Epidemiology and Pathogenesis of Myopia

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1.1 Trends in Myopia Epidemics

1.1.1 Global

Myopia has currently become a global epidemic issue, affecting nearly 34% (2.6 billion) of the total world's population as of the year 2020 [1]. It has been predicted that half of the world's population (nearly five billion) will become myopic by the year 2050. With regards to the regional differences, the estimated prevalence of myopia is reported to be lowest in East Africa with a prevalence rate of 8.4% in 2020, which is predicted to rise to 22.7% by 2050. In contrast, myopia prevalence in the developed countries of the Asia-Pacific regions, East Asia, and South-East Asia is estimated to be 53.4%, 51.6%, and 46.1% in the year 2020, and will rise to 66.4%, 65.3%, and 62.0%, respectively, by the year 2050.

1.1.2 East Asia

East Asian countries such as Singapore, China, Korea, and Taiwan have witnessed a steep rise in the prevalence of myopia in the last few decades. The prevalence of myopia was as high as 96.5% among 19-year-old teenagers in Korea [2], 79.3%

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among 17–19 years young adults in Singapore [3], and 86.1% among 18–24 years young military conscripts in Taiwan [4]. The prevalence has increased by fivefold in 7-year old (5.37–25.41%), and two to threefold in 12- (30.66–76.67%) and 15-year-old (44.3–92.9%) children from 1983 to 2016 in Taiwan [5]. In China, myopia prevalence among young adults aged 18.46 ± 0.69 years has increased from 79.54% to 87.7% in the urban regions over a period of 15 years (between 2001 and 2015) [6], and in university students aged 20.20 ± 2.80 years, it has escalated to 95% [7]. It has been predicted that nearly 84% of children between 3 and 19 years old will become myopic by the year 2050 in China [8].

1.1.3 South Asia

The South Asian region has observed relatively lower myopia prevalence in school-aged children below 20 years compared to the East Asian region in the last decade, ranging from as low as 2% in Nepal [9], 4.8% in Sri Lanka [10], 6.6% in Bhutan [11], 5.8% in Bangladesh [12], 12.7% in Pakistan [13], and as high as 35.5% in India [14]. A meta-analysis reporting the pooled prevalence of myopia in the last four decades in India revealed an increment of two-fold, from 6.6% between 1980 and 2008 to 14.2% between 2009 and 2019 in children aged 11–15 years [15]. According to a recent study from North India, 21.1% of schoolchildren aged 5–15 years had myopia [16]. If the current incidence rate of myopia continues, the prevalence in such urban regions is estimated to rise to 32% in 2030, 40% in 2040, and 48.14% in 2050 [17].

1.1.4 Middle East, Europe, Africa, and America

Although the epidemic of myopia is high in East Asian countries, other parts of the world also testify to the growing prevalence of myopia. In an age group below 21 years, the myopia prevalence ranged from 3.4 to 7% in Africa [18, 19], 6.5–9% in the Middle East [20, 21], 1.4–14.7% in South America [22–25], 14.8–17.3% in Australia [26], 29% in Canada [27], and 2.4–42.7% in Europe [28–30]. In the United States, the myopic population aged 25–54 years almost doubled (25.0 vs. 41.6%) in a period of three decades between 1971 and 72 to 1999 and 2004 [31]. Fig. 1.1 depicts the trend of increasing myopia prevalence at different time points in different countries.

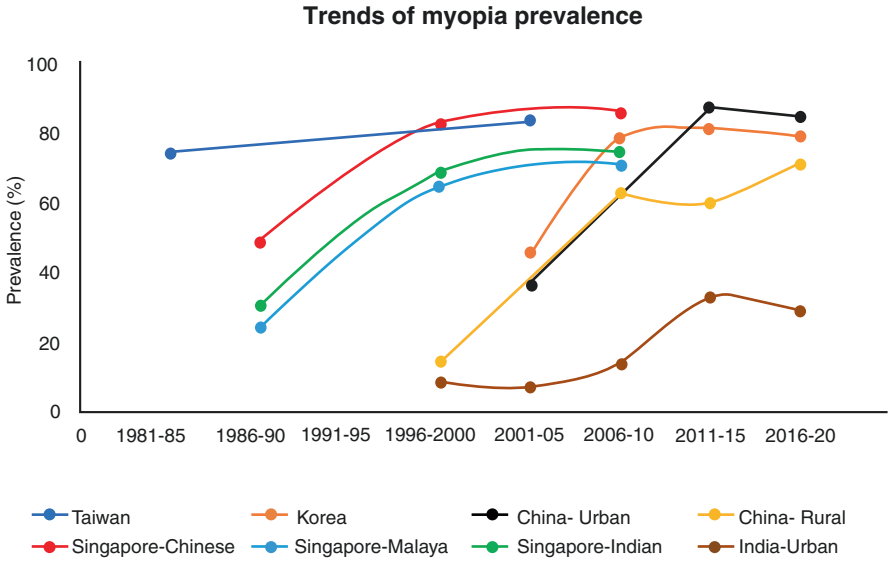

Fig. 1.1 Trends of myopia prevalence within different time points between 1981 and 2020 in different countries

1.2 High Myopia

1.2.1 Definition

High myopia is defined based on the magnitude of myopic refractive error. The World Health Organization (WHO) has indicated a threshold of ≤−5.00 D to define high myopia based on the diagnostic approach, as the predicted uncorrected distance visual acuity due to −5.00 D myopia would approximately equate to <20/400 which is considered as a threshold for blindness. However, to maintain consistency, the International Myopia Institute has proposed ≤−6.00 D as a threshold to define high myopia, considering most of the epidemiological and intervention studies applied this threshold [32].

