Myopia and Cataract

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Abstract

The rising global incidence of myopia warrants urgent attention due to its role in predisposing individuals to vision-threatening ocular conditions, including but not limited to cataracts and glaucoma. This review seeks to delineate the current understanding of the complex relationship between myopia and cataracts, exploring both epidemiological and pathological perspectives. Notably, there is a recognized association between myopia and early-onset cataract. Persistent progression of myopia over a lifetime can induce chronic alterations in the lens, encompassing shifts in both its microenvironment and structural attributes. Moreover, managing cataracts in myopic eyes presents significant challenges due to increased surgical difficulty and a higher likelihood of perioperative complications. Consequently, it is crucial to facilitate early detection of complications, forge apt management strategies, and implement targeted interventions to mitigate the adverse effects of both cataract and cataract surgery-related visual impairments in individuals with myopia. The overarching goal remains to enhance the quality of life for those affected by myopia, especially during their most productive working years.

Keywords: Myopia; Cataract; Proinflammation; IOL malposition; Lens epithelial cell.

Introduction

Myopia, also known as nearsightedness, is a refractive error caused by the elongation of the eyeball or the excessive curvature of the cornea, resulting in the focal point of distant objects falling in front of the retina. It has emerged as a global epidemic, affecting nearly half of the world’s population by the year 2050,1,2 and 80–90% of the young adults in East and Southeast Asia.3,4 Traditionally, myopia is categorized into two types: slight to moderate myopia and high myopia. Slight to moderate myopia is defined with eyes with refraction over −6.0 diopters (D) or an axial length (AL) under 26 mm, while high myopia is characterized by continuous and extreme elongation of the eyeball length throughout its lifetime. The progressive elongation of the eyeball in high myopia results in the atrophy of eye tissues and poses a significant risk of blindness. Consequently, high myopia should not be regarded simply as an increase in refraction compared to slight to moderate myopia but rather as a severe and unresolved ocular condition. The myopia-related pathological changes, including myopic maculopathy and optic neuropathy, are now the leading causes of severe visual impairments.5 Due to abnormal structures and microenvironments in myopic eyes, it is associated with many other ocular comorbidities and worse prognosis, such as glaucoma, retinal detachment, chorioretinal atrophy, macular hemorrhage, and cataracts.6

Cataracts, the progressive opacification of the eyes’ natural lens, lead to a decline in visual acuity and quality. It is the primary cause of blindness worldwide, affecting about 95 million people worldwide.7 Cataract is typically associated with aging but may also be caused by various genetic or environmental factors.7 The World Health Organization’s VISION 2020 project has targeted cataracts as one of the major avoidable eye conditions.8 Therefore, cataract prevention and successful completion of cataract surgery with fewer surgical complications and precise prognosis management are crucial for controlling and preventing cataract-related visual loss.

The relationship between myopia and cataracts is both complex and multifaceted. Numerous studies have demonstrated a significant association between myopia and a heightened risk of developing early-onset cataracts.9,10 Concurrently, literature extensively documents the pronounced challenges of managing cataracts in individuals with myopic eyes.1,12 This review aspires to consolidate both epidemiological and pathogenetic evidence establishing myopia as a risk factor for cataracts. Furthermore, it sheds light on the challenges and potential solutions concerning cataract diagnosis, management strategies, and postoperative prognosis in myopic patients.

