11, 2.42 and 0.91 mm respectively. The amplitude of accommodation was reduced by 3.6, 6 and 11.7 D with atropine concentrations of 0.01, 0.1 and 0.5 % respectively 60, 61. The rebound effect was considerably less with 0.01 %. Compiling 2 years of treatment and 1 year of washout, the overall progression of myopia was smallest in the 0.01 % atropine group (-0.72+-0.72 D). The limitation of the ATOM 2 study was the lack of a placebo control group.

Based on the ATOM2 study, the application of 0.01 % atropine drops has been widely used for pharmacological prevention of myopia progression5,6 .

The low- concentration atropine for myopia progression study (LAMP) was conducted in 2019 to address the limitations of the ATOM2 study in children aged 4 to 12 years by Yam J C et al7. Atropine in concentrations of 0.05, 0.025, 0.01 % and placebo. Over a follow up of 2 years, the efficacy of 0.05 % atropine eye drops was double that of 0.01 % atropine eye drops with respect to reduction of myopic progression, It was inferred that 0.05 % was the optimal concentration among the studied atropine concentrations for slowing the progression of myopia.

In a recent Cochrane review, Walline and associates8 summarised those children receiving atropine eye drops, pirenzepine gel or cyclopentolate eye drops showed a significant reduction in the increase of myopic refractive errors as well as axial length elongation was also less pronounced in these children as compared to placebo group.

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Low dose Atropine eye drops; Review of recent randomized clinical trials

Topical atropine has emerged as the most effective and promising treatment modality in myopia control for over several decades. It blocks muscarinic receptors non selectively via a neurochemical cascade on the retina, acts directly on scleral fibroblasts by inhibiting the synthesis of glycosaminoglycans via a non-muscarinic mechanism and also, increases dopamine released from (RPE) cells, - which in turn might cancel out a retinal signal that controls eye growth.

The Atropine for the Treatment of Childhood Myopia-1 (ATOM-1) was a

- Placebo-controlled, randomized, double-masked study conducted in Singapore which recruited 400 children aged 6-12 years with
- Moderate myopia (-1 D to -6 D, over 3 years (2-year treatment period and 1-year washout period).
- Ttreatment group received atropine 1% at bedtime in one eye while the control group received vehicle eye drops in one eye.
- There was progression of -1.29D of myopia in placebo and -0.28D in 1% atropine group over 2 years.
- There was 77% reduction of myopia in the study.
- At 3 years, a significant rebound seen for myopia progression and AL elongation after cessation of atropine 1% for 1 year.

Atropine for the Treatment of Myopia (ATOM 2) study Chia et al

- Randomized, double-masked clinical trial without placebo
- A total of 400 children randomized to receive atropine
- 0.5%, 0.1%, or 0.01% once daily in both eyes in a 2:2:1 ratio
- Study compared the safety and efficacy of 3 lower doses of atropine

	Myopia progression after 2 years of treatment	%age of children with progression after 1 year of washout (end of 3years)	total myopia progression in 5 years (children who continued to progress were restarted on 0.01%)
0.5%	-0.30D	68%	-1.98D
0.1%	-0.38D	59%	-1.83D
0.01%	-0.49D	24%	-1.38D
	2 years	3 years	5 years

- Results of the study showed that 0.01% atropine had similar efficacy compared to the higher concentration of 0.1% and 0.5%.
- Side effects with atropine 0.01% were minimal compared to the 2 higher concentrations.
- Negligible effects were seen on accommodation (mean residual accommodation was 11.8 D in the 0.01% group, compared to 6.8 D and 4 D in the 0.1% and 0.5% groups, respectively). No effect on near visual acuity in the 0.01% group.

