Myopia, also known as short-sightedness, is an emerging pandemic worldwide. Its prevalence is rising steadily and has reached alarming levels, especially in South-east Asia. The structural difference in myopic eyes includes steeper corneal curvature or a longer axial length as compared to non-myopic eyes. Mild myopia is a relatively benign condition, and blurring of vision can be corrected with spectacles, contact lenses, or refractive laser surgeries. However, severe myopia can predispose individuals to vision-threatening conditions such as retinal detachment, retinal degeneration, and choroidal neovascularization.

INTRODUCTION
Myopia is also associated with an increased risk of age-related eye disorders in the long run, including glaucoma or cataract. Many studies reported the prevalence of myopia in population-based samples with different ages, ethnicity and significant differences were observed. A systematic review published in 2016 summarised the prevalence of myopia in 145 population-based studies. It focused on increasing prevalence of myopia in future and estimated that it will affect nearly 5 billion people by the year 2050 based on the same trend. Factors that predict myopia occurrence and its progression have been widely investigated. It has been seen that the amount of time spent outdoor has protective effects on myopia. It has particularly become a topic of interest as it is an indirect marker of sunlight exposure and is a modifiable lifestyle-related risk factor for myopia. It has important public health implications in disease prevention.

REVIEW OF LITERATURE:
Epidemiology
Myopia prevalence varies across different regions, ethnicities and age groups. The prevalence of myopia has dramatically increased in the last decades in Asia as well as the Western world. Estimates show that its prevalence is around 2% in European children aged six years and 12% in children of Asian descent. Studies on Indian populations showed that the incidence of myopia in Indian children is 5.3% and 35.6% in adults. Other studies estimated that myopia prevalence reaches up to 69% by the age of 15 years in the urban population of East Asia. There is a near doubling in the prevalence of myopia in India i.e., from 7.4% to 13.1%, as compared to the past decade in urban schools of Delhi.

Pathophysiology of Myopia
- Failure of emmetropization
During the natural process of emmetropization, the eye expands in all directions, be it equatorial or axial plane. This process is associated with mechanical stretching and thinning of the lens in the equatorial plane, consequent thinning and a decrease in the power of the crystalline lens. Decoupling between axial length elongation and flattening of corneal and lens curvature causes escalated axial growth and arrest of lens thinning by disruption of the equatorial expansion leading to myopia. In an observational cohort study, it was noticed that there was accelerated axial length elongation (almost three
times faster) in myopic subjects one year prior to and after the onset of myopia, making axial length elongation a major determinant of the refractive status of the eye.6

-Peripheral retinal hyperopic defocus
The role of retinal defocus and peripheral hyperopia as a precursor for onset and progression are also well studied. Animal studies have shown that the location of the image plane regulates eye growth. If the image plane is defocused from the retina, eye grows towards that defocused plane of the image and tries to compensate for it. In these studies, it has been observed that the chicken eye occluded with a hyperopia lens (negative lens), and the eye length grows towards the image plane, which is behind the retina and becomes myopic as a result. Axial length elongation and, consequently, myopia have not been seen in central macular pathologies. However, children having laser ablation of the mid-peripheral retina following retinopathy of prematurity develop myopic shift, depicting a biological basis of the emmetropization with the sensory stimulus located somewhere in the mid-peripheral retina.

It is believed that the target tissue and sensory stimulus are linked with a sort of biological messenger molecules like dopamine so that the persistent stimulus i.e., defocused image, is followed by an effect in the target tissue i.e., axial length elongation of the eyeball and this is where the role of muscarinic receptors and their antagonists such as atropine and pirenzepine comes into play.7-8 Different studies have proposed different target tissues, such as the sclera, the choroid, and, more recently, Bruch’s membrane. However, there is an ambiguity regarding the exact target tissue that drives this feedback loop.