1.2.2 Influence of Age and Urbanization

The prevalence of high myopia is reported to be higher in adults than in children, in urban regions than in rural regions. A study conducted in China in 2009, which included 5083 university students, showed 23% of students aged 24 ± 2.5 years had high myopia (≤−6.00 D) compared to 18.12% in students aged 18.8 ± 0.8 years [7]. Likewise, another study has found high myopia in 1.39% in 12-year-old, 4.37% in

15-year-old, and 24.16% in 18-year-old Taiwanese children [5]. The epidemiological studies reported high myopia of 0.3% in children aged 3–10 years [33] and 19.3% of young teenagers aged 18 years [6] in urban regions compared to 0.1% in 3–6 years [34] and 8.6% in 6–18 years old young children in rural regions [35].

1.2.3 Current and Predicted Trends of High Myopia

Bullimore and Brennan reported that each diopter increase in myopia increases the likelihood of developing myopic maculopathy by 40%, irrespective of the degree of myopic refractive error [36]. This indicates the alarming condition that can arise due to high myopia. Globally, 5.2% of the total world's population is predicted to have high myopia in 2020, and these estimates are likely to rise to nearly 9.8% (938 million people) by the year 2050 [1].

The temporal prevalence of high and very high myopia (defined as SER ≤−10.00 D) among adults aged 18.5 ± 0.7 years showed an increment of greater than twofold (7.9% from 16.6%) and greater than 11-fold (0.92% from 0.08%) respectively, over a period of 15 years (2001–2015) in China [6]. A similar trend was reported from Taiwan, where the high myopia prevalence rate increased from 1.39% to 4.26% in 12-year-old children, 4.37–15.36% in 15-year-old children, and 16.87–24.16% in 18-year-old children within a period of three decades [5]. In the Korean population aged 18–35 years, there was a minimal increase in high myopia prevalence (from 11.3% in 2009 to 12.9% in 2013) over a period of 5 years [37]. In the US, the prevalence of high myopia (≤–8.00 D) increased eightfold in a period of three decades, from 0.2% to 1.6%, between 1971 and 1972 to 1999 and 2004 [31].

1.3 Pathological Myopia

1.3.1 Definition

Pathological myopia is sometimes interchangeably used with high myopia; however, both of these terminologies have different meaning. High myopia is solely defined based on the degree of myopia (≤−6.00 D) and is not necessarily associated with the presence of any pathological signs [32]. The International Myopia Institute has defined pathological myopia as "excessive axial elongation associated with myopia that leads to structural changes in the posterior segment of the eye (including posterior staphyloma, myopic maculopathy, and high myopia-associated optic neuropathy) and that can lead to loss of best-corrected visual acuity. The META-PM (Meta-analysis of Pathological Myopia) study has defined and classified pathological myopia based on the presence of signs associated with myopic maculopathy as (i) Category 0—no macular lesions, (ii) Category 1—tessellated fundus, (iii) Category 2—diffuse chorioretinal atrophy, (iv) Category 3—patchy chorioretinal atrophy, and (v) Category 4—macular atrophy [38]. The plus signs are lacquer cracks, myopic choroidal neovascularization, and Fuch's spot. Pathological myopia is defined if fundus photographs reveal any of these signs with and above category 2.

1.3.2 Current and Predicted Trends of Pathologic Myopia

The prevalence of pathological myopia ranges from 0.9 to 3.1% in China [39, 40], 1.2% in Australia [41], 1.7% in Japan, 3% in Taiwan [42], and 2.2% in India [43] (Fig. 1.2). Pathologic myopia lesions are reported to be equally prevalent in both low and high myopes (2.2% in low vs. 2.5% in high myopes); however, serious complications such as retinal detachment and posterior staphyloma were found to be higher in high myopes [44]. Among only high myopes, pathologic myopia lesions are found in 28.7%–72.7% of adults or older aged people >30 years in East Asian countries and Australia [39–41, 45, 46]. A systematic review and meta-analysis that included four population-based and three clinic/school-based studies reported the pooled prevalence of myopic macular degeneration (MMD) to be 0.4% in rural India, 0.5% in Beijing, 1.5% in Russia, and 5.2% in Singapore [47]. Another systematic review has indicated a nearly threefold increase in the pooled prevalence of MMD (1.3–3.5%) from 1993–2006 to 2007–2017 [48].