Epidemiology evidence

Myopia and nuclear cataract

The association of myopia and the nuclear type of cataract
Disease Study; Lens Opacity Classification System (LOCS) severe nuclear grade (OR = 9.10 in the Andhra Pradesh Eye Disease Study; Lens Opacity Classification System [LOCS] HI nuclear cataract grade ≥ 3.5, OR = 10.16 in Tanjong Pagar Survey; LOCS III nuclear cataract grade 5–6). Furthermore, Pan et al. conducted a meta-analysis of 7 cross-sectional studies and 1 case-control study and confirmed that myopia was associated with increasingly prevalent nuclear cataracts (pooled OR, 2.81; 95% confidence interval [CI] 1.94–4.06). However, the cross-sectional association can somehow be explained by the increase in lens power caused by an increase in nuclear density of the aging lens, thus, evidence from a prospective cohort study may be needed. The Los Angeles Latino eye study showed that the independent risk factor for the 4-year incidence of nuclear lens opacities was myopic spherical equivalent, while no such risk factors were found in cortical or posterior subcapsular opacities. Similarly, an associated risk between myopia at baseline and incident nuclear cataract was also reported in the Barbados Eye Study after a 4-year follow-up and Age-related Eye Disease Study after a 9-year follow-up. Particularly, high myopia (defined by ≤−6D) was associated with an increased 10-year incidence of nuclear cataracts, as revealed by the Blue Mountains Eye Study, while no such association was found in low and moderate myopia. A meta-analysis also showed a significant association for any myopia (OR, 2.51; 95% CI, 1.53–4.13, no heterogeneity); low myopia (OR, 1.79; 95% CI, 1.08–2.97, no heterogeneity); moderate myopia (OR, 2.39; 95% CI, 1.03–5.55, no heterogeneity); and high myopia (OR, 2.86; 95% CI, 1.43–5.73, no heterogeneity) with nuclear cataract. Based on this evidence, it is well-documented that baseline myopia is significantly associated with an increased risk of developing nuclear cataracts.

Myopia and cortical and posterior subcapsular cataract

Previous studies have shown inconsistent and conflicting results about the association of myopia and other two types of cataracts, the cortical and posterior subcapsular (PSC) cataract. For example, the Tanjong Pagar Survey found no significant association between cortical cataract and refractive errors but found that PSC cataract correlated with myopic refraction. However, the Blue Mountains Eye Study showed that high myopia was significantly associated with cortical cataracts, and also with PSC, particularly in eyes with early-onset myopia, defined as a history of wearing distance spectacles before the age of 20 years. Furthermore, the Beaver Dam Eye Study reported that incident cortical cataract was only associated with hyperopia after adjustment. The meta-analysis by Pan et al. showed that myopia was associated with PSC cataracts (pooled OR, 1.93; 95% CI 1.49–2.49), but not with cortical cataracts (pooled OR, 1.08; 95% CI 0.90–1.30). Similar conclusions were also generated from another new meta-analysis of 3 prospective and 8 cross-sectional studies conducted by Haarman et al. These findings indicate that the relationship between myopia and cortical or posterior subcapsular cataracts may be intricate, highlighting the need for further research to comprehend this association.

Myopia and cataract-surgery-related complications

While modern cataract surgery generally maintains a high safety and efficacy profile for patients with myopia, it entails notable challenges, including a higher incidence of complications related to phacoemulsification. Chief among the concerns is the escalated risk of pseudophakic retinal detachment seen in individuals with high myopia during phacoemulsification. This risk arises due to the diminished retinal quality and reduced fundus blood supply typical in high myopia cases, predisposing these individuals to greater vulnerability to intraocular pressure fluctuations and environmental disturbances during cataract surgery. Regarding anterior segment complications, our group’s prior meta-analysis identified a comparatively higher occurrence of several issues in highly myopic cataract patients versus emmetropic age-related cataract patients. These include posterior capsular rupture (3.91%), capsular contraction syndrome (2.1%), intraocular lens dislocation (0.58%), and a significant rate of transient intraocular pressure elevation (28.15%). Accordingly, cataract management in myopic patients demands heightened vigilance and a careful approach.

Risk factors of early-onset cataract in myopia

Identifying risk factors and therapeutic challenges for myopic complications, particularly early-onset cataracts, is paramount in understanding the pathogenesis and developing effective preventive strategies. Recently, a meta-analysis showed that myopic patients’ visual impairment risk was strongly related to longer axial length, higher myopia severity, and age older than 60 years. However, what is of particular concern is the potential loss of vision among myopic patients during their later years, often referred to as the working age (30–45 years of age). This period is characterized by an increased susceptibility to age-related eye diseases, such as cataracts, glaucoma, and macular degeneration, which can significantly impact visual function and quality of life. The distinct challenge of the discernability of creating socioeconomic value during this particular age group due to visual loss highlighted the importance of prioritizing early detection, implementing appropriate management strategies, and adopting preventive measures to address the complications of myopia.

