Natural Ways of Myopia Control: A Public Health Approach for the Prevention of Myopia

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Natural Ways of Myopia Control: A Public Health Approach for the Prevention of Myopia

Abstract
INTRODUCTION: The prevalence of myopia has increased to 90% of the young adult population in some Asian countries, and according to the recent studies, fifty percent of world population will become myopic by 2050. Some studies believe that this recent increase in prevalence of myopia is a manifestation of sedentary lifestyle and poor diet. Myopia has already become a public health issue for the world population.

PURPOSE: The purpose of this paper is to examine the mechanisms responsible for the development of myopia, identify the public health recommendations to modify modern lifestyle behaviors, review the literature that provides a basis for the recommendations and identify the knowledge gaps.

METHODS: A systematic literature search was performed using Web of Science and Ovid Medline, with Population, Intervention, Control and Outcome (PICO) search strategy.

RECENT FINDINGS: Myopia can be corrected or controlled by conventional or custom designed eye glasses or contact lenses, or even with eye drops. However, myopia may reoccur if these interventions are discontinued. Moreover, they may not be suitable for some people due to their complications and need of consistent compliance. Myopia may be prevented or controlled through lifestyle changes.

Exposure to sunlight has been shown to lead to normal eye growth. Prevalence of myopia is lower in children who spend more time outdoors. The location of eye growth cues appear to be in the periphery in the retina. Hyperopic peripheral defocus stimulates eye growth and myopic peripheral defocus retards eye growth. If a child spends a sufficient amount of time outside, the whole retina will be in focus and the eye appears to grow normally. The modern lifestyle is also a risk factor for myopia. Children spend more time indoors performing near tasks. As a result they are in a constant peripheral blur state which may lead to excess axial length growth. In the past thirty years has seen the introduction of highly processed foods. Refined sugar and starches are the main elements of the diet which may lead to excess insulin secretion. Insulin is a known growth factor which has cell receptors in the sclera potentially leading to unregulated eye growth.

CONCLUSION: We conclude that a natural approach to a myopia prevention strategy should be implemented which emphasizes spending time outdoors, promoting full spectrum indoor lighting, encourage proper reading and writing ergonomics, and increasing consumption of a nutrient dense diet.

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Degree Name
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Committee Chair
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Keywords
myopia, peripheral defocus, sunlight, modern lifestyle, insulin, metabolic syndrome, unregulated eye growth, balanced diet, and public health

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NATURAL WAYS OF MYOPIA CONTROL: A PUBLIC HEALTH APPROACH FOR THE PREVENTION OF MYOPIA

By

HARDEW MAHTO, B.OPTM, OD, MS

A THESIS

Submitted to the Graduate Faculty of Pacific University Vision Science Graduate Program, in Partial Fulfillment of the requirements for the degree of Master of Science

In Vision Science

PACIFIC UNIVERSITY
COLLEGE OF OPTOMETRY
FOREST GROVE, OREGON

July, 2016
This thesis of Hardew Mahto titled “Natural Ways of Myopia Control: A Public Health Approach for the Prevention of Myopia”, is approved for the acceptance in partial fulfillment of the requirements of the degree of Master of Science

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processed foods. Refined sugar and starches are the main elements of the diet which may lead to excess insulin secretion. Insulin is a known growth factor which has cell receptors in the sclera potentially leading to unregulated eye growth.

**CONCLUSION:** We conclude that a natural approach to a myopia prevention strategy should be implemented which emphasizes spending time outdoors, promoting full spectrum indoor lighting, encourage proper reading and writing ergonomics, and increasing consumption of a nutrient dense diet.

**KEYWORDS:** myopia, peripheral defocus, Sunlight, modern lifestyle, insulin, metabolic syndrome, unregulated eye growth, balanced diet, and public health
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INTRODUCTION

Myopia is a common refractive error in which a person is not able to see distant objects clearly because their eye is overpowered. An over-powered eye bends the light more and forms an image in front of the back of the eye (retina) -whereas a normal eye forms an image on the retina. Myopia occurs during the developmental stage of a child. It may be inherited from parents or may be caused by environmental factors. At birth, eyes are hyperopic (underpowered) and as age progresses the eye ball grows to decompensate for the hyperopia and become a normal emmetropic eye. This phenomenon is called emmetropization. However, in some children eye ball growth continues beyond emmetropia and causes the development of myopia. In recent times, myopia has become a global public health issue leading to visual impairment. Myopia is one of the most common causes of blindness. The complications of myopia include vision threatening conditions such as cataract, glaucoma, myopic macular degeneration and choroidal neovascularization. In addition, uncorrected refractive errors may also impair the vision related quality of life and cause difficulty in performing vision related tasks. The economic cost of myopia is also high due to associated complications. In Singapore, the mean annual direct cost of myopia was estimated to be US$148 for each school child aged 7-9 years. In the United States, the annual direct cost of correcting distance vision impairment is between US$3.9 and 7.2 billion, reported by the National Health and Nutrition Examination Survey (NHANES). The prevalence of myopia is increasing very rapidly, especially in Asian countries.

Prevalence of myopia worldwide

Pan et al reviewed a number of studies compiling the prevalence of myopia in several countries in the world. In 2008, the prevalence of myopia in Nepal ranged from 10.9%, 16.5% and 27.3% in 10, 12 and 15 year old children in urban region respectively whereas in 2000, it was less than 3% in 3-15 year old children in rural areas. In 2002, the prevalence of myopia was 4.7% in 5 year olds, 7% in 10 years old, and 10.8% in 15 year old children in urban India whereas, in rural India, it was 2.8%, 4.1%, and 6.7% in 7, 10, and 15 year old. In urban China, the prevalence of myopia ranged from 5.7% in 5 year old to 78.4% in 15 years old in 2004. On other hand, it was almost nil in 5 year old children in rural parts northern China and consistently increased to 36.7% and 55% in males and females population respectively in 2000. The prevalence of myopia in 2002 was 29%, 34.7% and 53% in 7 year, 8 year and 9 year old school based children in Singapore. A large cross sectional study in Hong Kong reported that the prevalence of myopia was 17% in children less than 7 years old and increased to 53.1% in children aged more than 11 year old 2004. In Taiwan, the prevalence of myopia changed drastically over the years. The prevalence of
myopia was 5.8% in 1983, 3% in 1986, 6.6% in 1990, 12% in 1995 and 20% in 2000 in Taiwanese primary school children. Studies in 1995 and 2000 reported that the prevalence rate increased to 84% in children aged 16-18 years old.

The prevalence of myopia in South African children was 3 or 4% and increased to 6.3% and 9.6% in 14 year old and 15 year old children in 2003. The prevalence rate in Chile increased from 3.4% in 5 year old children to 19.4% and 15.7% in males and females respectively in 2000. In the USA, Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study, reported that Asians populations were more myopic (18.6%) followed by Hispanics (13.2%). White populations were less myopic (4.4%) in 2003. In Swedish school based population, the prevalence of myopia was 49.7% in 2000.

Table 1: Prevalence of myopia worldwide

<table>
<thead>
<tr>
<th>Country</th>
<th>Study</th>
<th>Myopia First year (Prevalence)</th>
<th>Myopia Last year (Prevalence)</th>
<th>Age</th>
<th>Source</th>
<th>Location</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Vitale97</td>
<td>1971-1972 (25%)</td>
<td>1999-2004 (41.6%)</td>
<td>12-54 years</td>
<td>NHANES</td>
<td>Nationwide</td>
<td>All Except Hispanic</td>
</tr>
<tr>
<td>China,</td>
<td>He100,</td>
<td>2004 (78.4%)</td>
<td>2012, 2015 (95.5%, 80.7%)</td>
<td>&gt;15 years</td>
<td>SJUSM</td>
<td>Southern China, Shanghai, Beijing</td>
<td>Chinese</td>
</tr>
<tr>
<td></td>
<td>Sun98,</td>
<td></td>
<td></td>
<td></td>
<td>CMU</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wu99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>Lin101</td>
<td>1983 (74%)</td>
<td>2000 (84%)</td>
<td>16-18 years</td>
<td>DENTW</td>
<td>Nationwide</td>
<td>Taiwanese</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>Lam102</td>
<td>1994 (29%)</td>
<td>2004 88 %</td>
<td>&gt;13 years</td>
<td>HKPUHK</td>
<td>Nationwide</td>
<td>Chinese</td>
</tr>
<tr>
<td>Singapore</td>
<td>Au103,</td>
<td>1987-1992 (44.2%)</td>
<td>1996-1997 (79.3%)</td>
<td>15-25 years</td>
<td>MCCSAF</td>
<td>Nationwide</td>
<td>Chinese, Indian, Malay</td>
</tr>
<tr>
<td>India</td>
<td>Murthy104,</td>
<td>2000-2001 (10.8%)</td>
<td>2014 (13%)</td>
<td>5-15 years</td>
<td>AIIMS</td>
<td>New Delhi</td>
<td>Indian</td>
</tr>
<tr>
<td></td>
<td>Saxena105</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>Junghans106</td>
<td>1975 (5.4 %)</td>
<td>1990 (6.5%)</td>
<td>4-12 years</td>
<td>UNSW</td>
<td>Sydney</td>
<td>Australian</td>
</tr>
</tbody>
</table>

* NHANES: National Health and Nutrition Examination Survey, USA
* SJUSM: Shanghai Jiaotong University School of Medicine
* CMU: Capital Medical University, the Beijing Municipal Commission of Education and the Beijing Center for disease Control and Prevention.
* DENTW: Department of Epidemiology, National Taiwan University
* MCCSAF: Medical Classification Center, Singapore Armed Forces
* AIIMS: All Indian Institute of Medical Sciences
* UNSW: University of New South Wales, Sydney
Table 2: Prevalence of diabetes

<table>
<thead>
<tr>
<th>Study Country Year</th>
<th>Diabetes First year (prevalence)</th>
<th>Diabetes Last year (prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank China (2011)</td>
<td>1980 (1%)</td>
<td>2008 (10%)</td>
</tr>
<tr>
<td>Menke USA (2015)</td>
<td>1990 (3.5%)</td>
<td>2012 (14%)</td>
</tr>
</tbody>
</table>

Table 3: Amount of time spent per week on home works by 15 years old children worldwide

<table>
<thead>
<tr>
<th>Countries</th>
<th>Hours/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>13.8</td>
</tr>
<tr>
<td>Singapore</td>
<td>9.4</td>
</tr>
<tr>
<td>USA</td>
<td>6.1</td>
</tr>
<tr>
<td>Australia</td>
<td>6</td>
</tr>
</tbody>
</table>