LOW-CONCENTRATION ATROPINE FOR MYOPIA PROGRESSION (LAMP) STUDY

- 438 children
- Aged 4 to 12 years
- Myopia of at least -1.0 D
- Randomized in a 1:1:1:1 ratio to receive atropine 0.05%, 0.025%, 0.01%, and placebo
- After 1 year, the mean SE change was -0.27 -0.46, -0.59, and -0.81 respectively ($P < 0.001$)
- Mean AL change after 1 year was 0.20 mm, 0.29mm, 0.36 mm, and 0.41 mm, ($P < 0.001$)
- The 0.05%, 0.025%, and 0.01% atropine eye drops reduced myopia progression along a concentration-dependent response. Among them, 0.05% atropine was the most effective for controlling myopia progression and axial elongation during the study period
- 0.01% reduced AL elongation by 12%, compared with the placebo group, and that the difference did not reach statistical significance. Nevertheless, it achieved a 27% reduction in SE progression.
- The study concluded that all concentrations were well tolerated without an adverse effect on vision-related quality of life and of the 3 concentrations used, 0.05% atropine was most effective in controlling SE progression and AL elongation over a period of 1 year.

Two-Year Clinical Trial of the Low-concentration Atropine for Myopia Progression (LAMP) Study: Phase 2 Report

- Over the 2-year period, the mean SE progression was 0.55±0.86D, 0.85±0.73D, and 1.12±0.85D in the 0.05%, 0.025%, 0.01% atropine groups, respectively ($P=0.015$, $P<.001$, and $P=0.02$ for pairwise comparisons);
- mean AL changes over two years of 0.39±0.35mm, 0.50±0.33mm, and 0.59±0.38mm ($P=0.04$, $P<0.001$, and $P=0.10$).
- Compared with the 1st year, the 2nd year efficacy of 0.05% and 0.025% remained similar ($p=0.45$ and $p=0.31$), but mildly improved in the 0.01% atropine group ($P=0.04$).
- For the phase 1 placebo group, the myopia progression was significantly reduced after switching to 0.05% atropine (SE change 0.18D in second year vs. 0.82D in first year, $p<0.001$; AL elongated 0.15mm in 71 second year vs 0.43mm in first year, $p<0.001$).
- Accommodation loss and change in pupil size in all concentrations remained similar to the first-year results, and were well tolerated. Visual acuity, and vision related quality of life remained unaffected.
- The study concluded that over two years, the observed efficacy of 0.05% atropine observed was double that observed with 0.01% atropine, and it remained the optimal concentration amongst the studied atropine concentrations in slowing myopia progression

I-ATOM

- Multicentric, double-blinded, placebo-controlled randomized clinical trial
- 100 recruited Indian children with mild to moderate myopia
- reported 1-year data proving efficacy of 0.01% atropine drops in reducing myopia progression and axial length elongation
- MP was -0.16±0.4D (P=0.005) in atropine group and -0.35±0.4D (P=<0.001) in placebo group; difference between the two groups was 0.19D (P=0.021)
- MP reduction was 54% at 1 year in myopic children with no side effects.
- Mean ALE was 0.22±0.2mm (P=<0.001) in atropine and 0.28±0.28mm (P=<0.001) control; ALE between the groups was (0.06mm P=0.19)
- Mean AL reduction was 21% in atropine group than placebo but was not statistically significant

Other Prospective Placebo controlled interventional Indian clinical trial (PGIMER)

Rationale of study with one eye of individual as treatment and other as control): Limited study (LAMP) documented the results after matching the confounding factors (baseline near work, outdoor time, and accommodation). The effect of various confounding factors can be diminished if one eye of an individual receives the treatment and another eye of the same individual can act as the control to study true efficacy of drug in progressive myopes.