Early-onset cataracts are developed between the ages of 20 and 55, and there is a progressive increase in the incidence over time. Numerous studies have endeavored to elucidate the risk factors for early-onset cataracts in myopia, which could be attributed to axial length elongation, genetic predisposition, and environmental factors. A better understanding of the etiology and progression of early-onset cataracts in myopia can be achieved by comprehensively investigating and delineating these risk factors, leading to targeted interventions and improved clinical management strategies.

Axial length and early-onset cataract

In an early study, researchers reported that unexplained...
visual loss in young individuals with axial myopia could be attributed to discrete nuclear sclerosis. Two observational studies in India and Taiwan both showed that axial myopia (axial length more than 26 mm) was a significant risk factor for early-onset cataract. Moreover, a significant association was observed between the axial length and age at the time of cataract surgery, as well as the axial length and the nuclear cataract severity. The findings from these data suggest that managing axial length in young adults as part of myopia control strategies may hold potential for mitigating the development of early-onset cataracts in adults of working age groups.

Genetic predisposition and early-onset cataract

Family-based studies have consistently demonstrated that myopia exhibits a substantial heritability characteristic, particularly high myopia. Several genome-wide significant associated loci and a dozen linkage regions have been identified in families with high myopia or through case-control studies involving sporadic cases. Notably, Guo et al. based on an autosomal-recessive high myopia family and identified a homologous nonsense mutation in the LEPREL1 gene, which plays an essential role in the formation of severely high myopia and early-onset cataracts. LEPREL1 gene mutation may cause abnormal post-translational modification for several collagens, such as collagens I, II, IV, and V, and thus interferes with the process of lens fibroblast or fiber differentiations, leading to early-onset nuclear cataract. Zhao et al. also identified a novel missense variant of the CCDC111 gene in a high myopia family by exome sequencing. Notably, Guo et al. reported polymorphisms in TRIB2 and CAPRIN2 genes contribute to the susceptibility to cataracts in patients with high myopia in the Chinese Han population. It displayed widespread expression in primary cell cultures derived from various human eye tissues, including lens epithelial cells. It may play a role in the cataractogenesis in high myopia. However, the specific functions of these mutations are still uncertain, and further investigations into the underlying mechanisms are warranted to gain a deeper understanding.

Environmental factors and early-onset cataract

Environmental risk factors for early-onset cataracts mainly included dietary vitamins and carotenoids, ultraviolet exposure, and lifestyle changes. Interestingly, reduced physical activity and subsequent low-grade intraocular inflammation may be involved in myopia development. It is reported that the level of Irisin, a hormone induced by exercise, in the aqueous samples of the highly myopic cataract eyes was significantly higher, which opened a new direction to discover the relationship between physical activity and cataractogenesis in myopia. Previous studies have consistently documented evidence suggesting that reduced physical activity is an independent risk factor for developing cataracts. However, the exact contribution of physical activity to developing early-onset cataracts in myopia remains unclear, highlighting the need for additional research to investigate the underlying pathological connections.

Pathophysiology evidence

Microenvironmental changes of lens in myopia

Oxidative stress

The alternation of various age-related lens changes is associated with oxidative damage caused by oxidative stress, which arises from an imbalance between the production of free radicals and antioxidant defenses. Early in 1989, Simonelli et al. first demonstrated that cataractous lenses contain higher levels of malondialdehyde (MDA) compared to clear lenses and that the MDA level is further elevated in cases of diabetes and severe myopia compared to idiopathic forms. Recently, the aqueous humor of myopic eyes was verified to present lower total antioxidant capacity and higher total nitrite levels, which was more significant in highly myopic eyes. Furthermore, lower level of protein sulfhydryl has been observed in myopic cataracts, which reflected oxidative damage of the lens. The oxidative stress could be explained by increased oxygen exposure of the lens due to earlier vitreous liquefaction in myopic eyes, resulting in greater susceptibility to oxidative damage in the lenses. Additionally, elevated levels of glutathione oxidation have been observed in the lens and vitreous humor of individuals with myopia, while animal studies have demonstrated that injection of peroxidative substances into the vitreous resulted in cataract formation. These findings also support the involvement of the vitreous and retina in the development of cataracts in myopia.