Because of the rapid increase in prevalence of myopia in recent years; many vision scientists are investigating the root cause of myopia progression. A range of factors including genetics, insufficient near accommodation response, high AC/A ratio, esophoria, excessive near work, light levels, chromaticity of light, less time spent outdoors, magnitude of peripheral defocus and diet are associated with onset and progression of myopia. However, the exact mechanism behind onset and progression of myopia is not yet fully understood. A study in Taiwan has shown that the average age of onset of myopia in 1983 was 11 years. This average of onset age decreased to 8 years in 2000. On the basis of degree, myopia is classified as low(<-3D), medium (3D-6D) and high myopia (>6 D). Sankaridurg et al suggested that the early onset of myopia results in faster annual progression, and increases risk of high levels of myopia, which leads to sight threatening diseases. They estimated that if the onset of myopia was at the age of 6 years, the annual progression of myopia is approximately -1.00D. However, if the myopia developed at 15 years the annual progression was only about -0.36 D. If a child develops – 1.00D myopia at the age of 6 years, he is most likely to develop – 6.00 D at 12.9 years and -7.00 at 16 years. If a myopia control strategy, which is started at 6 years of age slowed progression by 30% then myopia will reach up to -5.67
D by the age of 16 years.\textsuperscript{10} Hence, there is a need to implement some strategies to prevent or delay the onset and control of myopia progression in the early developmental stage of a child. Several studies even stated that protective effect of outdoor activity is more evident at an early stage of refractive error development. \textsuperscript{2, 1}

Single vision spectacles and contact lenses correct refractive error. However, they either accelerate the myopia progression by causing hyperopic defocus in the periphery or show no significant effect on the progression of myopia.\textsuperscript{17, 18}

Several options are available to correct myopic refractive error and control the progression with various degrees of success including multifocal (PALs) spectacles, multifocal contact lenses, Orthokeratology (OK) contact lenses and pharmaceutical agents. \textsuperscript{10, 8, 2} OK lenses and pharmaceutical agent – atropine are very effective and control the progression by about 50% and 60% respectively. \textsuperscript{14, 2, 3, 19, 20} However, atropine has limitations and complications \textsuperscript{2} and OK lenses are expensive and require a detailed regimen. In addition, in order to delay the onset of myopia; myopia control strategies have to be introduced at an early age. Contact lenses, spectacles or pharmaceutical agents may be inconvenient for a very young child and if the child discontinues the use of atropine or OK lenses, the myopia progression reoccurs.

In recent years, several environmental and nutritional factors have been linked to myopia progression and control.\textsuperscript{2, 21} Numerous studies indicate that more time spent indoors, excessive near work, less exposure of natural sunlight or high intensity light and western diet are related to myopia development.\textsuperscript{1, 22, 23, 24, 25} Accumulative evidence suggests that outdoor activity reduces myopia progression by about 35%. Vitamin D and dopamine have been shown to be correlated with reduced myopia progression.\textsuperscript{26, 27, 28, 29} Insulin has been linked with development and progression of myopia in many animal studies.\textsuperscript{13, 30, 24, 31}

\textit{In this review paper, we address the following questions: (a) Should we encourage the development of public health policies that increases outdoor activity in children in order slow or stop the progression of myopia? (b) Should we encourage the development of public health policies that modify diet in order to reduce myopia?}
METHODS

Search Strategy and Inclusion Criteria

Online databases, WEB OF SCIENCE and OVID MEDLINE were used for electronic search. The electronic search has been conducted separately for three topics: Time outdoors and Myopia (TOM), Peripheral Defocus and Myopia (PDM) as well as Modern Life Style and Myopia (MLM). The search was based on PICO (Population, Intervention, Control and Outcome). The following keywords are used as PICO: Population: “Children” and “animal’.

Intervention: “Illuminance,” “time outdoors,” “dopamine,” “ Progressive addition lenses,” “ contact lenses,” “ foveal ablation,” “ nutrition,” “ diet,” “ insulin” and “hyperglycemia”.

Control: Comparison group in the articles.

Outcome: “Myopia,” “hyperopic defocus,” “myopic defocus,” “peripheral defocus” and “peripheral refractive error”. Detailed search strategies are given in Table 1. Some additional articles were obtained from retrieved articles and reviews by screening their reference lists manually.

Article inclusion criteria were restricted to (1) peer reviewed articles (2) randomized control trials, case control or prospective cohort studies evaluating the association among light, time outdoors, peripheral defocus, nutrition and myopia as well as hyperglycemia, and abnormal body growth. (3) Studies in children or animals. (4) ‘Time outdoors and Myopia’ as well as Peripheral Defocus and Myopia Studies published in English from 2010 to current (2016). A review article updated on myopia and myopic progression in children was published in 2010 and taken as a baseline article for this review. 32 This review article did not include information about myopia and nutrition so our search for ‘Nutrition and Myopia’ articles was not restricted by year.

Articles included in this review paper are graded: A, B, C, D or R on the basis of study design. Grade A includes: Randomized control trials (RCTs) or Meta-analysis (systematic reviews), Grade B: Weaker RCTs (weak design but multiple studies confirm) and Cohort studies( Prospective and retrospective), Grade C: Studies with strong design but with significant doubt about the conclusion, serious uncertainty about bias, sample size and research design and studies with small sample size. Grade D: Observational descriptive cross sectional surveys, case control and case report and Grade R: Reviews. In addition, recommendations for the prevention of myopia are categorized into strong, moderate and weak on the basis of strength of the evidence.
Table 1. Search Strategies

<table>
<thead>
<tr>
<th>1(a)</th>
<th>Myopia* AND Children* AND (Illuminance OR Outdoors* OR Dopamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(b)</td>
<td>(Myopia* AND Animal* AND illuminance*)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2(a)</th>
<th>Children* AND (Myopic defocus* OR Hyperopic defocus* OR Peripheral Defocus*) AND (Contact lenses OR Progressive addition lenses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(b)</td>
<td>Animal* AND (Hyperopic defocus OR Myopic Defocus OR Peripheral refractive error*) AND (Contact lenses OR Progressive addition lenses OR Foveal ablation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3(a)</th>
<th>Children* AND (Nutrition* OR Diet* OR Insulin* OR Hyperglycemia*) AND (Juvenile-Onset Myopia OR Myopia*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3(b)</td>
<td>Animal* AND (Nutrition* OR Diet* OR Insulin* OR Hyperglycemia*) AND (Juvenile-Onset Myopia OR Myopia*)</td>
</tr>
<tr>
<td>3(c)</td>
<td>Children* AND (Indoors* OR Studying* OR TV) AND Myopia</td>
</tr>
</tbody>
</table>

Table 4: Search strategies
Table 5: Flow chart of the review inclusion

323 articles identified:
- 149 from Ovid Medline
  - TOM: Children (n=58) + Animal (n=9)
  - FDM: Children (n=11) + Animal (n=9)
  - MLM: Child Diet (n=19) + Insulin Animal (n=25) + Near work (n=18)
- 174 from Web of Science
  - TOM: Children (n=72) + Animal (n=6)
  - FDM: Children (n=32) + Animal (n=6)
  - MLM: Child Diet (n=28) + Insulin Animal (n=7) + Near work (n=23)

127 Duplicates removed

196 Articles remained after duplicates removed

100 Irrelevant articles excluded

96 Articles are included for the review
RECENT FINDINGS

TIME OUTDOORS AND MYOPIA (Published since 2010)

Recent studies suggested that time spent outdoors is effective in delaying onset of myopia.\textsuperscript{33, 34, 35, 36, 37, 38, 34, 39, 40, 35, 41, 42, 43, 44} Outdoor activities have two characteristics that have been studied. One is high intensity light which on a sunny day has 110,000 lumens per meter\textsuperscript{2} (lux) and on a cloudy day has 1000-2000 lux.\textsuperscript{45, 46, 47, 48, 22, 49, 50, 51, 52} This is a substantial amount of light compared with indoors (150-500 Lux). The other characteristic of being outdoors is the dioptric pattern of outdoor visual environment. In an outdoor scene, the objects are typically further away with less dioptric variations. Hence the outdoor visual environment has a more uniform dioptric pattern. Hence the retinal image is formed with a uniform peripheral focus compared to indoor viewing which may alter normal axial length growth.\textsuperscript{53} We believe that the high intensity light outside and uniform dioptric pattern of outdoor visual environment regulates normal eye growth.

The protective effects of outdoor activity appear more linked to the time spent outdoor rather than physical activity.\textsuperscript{54, 37} Guggenheim et al found that myopia occurrence was less in children who spent more time outdoor, but indoor sports activity did not prevent myopia development. Time spent outdoors predicted myopia development independent of physical activity.\textsuperscript{37} Children who spent less time outdoors were 40\% more likely to develop myopia than children spending more time outdoors. In a similar study children with low levels of physical activity were only 10\% more likely to develop myopia than children with high levels of physical activity.\textsuperscript{55}

**Time spent outdoor and reduced rate of myopia incidence: Evidence from interventional studies**

He et al conducted a cluster randomized trial on outdoor activity in China. For this study, children from 29 schools were selected. From these 29, six groups of two schools matched on visual acuity were selected to be randomly assigned to an intervention of increased outdoor activity or control. Baseline data were gathered from grade 1 (6-7 years) to grade 4 with annual follow up. Before collecting the baseline data, information sessions were conducted in schools participating in this study. During that session information was given about the study to principals and teachers of the schools and parents. Increasing time spent outdoors was implemented in two ways. An additional 40 minutes were added in the school schedule for outdoor activities and children were encouraged to spend time outdoors during holidays. Visual acuity was measured using ETDRS chart and cycloplegic refraction using an auto refractor. The primary outcome of this study was the three year cumulative incidence of myopia in experimental and control groups. The secondary outcome was change in mean spherical error and axial length over 3 years. Time spent outdoors during holidays was recorded by questionnaire where average daily time spent
outdoors was calculated by adding the time outdoors in school and outside school. In the descriptive
analysis of baseline characteristics, t tests revealed no difference in initial spherical equivalent and axial
length between control and experimental group. Changes in spherical equivalent refraction and axial
length between control and experimental group were compared using mixed model analysis of
covariance. In primary outcome analysis, the cumulative incidence rate of myopia was 24.2% in the
experimental group and 31.1% in the control group. Using a post hoc logistic regression model adjusting
for parental myopia, there was a significant decreased risk (odds ratio was 0.73; 95% CI, 0.57 to 0.92; P = .01) for the three year incidence rate of myopia in the experimental group compared with the control
group. Cumulative change in spherical equivalent refraction (myopic shift) after three years was
significantly less in the experimental group than in the control group (mean of −1.42 D vs −1.59 D,
respectively; difference of 0.17 D) [95% CI, 0.01 D to 0.33 D]; P = .04). These data suggested that the
policy of adding about 40 minutes of additional outdoor activity during school hours for three years may
reduce the incidence rate of myopia.35