- Participants received treatment with 0.01% atropine eye drops every night in the right eyes as treatment group/eyes carboxymethyl cellulose drops in left eyes as control eyes/group.
- Reported the efficacy and safety of low-dose atropine compared to placebo in the Indian population over 1-year and also to study the impact of various modifiable and non-modifiable factors on myopia progression (MP) and drug efficacy (DE).
- myopic children (80 eyes of 40 patients) with age 6-16 years, myopia -1D to -7D , progression ≥0.5 D in the preceding year, stable astigmatism ≤1.5 D, anisometropia of ≤ 2 D were recruited
- MP was 0.25D (0.13-0.44 D) in treatment eyes and 0.69 D (0.50-1.0 D) in control eyes (p=0.001)
- ALE was 0.14 mm (0.05-0.35mm) in treatment eyes and 0.32mm (0.19-0.46mm) in control eyes (p=0.001)
- Pupil size was 3.5mm (3.5-4mm) in treatment eyes and 3mm(3-3.38mm)in control eyes (p=0.000)
- Median reduction in myopia progression in treatment eyes compared to control eyes (TRMP) was 0.45 DS (0.25DS -0.59 DS).
- Median reduction in axial length elongation in treatment eyes compared to control eyes (TRALE) was 0.13mm (0.09mm-0.18mm).
- % Median TRMP between two eyes 66.67% (50%-79.19%)
- % Median TRALE between two eyes 52.08 % (30.31%-75.70%)
- The study concluded that once-nightly dose of 0.01% atropine eye drops is safe and effective in achieving a statistically significant reduction in MP and ALE in low and moderate childhood myopia compared with placebo treatment in Indian eyes

Reduction in MP and ALE was statistically significant in all children irrespective of age-group, baseline MP, family history, screen-time, near and outdoor-time. The strongest

determinants of annual MP were age and baseline MP. Screen-time in control eyes was associated with greater ALE (r=0.620, p=0.042). Drug efficacy was higher when outdoor time exceeded 2hours/day (p=0.035) while the efficacy was lower with prolonged near activities (p=0.03), baseline fast-progressors (p<0.05) and history of parental myopia (p<0.05).

Questions that need to be addressed:

1. When to start atropine therapy
2. Age for starting
4. Optimum dose of atropine eye drops
3. Non -responders / poor response and how to handle them
4. Frequency and time of application
5. Duration of treatment, up to what age
6. Potential rebound phenomena after cessation of therapy and relationship to dosage
7. Tapering schedule for higher concentrations of atropine to address rebound phenomenon.
8. At what age therapy can be stopped.
9. Long term effects including safety
10. Ethnicity on response to therapy
11. Mode of action of atropine/ antimuscarinic eye drops.
12. Combination therapy, indications / safety / efficacy

Recommendation:

There is robust evidence fron clinical and experimenta studies that low dose atropine drops retard progression of myopia. There is a dose response relationship , the higher the dosage more effect but side effects also multiply. Low dose atropine ion concentrations of 0.01- 0.1 % may carry an efficacy of 30-60 % for myopia control. About 20 to 30 percent of children especially those who have an early onset and may benefit from a higher concentration of atropine. High concentration of atropine 0.5 % to 1 % is significantly more efficacious (60-80 %) but side effects like blur at near and photophobia mount disproportionately and theses children may require photochromatic glasses and may be a near aid. About 10 % for poorly understood reasons may still respond poorly.Lower dosages may also have less rebound effect and may be stopped abruptly, higher doses have more pronounced rebound effect and may need to be tapered. The risk of adverse effects rises linearly as concentration is increased. One may also need different dosages at different age groups and ethnicity, geographical location and other compounding factors could be at work and need to be studied. For overall myopia retardation of progression 0.05 % seems to be most advantageous and safe concentration.

The role of low dose atropine in prevention of onset of myopia (premyopia) is debatable but likely it has a role and that opens up future avenues for low dose atropine drops widespread usage in preventing and stalling myopia epidemic, should it work.

More work is required to delineate the role of low dose atropine in the prevention of onset and retardation of myopia, the challenges are formidable as is the magnitude of the projected impending epidemic. The future holds promise for use of low

dose atropine in myopia control, combined therapy with optical devices is also being explored in non responders and those with high myopia.

Low dose atropine is safe to be used for controlling myopia progression and axial elongation in children 4-16 years of age with progression ≥0.5 D. Efficacy of drug is more if child participates in outdoor activity in sunlight >2 hours/day and refrain digital screen and prolonged near activities.