Role of outdoor and sunlight exposure on Myopia
Multiple studies conducted among different geographical areas and continents demonstrated an inverse relation between time spent outdoors and the onset or myopia progression. A population-based cohort study in Western Australia measures the inverse correlation between objective sun exposure and myopia even after adjustments for confounders.9 A school-based study from Singapore showed that reduced time spent outdoors, less physical activity and lack of exposure to greenery and daylight with increased engagement in near work were associated with myopia progression. Furthermore, randomized clinical trials in Chinese school children showed that the extra time spent outdoors during recess prevented the onset of myopia in some children.10 However, it is unclear whether sunlight exposure, increased retinal illumination, or visualizing objects at a distance is responsible for this beneficial effect. Multiple objective and subjective measures of recent and cumulative sun exposure were collected. Saxena et al. in North India Myopia Study (NIMS) reported that more than 2 hours of outdoor exposure is associated with reduced myopia progression.4 This myopia progression might not be linked to increased physical activity, but exposure to bright light (>1000 lux) or UV light, as it is supported by the finding in a few studies that myopia progression has sessional variation i.e., more in winter than summer.

The increased amount of time spent outdoors is associated with reduced incidence or progression of myopia might be due to a number of possible mechanisms:

1) Light dopamine hypothesis: It says that bright light or UV exposure is associated with dopamine release, which ultimately modifies axial length via the dopamine signalling pathway

2) Distant focus with the relaxation of accommodation

3) Increased Vitamin D synthesis11

However, the role of vitamin D in the development of myopia is under much scrutiny.
Vitamin D and Myopia

Recently since the last few years, after the publication of some review articles on the role of vitamin D in ocular disorders, more and more studies investigating this relationship have been published, including some prospective studies examining this relationship and therapeutic effects of vitamin D. Recent studies show the association between serum 25-hydroxyvitamin D [25 (OH) D3] levels and adolescent myopia. Whether it is due to outdoor exposure or there is a direct role of vitamin D in myopia pathophysiology is still debatable. Studies focusing on vitamin D receptor polymorphism and its relation with myopia are with inconsistent results. Serum 25(OH) D3 is derived from multiple sources. Vitamin D3 (cholecalciferol) is formed in the epidermal layer of the skin after exposure to a particular spectrum of sunlight and is absorbed from the intestine after dietary intake. However, Vitamin D2 (Ergocalciferol) is derived from the dietary intake of foods such as yeast and fungus. Both types of vitamin D undergoes hydroxylation in the liver followed by hydroxylation in the kidneys and become active metabolite i.e., 1,25 (OH)2 D3. If not supplemented in the diet, sunlight exposure is believed to be the major source of vitamin D. Besides its main role in regulating calcium and phosphate metabolism of the body, it can be involved in immune responses, DNA transcription and methylation in some neuronal disorders like cognitive decline and Parkinsonism. However, its direct role in eye growth is unclear. One cohort study on young children in the Netherlands found a significant association between serum vitamin D levels and axial length & myopia. The study showed that children with low serum 25 (OH) D3 have longer axial lengths, and those with higher 25 (OH) D3 had a lower risk of myopia. This association remained significant even after adjusting for outdoor exposure, indicating that these two factors can have overlapped as well as different effects on the development of myopia. Genetic variants in Vitamin D pathway genes appeared not to be related. Although SNPs in the Vitamin D receptor (VDR) and CYP24A1 show some association with axial length and myopia, however, the result wasn’t consistent after adjustment for multiple testing. Vitamin D production is stimulated by UV light, not by mere light. Animal studies have shown that artificial light deprived of UV light can prevent myopia development. This might suggest that outdoor exposure and Vitamin D are independently related with elongation of axial length and myopia development. A South Korean and an Australian study showed a positive association between the role of vitamin D in the development of myopia. There are many theories regarding the role of Vitamin D in eye growth. One of them relates Vitamin D with dopamine. According to this theory, light exposure stimulates dopamine release from retinal amacrine cells. This dopamine affects the gap junctions and the size of receptive filed, two important determinants of eye growth and Vitamin D is believed to influence dopamine metabolism is many neurological disorder, such as Parkinson and restless leg syndrome. In Parkinson, Vitamin D protects against dopamine secreting neuronal death in substantia nigra. In animals it has been seen that vitamin D favours increased dopamine metabolism. In developing rat brain vitamin D upregulates the glial-derived neurotrophic factor (GDNF) which in turn increases the dopamine neurons. It means vitamin D enhances the function of dopamine and dopamine-secreting neurons. Whether Vitamin D also favours dopamine release in amacrine cells is still intriguing.