Vision impairment or blindness due to sight-threatening complications of pathologic myopia is known to affect one in one thousand to one in one hundred individuals of different ethnicities [49]. Although there is no direct evidence predicting the future epidemic of pathological myopia, given that 10% of myopes globally will be high myopic by the year 2050 [1] and the manifestation of pathologic lesions even in low grades of myopia, the epidemic of myopia associated with sight-threatening complications might upsurge in the future.

1.3.3 Myopia Incidence and Progression

Myopia incidence and progression are found to be associated with ethnicity. Unlike myopia prevalence, the evidence on myopia incidence is scarce owing to the need for longitudinal studies. The incidence of myopia among 6-year-old

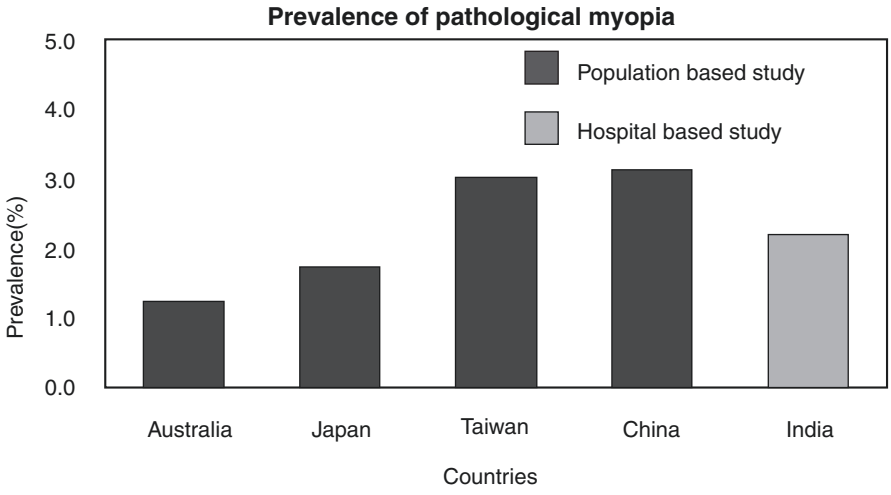

Fig. 1.2 Prevalence of pathological myopia in different countries

Chinese children was 39.5% over a period of 3 years [50]. In Singapore, the cumulative 3-year myopia incidence ranged from 32.4% to 47.7% in children aged 7–9 years [51]. The Northern Ireland Childhood Errors of Refraction (NICER) study conducted in the UK during 2012–2014 (baseline data from 2006–2008) reported an annual incidence rate of 2.2% in the younger cohort (6–7 years at baseline) and 0.7% in the older (12–13 years at baseline) cohort. Conversely, in the same age group of Australian children, an opposite trend was seen where only 1.3% of children aged 6–7 years and 2.9% of children aged 12–13 years developed myopia [52].

Annual incidence rates were higher in East-Asian ethnicity in both younger (6.6% in East Asians vs. 0.7% in European Caucasians) and older (3.2% vs. 1.2%, respectively) cohort of children than European Caucasians [52]. A significantly lower number of Indian and Malayan children (27.2%) developed myopia compared to Chinese children (49.5%) of a similar age group in Singapore, indicating higher incidence rates in individuals of Chinese ethnicity [51]. In the South Asian region, urban schoolchildren aged 5–15 years had an annual incidence rate of 3.4% [16].

With regards to myopia progression, the shift in myopic refractive error in Chinese children aged 6 years was reported to be −1.59 D over a period of 3 years, whereas the annual rate of progression ranged from −0.28 to −0.30 D among 6–13 years old school-aged children [53]. The amount of progression was higher in Australian children (baseline) that ranged from −0.31 to −0.41 D/year in children aged 6–13 years [54]. Compared to this, Irish children showed a lesser annual shift in myopia (ranging from −0.09 to −0.18 D/year) in the NICER study across the same age cohorts [55]. Mean annual change in myopic refractive error in North Indian urban children aged 5–15 years (who were already myopic at baseline) was reported to −0.27 ± 0.42 D/year [16]. Another retrospective study involving Indian children and young adults aged 1–30 years indicated an annual progression of −0.07 D to −0.51 D/year [56].

1.3.4 Emmetropisation and Refractive Development

Emmetropia refers to a refractive condition when the incident parallel rays of light from distant objects focus on the retina while accommodation is at rest. Emmetropisation is an active process where refractive components and the axial length of the eye (the linear distance from the anterior surface of the cornea to the retina along the visual axis) come into balance to achieve the emmetropic condition [57, 58]. Any disruption in this process or emmetropisation leads to the development of refractive errors [58].

Myopia can be broadly classified into two qualitative categories as either a) axial myopia—refractive state that can be attributed to excessive axial elongation or b) refractive myopia—refractive state that can be attributed to changes in the structure or location of the image forming structures, i.e., the cornea and/or lens [32]. Similar to the axial growth observed in a variety of animal experiments [59, 60], myopic

eyes in children [25, 61], young adults [62], and the elderly [63, 64] were reported to have a deeper vitreous chamber depth, indicating that axial myopia is primarily due to elongation of the vitreous chamber, with nominal changes in corneal curvature and crystalline lens power [65].