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Annexure 1

History taking, Evaluation and follow up.

1. Age, gender, age of onset of myopia, past history of myopia progression, previous myopia control measuresundertaken if any, their efficacy / side effects, history of use of spectacles, last refraction done, cycloplegic used, time spent outdoors and time spent reading doing near work Reading more than 45 minutes continuously and / or at a distance of less than 20 cms.. History of parental myopia of more than 3 D in one eye, one or both parents. Family history of myopia, ethnicity. History of prematurity, low birth weight, ROP including it's treatment and response. Systemic conditions associated with myopia
2. Best corrected VA, Binocular vision, accommodative lag and amplitude of accommodation. Anterior segment evaluation Including pupil size and pupil responses.
3. Age appropriate cycloplegic refraction, Keratometry, anterior chamber depth, lens thickness.
4. Accommodative and binocular vision assessment.
5. Corneal topography if indicated for contact lens fitting, for example.
6. Axial length measurement- Axial elongation is more rapid in children 6-12 years and slower in older children, 12-16 years. Emmetropes typically have axial length of 22 -24.5 mm whereas myopes typically have axial lengths of more than 25 mm. Axial length may normally grow by 0.1 mm / year, an increase of 0.2 – 0.3 mm is associated with myopia progression.
7. Detailed Fundus examination(annual or as indicated) should be done including assessment for any changes associated with high myopia / degenerative myopia.
8. Age normal cut offs for myopia onset-
    a. Six years +0.75 D or less
    b. 7-8 years + 0.5 D or less
    c. 9-10 years +0.25 D or less
    d. 11 years Emmetropia.
9. Treatment specific parameter-
    a. Atropine- Pupil size, accommodation and IOP
    b. Orthokeratology-
    c. Corneal topography
    d. Spectacles / contact lenses- to be worn full time. OK lenses for at least 8 hours
    e. Any blur in distant VA.
10. Informed consent from parents, expected response, potential risks and side effects, and prognosis to be explained.
11. If myopia progression not adequately controlled, treatment could be stopped, another mode of therapy undertaken or augmented / combined with another form of therapy, Close monitoring on treatment cessation for any rebound effect.
12. Review schedule for low dose atropine-
    a. Four – 7 days, 1 month. 3 months, 6 months thereafter.

SALIENT FEATURES AND SUMMARY OF GUIDELINES:

Risk Factor Assessment:

Myopia is known to result from an interplay of genetic, ethnic and environmental risk factors. Evaluating these risk factors may shape the management strategy-

- Younger age at Myopia onset- The age normal refractive error in a child can be computed. This factor being independent of gender, ethnicity, school, time spent reading and parental myopia. Lower hyperopia than age normal can indicate risk of myopia development.
- Myopic parents- having one or both myopic parents (SER >3 D) increases risk of myopia development.
- Asian ethnicity- Asian ethnicity has a prominent role in myopia development and progression.
- Binocular vision disorders- Conditions like reduced accommodative responses, increased accommodative lag and high AC / A ratio may have a bearing on myopia development and need careful evaluation.
- Visual environment- The risk is closely related to reading at closer than 20 cm and continuously for periods of time exceeding 45 minutes.
- History should record the age of onset of myopia, history of myopia progression, previous myopia control measures adopted and their outcomes and details about time spent outdoors and near work habits.

Treatment Strategy to be Adopted:

1 - Identify pre- myopes and follow them, manage them by modulating environmental factors or by pharmacologic means (0.01 % atropine eye drops).

2 - Assess rate of progression- An understanding and estimation of rate of progression in an individual may help identify treatment strategy.

3 - Children with added risk factors require more aggressive management and more frequent follow up. Younger age often leads to faster progression. Greater myopia control with PAL lenses was demonstrated for example in children with accommodative lag and near esophoria.

4 - Greater myopia control with atropine in children of Asian than European ethnicity.