In suburban area of Taiwan, A prospective interventional study has been performed in children aged 7 to
11 years, to investigate the effect of outdoor activities during the class recess on myopia. Two schools
with same socioeconomic status were selected for this study. 333 students from one school served as an
interventional group and 238 from the other school participated as a control group. The purpose of the
intervention was to bring a recess outside the classroom (ROC) program wherein all the children were
encouraged to go outside; lights of the class rooms were turned off and class were emptied. The total
recess time was 80 minutes per day and 6.7 hours weekly in the intervention group. However, control
group did not have any special program for outdoors. The cycloplegic auto refraction and axial length
measurement were taken at the beginning and end of the study. There was no significant difference
between intervention and control group at the baseline with regard to age, gender, baseline refraction and
prevalence of myopia (47.75% vs. 49.16%). However, there was significantly less onset of new myopia in
the intervention than control group (8.41% vs. 17.65%; P<0.001) after one year. In addition, the myopia
progression was significantly lower in the intervention compared to control group (−0.25 diopter [D]/year
vs. −0.38 D/year; P = 0.029). This study concluded that outdoor activity during class recess has protective
effect on both development and progression of myopia.56

**High intensity light levels are protective: evidence from animal studies**

Light intensity as a potential control mechanism has been supported with animal studies.46, 45, 57, 58, 58
Cohen et al raised chicks for 90 days under three different light intensities (50 Lux, 500 Lux and 1000
Lux) during the day. They did not manipulate defocus. They found that the chicks raised in dim light
intensity (50 Lux) developed emmetropization in 30 days and become myopic in 90 days. Chicks that
were raised under medium light intensity developed emmetropization in 55 days and remained emmetropic for up to 90 days. Chicks that were raised in high intensity (1000 Lux) were remained hyperopic beyond 90 days.\(^5\)

A similar study was conducted in rhesus monkeys by Smith et al. Data presented for 58 rhesus monkeys. Out of 58, eight monocular form deprived rhesus monkeys were primary subjects and were reared under normal lighting condition (15-630 Lux) to high lighting condition (2500 Lux). The data of 32 normal and 18 monocular form deprived monkeys served as control and were raised in normal light. Monocular form deprivation was created by fitting goggles in infant monkeys that contained zero powered spectacles in front of one eye and zero powered diffuser spectacles in front of the treated eye for 6 hours a day for 23 to 136 days. The zero powered diffuser spectacles consisted of light perception bangerter occlusion foil that reduced the retinal image contrast dramatically but did not affect the spectral composition of the retinal image. Refractive status and axial length growth were assessed after the study by retinoscopy and ultrasound respectively. They found that high intensity light levels retarded the progression of myopia development. Sixteen out of 18 normal lights reared, form deprived monkeys developed myopia. Whereas, only 2 out of 8 form deprived monkeys developed myopic anisometropia (eyes differ in amount of refractive error) under high intensity light condition. At the beginning of the study (3 weeks of age), the refractive errors of the right and left eyes were closely matched in all animals (all subject groups combined; OD versus OS average ± SD: +4.12 ± 1.77 D vs. +4.18 ± 1.71 D; \(t = −1.38; P = 0.17\)). There were no differences in mean refractive errors between the control eyes in groups (right eyes: \(P = 0.16−0.54\)). Form deprived monkeys raised in normal light condition showed consistent axial length growth in treated eyes. This study concluded that time spent outdoor could be protective against myopia progression in children because of high intensity light exposure.\(^4\)

Smith et al conducted another study to determine whether high intensity light retarded development of myopia caused by lens induced hyperopic defocus. For this study, hyperopic defocus was induced in 27 monkeys by putting -3.0 D lens in front of one eye. Fifteen out of 27 treated monkeys raised in normal light condition (350Lux) and another 12 treated monkeys reared in artificial high intensity light (2500 Lux) for 6 hours from 50 to 123 days. Refractive errors, corneal curvature and axial length were assessed by retinoscopy, keratometry and ultrasonography, respectively. Data were obtained from previous studies also of 37 monkeys four of which were exposed to high ambient light. They found that in both normal and high light-reareded monkeys, lens induced hyperopic defocus triggered vitreous chamber growth and developed myopia. The high intensity light levels did not retard the development of myopia due to lens induced hyperopic defocus (high light: -1.69 +/- 0.84D vs normal light: -2.08 +/- 1.12 D ; \(P= 0.40\)).
concluded that the mechanism responsible for form deprivation myopia and lens induced myopia were different.\textsuperscript{59}

However, Wong et al conducted two experiments in rhesus monkey to assess the protective effect of bright sunlight on myopia. In this study, hyperopic defocus was imposed by putting -3.00D lens in right eye and zero power in left eye. Three groups were studied. Two groups with -3D lens in one eye and one group had no minus lens in either eye. Of the two groups with -3D in one eye, one group was exposed to 12 hours of artificial lighting each day and the other group had 12 hours of artificial light with 3 of those hours in natural light. The animals were followed for 3 months and the difference in refraction between eyes was measured. The group with 3 hour exposure to natural light was equivalent to the control with no -3D lens in either eye. The group with only artificial light had significantly more myopia in the -3D lens (-1.66D +/-0.87D). The group raised under natural light was more hyperopic compared to the group raised under artificial light showing that natural light was protective against hyperopic defocus induced myopia in children(-0.22±0.44D; \(P=0.002\)). A difference between the Smith and Wang studies was the spectral distribution of the light sources and light intensity levels. In the Smith study, metal halide lamp was used with color temperature 3500K, which strongly emits full spectrum of light but this source is stronger in longer and middle wavelengths but weaker in short wavelengths. Whereas, the Sunlight outside is typically short wavelength blue light and the Wang study’s artificial light had a peak in the blue light area (453nm plus peaks at 545nm and 611nm) with a color temperature 6500K. In addition, the averaged illuminance levels in Smith’s study was 25,000 lux however, the illuminance levels of natural sunlight in Wang study varied widely from 6000 lux to 70,000 lux from cloudy to clear sunny day and the mean illuminance level was higher in Wang study from 25,000 to 40,000 lux. The differences in the studies may support the hypothesis that blue light (light in the shorter wave length portion of the visible spectrum) affecting s-cones in the periphery or high intensity light may be part of the mechanism controlling myopia progression.\textsuperscript{51}

**Increased Vitamin D levels**

The chief source of vitamin D is endogenous synthesis after skin is exposed to the Sun. Vitamin D deficiency has become well known condition in many populations and level of 25(OH) D is decreasing over time perhaps, due to behavioral changes to less outdoor activity. Taking into consideration, the genetic and environmental factors and correlated temporal pattern offer compelling evidence that risk of myopia development is associated with vitamin D related factors.\textsuperscript{28} Numerous studies linked vitamin D with myopia development.\textsuperscript{26, 27, 28, 29} A study conducted in Australia demonstrated the association of myopia with lower level of vitamin D. Twenty nine hundred pregnant women attending the public antenatal clinic at King Edward Memorial Hospital or nearby private practices were selected for the Raine...
A study between May 1989 and November 1991. A total of 2868 of their children have undergone serial assessment since birth. 1344 children attended the eye examination however, 198 children did not have their serum 25(OH) D measured and there was incomplete clinical or questionnaire data for 200 participants. 25(OH) D is a (pre hormone produced in liver) metabolite used to determine the status of vitamin D. 946 had data for serum 25(OH) D3 along with potential confounders including age, sex, ethnicity, parental myopia, education and ocular Sun exposure. However, only 837 children had data for time spent outdoors and potential confounders. Of the 946 children who received an eye examination, 221 were myopic and 725 non-myopic. Lower serum 25 (OH) D3 concentration was found in myopic children compared to non-myopic children. (Median 67.6 vs. 72.5 nmol, P = 0.003). In univariate analysis, lower concentration of serum 25(OH) D3, less than 50 nmol/L, was related to higher risk of myopia development (OR = 2.63; 1.71–4.05 95% CI, P < 0.001). This association remained after adjustment of potential confounders comprising age, sex, ethnicity, parental myopia, education and ocular Sun exposure biomarker score (adjusted OR 2.07; 1.29–3.3295% CI, P = 0.002). The study suggested that less exposure to sunlight was associated a with higher prevalence of myopia.

Table 6: Time spent outdoors and myopia: Evidence from unsystematic reviews.

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Design</th>
<th>Number of references</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMonnies¹ (2015)</td>
<td>Review</td>
<td>71</td>
<td>Outdoor activity is protective whereas too much near work is a risk factor for normal eye growth. Risk estimation prior to onset of myopia and early implementation of interventions could significantly decrease the chance of progression to pathological myopia.</td>
</tr>
<tr>
<td>Mihelcic² (2013)</td>
<td>Review</td>
<td>27</td>
<td>Before onset and in the beginning stage of myopia, spending time outside reduces the risk of development and progression of myopia. In addition, sustained near work should be avoided.</td>
</tr>
<tr>
<td>Myrowitz³ (2012)</td>
<td>Review</td>
<td>58</td>
<td>Children who spend more time outdoor are less likely to develop myopia.</td>
</tr>
<tr>
<td>Pan⁴ (2011)</td>
<td>Review</td>
<td>94</td>
<td>Less time outdoors and more time spent on near work, higher educational level and parental myopia are the risk factors for development of myopia.</td>
</tr>
</tbody>
</table>
Spending more time outdoor protects young children from myopia. This protective effect of time outdoors may be due to high intensity of light, chromaticity of day light or higher levels of vitamin D.

High intensity light is protective against myopia.

Increased outdoor activity prevents the development of myopia and provide substantially risk free environment for normal eye growth.

Worldwide increase in prevalence of myopia is associated with educational pressure and life style changes which reduced the time that children spend outside.

Bright light stimulate dopamine production, Increased level of dopamine in the retina generates a signal that inhibits eye growth.

Increase outdoor activity is the best potential intervention we have at this time to recommend to children to control myopia.

Children who spend more time outside are less likely to develop myopia. Dopamine release is stimulated by bright light outside inhibits eye growth.