1.4 Ocular Expansion Models

Ocular stretching causes structural changes in the myopic eye, notably in the posterior region of the eye (vitreous chamber depth, retina, choroid, and sclera). The ocular stretching is observed not just along the visual axis but in a variety of ways (Fig. 1.3), such as (a) "Global expansion" where ocular expansion occurs in all directions from the limbus towards the posterior pole [66], (b) "Equatorial expansion" where ocular stretching occurs parallel to the optic axis and is limited to the equatorial region of the eye [67], (c) "Posterior pole expansion" where ocular elongation is limited to the posterior pole typically owing to increased tension at the level of zonules and ciliary body [68], (d) "Axial expansion" or the hybrid model of elongation where the globe expands along both posterior pole and equatorial directions [69], and (e) "Asymmetrical expansion" where the eyeball could follow the global expansion model, but undergo unequal/uneven stretching from anterior to posterior pole [70].

1.4.1 Role of the Retina in Regulating the Ocular Growth

The retina is the light-sensitive layer located as the innermost layer of the posterior coat [71, 72]. The fovea (central region of the retina) is a depression in the inner retinal surface about 1.5 mm wide, whereas the rest is referred to as the peripheral retina (approximately about 21 mm from the fovea to ora-serrata) [73].

Humans [74–78] and various animal species such as chicks [59, 79–85], monkeys [86–91], tree shrews [92, 93], mice [94, 95], guinea pigs [96], marmosets [60], kittens [97, 98], and squids [99] are capable of detecting the retinal image defocus and accordingly regulating ocular growth [58, 100]. This retinal image defocus detection system appears to operate independently and locally within the eye. Despite an absence of input from the accommodative system (induced via cycloplegia, ciliary nerve section, or damage to the Edinger-Westphal nucleus) [82, 101] or higher visual centers (induced

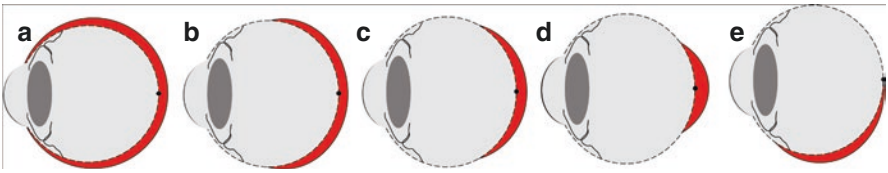

Fig. 1.3 The figure above shows various globe expansion models for myopic eyes. Global expansion (**a**), equatorial expansion (**b**), axial expansion (**c**), posterior pole expansion (**d**), and asymmetrical expansion (**e**)

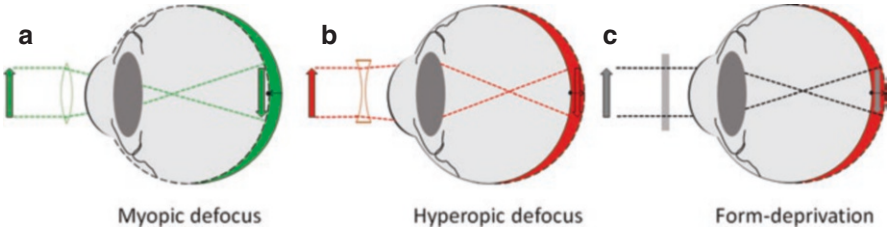

Fig. 1.4 The figure above shows the directional change in axial length in response to myopic defocus (**a**), hyperopic defocus (**b**), and form-deprivation (**c**). The green and red color indicates decrease and increase in axial length, respectively

via optic nerve section) [102], the eye still responds to the imposed form-deprivation (retinal image quality degradation) [81, 102], and detects the sign of optical defocus (Fig. 1.4) [82, 85, 101–103]. This suggets that the blur signal at the retinal level may initiate complex signaling cascades responsible for cellular and biochemical changes in retinal structures for refractive development [71, 100, 104, 105].

Morphologically, the thickness profile of the ganglion cell-inner plexiform layer and retinal nerve fiber layer (RNFL) in children with myopic refractive error is reported to be thinner compared to that of non-myopes [106, 107]. The total thickness of the peripheral retina was found to be thinner in high myopic eyes compared to emmetropes, attributable to a thinner inner nuclear layer, combined Henle fiber layer, outer nuclear layer, and outer segment of the photoceptor layer [108]. High myopic eyes were shown to have thinner RNFL and Ganglion cell complex (GCC) thickness compared to low and moderate myopia [109].

Overall, axial growth is associated with retinal thinning, mainly in the equatorial and pre-equatorial regions, with no changes in foveal retina thickness [110]. It is noteworthy that the changes in macular retinal thickness in mild to moderate myopia are relatively small (6 microns) and unlikely to be of clinical significance [111]. More importantly, the proportion of the decline in sub-foveal choroidal thickness is higher than the retinal thickness, indicating that changes in choroid thickness occur earlier and more rapidly during myopia development or progression [111–113].