5 - Safety, costs, availability of treatment, follow -up required and compliance considerations.

6 - Patients and parents need to be informed about the risk factors for myopia onset and progression in order to understand the risk profile and take preventive / therapeutic measures.

7 - Expected outcomes, efficacy, alternative modalities, risks and side effects of treatment need to be communicated.

8 - No current therapeutic modality can permanently stop or reverse the progression.

9 - No current therapeutic modality can permanently stop or reverse the progression.

10 - The myopia treatment outcomes for an individual child can be lower or higher than average. The efficacy may vary with time as treatment progresses.

11 - Long term efficacy is not established as available data are from 1 to 5 years of treatment only as of now.

SPECIFIC GUIDELINES

Spending more time outdoors-

Encourage children to spend more time outdoors at least 80 to 120 minutes / day. This may be particularly important for children with pre myopia who may not progress to myopia. More work needs to be done on this area of vast public importance. Less near work with frequent breaks may help. A meta analysis by Sherwin reported that every 1 hour of outdoor time per week brings down development of myopia by 2 %.

Reduced time on smart phones, near digital devises like tablets and laptops and near tasks:

A meta-analysis of published literature reveals unequivocally that more time spent doing near work is associated with high risk of myopia. The risk of myopia increased by 2 % for for 1 diopter hour of near work per week. A working distance of < 20 cm has been shown to be the culprit irrespective of light intensity used. Television / projector are less myogenic as compared to smart phones and laptops. Near work in dim light is likely another myogenic factor. Avoiding dim illumination, laptops and tablets and smart phones having a reading distance of at least 20 cm may be protective. A 20 20 rule, after 20 minutes of close work looking at a distance of 20 feet for 20 seconds has been recommended.

Low Dose Atropine Drops:

1 -Low dose atropine eye drops to be applied daily at bedtime. Concentrations 0.05, 0.025 and 0.01 are found to be effective.0.01 are found to be effective.

2 - The o.05 % drops were more efficacious as compared to 0.025 and 0.01 % drops.

3 - The rebound phenomena were least with 0.01 % drops

4 - Two-year LAMP study reported mean myopic refractive error progression was least in 0.05 % atropine group. Both 0.05 and 0.025 are more effective as compared to 0.01 % which showed little slowing

5 - Treatment can be continued for 2 years with a washout period of 1 year.

6 - Non responders can be treated with higher concentrations and with combination therapy. About 10 % remain as non-responders despite higher dosages.

7 - Patients should be closely monitored for side effects like mydriasis and reduced amplitude of accommodation.

8 - Rebound effect is more than double with 0.5 and 0.1 % than with 0.01 % eyedrops. Age is also a factor with younger children experiencing more rebound effect.

9 - Efficacy in high myopes may be less.

10 - Some trials have also evaluated 0.01% atropine with orthokeratology and have shown better results with dual therapy rather than with monotherapy (OK).

12 - Efficacy may be more in Asian Children.

13 - Atropine therapy may be better than alternative therapies in Asian context.

14 - Guidelines for atropine therapy are still evolving.

Defocus incorporated multiple segment Spectacle Lenses:

significantly reduced myopia progression in Chinese children after 2 years of treatment. . The Progression was -0.41+- 0.06D as compared to -0.85+- 0.08 D in the control group. The mean axial length was significantly less than in single vision spectacle lens group ((0.21 +- 0.02mm and 0.55 +- 0.02 mm. The myopia retardation of progression was better in children with baseline hyperopic relative peripheral refraction than in those with myopic relative refraction. Visual acuity with DIMS lenses may drop in temporal and nasal gaze conditions a decrease in contrast sensitivity in nasal and temporal gaze conditions can also take place with DIMS lenses. Mid peripheral blurred vision may be a symptom that may be noticed occasionally. Randomized prospective controlled trials are required to clarify the efficacy, safety and long-term effects. High costs in Indian setting may be a deterrent for mass application. Other lens designs like Zeiss MyoVision are not as effective.