<table>
<thead>
<tr>
<th>Study/(Year)/Region</th>
<th>Design</th>
<th>Control (N)</th>
<th>Treatment (N)</th>
<th>Primary outcome</th>
<th>Effect size/ OR/RR/ significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read22 (2015) Australia</td>
<td>Cohort</td>
<td>Non myopes(N=60)</td>
<td>Myopes (N=41)</td>
<td>Bright light retards axial length growth</td>
<td>Mean axial eye growth: Non myopic: (0.05 ± 0.05 mm) Myopic: (0.19 ± 0.20 mm), Effect size: 1.12 ** for p&lt;0.001</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Setting</td>
<td>Group 1 (N)</td>
<td>Group 2 (N)</td>
<td>Findings</td>
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<tr>
<td>Choi (2014) Korea</td>
<td>Cross sectional survey</td>
<td>Non-myopic children (N=405)</td>
<td>Myopic (N=1633)</td>
<td>Serum 25(OH) D is lower in myopic children especially in high myopes</td>
<td>* for p=0.054, Non-myopes: 16.3 ± 0.3. High myopes: 15.2 ± 0.4 Effect size= 3.14</td>
</tr>
<tr>
<td>Guggenhiem (2014) UK</td>
<td>Cohort</td>
<td>Not likely myopic(N?) children</td>
<td>Likely myopic (N=?)</td>
<td>lower 25(OH)D in likely myopic group</td>
<td>Likely myopic vs not likely myopic :58.1 (95% CI = 56.7–59.5) vs. 60.3 [95% CI = 59.6–61.0] nmol/L; ** for P = 0.007</td>
</tr>
<tr>
<td>Parssinen (2014) Finland</td>
<td>RCT</td>
<td>Outdoor activity &lt; 3 hours (N=96)</td>
<td>Outdoor activity &gt; 3 hours (N=50)</td>
<td>Less myopia with more time spent outdoor</td>
<td>* for p= 0.041</td>
</tr>
<tr>
<td>Yazar (2014) Australia</td>
<td>Cohort</td>
<td>Non-myopic children (N=725)</td>
<td>Myopes (N=221)</td>
<td>Lower serum 25(OH) D concentration in myopes</td>
<td>(median 67.6 vs. 72.5 nmol, P = 0.003), (adjusted OR 2.07; 95% CI 1.29-3.32; ** for P = 0.002)</td>
</tr>
<tr>
<td>Guo (2013) China</td>
<td>Cross sectional</td>
<td>Rural (N=311)</td>
<td>Urban (N=370)</td>
<td>Less time spent outdoors in urban region was associated to myopia</td>
<td>(**P&lt;0.001; OR, 0.32; 95% CI, 0.21–0.48). The total outdoor time: Urban vs rural (1.1+/-.4 vs. 2.2+=/.8 hours) ** for P=0.001</td>
</tr>
<tr>
<td>He (2015) China</td>
<td>RCT</td>
<td>No additional time for outdoor activity (N=951)</td>
<td>Additional 40 minutes class of outdoor activities (N=952)</td>
<td>Lower incidence of myopia in intervention group</td>
<td>Control vs Intervention (39.5% vs 30.4%), RR= 0.769, (difference of -9.1% [95% CI, -14.1% to -4.1%]; ** for P&lt;.001)</td>
</tr>
<tr>
<td>French (2013) Australia</td>
<td>Cohort</td>
<td>Less time spent outdoors (N?)</td>
<td>More time spent outdoors (N?)</td>
<td>Children who spent less time outdoor became myopic.</td>
<td>Myopic vs non-myopic : younger cohort(16.3 vs. 21.0 hours/week, ** P &lt; 0.0001),older cohort: (17.2 vs. 19.6 hours/week), ** for P=0.001</td>
</tr>
<tr>
<td>Guggenheim (2012) England</td>
<td>Cohort</td>
<td>Less time spent outdoors (N=?)</td>
<td>more time spent outdoors (N=?)</td>
<td>Children who spent less time outdoor are</td>
<td>Hazard ratio for incidence of myopia: More time spent</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Findings</td>
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<tr>
<td>Guo(^{39}) (2013) China</td>
<td>Cross sectional</td>
<td>Less time spent outdoors (N=570)</td>
<td>More time spent outside (N=73)</td>
<td>Less time spent outdoors was significantly associated with axial length growth</td>
<td>(* for (P=0.02); OR: 0.53; 95%CI: 0.32, 0.88)</td>
</tr>
<tr>
<td>Gwiazda(^{40}) (2014) United States</td>
<td>RCT</td>
<td>Winter visits (N = 146)</td>
<td>Summer visits (N= 212)</td>
<td>Myopia progression was lesser in summer</td>
<td>Myopia progression: (Winter vs Summer) ((-0.35 \pm 0.34 , \text{D} \text{vs} -0.14 \pm 0.32 , \text{D})); Effect size: 0.63 Significant difference (0.21 D ** for (P &lt; 0.0001))</td>
</tr>
<tr>
<td>Jin(^{41}) (2015) China</td>
<td>Cohort</td>
<td>School without recess outside program (N= 1316)</td>
<td>School with recess outside program (N=1735)</td>
<td>Onset of myopia was lower in intervention group</td>
<td>Onset of myopia: Intervention vs control (3.70 % vs. 8.50 %), RR = 0.43 * for (P = 0.048)</td>
</tr>
<tr>
<td>Lin(^{43}) (2014) China</td>
<td>Cross sectional</td>
<td>Myopes (N=252)</td>
<td>(Emmetropes+ Hyperopes) (N= 118)</td>
<td>Myopes had less outdoor activity</td>
<td>Time spent outside(h/d)): 0.00 vs (2.29-6.21); SE in D (-1.34 +/- 2.45) vs (-0.25 +/- 2.06) respectively, Effect size: 0.48 ** for Ptrend=0.0003</td>
</tr>
<tr>
<td>Backhouse(^{46}) (2013) New Zealand</td>
<td>Cohort</td>
<td>Low illumination (300Lux) (N= 11)</td>
<td>High illumination (2000 lux) (N= 11)</td>
<td>Less myopia development in the treatment group</td>
<td>SE of high illumination vs low illumination(-4.94 +/- 1.21 , \text{D}) vs (-9.73 +/- 0.96 , \text{D}); Effect size: 4.41 * for (p = 0.022)</td>
</tr>
<tr>
<td>Smith(^{47}) (2012) United States</td>
<td>Cohort</td>
<td>Monocular form deprived monkeys under ordinary light (N=18)</td>
<td>Monocular form deprived monkeys under high artificial light (N= 8)</td>
<td>Less myopia development in treatment group</td>
<td>No. of monkeys developed myopia: [Treatment group vs control group; 2(25%) vs 16(88.88%), RR=0.28]</td>
</tr>
<tr>
<td>Mcknight(^{48}) (2014)</td>
<td>Cross sectional</td>
<td>Myopic (N=311)</td>
<td>Non myopic (N=1017)</td>
<td>Less prevalence of myopia with</td>
<td>Prevalence of myopia in the lowest</td>
</tr>
<tr>
<td>Country</td>
<td>Study Type</td>
<td>Cohort</td>
<td>Exposure/Outcome</td>
<td>Findings</td>
<td></td>
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<tr>
<td>Australia</td>
<td>Cohort</td>
<td>Emmetropes (N=13)</td>
<td>Stable myopes + progressive myopes (N=22)</td>
<td>Increased light (UV) exposure quartile of conjunctival auto fluorescence vs highest quartile of conjunctival auto fluorescence; (33.0% vs 15.6%, OR=0.47)</td>
<td></td>
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<tr>
<td>Schmid (2013) Australia</td>
<td>Cross sectional</td>
<td>Lowest UVAV quartile</td>
<td>Highest UVAV quartile</td>
<td>Prevalence of myopia was less in highest UVAF quartile UVAF quartile was associated with an OR of myopia of 0.76, 95% CI = 0.66–0.96, P_trend = 0.015 (SE ≤ −0.5 D); and OR of myopia 0.68 (95% CI = 0.54–0.86), **P_trend = 0.001 (SE ≤ −1.0 D)</td>
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<tr>
<td>Sherwin (2012) Australia</td>
<td>RCT</td>
<td>Artificial Light Group (AL): (25000-4000 lux) (N=4)</td>
<td>Natural Light group(NL): AL + 3 hours natural sunlight (N=4)</td>
<td>NL group were more hyperopic than those in the AL group (F=5.726, *P=0.032) (AL vs NL: -1.66+/-.087D vs -0.22+/-.44D;) Effect Size: 2.19 ** for p=0.002</td>
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<tr>
<td>Deng (2010) United States</td>
<td>Cross sectional</td>
<td>Myopes (N= 33)</td>
<td>Non-myopes (N= 114)</td>
<td>Non Myopes spent more time outside during school year Time spent outdoor/week: myopes vs non myopes; (8.25 ± 6.24) vs (10.95 ± 5.95), Effect size: 0.44 * for (p &lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td>Read (2014) Australia</td>
<td>Cohort</td>
<td>Myopes (N=41)</td>
<td>Non-myopes (N=61)</td>
<td>Higher light exposure in non-myopic children Mean daily light exposure: myopic vs non-myopic; (915 +/- 519 lux) vs (1272 +/- 625 lux), Effect size: 0.62 ** for p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Wu (2013) Taiwan</td>
<td>Cohort</td>
<td>School without recess outside program (N= 238)</td>
<td>School with recess outside program (N=333)</td>
<td>Prevalence of myopia was less in treatment group Treatment vs control : (8.41% vs. 17.65%), RR: 0.47 ** for P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cohen^{57} (2011) Israel</td>
<td>Cohort</td>
<td>Medium and low intensity light (50 and 500 lux) (N=27)</td>
<td>High intensity (10,000 lux) (N=13)</td>
<td>Chicks under high intensity were more hyperopic</td>
<td>SER on 90 days, Low intensity vs high intensity; [-2.41D (95% CI -2.9 to -1.8D)] vs +1.1D</td>
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<tr>
<td>Cohen^{58} (2012) Israel</td>
<td>Cohort</td>
<td>Light-dark cycles N=46</td>
<td>Continuous light N=42</td>
<td>Under light-dark cycles, low vitreal concentration of DOPAC (dopamine) was associated with myopia</td>
<td>SER on 90 days: (Light-dark cycles vs continuous light); (-2.41 ± 1.23) vs (+0.63 ± 3.61), Effect size: 1.25</td>
</tr>
<tr>
<td>Smith^{59} (2013) United States</td>
<td>Cohort</td>
<td>Monkeys raised in low illumination (350 lux) (N=15)</td>
<td>Monkeys raised in high illumination (2500 lux) (N=12)</td>
<td>High illumination did not retard the eye growth</td>
<td>(High light: -1.69 ± 0.84 D versus normal light: -2.08 ± 1.12 D; Effect size: 0.39 * for p=0.40)</td>
</tr>
<tr>
<td>Wu^{73} (2015) China</td>
<td>Cross sectional survey</td>
<td>Myopic shift (N=2170)</td>
<td>No myopic shift (N=2122)</td>
<td>Greater shift towards myopia was associated to less time spent outdoors</td>
<td>(OR=0.87, 95% CI=0.78-0.97,** for P&lt;0.013).</td>
</tr>
<tr>
<td>Saxena^{76} (2015) India</td>
<td>Cross sectional</td>
<td>Myopes (N=1297)</td>
<td>Non-myopes (N=8587)</td>
<td>Less prevalence of myopia was associated with outdoor activities/playing &gt; 2 hours in a day.</td>
<td>** for P &lt; 0.001</td>
</tr>
<tr>
<td>Foulds^{85} (2013) Singapore</td>
<td>Cohort</td>
<td>Chicks raised under red wavelengths (N=16)</td>
<td>Chicks raised under blue wavelengths (N=19)</td>
<td>Chicks under red wavelength developed myopia</td>
<td>SER on days: Red vs Blue; (-2.83 ± 0.25 D) vs (+4.55 ± 0.21 D) Effect size: 7.47</td>
</tr>
<tr>
<td>Lan^{90} (2013) Germany</td>
<td>Cohort</td>
<td>Chicks raised under normal light (N=14)</td>
<td>Chicks raised under bright light (N=14)</td>
<td>Bright light stimulates the choroidal thickening.</td>
<td>Choroidal thickness: Bright light vs normal light; (+7.6 +/- 26.0%) vs (-18.6 +/-26.9%), * for p=0.039)</td>
</tr>
</tbody>
</table>
PERIPHERAL DEFOCUS AND MYOPIA