Elevated oxidative stress plays a pivotal role in facilitating the onset of early cataract development through several mechanisms. Epigenetically speaking, the oxygen-rich environment prevalent in myopic eyes can induce DNA hypermethylation. Modifying antioxidant genes could instigate a perilous cycle of amplified oxidative stress coupled with diminished enzymatic antioxidants, fostering a hostile environment for lens health.

From a proteomics standpoint, lipid peroxidation products spurred by oxidative stress can promote the aggregation of soluble proteins, subsequently leading to fragmentation and compromised integrity of the lens membrane structure. This process effectively hastens the lens’ opacification, exacerbating the progression towards cataract formation.

Proinflammatory status

Myopia has been reported to be closely associated with inflammatory disorders, such as choroidal neovascularization, multiple evanescent white dot syndrome, and multifocal choroiditis. However, whether inflammation plays a role in myopia development and myopic complications remains unknown. Yuan et al. reported a significant positive association between levels of Interleukin 6 (IL-6) and matrix metalloproteinase-2 in aqueous humor and the axial lengths. Notably, our group has previously found proinflammatory cytokines expressed in the aqueous humor in highly myopic cataract eyes, represented by monocyte chemoattractant protein-1, regulated on activation, normal T-cell expressed and presumably secreted, IL-8, platelet-derived growth factor-BB, and IL-6, suggesting an intraocular inflammation may play an essential role in the development and progression of cataract formation in highly myopic eyes.

On the other hand, the chronic inflammation status in aqueous humor may also play a role in developing phacoe-
multisification-related complications in the anterior segment. For example, capsular contraction syndrome, a rare fibrotic post-surgical complication, occurs more frequently in eyes with high myopia, which is related to the decrease of anti-inflammatory cytokine interleukin-1 receptor antagonists in high myopia.\(^{54}\) As an antagonist of the IL-1 receptor, IL-1ra blocks IL-1 downstream signaling and also decreases other proinflammatory cytokines, such as IL-1α, IL-1β, IL-12, IL-2, and interferon γ,\(^{55,56}\) and therefore mediates the myofibroblast formation.

### Enrichment of the growth factors

Studies have shown that several growth factors were related to myopia and myopia-related complications. Of note, elevated transforming growth factor-beta 1 (TGF-β1) and TGF-β2 levels were widely reported in the lens of myopic eyes.\(^{57–60}\) Which may play an essential role in not only the pathogenesis of cataract development but also cataract-surgery-related lens complications. Specifically, TGF-β1 may mediate myofibroblast formation and lead to higher frequencies of capsular contraction syndrome after cataract surgery.\(^{61}\) Additionally, TGF-β2 may mediate injury-induced epithelial-mesenchymal transition and lead to aggregated posterior capsule opacification after cataract surgery.\(^{62}\) Therefore, potential prevention and therapeutic targets may be to control the expression of growth factors in managing postoperative myofibroblast complications in highly myopic cataract patients.

Furthermore, fibroblast growth factor-2 (FGF-2, also known as basic-FGF) is upregulated in the choroid/retinal pigment epithelium of the minus lens-treated myopia model of marmosets.\(^{63}\) FGF-2 also plays a vital role in lens development, lens fiber differentiation, and cataract development.\(^{57,62,64}\) However, specific mechanisms and direct evidence of the role of FGF-2 in cataract development in myopic eyes remained unclear.

### Structural changes of the lens in myopia

#### Biological behaviors of lens epithelial cells

Under the influence of these environmental factors, biological behaviors of lens epithelial cells may likely be triggered in lens epithelial or fiber cells in myopic eyes.