1.4.2 Central vs. Peripheral Retina

Fovea possesses high-contrast visual acuity, cone-receptor density, and high resolution. As a result, it was long assumed that the visual signals from the fovea largely influence the ocular growth and subsequent refractive development [100, 104]. However, since the fovea corresponds to only a small area in the central visual field ($\approx 10^{\circ}$), it is reasonable to presume that the peripheral retinal area might also be important in driving the refractive status.

In animal studies, it was observed that eyes with form-deprivation (induced via diffusers/Bangerter filters) imposed on the peripheral retina and having unrestricted clear central vision led to an increase in axial length and resulted in form-deprivation myopia (FDM) [87, 114]. Furthermore, ablating the central 10° diameter of the retina around the fovea while leaving the periphery intact resulted in an emmetropic refractive state [91] and also compensated for form-deprivation (FDM), optically induced hyperopic [115], and myopic defocus [89]. These studies indicated that the visual signals from the retinal periphery are also indeed critical for visually guided eye growth and that refractive development is susceptible to local and regionally selective mechanisms in the peripheral retina [90].

1.4.3 Theories Related to Peripheral Optics and Retinal Shape in Myopia

Various animal and human studies have reported that myopes exhibit relative peripheral hyperopia (the peripheral retinal image is focused behind relative to the central focus), and emmetropes and hyperopes exhibit relative peripheral myopia (the peripheral retinal image is focused in front relative to the central focus) [69, 100, 104, 116, 117]. The optically induced peripheral hyperopic and myopic defocus, respectively, accelerated and decelerated the eye growth, indicating the role of that relative peripheral hyperopic defocus in the development of myopia (myopiagenesis) and myopia progression [100, 118–124]. When the form-deprivation [125–128] or optically induced peripheral hyperopic defocus is imposed to a specific retinal region of chick and guinea pig eyes, only the region imposed by the hyperopic defocus exhibited maximum elongation of axial length [125, 127, 128], and resulted in alteration of posterior eye shape, indicating a local regulation of ocular growth [69, 117, 126].

Considering that the refractive state of the eye is always based on the presence of the focal plane in relation to the retinal plane, several studies have attempted to anticipate the peripheral retinal shape variations based on the type and magnitude of refractive error in the periphery of the eye. As shown in Fig. 1.5, myopic eyes with relative peripheral hyperopia are known to exhibit a steeper or prolate retinal shape, whereas hyperopic or emmetropic eyes with relative peripheral myopia exhibit a flatter or oblate retinal shape [69, 118, 129–132]. Retinal shapes have been shown to differ depending on factors such as ethnicity and primary refractive meridians [117, 133], with the East Asian myopes exhibiting steeper (prolate) retinal shape and greater relative peripheral hyperopia than Caucasians, along horizontal than in vertical meridian.

In high myopic eyes, the baseline shape of the posterior pole had a substantial impact on the speed with which the posterior pole shape changed. Eyes having a flatter shape at baseline tended to change shape more slowly, whereas an eye with restrained shape deformation tended to change shape rapidly [134].

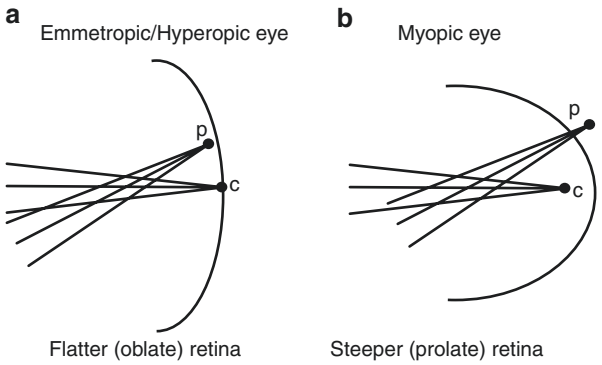

Fig. 1.5 The figure above shows the comparison of central and peripheral optics in the emmetropic eye (**a**) and myopic eye (**b**). Note that the peripheral rays may not always be hyperopic as shown in panel **b**

1.4.4 Changes in the Choroid

The choroid, a highly vascular tissue that lies between the retina and sclera, is the primary source of oxygen and nutrients to the outer retina and is considered to play a major role in the regulation of ocular temperature, intraocular pressure, modulation of vascularization, and growth of the sclera [135]. Experiments in a wide range of animal species [136–139] and humans [74, 77, 140–142] investigating the effect of retinal defocus on choroidal response indicated that the choroid plays a critical role in the regulation of ocular growth and refractive development. Overall, thickening of the choroid has been observed in response to myopic defocus, whereas thinning has been observed in response to hyperopic defocus. Studies have also demonstrated that thinning of the choroid is a structural hallmark feature of human myopia [143], with a negative correlation between choroidal thickness and axial length, suggesting that the change in choroidal thickness may be a predictive biomarker for long-term changes in ocular elongation. Choroidal thickness has been shown to decrease approximately by 26 microns with each additional millimeter increase in axial length [144]. Since the choroid is primarily a vascular structure capable of rapidly changing blood flow, variations of choroidal thickness are considered to be associated with changes in choroidal vascularity [145].