Peripheral refractive error can be classified into hyperopia (image formed behind the retina) and myopia (image created in front of the retina). Relative peripheral defocus is defined as the difference between off-axis (peripheral retina-away from the center) and on-axis (central retina) refraction. Peripheral optics may influence the onset of myopia either by peripheral refraction pattern or retinal shape.\textsuperscript{61, 62, 63} Researchers suggested that central refractive error can be controlled by altering peripheral retinal defocus. Hyperopic defocus at the peripheral retina accelerates axial length growth while myopic defocus retards eye growth.\textsuperscript{64, 65, 66, 18} In addition, it has been reported that the central retina does not contribute in an essential way to the changes in the eye shape during the development of vision induced myopia.\textsuperscript{67} A study has been conducted in 820 children aged between 5 and 15 years to define their eye shape. Peripheral refraction was measured at 30 degrees in the nasal visual field. Ocular shapes were described on the basis of relative peripheral refraction at this position. Myopic eyes had a mean relative peripheral hyperopia of $+0.80 \pm 1.29$D and were most often considered prolate (elongated along the visual axis eye relative to the axis on the equator). Emmetropic eyes with relative peripheral refraction had a mean of $-0.41 \pm 0.75$D and considered primarily spherical or slightly oblate and hyperopic eyes with relative peripheral myopia of $-1.09 \pm 1.02$D were oblate (wider in the equator). In some studies, eye shapes were investigated using MRI, X-rays, computerized topographies and ultrasonography. In these studies, axial length of the eye was compared with one or both height and width of the eye. Most of these studies reported greater increase in length than height and width with increase in myopia.\textsuperscript{61} Huang et al conducted a study in rhesus monkeys to assess the ocular shape after inducing myopia and form derivation experimentally. Myopia and form deprivation have been induced in two groups of monkeys by putting -3D and zero powered diffusers in one eye and plano lenses in fellow eye. The treatment was started at 22 +/- 2 days of age and continued until 158 +/- 22 days of age. Consequently, lenses were removed and monkeys were allowed unrestricted vision until 340 days of age. Ocular biometry and MRI have been performed to assess the change in axial length and ocular shape. This study found that during treatment period, axial length has increased and at the same time width of the eye decreased and eye become prolate. On other hand, during recovery period, axial length growth has stopped but eye has become wider at equator and become oblate. This study suggested that peripheral refraction is not constant; it changes over time as central refraction changes and eventually shape of the eye changes.\textsuperscript{68} Lining up the focal plane with the retina requires lens and corneal power to be able to compensate for the length of the vitreous chamber. When the myopic eye is prolate the width of the eye does not allow the radius of the lens to grow to provide sufficient power to compensate for the axial length. Smith et al induced myopia in young primates. After removing the lens the myopic chimps developed normal emmetropic vision. We suspect
that rather than shortening their axial length, their eyes became more prolate and provided more lens power.

A study with Singapore Chinese children determined whether relative peripheral hyperopia was associated with an increased risk of developing myopia or myopia progression. The study was a follow up report of the Peripheral Refraction in Preschool Children study (PREP). PREP study examined peripheral refraction and central refractive error of 250 Singapore Chinese children in single visit and detail data has been published. The 250 children who participated in the PREP study were contacted for their clinical examination approximately 1 year after their initial assessment. The data obtained from the PREP study was considered as baseline and compared with data taken during follow-ups visits. Cycloplegic refraction was performed by infrared ray auto refractometer along central, 15 degree, and 30 degree nasal and temporal eccentricities. Of the 250 children who participated in the PREP study, 187 were recruited for this study with a mean age of 7.2 years (range 3.4 -15.8 years). The spherical equivalent (SE) for all children was significantly more negative at the follow-up visits than baseline visit at all eccentricities. (all P < 0.001). Ninety six children, who were myopic in baseline visit, were more myopic in follow-up visits. Sixty-seven children have become-myopic after registering hyperopic or emmetropic at baseline. Twenty four children remained non-myopic who were emmetropic or hyperopic at baseline. At the follow-up visits, children who became- myopic were myopic at all peripheral eccentricities whereas children who remained non-myopic were hyperopic at all peripheral eccentricities. However, numerous studies suggested that myopic eyes are prolate and have hyperopic defocus at the periphery. At the baseline visit, those who remained non- myopic and those who became- myopic had relative peripheral myopia at all eccentricities. However, those who remained non- myopic maintained relative peripheral myopia but those who became- myopic children had relative peripheral hyperopia at nasal and temporal the 30 degree point at follow up visits. At the baseline visit, myopic children had relative peripheral hyperopia at nasal and temporal 30 degree and at the follow-up visits; myopic-children had relative peripheral hyperopia at 15 degree nasal and temporal and developed more relative peripheral hyperopia at 30 degree nasal and temporal eccentricities. This study found no significant association between relative peripheral SE and central SE for children who became myopic in follow up visits and suggested that relative peripheral hyperopia was not an important factor for development of myopia. Relative peripheral hyperopia rather occurred due to axial length elongation as the eye changes its shape from oblate to prolate. However, compelling evidence has been found from animal studies that peripheral retina might play an important role in myopia development.

Huang et al conducted a study in 18 monocular form deprived rhesus monkeys. The form deprivation was implemented by securing diffusers in front of their treated eyes between 22 +/- 2 and 155 +/- 17 days of
age. The fovea and most of the parafoveal region of treated eyes were ablated by laser photocoagulation at the beginning of the diffuser rearing period. Each eye’s refractive status was measured using a retinoscope along the pupillary axis and at 15 degree intervals to eccentricities 45 degree along horizontal meridian. Data from 12 normal monkeys and five monkeys that had monocular foveal ablation were treated as control. This study found that the foveal ablation did not interfere with either the central or peripheral refraction of treated eyes. Moreover, foveal ablation did not interfere with the pattern of peripheral refractions in form deprived monkeys. This study suggested that foveal input does not contribute in an essential way to the alterations in eye shape that occur during development of FDM. This study also suggested that peripheral vision or peripheral refractive status may play a significant role in development central refractive error.67

Near work and myopia
Several epidemiological cross-sectional and cohort studies linked near work with myopia.70, 36, 71, 72, 73 Even though, numerous studies conducted to identify the relationship between near work and myopia, the mechanism is still unclear, with some studies reporting positive findings.70, 36, 71, 72, 73 and other revealing no relationship 74, 43.

The Beijing eye pediatric eye study conducted in 15066 school children with mean age 13.2 +/- 3.4 years. This study reported that long reading duration (OR:1.10;95%CI:1.06,1.15), shorter distance watching TV or computer (OR:0.93;95%CI:0.89,0.97), dim reading illumination (OR:0.93;95%CI: 0.88,0.98) are significantly associated with myopia. 75 In North India Myopia (NIM) study, prevalence of myopia and its risk factors on 9884 urban school children with mean age of 11.6 +/- 2.2 years was investigated in Delhi. Studying > 5 hours/day (p < 0.001), watching TV > 2 hours/day (p < 0.001) and playing games with computer/video/mobile games (p < 0.001) were shown significantly associated with myopia. 76 A study in Taiwan, conducted on 5048 male military conscripts aged 18-24 years and reported that high levels of education ((p = 0.001), more time spent in studying (p = 0.001), and higher levels of urbanization (p = 0.010) were associated significantly with myopia. 72 On other hand, some studies did not find positive correlation between myopia and near work. Near was not significantly related to myopia in Chinese children and axial length progression in children with various ethnic groups.74, 43 The mean refractive error of Chinese children was not significantly different with various levels of near work. With 10 hours of additional near work, myopia progression did not increase in children with diverse ethnicities.74 Current evidence suggests that long duration of near work that is consistent at a distance < 30 cm with
lesser breaks are more important than total number hours. However, exact quantification of near work is difficult because the available evidence are based on questionnaire based approach which subjective and may be memory biased.

**Outdoor Vs Indoor**

In outdoor visual environment, mostly targets are present at a distance with less dioptic variation. Hence, peripheral retina always gets a point where it is in focus. Whereas animal studies suggested that retinal image defocus play a vital role in eye growth and refractive error development in chicks. Positive lens induced myopic defocus retards eye growth however negative lens induced defocus leads to axial elongation and myopia. In positive lens imposed defocus, choroid thickens and brings the focal plane forward in order to make the image clear. On other hand, negative lens causes choroidal thinning and pull the retina backward, results in myopia. In human, reduced accommodative response (lag of accommodation) which forms an image behind the retina is similar to the negative induced defocus in animals. The hyperopic defocus due to lag of accommodation, may stimulate the growth of posterior part of the eye to shift the retina toward the point of clear focus, results in axial length elongation. Therefore, with high deficit of accommodation during too much near work will cause hyperopic defocus, which might act as a stimulus for eye growth.

In addition, a review article reported that non-presbyopic eye adjust the near task by accommodating according to the object distance. However, this adjustment is not accurate and lags behind the retina by 0.50D for the 40cm object distance and forms hyperopic defocus. Moreover, if we believe that central vision is clear at the point of fixation due to sustained effort of accommodation, most of the periphery will be out of focus for the objects present at variable short distances in indoor visual environment, therefore leading to a form of deprivation myopia. Figure: 1.

**Abnormal reading posture and peripheral defocus**

Neil et al stated that the range of dioptic stimuli will depend on the environment itself, head position and orientation within that environment. Short reading distances are likely to increase the stimulus range. Children adopt reasonable long reading distance however; children preferred their relaxed posture when they get tired particularly for long reading duration. Due to short working distance and pronounced head turn, the spatial distribution of dioptic stimuli available will be different for each eye. The eye which is closer will have higher dioptic stimuli. Even with equal convergence, wide variation of vergence can be seen due to obliquity of the line of sight with respect to the child’s workbook and desk. Considering that accommodation is maintained at the point of fixation, most of the periphery will be out of focus. In this situation, where most of periphery is badly out of focus, emmetropization process could not function normally and therefore, a type of form derivation myopia occurs as mentioned earlier.
It appears that it is blur that is a factor promoting myopia. The most common environment with peripheral blur is indoors. Hence outdoor visual environment seems to be suitable for normal eye growth.

