E-ISSN: 3025-2326
DINASTI HEALTH AND PHARMACY SCIENCE
https://dinastires.org/DHPS dinasti.info@gmail.com +62 811 7404 455

DOI: https://doi.org/10.38035/dhps.v4i1

Refractive Errors in Down Syndrome: An Integrative Review of Emmetropization Failure, Corneal Biomechanics, and Accommodative Dysfunction

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Abstract: Down syndrome is the most common chromosomal disorder compatible with life and is associated with multisystem manifestations, including visual abnormalities. Refractive errors are among the most frequent ocular manifestations in Down syndrome, occurring at substantially higher rates than in the general population. Unlike typically developing children, who largely achieve emmetropia through a homeostatic process called emmetropization, children with Down syndrome show a low proportion of emmetropia and persistently heterogeneous refractive errors. This integrative review searched PubMed/MEDLINE, Scopus, Google Scholar, and the Cochrane Library to synthesize evidence on three domains hypothesized to interact in producing emmetropization failure in Down syndrome: corneal biomechanical alteration, accommodative dysfunction, and disrupted retinal blur signalling. Available evidence suggests that trisomy 21 is associated with dysregulated extracellular matrix and collagen organization that reduces corneal biomechanical stability, together with accommodation lag markedly greater than in children without Down syndrome. Both mechanisms appear to converge on persistent retinal image degradation, which may disrupt the visual signals required for refractive growth regulation and contribute to persistent ametropia, increased amblyopia risk, and long-term impairment of visual development. An integrated understanding of these mechanisms has important implications for longitudinal ophthalmologic screening strategies, early amblyopia detection, and more routine evaluation of accommodative function in the Down syndrome population.

Keywords: *Down Syndrome, Refractive Error, Emmetropization, Corneal Biomechanics, Accommodation*

Indonesian Abstract: *Sindrom Down merupakan kelainan kromosom yang paling sering ditemukan dan masih memungkinkan kelangsungan hidup, serta berkaitan dengan manifestasi multisistem, termasuk kelainan penglihatan. Kelainan refraksi termasuk salah satu manifestasi okular yang paling sering dijumpai pada sindrom Down, dengan angka kejadian yang jauh lebih tinggi dibandingkan populasi umum. Berbeda dengan anak dengan perkembangan tipikal yang sebagian besar mencapai emetropia melalui proses homeostatik yang disebut emetropisasi, anak dengan sindrom Down menunjukkan proporsi emetropia*

yang rendah serta kelainan refraksi yang heterogen dan menetap. Kajian integratif ini menelusuri PubMed/MEDLINE, Scopus, Google Scholar, dan Cochrane Library untuk merangkum bukti pada tiga domain yang diduga saling berinteraksi dalam menyebabkan kegagalan emetropisasi pada sindrom Down, yaitu perubahan biomekanik kornea, disfungsi akomodasi, dan gangguan sinyal blur retina. Bukti yang tersedia menunjukkan bahwa trisomi 21 berkaitan dengan disregulasi matriks ekstraseluler dan organisasi kolagen yang menurunkan stabilitas biomekanik kornea, disertai dengan lag akomodasi yang jauh lebih besar dibandingkan anak tanpa sindrom Down. Kedua mekanisme tersebut tampak bermuara pada degradasi bayangan retina yang menetap, yang dapat mengganggu sinyal visual yang diperlukan untuk regulasi pertumbuhan refraksi serta berkontribusi terhadap ametropia persisten, peningkatan risiko ambliopia, dan gangguan jangka panjang pada perkembangan penglihatan. Pemahaman terintegrasi mengenai mekanisme-mekanisme ini memiliki implikasi penting bagi strategi skrining oftalmologis longitudinal, deteksi dini ambliopia, dan evaluasi fungsi akomodasi yang lebih rutin pada populasi sindrom Down.

Keywords: Sindrom Down, Kelainan Refraksi, Emetropisasi, Biomekanik Kornea, Akomodasi

INTRODUCTION

Down syndrome is the most common chromosomal disorder in humans, caused by free trisomy 21, with an estimated incidence of 1 in 700 to 1 in 1,000 live births (Catalano, 1990). Advances in neonatology, pediatric cardiology, and the management of systemic comorbidities have substantially increased the life expectancy of individuals with Down syndrome, making
attention to quality of life and visual function increasingly important.