However, the underlying mechanism of how the choroid plays a role in ocular growth and refractive development is still unknown. It has been suggested that since the choroid lies between the retina and sclera, it acts as a channel to transfer the retinal signalling molecules or growth factors from the retina to the choroid. Apart from the effect of defocus, several other factors like muscarinic antagonists such as homatropine and atropine [146, 147], dopamine agonists such as apomorphine and quinpirole [148], accommodation [149, 150], and increased light exposure [151, 152] have resulted in changes to the choroidal thickness.

1.4.5 Changes in the Sclera

The sclera is considered as the skeleton of the eye, which forms the outer coat of the eyeball. It comprises the fibrous shell of collagen and fibroblasts, which helps in the production and maintenance of extracellular matrix (ECM) [153], serves as an attachment for the extraocular muscles, allows passage for the optic nerve, channels for arterial blood supply, venous drainage, nerves for interocular structures, and drainage of aqueous humour [153]. It is also known to neutralize the short-term fluctuation in intraocular pressure and act as a mechanical barrier [153]. The disturbance in the structure and function of the sclera can lead to an alteration in refractive development. Ocular enlargement in myopic eyes is shown to be associated with progressive thinning of the sclera [70, 154]. Overall thinning of the sclera is associated with thinning of the collagen fiber bundles along with the reduction in the glycosaminoglycan and collagen contents and the size of the individual collagen fibrils particularly the small diameter fibrils, rendering the sclera biochemically weaker in myopic eyes [155, 156]. Given that longitudinal fibers of the ciliary body run adjacent and parallel to the sclera with tendons connecting equatorial sclera and choroid extending anteriorly to the sclera spur [157], sustained accommodation during close distance near work is shown to result in thinning of the anterior sclera, mainly 3 mm posterior to the scleral spur [158]. Furthermore, high myopes are shown to exhibit a greater sagittal height of the anterior sclera in the nasal region than emmetropes, indicating high myopes have a different anterior eye shape [159]. Adding to the evidence, inferior anterior scleral thickness was found to decrease with an increasing degree of myopia [70].

1.4.6 Optical, Biomechanical, and Neural Mechanisms in Myopiageneis

Accommodation is the fundamental part of any near work activity, which is defined as "the ability of the eye to change its optical power to focus on objects at different distances." The structural changes that occur during accommodation include the shape of the crystalline lens (principally the anterior surface), where the anterior surface becomes more curved with little changes in the posterior surface, the central thickness of the crystalline lens increases, the equatorial diameter decreases, and lens volume remains constant with the decrease in surface area [160, 161]. Accommodative response reflects the change in the dioptric power of the crystalline lens in response to a stimulus (accommodative demand). If the accommodative response is lower than the accommodative demand during near-viewing conditions, this results in an error known as the lag of accommodation. And if the accommodative response is higher than the accommodative demand, this results in an error known as the lead of accommodation.

Given that near work plays a major role in myopiagenesis, accommodation during near work has been considered to be the potential cause for ocular growth. Moreover, several other non-accommodative mechanisms explain the role of near work and myopia. All proposed theories related to near work and myopia are discussed below (Fig. 1.6).

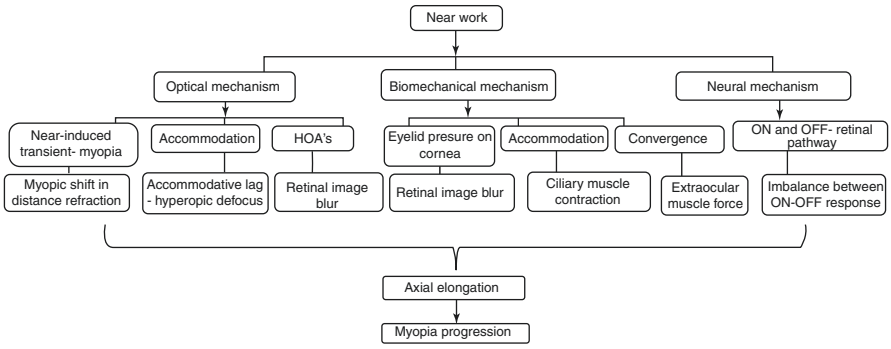

Fig. 1.6 The flowchart above shows the various theories proposed related to near work and myopia

1.4.6.1 Accommodative Lag Theory

Myopia has been linked to central hyperopic retinal defocus associated with the lag of accommodation during near-work activities, and the lag theory indicates *that* such a hyperopic defocus could trigger ocular growth (Fig. 1.7). This is based on the findings from studies in a wide range of animal species, including guinea pigs [162], chicks [81], and monkeys [86] that chronic hyperopic retinal blur triggered axial elongation to compensate for the blur stimulus. The fact that myopic eyes have a higher lag of accommodation (i.e., reduced accommodative response to blur) compared to non-myopic eyes [163, 164], supports the theory that myopic eyes experience a greater amount of hyperopic blur during near work, which might lead to excessive axial growth. Evidence suggests that children who use bifocals [165, 166] and progressive addition lens (PALs) [167, 168] showed less myopia progression compared to children wearing single vision spectacle lenses. However, the consensus regarding the association between the lag of accommodation and the progression of myopia has so far been conflicting. Few studies have shown that lag of accommodation is associated with progression of myopia [169, 170], few suggest that greater myopia progression in adults is associated with a low lag of accommodation [171], and others found no significant association between lag of accommodation and myopia [172, 173]. It is indicated that lag of accommodation can be the consequence rather than a cause of myopia, since lag of accommodation was not significantly different before the onset or during the onset of myopia between children who became myopic and emmetropic children [174].