Figure 1: Peripheral defocus

Table 8: Peripheral defocus and myopia: Evidence from unsystematic reviews

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Design</th>
<th>Number of references</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sankaridurg (2014)</td>
<td>Review</td>
<td>73</td>
<td>Peripheral myopic defocus retards the eye growth</td>
</tr>
<tr>
<td>Pan (2011)</td>
<td>Review</td>
<td>94</td>
<td>Relative peripheral hyperopia can stimulate the compensating eye growth in the center. More time spent on near work, higher educational level and parental myopia are the risk factors for development of myopia.</td>
</tr>
<tr>
<td>Sivak (2012)</td>
<td>Review</td>
<td>155</td>
<td>There is a possible connection between relative peripheral hyperopia and onset of myopia. Reduction in peripheral hyperopia show significant reduction in progression of myopia.</td>
</tr>
<tr>
<td>Smith (2013)</td>
<td>Review</td>
<td>117</td>
<td>Imposed peripheral myopic defocus retards progression of myopia</td>
</tr>
<tr>
<td>Charman (2023)</td>
<td>Review</td>
<td>64</td>
<td>Indoor visual environment is unfavorable for normal eye.</td>
</tr>
</tbody>
</table>
growth. Due to presence of many objects with various dioptic stimuli indoors, most of the peripheral retina will be out of focus, which triggers myopic growth.

Table 9: Peripheral defocus and myopia: Evidence from epidemiological studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Control group</th>
<th>Human/animal</th>
<th>Primary outcome</th>
<th>Effect size/OR/Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu&lt;sup&gt;62&lt;/sup&gt; (2012) United States</td>
<td>Cohort</td>
<td>Two zones contact lens (-5 D central/-10 D Periphery) (N=7)</td>
<td>Two zones contact lenses (-10D Central/-5D Periphery) (N=7)</td>
<td>Less myopic growth in treatment group</td>
<td>SER: Treatment vs control group: ((-4.73 \pm 0.89 \text{ vs } -8.86 \pm 0.70 \text{ respectively})) Effect size: 5.19</td>
</tr>
<tr>
<td>Liu&lt;sup&gt;63&lt;/sup&gt; (2011) United States</td>
<td>Cohort</td>
<td>Plano lens (N=9)</td>
<td>2- zones contact lens: Plano at the center and + 5 D in the periphery (N=6)</td>
<td>Chicks in the treatment group were more hyperopic</td>
<td>SER: Treatment vs control (+4.25 ± 0.35D vs +0.19 ± 1.14 D) Effect size: 5.44</td>
</tr>
<tr>
<td>Benavente&lt;sup&gt;64&lt;/sup&gt; (2014) United States</td>
<td>Cohort</td>
<td>Plano lens at the center and −5.0 D at the periphery N= 10</td>
<td>Plano at the center and + 5 D at the periphery N= 10</td>
<td>More hyperopic eyes in the treatment group.</td>
<td>SER: Treatment vs control (+0.94 ± 0.65D vs −1.28 ± 0.37 D) Effect size= 4.35 * for P &lt; 0.05</td>
</tr>
<tr>
<td>Huang&lt;sup&gt;67&lt;/sup&gt; (2011) United States</td>
<td>Cohort</td>
<td>Form Deprivation (FD) (N= 10)</td>
<td>Form deprivation + Foveal ablation (FD+FA) (N= 8)</td>
<td>No significant difference between treatment and control in SER</td>
<td>SER: Treatment vs control ((-1.76 \pm 2.75 \text{ D vs } -4.08 \pm 3.94 \text{ D})), Effect size: 0.69 (T= 1.47,)</td>
</tr>
</tbody>
</table>
### MODERN LIFESTYLE AND MYOPIA

In last 150 years the world has changed due to urbanization and industrialization. Life has become more demanding and stressful and people do not find time even to exercise on a regular basis. People spend more time indoors performing near work tasks such as studying, playing games on mobile devices and watching TV. Eating behaviors have changed from low glycemic (low sugar content), protein and vitamin rich food to high glycemic index, processed food (high sugar, additives, and less nutrition). The rapid urbanization and lifestyle changes including diet, prolonged reading, less physical activities, and less time spent outdoor are thought to be risk factors of abdominal obesity, insulin resistance, type2 diabetes and perhaps leads to unregulated eye growth.\(^{13}\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Baseline</th>
<th>Remained</th>
<th>Peripheral refraction at baseline did not influence the myopia progression</th>
<th>Baseline Remained non myopic vs became myopic: 0.32 +/- 0.96 vs +0.19 +/-1.09</th>
<th>Effect size: 0.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sng(^{69}) (2011) Singapore</td>
<td>Cohort</td>
<td>Became myopic (N=67)</td>
<td>Remained non- Myopic (N= 24)</td>
<td>Peripheral refraction at follow-up &gt; for became-myopic</td>
<td>+0.32 +/- 0.96 vs +0.19 +/- 1.09</td>
<td>Effect size: 0.12</td>
</tr>
<tr>
<td>Kang(^{17}) (2012) Australia</td>
<td>Cohort</td>
<td>Myopic Subjects without correction (N=34)</td>
<td>Myopic subjects corrected with Single vision contact lens(SCL) (N=34)</td>
<td>Full correction of myopia with SCL caused greater peripheral hyperopia, which may stimulate eye growth</td>
<td>F = 5.090, <strong>p = 0.003</strong></td>
<td></td>
</tr>
</tbody>
</table>
Refined sugars and cereals are main components of urban diet. However, these carbohydrate rich foods were not eaten regularly or at all prior to the mid-20th century. Now they are readily available everywhere. In the past 20 years, numerous studies have reported that the regular intake of hyperglycemic foods containing starch and refined sugar cause acute and chronic hyperinsulinemia (sudden or long standing increased blood insulin level).\textsuperscript{24}

Lifestyle of the people has changed in past 30 years. People spend more time indoor in reading and watching TV. They do not perform physical activities or spend time outside. Prevalence of diabetes is epidemic worldwide now and incidence of myopia increased to 85\%-90\% in some Asian countries. We propose that the modern lifestyle is a risk factor of insulin resistance causing diabetes and abnormal eye growth.

**Insulin and eye growth: Evidence from animal studies:**
Numerous studies have been conducted in animals to determine the effect of insulin on eye growth.\textsuperscript{30, 77, 78, 79, 80} It has been stated that visually guided emmetropization involves changes in protein and gene expression across the different fundal layers of the eye. Spectacle treatment caused biochemical changes in the chick’s eye. It altered the abundance of the mRNA and protein of the transcription factor ZENK (transcription factor that retards the eye growth) especially in the glucagon expressing amacrine cells. Only 40 minutes of defocus exposure of positive lens wear increases the number of ZENK expressing cells. Negative lens wear correspondingly decreased ZENK expressing cells. In addition, spectacle treatment altered glucagon mRNA and peptide levels in the retina in sign of defocus dependent manner. Moreover, glucagon and glucagon agonist inhibited lens induced myopia development in many animal studies. Therefore, glucagon may act as a STOP signal for eye growth, at least in chicken. To investigate the effect of insulin on eye growth, Marita et al reared 172 male white leghorn chickens in groups of 6-8 animals under 12/12 hour light/ dark condition. Chicks were treated with positive and negative lenses and injected in their eyes with either saline water or different amounts of insulin. The effect of insulin was studied on refractive error development, axial length growth, corneal curvature, vitreal glucose and chemicals which have been associated with tissue growth (e.g. ZENK). The study showed that:

- The development of myopia was stimulated by the intravitreal insulin.
- Myopic growth was enhanced when chicks wore negative lenses in addition to the insulin injections. When positive lenses (creating myopic defocus), were combined with injections the expected hyperopia was not only inhibited, it reversed the refractive error and caused myopia.
• The development of myopic refractive error by insulin was associated with increased axial length. However, the axial length increase was due to lengthening anterior structures of the eye such as anterior chamber depth and thickening of crystalline.

Most studies in myopia growth have shown axial change in the vitreous chamber; nevertheless this study concludes that the insulin is a powerful stimulator of axial length growth.\textsuperscript{30}

Sheng et al studied in vitro effects of insulin on choroidal thickness and scleral GAG synthesis by using eye cups consisting of RPE, choroid and Sclera (RCS), choroid and sclera (CS) or just sclera from pair of eyes. One eyecup was cultured with different amounts of insulin and its pair was cultured in L-15 medium without insulin. A scan ultrasonography was used to measure the choroidal thickness in the eye cups before and after 20 hours of incubation. To measure the scleral GAGs synthesis, sulfate was incorporated into the sclera after 40 hours of incubation. To further study the effect of insulin and RPE on choroid, two pairs of CS eye-cups were prepared with vs. without RPE transplanted from donor eyes in the presence or absence of 37 $\mu$M insulin. In order to study whether insulin caused RPE to secrete the diffusible factor which affects the choroid, medium conditioned RPE was prepared in the absence or presence of 37 $\mu$M insulin for 20 h. Choroidal thickness increased in all eye cups after 20 h of incubation. Thickening of the choroid seen in the culture is reduced by insulin significantly, but only in the eye-cups where RPE was present. Scleral GAGs synthesis increased in both RCS and CS eye cups in the presence of insulin but the effect was greater in CS eye cups. There was no scleral GAG synthesis due to insulin in scleral eye-cups. In CS eye-cups cultured with transplanted RPE or without RPE, Insulin thickened the choroid significantly less in the presence of RPE than without RPE. The decrease in choroidal thickness was similar to the thickness seen in RCS cups with intact RPE. This study demonstrated that in vitro as in vivo, insulin prevents the choroidal thickening and promotes scleral GAGs synthesis. Insulin causes RPE to produce diffusible substances that inhibit the choroidal thickening. Insulin may also cause the choroid to generate secondary signal via RA to sclera to promote GAGs synthesis.\textsuperscript{77}

**Nutrition and myopia: evidence from human studies**

Several studies have been conducted to study the impact of diet on eye growth.\textsuperscript{81,82} Jacobsen et al studied poor glycemic control in diabetic patients as a risk factor for myopia development. Three hundred twenty three (323) type 1 diabetic patients were selected from eye clinic at Steno Diabetes Center, Copenhagen in 1995-1997. Age at onset, age at baseline, sex, weight, HbA(1c), insulin dosage, refractive error, visual acuity and ocular complications due to diabetes were collected from baseline to 2005. This study found that the prevalence of myopia was considerably higher in diabetic patients than background Danish population. This study reports that poor metabolic control of glucose is a risk factor of myopia and myopia can be considered as a complication of hyperglycemia in diabetes.\textsuperscript{81}
Another study has been conducted to investigate whether the variation in normal nutrition plays a role in development of myopia. The nutritional data of 24 myopic children aged 7 to 10 years were compared to 68 children who were not myopic at the age of 10 years. There was a significant difference between myopic and non-myopic children for protein intake, fat, vitamin B1, B2 and C, phosphorus, iron and cholesterol. Therefore, we may speculate that children who developed myopia had a less nutrient dense diet and perhaps, consumed more highly processed foods which is a risk factor for metabolic syndrome, which may cause myopia.