Commonly, the pathogenesis of conventional age-related cataracts is usually associated with “negative” biological behavior such as programmed cell death of lens epithelial cells, including apoptosis,\(^{65–67}\) ferroptosis,\(^{68,69}\) and autophagy.\(^{70}\) However, unlike age-related cataracts, the lens epithelial cells in myopic eyes mainly exhibit “positive” biological behaviors. As characterized by extensive eyeball growth, it is reasonable to speculate that the lens growth may also be aggregated in highly myopic eyes. As documented, an increased lens size in highly myopic eyes is reported, and it is associated with up-regulation of β/γ-crystallin expressions, mediated by the dysregulation of MAF-TGF-β1 axis.\(^{58}\) Furthermore, down-regulation of α-crystallin in human high myopia-related cataract lens epithelium has also been reported.\(^{71}\) Our group has conducted a single-cell RNA sequencing on lens cells from highly myopic eyes and found that the proliferation and differentiation of lens epithelial cells were more amplified, resulting in a larger proportion of lens fiber cells mediated by the Notch2 signaling pathway.\(^{72}\)

Moreover, by whole transcriptome sequencing of Circular RNAs of a highly myopic lens, our group has identified circ-AFF1 in the pathogenesis of highly myopic cataracts, which promoted cell proliferation and migration and inhibited cell apoptosis.\(^{73}\)

Given this evidence, it can be inferred that myopia, especially high myopia, may induce various “positive” biological behaviors, including enhanced cell proliferation, differentiation, and migration. Nevertheless, there is still a need for further exploration and investigation into potential interventions targeting this specific aspect.

### Lens size in high myopia

Considering that high myopia is often associated with excessive eyeball growth, primarily characterized by axial elongation, it is reasonable to speculate that lens growth in high myopes may differ from non-myopes. Nevertheless, various previous studies concentrating on the lens thickness measured by IOLMaster reported no significance between highly myopic and emmetropic patients,\(^{74–77}\) may be due to the insufficient accuracy of the instrument. Recently, Muralidharan et al. used 3-D optical coherence tomography to investigate the morphological changes of the human lens in myopia and found that the lens exhibits thinning, equatorial stretching, and capsular stretching but maintains a constant volume in myopic eyes.\(^{78}\) However, this study still had a problem with insufficient sample size (only 8 emmetropia vs. 13 myopia).

Our group recently established increased lens dimensions in highly myopic eyes using magnetic resonance imaging in large samples (144 emmetropia vs. 105 high myopia).\(^{58}\) Furthermore, a significantly larger maximum cross-sectional area of the lens was also verified by a defocus-induced myopic mouse model.\(^{58}\) This evidence suggested that the lens development might be aberrant in highly myopic eyes, resulting in pathologically larger lens size and, consequently, larger capsular bag volume.

### Structural changes and IOL (intraocular lens) related complications

We believe that the pathological growth of the lens in high myopia may contribute to significant structural changes that can lead to various perioperative challenges in cataract surgery. Severe IOL-related complications may render reduced vision or visual quality and warrant secondary surgery such as IOL replacement. Here, we conclude the incidence, etiology, and prevention of these IOL-related complications in high myopia (Table 1).\(^{79–89}\)

IOL malposition may occur due to the larger capsular bag volume in highly myopic eyes. Various studies have reported that the greater inferior decentration of IOLs was found in highly myopic eyes.\(^{51,90}\) Wang et al. also suggested that cataract eyes with AL > 30 mm are at an increased risk of experiencing clinically significant IOL decentration and tilt.\(^{79}\) As for toric IOLs, the rotation may be more frequent in myopic eyes,\(^{54,59}\) and it was more significant in eyes with larger white-to-white (WTW) distance.\(^{80}\) These indicate that there might be an increasing incompatibility between IOL and capsular bag size with axial length elongations. The malposition of IOL in myopic patients may result in worse visual quality and more subjective symptoms, ultimately impacting surgical outcomes and patient satisfaction. Hence, careful consideration should be exercised when contemplating the implanta-
tion of multifocal or toric IOLs in highly myopic patients with AL > 30 mm or a large WTW distance. Plate-haptic design of IOLs may help with better stability.81 and extended-depth-of-focus design of IOLs may have better tolerance to IOL malposition.82 Additionally, combined capsular tension ring (CTR) implantation is also reported to increase the rotational stability of a toric IOL effectively.83 Moreover, reducing the polishing of the anterior capsule may improve the rotational stability of a toric IOL, as the anterior capsular opacification may increase the friction of IOLs.84