While it has been considered that stimuli presented to the foveal area can elicit an accommodative response, there is also evidence suggesting that stimuli presented at the peripheral retina can also produce accommodative responses (in the absence of a central stimulus), termed as peripheral accommodation [175–177]. It is shown that the accommodative response to the target decreased with the increase in the eccentricity (5°, 10°, and 15°) of the target [177]. Furthermore, It has been speculated that although the image is well focused on the retina accompanied with image-focused in front of the perifoveal retina, the eye will relax to bring the image closer to the retina, which in turn, causes lag of accommodation and may trigger myopia [176].

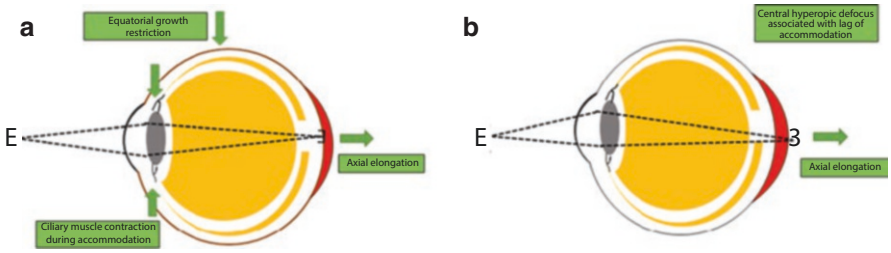

Fig. 1.7 Illustration of mechanical tension theory (**a**) and accommodative lag theory (**b**)

1.4.6.2 Mechanical Tension Theory

This theory explains the role of "mechanical stress" or "force" created by the ciliary body or the crystalline lens at the anterior part of the globe during accommodation in accelerating axial ocular growth by restricting the equatorial ocular growth to a point where proportional globe expansion is no longer possible (Fig. 1.7) [178, 179]. Accommodation can promote ocular growth by choroidal or scleral action, or with a combination of both. Because the fibers of the ciliary body extend posteriorly till the choroid, contraction of the ciliary body during accommodation (ciliary-choroidal tension) causes forward pulling of the choroid with a reduction in the circumference of the sclera and results in axial elongation [180]. Several human studies have found a significant transient increase in axial length and thinning of the choroid associated with short-term near work, supporting the mechanical tension theory [150, 181, 182]. Sustained accommodation has been found to induce a hyperopic shift in relative peripheral refraction, implying that the ciliary muscle's mechanical influence on the choroid can result in a more prolate ocular shape during accommodation [183]. Adding further evidence, accommodation was found to cause significant thinning of the anterior sclera, particularly 3 mm posterior to the scleral spur [158]. These changes were found to be more prominent in myopes compared to emmetropes.

1.4.6.3 Higher-Order Aberrations

Accommodative response and higher-order aberrations have been demonstrated to be influenced by downward gaze during near work [184–186]. A shift in corneal optics during near work has been postulated as a possible connection between near work and myopia development [187–189]. Changes in corneal astigmatism and higher-order aberrations have been found to occur after a near task in the downward gaze, which significantly affects retinal image quality. These changes are likely to be caused by the eyelid pressure on the corneal surface.

The magnitude and sign of HOA, particularly negative spherical aberration, are thought to provide a directional cue to the retina, leading to compensatory eye growth to improve image quality. Positive spherical aberration, on the other hand, has been considered to be protective against myopia progression due to its action in reducing the hyperopic defocus associated with the lag of accommodation during near work, and improve the retinal image quality. In a study of Chinese schoolchildren, higher-order aberrations were reported to be significantly higher in children

with faster myopia progression (≥0.50 D/year) compared to children with a slower rate of myopia progression (<0.50 D/year), suggesting that higher-order aberrations could be the risk factor for myopia progression [190]. Furthermore, it has been demonstrated that the optical quality of the retinal image decreases with an increase in myopic refractive error [191].

1.4.6.4 Near-Induced Transient Myopia (NITM)

It is defined as a myopic shift in distance refraction (far-point) immediately after a period of extended or sustained near work [192–195]. It has been suggested that NITM acts as a myopic blur for distance vision immediately after a sustained period of near work and delayed decay to the baseline, which could lead to permanent myopia. Myopes show a greater level of myopic shift compared to emmetropes. Late-onset myopes have a longer NITM decay time to reach their baseline level than early-onset myopes following a shorter period of near work [196]. Progressive myopes tend to have a greater level of NITM than stable myopes and emmetropes [196, 197]. The manifestation of NITM was found to be associated with the sympathetic pathway of the autonomic nervous system. The autonomic nervous system has two pathways: (a) the parasympathetic pathway which innervates the synaptic muscarinic receptors (M3) in the iris sphincter and ciliary body and results in contraction of the ciliary body, (b) the sympathetic pathway which has alpha 1 and alpha 2 receptors resulting in pupillary mydriasis, and b1 and b2 receptors resulting in inhibition of accommodation. The present hypotheses indicate that NITM could be either due to a deficit in sympathetic input (resulting in delayed decay to the baseline), or it could be a deficit in both parasympathetic and sympathetic pathways, given that they function in a complementary manner [198].