Table 10: Modern lifestyle and myopia: Evidence from unsystematic reviews

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Design</th>
<th>Number of references</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galvis\textsuperscript{13} (2016)</td>
<td>Review</td>
<td>129</td>
<td>Insulin have direct effect on unregulated eye growth and indirect effect via increasing insulin like growth factor which further decreases insulin like growth factor binding protein. Recent increase in prevalence of myopia may be related to insulin resistance due to sedentary lifestyle and modern diet.</td>
</tr>
<tr>
<td>Cordain\textsuperscript{24} (2002)</td>
<td>Review</td>
<td>140</td>
<td>High glycemic carbohydrate diets may induce permanent change in development and progression of myopia particularly if it is consumed during developmental period of growth.</td>
</tr>
</tbody>
</table>

Table 11: Modern lifestyle and myopia: Evidence from epidemiological studies

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Design</th>
<th>Control Group</th>
<th>Treatment group</th>
<th>Primary outcome</th>
<th>Effect size/ OR/Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldkaemper\textsuperscript{30} (2009) Germany</td>
<td>Cohort</td>
<td>Eye without insulin (N=6-8)</td>
<td>Eye with insulin (N=6-8)</td>
<td>Less hyperopia in treatment group. Insulin stimulated the eye growth</td>
<td>SER: Treatment vs control (+2.09 ± 0.46 vs +3.32 ± 0.22), Effect size: 3.61 * for $P &lt; 0.05$</td>
</tr>
<tr>
<td>Sheng\textsuperscript{77} (2013) United States</td>
<td>Cohort</td>
<td>RPE+ Choroid + Sclera (RCS)</td>
<td>RCS eye cups with insulin (N= 81)</td>
<td>Insulin reduced the choroidal thickness</td>
<td>Choroidal thickness: High dose Treatment vs</td>
</tr>
<tr>
<td>Study</td>
<td>Cohort</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Control</td>
<td>Notes</td>
</tr>
<tr>
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</tr>
<tr>
<td>Penha\textsuperscript{78} (2012) Germany</td>
<td>Cohort</td>
<td>Animal wearing -7 D with intravitreal saline (N=6)</td>
<td>Insulin Injected group became more myopic</td>
<td>SER: Treatment vs control – -9.05±1.15 D vs -6.01±0.68 D, Effect size= 3.32 * for p= 0.019</td>
<td></td>
</tr>
<tr>
<td>Penha\textsuperscript{79} (2011) Germany</td>
<td>Cohort</td>
<td>Animal wearing no lens (N=6)</td>
<td>Myopic defocus in treatment group decreased the insulin receptors, IGF and mRNA levels in the RPE</td>
<td>* for p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Jacobsen\textsuperscript{81} (2008) Denmark</td>
<td>Cohort</td>
<td>HbA1c greater than median (&gt;8.8) (N= 118)</td>
<td>Patients with HbA1c &gt; (8.8%) had a 60% increased risk of a myopic shift and increased level of HbA1c were significantly associated with myopia</td>
<td>RR 1.6 (95% CI 1.19; 2.14) * for p=0.022</td>
<td></td>
</tr>
</tbody>
</table>

### POSSIBLE MECHANISMS OF REGULATED AND UNREGULATED EYE GROWTH:

#### Role of full spectrum light in regulated eye growth

Numerous animal studies indicated that the chromaticity and spectral composition of ambient light may influence the emmetropization process.\textsuperscript{83, 84, 85, 53, 86}

Rucker and Wallman reported that longitudinal chromatic aberration (LCA) causes dispersion of the white light. Due to LCA, some of the wavelengths focus close or on the retina however, others focus away from the retina, resulting a greater loss in contrast and form a blur retinal image which is most noticeable at borders. In hyperopic defocus, the image is focused behind the retina and long wavelengths are more blurred. Conversely, in myopic defocus, the image is focused in front of the retina and short
wavelengths are more blurred. The amount of blur changes at different wavelengths, changing the color of the blur with the change in the focal plane. Frances et al suggested that colored blur may guide the emmetropization process. In addition, eyes are shorter (hyperopic) at the birth and grow as the age of a child progresses. We believe that, when a child is in his developmental years, having hyperopic defocus of full spectrum of light but short wavelength are closer to the retina than long wavelengths. As the eye grows, the short wavelength light comes closer to the retina and after certain time, may come into the focus, which sends a stop signal to the eye to stop the growth. In addition, the changes in color or luminance contrast provide us the knowledge of our surroundings. The detection of contrast initiates with the detection of a difference in cone excitation as the eye moves across the border of the image. Image movement in retina is necessary in chicks to originate emmetropization response.\cite{83}

The LCA changes the cone contrast with defocus. Wavelength 555 nm was considered to be in-focus plane with highest sensitivity of detecting changes in luminance. When eye is hyperopic and moving toward emmetropization, the cone contrast of S-cones is greater than L and M cones due to more short wave length closer to the retina. When the eye is starting to become myopic, the cone contrast of the L and M cones (long wave lengths cones) is greater than S-cones (short wavelengths cones) because of the focal plane for the L and M cones is closer to the focal plane than the s-cones. Hence the relative difference in cone contrast caused by longitudinal chromatic aberration may provide an indicator of sign of defocus and guide the axial length growth.\cite{83}

**Regulated eye growth by a chemical Cascade**

Nebbioso et al stated that number of hours spent outdoor is directly proportional to inhibition of axial length growth. The natural sunlight stimulates dopamine release which retards the eye growth. However, blurred vision also initiates a signaling cascade that from the retina reaches to sclera through retinal pigment epithelium (RPE) and inhibits eye growth. Various animal studies showed that several chemicals are involved in regulation of eye growth: dopaminergic system, muscarinic and glucagonic system. In addition, the existence of \textit{go} and \textit{stop} signals has been proposed that regulate eye growth. \textit{Stop} signals include dopamine, glucagon and fibroblast growth factor. \textit{Go} signals include acetylcholine, transforming growth factor beta, nitric oxide and retinoic acid (RA). Nitric oxide and retinoic acid have also been found to have inhibitory function on eye growth. These double effects of nitric oxide and RA suggest that there is a very complicated multifactorial mechanism guided by environmental and genetic factors.\cite{21} We believe that peripheral defocus and dopaminergic system, which is stimulated by natural sunlight play important role in guiding the eye for its normal growth.

Zhong et al conducted a study in Macaque retina to investigate the activity of bipolar and amacrine cells when the retinal image is either in- focus or defocus. They reported that activity of ON-bipolar cells and
GABAergic amacrine cells was more when image was in focus or myopic defocus. In addition, Nebbioso et al stated that positive lenses increased dopamine level whereas negative lenses reduced the dopamine level in the retina. Moreover, positive lens induced myopic defocus increases the number of ZENK expressing cells in the chick’s retina. In addition, ZENK expression is up-regulated by dopamine agonist and atropine. Furthermore, the ZENK expression is inversely proportional to the axial length growth. Fig. 5 Atropine increases ZENK expression. Hence, it may interfere the same chemical cascade which is initiated by bright light. Moreover, atropine can dilate the pupil and allow more light to the eye which stimulates the dopamine and control myopia.

Dopamine is produced and released by dopaminergic amacrine and interplexiform neurons. Light stimulated amacrine and interplexiform cells release dopamine and nitric oxide. Dopamine and nitric oxide activate several intercellular pathways including adenosine monophosphate cycle and adenosine guanosine monophosphate cycle. These cycles’ phosphorylarize or dephosphylaze of gap junctions connexines which alter the conductance of gap junction into ionic current. This conductance of the gap junction can be increased or decreased in the presence of the light depending on brightness level.

Dopamine binds with 5 different receptors from D1 to D5. These receptors are grouped into two different families: D1 like receptors which include D1 and D5, and D2 like receptors which include D2, D3 and D4. Receptor D1 is present in bipolar, amacrine and horizontal cells in the retina. Retinal pigmentary epithelium has D2 and D5 dopamine receptors. In addition, D2 receptor present in dopaminergic neuron acts as an auto receptor and inhibits dopamine secretion. The extracellular concentration of dopamine across the retina is variable due to different degree of local diffusion and distance between dopamine receptors. This fact correlates with the sensitivity of dopamine receptors. D5 dopamine receptors are 10-20 times more sensitive than D1 so that D5 can react even with small amount of dopamine reaches to RPE from dopaminergic amacrine cells. D2 receptors also have greater sensitivity than D1 which allows them to bind with dopamine at night when dopamine concentration is very less due to inhibitory effect of melatonin.

The daily rhythms of dopamine synthesis and release are maintained by interaction between retinal photoreceptors and dopaminergic neurons. Dopamine concentration varies throughout the day because it is produced under the influence of light and dark cycle. Dopamine itself retards the synthesis of melatonin which is a hormone secreted by pineal gland and plays role in regulating our sleep cycle. In addition, melatonin was considered as a strong inhibitor of dopamine release and metabolism. Melatonin reaches its peak at night whereas dopamine reaches it during the day. Furthermore, it has been reported that melatonin acts locally in the retina and plays an important role in controlling circadian rhythm. The
Melatonin receptors called Mell were found in GABAergic and dopaminergic amacrine cells which inhibit the function of adenylate cyclase which results in reduction in concentration of cyclic adenosine monophosphate. The biosynthesis of melatonin is regulated by light and dark cycle. In the presence of light, acetalyting enzyme is inactivated. Acetalytic enzyme converts serotonin into N-acetyleserotonin which is a precursor of melatonin. Due to deactivation of acetalyting enzyme by light, concentration of melatonin decreases. Simultaneously, increase in the concentration of dopamine has been observed which suggests the elevation or reduction of these two hormones represents the basis of ocular circadian rhythm: darkness disables the dopaminergic transmission which activates the melatonin synthesis. Figure: 4.

It also has been stated that intrinsically photosensitive ganglion cells (IpRGC) containing melanopsin regulates circadian rhythm by elevating the dopamine concentration and suppressing the melatonin levels in the retina. The stimulation peak of IpRGC is 470 nm which is short wavelength blue light. Therefore, blue light is important for normal eye growth, which can stimulate IpRGC to produce melanopsin that further maintains ocular circadian rhythm for regulated eye growth. Hence we propose that ocular circadian rhythm regulates the homeostasis through defocus and light. Normal regulated eye growth or unregulated eye growth is a consequence of the status of this homeostasis. Figure (3)

It also has been demonstrated in chick studies that imposed myopic defocus, dopamine agonist and even bright light increased small, transient but significant choroidal thickness which brings the focal plane forward and reduces axial length growth figure 5. Therefore, we assume that a chemical cascade is involved which sends a signal from retina to sclera through choroid in order to regulate eye growth. Cycloplegic therapy (atropine) may affect the same chemical cascade and stop axial length growth.