Secondly, late spontaneous IOL dislocation is frequently observed in highly myopic eyes.82 This occurrence can be attributed to the gradual zonular dehiscence and subsequent contraction of the capsular bag over several years after uneventful surgery. Fernández-Buenaga et al. reported that 19.7% (12/61) of the late in-the-bag spontaneous IOL dislocation cases were presented with high myopia, which was considered the main predisposing factor.83 Therefore, during phacoemulsification in high myopic eyes, it is vital to evaluate the supportability of zonules, and caution should be taken to keep the integrity of zonules. While there is currently no definitive evidence supporting the use of CTRs to prevent late IOL dislocation in high myopia, their routine implementation offers a plausible preventive measure. This is supported by evidence demonstrating their role in safeguarding zonular integrity during surgery.85,84

Lastly, accurately predicting refractive outcomes in highly myopic eyes remains a substantial challenge, even with advancements in modern cataract surgery techniques.11 Our research has shown that highly myopic eyes exhibit greater hyperopic refractive errors than myopic refractive errors when utilizing traditional IOL calculation formulas. This discrepancy can be attributed to compromised fixation stability during preoperative biometry measurements.96

A primary obstacle is anticipating the effective lens position in highly myopic eyes, which often present with complex biometry characteristics such as pronounced lens thickness95 and wide WTW measurements.96 To achieve more precise biometry in cases of high myopia, newer swept-source OCT-based devices could offer improved results, given their ability to accurately measure even through dense cataracts and their reduced susceptibility to errors stemming from poor fixation stability.87

Regarding IOL calculations, employing the latest generation of formulas, opting for versions specially adapted for long eyes, or averaging the outcomes derived from multiple formulas might facilitate decreased refractive error in patients with high myopia.88,89

### Conclusion

In conclusion, a burgeoning body of evidence substantiates a significant correlation between myopia and cataracts. Particularly, high myopia routinely manifests as a salient factor in the onset of early cataracts, notably of the nuclear variety. Variables, including augmented axial length, genetic mutations, and environmental disturbances, have been causally implicated in the heightened prevalence of early-onset cataracts among myopic individuals.

Myopic eye lenses undergo complex microenvironmental and structural transformations, which complicate the perioperative management of cataracts in such scenarios. It is crucial to pursue further research to deepen our understanding of the underlying mechanisms and pinpoint effective strategies, emphasizing cataract prevention, refined perioperative management, and reducing surgical complications.

The primacy of early detection, well-curated management strategies, and pinpointed interventions cannot be overstressed, as they are vital to mitigating the repercussions of cataract-induced visual impairment. Such measures pave

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IOL: intraocular lens; SRK/T formula: Sanders, Retzlaff, Kraff formula; D: diopter; AL: axial length; WTW: white-to-white; OCT: optical coherence tomography.
the way for improved quality of life for individuals grappling with myopia.

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Conflict of interest
The authors have no conflict of interest to declare.

Author contributions
LW: article searching, analysis, and interpretation of data and manuscript writing; KKZ: critical revision and technical or material support; YL: critical funding and administration; XJJ: critical revision, critical funding, administration, and manuscript writing; KKZ: critical revision and technical support. All authors have contributed significantly to this study and approved the final manuscript.

Abbreviations
AL, axial length; CI, confidence interval; CTR, capsular tension ring; D, diopeters; FGF-2, fibroblast growth factor-2; IL-6, Interleukin 6; IOL, intraocular lens; LOCS, Lens Opacity Classification System; MDA, malondialdehyde; OCT, optical coherence tomography; OR, odds ratio; SRK/T formula, transforming growth factor beta 1; WTW, white-to-white.

References