Another mechanism is the regulation of DNA transcription by acting on genes responsible for the transcription of Vitamin D response elements (VDRE). Active intracellular 1,25 (OH)2 D3 binds to Vitamin D binding protein, enters into the nucleus and then binds with retinoid X receptors in order to bind with Vitamin D response elements to initiate transcription. Hence the presence of VDR suggests the local activity of Vitamin D. In a recent study, 25 (OH) D3 and 1,25 (OH)2 D3 generating 2- hydroxylase and 1 α-hydroxylase, as well as deactivating enzyme 24-hydroxylase, could be localized in various places in the eye including the complementary regions of the ciliary body, scleral fibroblasts, corneal epithelium and endothelium, retinal pigment epithelium, neural retina indicating that vitamin D is locally produced, activated and regulated in the eye. Retinal cells also metabolise active 1,25(OH)2 D3, and this active vitamin D may interfere with the
transcription of genes that promotes myopia signalling cascade. In a novel study, serial Pentacam images of vitamin D deficient children were taken. It was observed that children with Vitamin D deficiency have astigmatism that was mildly improved with supplementation. Additionally, the same was done on a pair of identical twins. One who spent most of his time indoors had myopia progression over the other child who spent most of his time outdoors.

While all these above studies show a positive correlation, a study tried to correlate the vitamin D levels in neonates with the development of myopia in young adulthood. The result of this case-control study however did not show any possible correlation. The only Indian study that attempted to correlate vitamin D deficiency as a risk factor for myopia tried to find a connection between Vitamin D3 receptor polymorphism and myopia. Unfortunately, they could not find a relation between myopia and receptor polymorphism of the tested genes.

**DISCUSSION**

It is now well known that increased sunlight exposure or increase time spent outdoors is associated with reduced risk of myopia. A recent cohort study from India by showed an inverse relation between myopia and the amount of time spent outdoors. This association of myopia with outdoor and sunlight exposure remains consistent among old studies as well as new studies and literature reviews, even after adjustments for multiple confounders.

However, the question of whether increased outdoor exposure also slowdowns the myopia progression is still debatable. A recent review concluded that increased outdoor exposure is associated with induced myopia incidence, but it did not slow down myopia progression.

The association between vitamin D and myopia is controversial in cross-sectional studies. Many studies suggest that there is an inverse relation between serum 25 (OH) D3 levels and myopia onset and progression. It may have a protective effect on myopia. However, several case-control studies from different countries, such as US, Denmark, Australia showed that the risk of myopia is not related to neonatal vitamin D levels.

However, it is crucial to establish the causation between vitamin D and myopia. A large longitudinal cohort study found that 25 (OH) D3 levels are correlated with self-reported time spent outdoors; however, there was no evidence suggesting that the vitamin D levels were independently associated with myopia. Another study on preterm children found that the amount of time spent outdoors has inverse correlation with myopia however again it failed to show its direct relation with serum 25 (OH) D3 concentrations. Although, an Australian perspective study on young adults demonstrated that myopia was strongly associated with current 25 (OH) D3 concentrations, which is an indirect marker of time spent outdoors.

A recent meta-analytical study found that the risk of myopia is inversely related to serum 25 (OH) D3 concentrations after adjusting for time spent outdoors or sunlight exposure. This result was consistent in populations above 18 years of age but was not significant under 18. It also showed no relation between Vitamin D receptor gene polymorphism and increased risk of myopia. On the other hand, studies on animals suggest that violet light can suppress myopia progression. However, there was no beneficial effect of UVB exposure suggesting that UVB exposure and its dependent vitamin D synthesis pathway may not have any protective role on myopia progression.

In conclusion, although evidence from the literature suggests that blood 25-(OH) D3 levels are inversely associated with myopia, it seems like vitamin D does not have direct protective effects on myopia. Instead, outdoor exposure is a confounder between the effects of vitamin D on myopia progression, and 25-(OH) D3 can be taken as a biomarker of outdoor exposure.
REFERENCES