The association between retinal images, choroid and sclera implies communication between these three layers. Retinoic acid was thought to be a messenger molecule which is actively synthesized in the choroid. Retinal defocus or some chemical cascade initiated in the presence of high intensity light, which may signal the choroid to produce RA. In addition, RA links the retinal image clarity to appropriate scleral tissue growth. The concentration of retinoic acid increases with hyperopic defocus due to minus lenses which results in myopic growth. Whereas plus lenses decrease the concentration of RA which leads to hyperopia. However, decreased choroidal synthesis of RA promotes the axial length growth and increased secretion of RA slows the axial length growth. Proteoglycan or GAGs are the glycosylated proteins in the sclera that determine the size of the eye. RA inhibits proteoglycan or GAGs synthesis in chicks. The natural retinoids: trans retinoic acid and 9-cis retinoic acid are present in the body. They bind the two families of nuclear receptors: retinoic acid receptors (RAR) and retinoid X receptors (RXRs) and activate gene transcription which controls growth of many cells.
Recently, it is has been shown that IGFBP-3 (Insulin like growth factor binding protein) is a ligand (a molecule that binds the nuclear retinoic receptors) and it enhances the growth inhibitory function mediated by RA receptors. Waldbillig et al demonstrated in chick sclera that Insulin like growth factor-1 (IGF-1) and insulin binding sites are present in the sclera. IGF -1 and insulin are growth stimulators but their receptor sites on the sclera decrease about 50 % in 2 weeks after the hatching. Therefore, we speculate that IGFBP-3 insulin and IGF-1 binding sites may present in the human sclera which receive growth inhibitory and excitatory signals from RA respectively and guide the Glycosaminoglycan (GAGs) synthesis in the sclera.\textsuperscript{93} Sheng et al demonstrated in chicks that insulin can promote the GAGs synthesis in sclera, if it is intact with choroid or choroid- RPE both and suggested that insulin may create a growth promoting signal from RPE and that reaches to sclera through choroid and regulate eye growth Figure 2.\textsuperscript{77}

Sheng et al and Waldbillig both conducted their studies in chicks. Sheng et al reported that sclera should be intact with either or both choroid and RPE. Whereas, Walding suggested that sclera has IGF binding sites, which decrease with the age.\textsuperscript{77, 93} Therefore, if IGF-1 binding sites are necessary for growth, then its reduction in number with age may limit the time period for growing eye. This is particularly important if we want to make an eye more oblate with therapy.
Figure 2: Chemical cascade induced by light or retinal defocus
Figure 3: Ocular circadian rhythm for normal eye growth
Unregulated eye growth by insulin

The possible mechanism of onset of myopia due to increased insulin is that the hyperinsulinemia suppresses the secretion of insulin like growth factor binding protein-1 and increases the production of free insulin like growth factor-1. The circulating levels of insulin and IGFBP-1 inversely vary throughout the day and the IGF-1 level maximized when the insulin level is more than 70-90 pmol/L. The elevation in insulin due to consumption of refined sugar and starch, results in increased IGF-1 and reduced IGFBP-3 levels in all peripheral tissue including sclera of the eye Fig. (8&9). Walding et al demonstrated that IGF-1 and insulin binding sites are present in the sclera during developmental period of chicks, but declines with the age. Therefore, we may assume that more consumption of hyperglycemic food during developmental period may increase the insulin level, which can further bind with its binding sites at the sclera and promote unregulated GAGs synthesis results in eye growth. In addition, it has been stated that excess IGF-1 may promote tissue growth all over the body and cause obesity and perhaps myopia. Moreover, it has been demonstrated that insulin resistance impairs the dopaminergic system in the brain.
and reduces dopamine concentration in the brain. Therefore, insulin resistance may affect the normal chemical cascade responsible for normal regulated eye growth by reducing dopamine level and causing unregulated eye growth. Figure: 5.

Another possible mechanism could be reduced synthesis of retinoic acid (Vitamin A) by choroid, resulting increase in axial length. Numerous studies suggested that the absence of clear retinal image during critical postnatal (after birth) development, triggers axial length elongation is called form deprivation myopia. This axial length elongation is due to proliferation scleral chondrocytes and fibroblast (scleral cells). As we stated earlier, RA is the chemical messenger which links the retinal image clarity to appropriate scleral tissue growth. Decreased choroidal synthesis of retinoic acid enhances the axial length growth and increased secretion of retinoic acid retards the axial length growth. Many food items such as carrots, broccoli, papaya and dairy products contain vitamin A. Therefore, we may speculate that less intake of Vitamin A rich diet affects the retinoic synthesis.

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**Modern LifeStyle**

- High glycemic and processed food - more time indoors
- Insulin resistance - long wave length light
  - Decreased Dopamine Synthesis
  - Decreased ZENK Expression
  - Retinoic Acid
    - Insulin and IGF-3 binding sites
      - IGF-3
        - More GAGs synthesis
        - More axial length growth

**Figure 5: Regulated and unregulated eye growth**
The prevalence of myopia reached to 90% in Asian countries. Uncorrected myopia is one of the main causes of visual impairment due to its vision threatening complications. The OK and cycloplegic therapy seem most effective in myopia control, however, it’s long term efficacy and side effects are still unknown and myopia may reoccur if they are discontinued.\(^\text{25}\) Hence, the consideration of environmental factors and lifestyle changes are necessary to prevent myopia. It has been shown that the time spent outdoor is protective against development and progression of myopia.\(^\text{33,76,95,40}\) Spending 2-3 hours outdoor everyday has been shown to significantly reduce myopia incidence by interventional studies where children had additional activities during the school hours.\(^\text{35,56}\) Physical activity is not correlated with myopia progression, however time spent outdoor is protective due to high intensity blue light, exposure of full spectrum of light, availability of vitamin D, UV radiation and uniform dioptic visual environment.\(^\text{53,49,55}\)

Peripheral retinal defocus plays an important role in regulating normal eye growth has been shown by many animal studies. Peripheral hyperopic defocus accelerates whereas myopic defocus deaccelerates the progression of myopia. In addition, it has been reported that outdoor activity and peripheral defocus may work together to guide the eye to grow in a normal direction. It is believed that myopic defocus induced by positive lens or sun light initiates a chemical cascade, which regulate the eye growth. Furthermore, the presence of blue light outside stimulates the IpRGC to secrete melanopsin. Melanopsin further forms an ocular circadian rhythm by stimulating dopamine synthesis and suppressing melatonin production and regulate normal eye growth. The uniform dioptic pattern outside due to less variation in distant object distances have also been associated with normal eye growth.\(^\text{21,88}\) These results suggest that multiple factors work together to regulate the normal eye growth and maintain the homeostasis.

Recently, urbanization, more time spent indoors doing near work and the western diet are linked with myopia.\(^\text{24}\) Watching TV, playing on mobile devices and computers are not linked with myopia in certain studies however, longer time spent (> 20-30 min) reading and writing at short working distance (< 30 cm) with fewer breaks and adopting abnormal reading posture is associated with myopia progression.\(^\text{96,75}\) Animal studies have shown that Insulin is a powerful stimulator of axial length growth.\(^\text{30}\) It has been stated that intravitreall injected insulin was able to cross the retina and choroid and affect the sclera and can cause unregulated eye growth by disturbing normal chemical cascade responsible for normal eye growth.\(^\text{2,30}\) In addition, free circulating insulin can inhibit IGFBP-3, which is a growth inhibitor and promote abnormal axial length growth.\(^\text{24}\)

Studies suggested that the modern diet and lifestyle is causing insulin resistance, which is a risk factor of cardio-vascular disease, obesity and myopia.\(^\text{13,24}\)
Refined sugar and starches are the main components of the western diet which disturbs the blood sugar metabolism and increases insulin resistance resulting in metabolic syndrome, obesity and perhaps myopia. Hence we speculate that development of myopia is a multifactorial refractive disease and it can be controlled by multiple environmental and lifestyle changes.

**CONCLUSION**

We conclude that a natural approach to a myopia prevention strategy should be implemented which emphasizes spending time outdoors, promoting full spectrum indoor lighting, encouraging proper reading and writing ergonomics, and increasing consumption of a nutrient dense diet.

**RECOMMENDATIONS**

Since cycloplegic and optical devices cannot totally prevent or slow the progression of myopia. We recommend that the following factors related to visual hygiene should be re-examined and implement into practice at early age (< 6 years) of a child. Recommendations are classified into: strong, moderate weak on the basis of evidence available:

1. Children should have 2-3 hours of daily outdoor activity [Moderate].
2. Schools should add additional outdoor activity or recess time outdoor program during school hours [weak].
3. Reading rule: 20-40-20-20 Take break after every 20 minutes and read at 40 cm and take 20 second break by looking at 20 feet [Moderate].
4. Maintain straight upright posture while studying [Weak].
5. A sufficient and cool temperature light source should be used for reading and writing [weak].
6. In addition, take balanced diet including protein rich food with less sugar, fruits, vegetables and drinks without sugar. In addition, avoid processed food. [Moderate].
FUTURE STUDIES NEEDED:

Time spent outdoors has been shown to be protective against myopia by many observational studies but few randomized clinical control trials (RCTs) have been conducted to investigate the protective effect of time spent outdoors. Hence, more RCTs should be conducted to validate the effect of outdoor activity for normal eye growth. Moreover, numerous studies reported that time outdoors are effective to delay the onset of myopia is due to high intensity sunlight. Few studies reported that high intensity artificial light indoors can prevent myopia development. Hence, researchers should conduct studies using high intensity light in school class rooms to find out the effect of cool temperature bright light on myopia.

Longer reading duration and shorter reading distance have been shown to be related to more prevalence of myopia by some questionnaire based cross sectional studies. Researchers believed that close reading distance causes peripheral hyperopic defocus, which further triggers the eye growth. However, the reliability of these studies may be compromised due to memory biased results. Hence, more research is needed with better study design to identify the relationship between near work, peripheral defocus and myopia.

In the chemical cascade for regulated eye growth, we did not find any evidence how dopamine reaches the sclera from retina and dopamine receptors in the sclera. Therefore, future studies should be performed to answers these questions.

Recent studies speculated that increased prevalence of myopia of myopia is due to modern lifestyle includes less physical activities and more sugar rich diet. Modern lifestyle is a risk factor of insulin resistance, which further increase the insulin level in the blood and promotes overall body growth including eye. In addition, animal studies have shown that intravitreal insulin can stimulate eye growth. However, the direct effect of insulin in human eye has not been reported and very few studies are available demonstrating the relationship between diabetes and myopia. Hence, further studies should be involved to find out the relationship between diabetes or HbA1c and myopia.
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