Visual impairment is among the most common comorbidities in Down syndrome. A wide range of ocular manifestations have been reported, including strabismus, nystagmus, blepharitis, nasolacrimal duct obstruction, cataract, keratoconus, amblyopia, and refractive error (Roizen et al., 1994; da Cunha & Moreira, 1996; Evereklioglu et al., 2002). Among these manifestations, refractive error is one of the most frequently encountered and can be identified from an early age, with a prevalence of ametropia that is consistently higher than in the general population, although the distribution of refractive error types varies considerably across studies (Woodhouse et al., 1997; Haugen et al., 2001; Akinci et al., 2009).

In the general population, refractive development during childhood proceeds through a dynamic process called emmetropization, a homeostatic mechanism that coordinates axial length growth, lens power, and corneal curvature so that the image falls precisely on the retina (Mutti et al., 2005; Troilo et al., 2019). Most children attain a refraction close to emmetropia by school age. In contrast, children with Down syndrome show a different pattern: a lower proportion of emmetropia, while ametropia tends to persist and shows greater variability throughout growth (Doyle et al., 1998; Cregg et al., 2003; Al-Bagdady et al., 2011).

This phenomenon raises a fundamental biological question. The high prevalence of refractive error in Down syndrome is unlikely to be explained by a single anatomical change. Emerging evidence points to a more complex interaction among disrupted regulation of refractive growth, altered corneal biomechanical properties, and accommodative dysfunction. Persistent accommodative deficits may cause degradation of retinal image quality and disrupt the visual signals required for emmetropization (Anderson et al., 2011; Woodhouse, 2010). At the same time, alterations in extracellular matrix and collagen organization associated with trisomy 21 are thought to affect the biomechanical properties of the cornea, increase optical aberrations, and contribute to refractive error (Little et al., 2009; Alió et al., 2018; Kristianslund & Drolsum, 2021).

The clinical implications of this phenomenon are significant. Suboptimal vision at an early age can impede visual development, increase the risk of amblyopia, disrupt the learning process, and affect the quality of life of individuals with Down syndrome, who rely heavily on visual information for learning and social interaction (McCullough et al., 2013; Haseeb, 2022).

Although the prevalence of refractive error in Down syndrome has been extensively reported, most publications have focused on descriptive epidemiology, while the biological mechanisms underlying the high incidence of ametropia remain relatively fragmented. Emmetropization failure, altered corneal biomechanics, and accommodative dysfunction are likely to interact synergistically, yet these three domains are rarely discussed in an integrative manner within a single coherent conceptual framework. This review was undertaken to synthesize current evidence on the epidemiology and spectrum of refractive error in Down syndrome, examine the evidence for emmetropization failure, analyze the roles of corneal biomechanics and accommodative dysfunction, and integrate these three domains into a conceptual model that can be translated into clinical practice.

METHODS

A literature search was conducted across PubMed/MEDLINE, Scopus, Google Scholar, and the Cochrane Library using combinations of the keywords "Down syndrome," "refractive error," "emmetropization," "corneal biomechanics," "accommodation," "keratoconus," and "amblyopia." Inclusion criteria comprised English- and Indonesian-language cohort, case-control, cross-sectional, systematic review, meta-analysis, and narrative review articles, as well as relevant clinical guidelines; foundational articles published before 2015 with important conceptual contributions were also included. An integrative narrative review design was chosen given the heterogeneity in study populations, examination methods, and outcome definitions across studies, which limits formal quantitative synthesis.

RESULTS AND DISCUSSION

Down Syndrome and the Spectrum of Ocular Manifestations

The clinical manifestations of Down syndrome are highly heterogeneous and involve nearly every organ system, including the visual system. This vulnerability of the visual system is likely multifactorial. First, eye development depends on a complex interaction among neuroectodermal, neural crest, and mesodermal tissues, so that disrupted regulation of embryonic development due to trisomy 21 can produce persistent structural and functional changes.

Second, various ocular structures such as the cornea, sclera, ciliary body, and lens capsule depend heavily on the integrity of the extracellular matrix and collagen organization, both of which are known to undergo altered metabolism in Down syndrome (Catalano, 1990; Little et al., 2009). Third, the visual system is a sensory system that undergoes progressive maturation throughout childhood, so that accommodative dysfunction and suboptimal optical quality may potentially disrupt this maturation process.