1.4.6.5 Role of Convergence and Extraocular Muscles

This theory suggests that stress generated by extraocular muscles during near work could potentially cause an increase in axial length. Mechanical pressure from the rectus and oblique muscles during convergence has been proposed as a possible cause for ocular growth [199]. Given, the scleral stiffness at the posterior pole is only 62% of that of the anterior pole [200], the oblique muscles might exert enough localized tension on the posterior sclera to elicit axial elongation due to their attachment site at the posterior part of the globe (in proximity to the optic nerve). It has also been hypothesized that the extraocular muscle's mechanical stress at the equator is than the ciliary muscle contraction during accommodation [199]. The axial length of the eye was shown to increase in inferonasal gaze, and this change was greater in myopic than emmetropic participants [201]. During downward gaze, the axial length increased for eye movement without head movement compared with primary gaze, suggesting that changes in axial length in downgaze are due to the influence of the extraocular muscles, particularly oblique muscles [201]. Recently, it has been found that the medial rectus was significantly thinner in myopic eyes compared to emmetropes, and the sustained stress during binocular viewing conditions could affect the anterior scleral shape [202] which could in turn lead to asymmetrical growth of the eye associated with myopia development or progression.

1.4.6.6 Role of ON-OFF Pathway

Retinal ganglion cells have circular fields which are organized into ON-center/OFF-surround and OFF-center/ON-surround pattern. The properties of ON-center cells show that when a small annulus of light falls at the center of the cell, it leads to the depolarization of the cell membrane resulting in activation of the cells, whereas hyperpolarization (i.e., inhibition of the cell) occurs when light is presented on the surrounding field of the cell, sparing the center. Conversely, the OFF-center cells depolarize by the light stimulus in the surrounding field of the cell (i.e., offset of stimulus in the center). Experiments in chickens and mice with deficient ON- or OFF-pathway signalling suggest that ON-pathway activity represents an inhibitory signal for eye growth, while the OFF-pathway may be stimulatory [203, 204]. Based on this information, recent studies in humans have reported that reading black text on a white background overstimulated the OFF-pathway, resulting in significant thinning of the choroid, whereas reading white text on a black background overstimulated the ON-pathway, resulting in significant thickening of the choroid [205].

1.4.7 Role of Genetics and Other Factors in the Refractive Development

The risk factors responsible for the development and progression of myopic refractive error can be broadly categorized into genetic and environmental factors [206]. There is a strong line of evidence indicating the role of hereditary etiology in myopia development [207]. It has been suggested that the heritability of myopia could be between 60% and 80% [207]. MYP1—a myopia-related gene locus, was one of the first recognized gene loci to be associated with high myopia [208]. To date, 200 gene loci have been identified related to myopic refractive error [207]. Parental history of myopia has been considered to be a risk factor for myopia development and faster progression in myopic children [209, 210]. The risk of developing myopia was reported to be two to threefold higher in children with two myopic parents compared to 1.5 times higher in children with one myopic parent, and lowes with no myopic parents [211]. Children with two myopic parents have been shown to have rapid myopia progression with single vision spectacles and atropine treatment, and children having one myopic parent progress less than the former but faster than the children with no myopic parents [209, 212].

Despite several indications of a relationship between genetics and myopia, the rapid rise in the prevalence of myopia over the last several decades cannot be just attributed to genetic influence, especially when such a dramatic rise in the prevalence is observed in a specific population or specific region. Apart from nearwork [213–215], several other factors such as closer reading distance (less than 30 cm) and longer periods of continuous near work (more than 30–45 min) [214, 216], posture and gaze angle during reading [217–220], time spent in outdoor activities [221–223], education level [224–227], intelligence [228–231], location (rural vs. urban) [232], digital screen time [233–235], level of physical activity [236], socioeconomic status [237], body stature [238], and low birth weight [239] have been identified to be associated with the development and/or progression of myopia.

Key Points

1. Prevalence, incidence, and progression of myopia vary with region and ethnicity.
2. The retina is capable of detecting the retinal image defocus and regulate ocular growth independently and locally within the eye via a series of complex cellular and biochemical mechanisms.
3. The visual signals from the retinal periphery are indeed critical for visually guided eye growth and corresponding refractive development.
4. The shape of the retina and the type and magnitude of peripheral retinal defocus may have a potential role in myopia development and progression.
5. Optical, biomechanical, and neural mechanisms are known to play role in myopiageneis.
6. The ocular growth is not just observed along the visual axis, but the expansion of eye can happen following any of the proposed models.

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