Highly Aspherical Lenslets (HAL) Spectacle lenses

One year results demonstrated 0.53 D and 0.33 D 67 % and 41 5 slowing of myopia progression by HAL and SAL (slightly aspherical lenslets) lenses as compared to single vision spectacle lenses. The axial elongation was slowed by 64 % and 31 % in HAL and SAL. After 2 years the HAL and SAL retarded myopia progression by o.80 D and 0.42 D respectively. Axial elongation plummeted by 0.35 and 0.18 mm respectively. Increased lenslet a- sphericity increased the retardation of myopia progression. Low contrast visual acuity and near vision may be marginally affected. For children who wore HAL for 12 hours the mean change in spherical equivalent refraction was brought down by 0.99 (0.12) D and increase in axial length slowed by 0.41 (0.05) mm in a study in 2022 by Bao et al.

Defocus and multifocal contact lenses

A reduction in myopia progression on an average of36.4% and a decrease in axial length of 37.9 % has been demonstrated. Optimum distribution of refractive power across the lens to maximize the slowing of myopia progression as well as to provide functional vision needs to be established. Costs and requirement for a regular follow up may be restraining factors

in the Indian context.

Orthokeratology:

OK is more effective in younger children with more rapidly progressive myopia.

The efficacy for retardation of progression of myopia may go up to 50 % in 2 years follow up with a high drop out rate. OK is thus modestly beneficial. The efficacy may decrease over time.

Toric OK effective in myopia in moderate to high corneal astigmatism

Potential complications like microbial keratitis have to be kept in mind. Rebound effect can take place if treatment is stopped early. Cost and availability of services in Indian context may be a deterrent.

OTHER CONSIDERATIONS

The risk / benefit ratio of interventions in pre myopia and for retardation of progression of myopia must be assessed on individual basis keeping age, health, lifestyle, ethnicity, geographical area, gender etc. in mind.

There may be additive effect by combining therapy as they act via different mechanisms. Studies are underway to combine therapy and in future, combined therapy may be more prevalent.

Treatment has to be adapted according to availability of treatment options in a particular setting and scope of practice and practice patterns.

The efficacy of interventions for retardation of progression of myopia is controversial in pathological myopia due to scleral thinning, retinal degenerative changes, vitreous degeneration and posterior detachment Myopia in retinopathy of prematurity and in myopia in children with pseudophakia.

WHAT IS KNOWN NOT TO WORK IN RETARDATION OF PROGRESSION OF MYOPIA OR HAS INSIGNIFICANT EFFECT

Pinhole glasses

Under-correction of myopia

Bifocal glasses

Blue light blocking glasses

Progressive addition spectacle lenses (PAL)

Daytime single vision soft contact lenses

Peripheral plus defocus correcting spectacle lenses.

Future Potential Pharmaceutical Agents:

Intraocular pressure and myopia could be linked and are under investigation. IOP may be a contributing factor for progression of myopia. Topical Latanoprost has been shown to block myopia caused by form deprivation in animal models. There are other topical drugs like Dopamine, timolol and caffein that are undergoing human clinical trials. The drug therapy turf for retardation of myopia progression is expanding exponentially and we are likely to catch up and stymie the imploding myopia epidemic.

Future studies are expected to focus on combination therapies working at different levels (afferent and efferent arms) to achieve cumulative effect on retardation of progression of myopia.

'Doubt is not a pleasant condition, but certainty is absurd':

Voltaire in a letter to Frederick The Great.

Conflated on behalf of Strabismological Society of India by Dr. P. K. Pandey, Secretary, SSI, incorporating inputs from SPOSO -ENTOD- FGM held on 3rd December 2022 at Chandigarh (India) and 24th June 2023 at Aurangabad (India).

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- These are based on our current understanding of trends and are bound to evolve as new evidence is established.
- These guidelines are mere suggestions and cannot be used in court of law to safeguard against or for any legal proceedings.
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Joint Initiative of:

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