Accordingly, ocular manifestations in Down syndrome likely do not represent an isolated single-organ abnormality, but rather a consequence of systemic disruption to neuro-ocular development and connective tissue. Refractive error is rarely found in isolation and is frequently associated with strabismus, reported in approximately 20-50% of individuals and predominantly esotropic, as well as with amblyopia, which is likely a consequence of combined strabismus, anisometropia, high ametropia, and congenital cataract (Roizen et al., 1994; Everekliogl u et al., 2002).

Keratoconus is a manifestation receiving increasing attention, with a reported risk several-fold higher than in the general population, thought to be related to altered corneal

biomechanics, disrupted collagen organization, and a higher frequency of eye rubbing (McMonnies, 2009; Kristianslund & Drolsum, 2021). Several studies have also shown that visual quality in Down syndrome is often poorer than would be predicted from the magnitude of refractive error alone, indicating a contribution from optical aberrations and accommodative quality (McCullough et al., 2013). Overall, the spectrum of ocular manifestations in Down syndrome indicates that visual impairment in this population is multidimensional, involving an interaction among anatomical, optical, and neurological factors (Table 1).

Table 1. Spectrum of Ocular Manifestations in Down Syndrome and Estimated Prevalence

Ocular Manifestation	Estimated Prevalence	Source
Refractive error (ametropia)	40-90%	Catalano (1990); Little et al. (2009)
Strabismus (predominantly esotropia)	20-50%	Roizen et al. (1994)
Amblyopia	10-36%	Everekliogl u et al. (2002)
Keratoconus	Several-fold higher than the general population	Kristianslund & Drolsum (2021)
Cataract (congenital or acquired)	5-15%	Roizen et al. (1994)
Nystagmus	5-30%	Catalano (1990)
Nasolacrimal duct obstruction	3-35%	Roizen et al. (1994)

Epidemiology of Refractive Error in Down Syndrome

Unlike the general population, in which most individuals achieve emmetropia during growth, children with Down syndrome show a markedly higher prevalence of ametropia and a more heterogeneous distribution of refractive error. Hyperopia, myopia, astigmatism, and anisometropia are all found more frequently than in the general population, although the predominant type of refractive error varies considerably across studies: Woodhouse et al. (1997) in the United Kingdom reported persistent hyperopia as the dominant finding, Haugen et al. (2001) in a Norwegian population-based study reported high astigmatism, while Akinci et al. (2009) in Turkey reported hyperopia influenced by age and examination method. Astigmatism appears to be the most consistently reported refractive error across studies, with a prevalence exceeding 50% in many studies (Little et al., 2009; Al-Bagdady et al., 2011).

Differences in prevalence across studies are often interpreted as reflecting biological differences, but such interpretation must be made cautiously, as it is influenced by substantial methodological heterogeneity: the age range of subjects (hyperopia is more common at younger ages, whereas myopia and astigmatism may increase with older age), the use of cycloplegic versus non-cycloplegic refraction, the diagnostic threshold used to define ametropia, variation in refraction measurement methods, ethnic heterogeneity, and generally small sample sizes in observational designs (Table 2).

Table 2. Methodological Factors Contributing to Variation in Prevalence Across Studies

Factor	Potential Impact on Study Findings
Age range of subjects	Hyperopia is more common at younger ages; myopia and astigmatism may increase with older age

Factor	Potential Impact on Study Findings
Cycloplegic vs. non-cycloplegic refraction	Non-cycloplegic refraction risks overestimating myopia and underestimating hyperopia
Diagnostic threshold for ametropia	Variation in dioptric cut-off values determines the reported prevalence
Refraction measurement method	Retinoscopy, autorefraction, and subjective refraction have differing precision
Ethnic characteristics of the study population	The distribution of astigmatism and myopia is known to vary across ethnic groups
Sample size	Studies with small samples are prone to unstable estimates
Selection bias in observational designs	Hospital-referred populations risk over-representation of severe cases

Source: synthesized from Woodhouse et al. (1997); Haugen et al. (2001); Akinci et al. (2009).

The most important epidemiological finding is not which type of ametropia is most frequently observed, but rather the fact that the proportion of emmetropia in Down syndrome is consistently lower than in the general population. In other words, children with Down syndrome appear to fail to achieve normal refractive regulation. This finding directs attention to the possibility of a more fundamental disruption of the emmetropization process, which is discussed in the following section.

Emmetropization Failure in Down Syndrome

At birth, most infants are in a state of mild hyperopia with considerable variability in refraction. During infancy and early childhood, the visual system undergoes a dynamic developmental process called emmetropization, a homeostatic mechanism that coordinates axial length growth, corneal curvature, anterior chamber depth, and lens power so that the optical focus falls precisely on the retinal plane (Mutti et al., 2005). Experimental evidence shows that the retina is capable of detecting optical defocus and converting it into a biological signal that regulates eye growth through retina-choroid-sclera interactions; the retina functions not only as a photoreceptor but also as a regulator of refractive growth (Troilo et al., 2019).

Animal model studies show that hyperopic defocus tends to stimulate axial elongation, whereas myopic defocus inhibits axial growth and can induce choroidal thickening, a feedback system involving retinal dopamine, retinoic acid, insulin-like growth factor, transforming growth factor beta, and various mediators in the choroid and sclera (Tkatchenko et al., 2018; Troilo et al., 2019).

Several longitudinal studies have shown that children with Down syndrome have a lower proportion of emmetropia than the general population, and that refractive variability tends to remain high throughout growth rather than narrowing with age as in the normal population (Haugen et al., 2001; Cregg et al., 2003; Al-Bagdady et al., 2011). This finding suggests that the principal problem in Down syndrome may not simply be a high prevalence of myopia, hyperopia, or astigmatism, but rather a failure of the visual system to undergo normal refractive developmental correction (Table 3).

To date, no single mechanism has been identified that fully explains emmetropization failure in Down syndrome; the available evidence suggests that this phenomenon is likely multifactorial. The first hypothesis highlights accommodative deficits: accommodative lag causes persistent retinal blur, particularly during near vision, which may disrupt the visual signals required to guide refractive growth (Anderson et al., 2011). The second hypothesis

highlights altered corneal biomechanics: a steeper cornea, high astigmatism, and increased higher-order aberrations can produce suboptimal retinal image quality (Little et al., 2009; Alió et al., 2018).

The third hypothesis highlights differences in neurological development, given that Down syndrome is a neurodevelopmental condition that may affect the processing of visual information required by the system that regulates refractive growth. The fourth hypothesis highlights a possible difference in the pattern of axial growth, although data on this remain very limited (Table 3).

Based on a synthesis of the available evidence, emmetropization failure in Down syndrome is likely not caused by a single anatomical abnormality, but rather is a consequence of the interaction among degraded visual input quality, differences in neurological development, and altered optical properties of the eye (Figure 1).

Refractive error in Down syndrome likely does not represent merely an increased prevalence of ametropia, but more accurately reflects the failure of a homeostatic system that regulates refractive development during growth, in which accommodative deficits, altered corneal biomechanics, and possible differences in visual processing produce persistent degradation of retinal image quality, thereby disrupting the biological signals required for normal emmetropization.

Table 3. Characteristics and Hypothesized Mechanisms of Emmetropization Failure and Accommodative Dysfunction in Down Syndrome

Aspect	Description	Source
Pattern of refractive development in Down syndrome	Refractive variability remains high throughout growth and the proportion of emmetropia is low, differing from the gradual narrowing pattern seen in the general population	Haugen et al. (2001); Cregg et al. (2003); Al-Bagdady et al. (2011)
Accommodation lag in Down syndrome	Mean of 1.81 ± 1.30 diopters, considerably greater than in children without Down syndrome	Anderson et al. (2011)
Accommodative deficit hypothesis (emmetropization failure)	Accommodative lag causes persistent retinal blur during near viewing	Anderson et al. (2011)
Corneal biomechanical hypothesis (emmetropization failure)	A steeper cornea and increased higher-order aberrations reduce retinal image quality	Little et al. (2009); Alió et al. (2018)
Neurodevelopmental hypothesis (emmetropization and accommodative failure)	Differences in central visual signal processing affecting the regulation of refractive growth and accommodative response	Conceptual; direct evidence still limited
Differential axial growth pattern hypothesis	A possibly different pattern of axial elongation in Down syndrome; quantitative data not consistently reported in the reviewed literature	-
Primary sensory deficit hypothesis (accommodation)	Already-degraded retinal image quality reduces the accuracy of the signal that triggers the accommodative response	Cregg et al. (2001)

Aspect	Description	Source
Accommodative effector dysfunction hypothesis	Possible differences in ciliary body, crystalline lens, or neuromuscular mechanism responses	Al-Bagdady et al. (2009)

Corneal Biomechanics in Down Syndrome

The cornea is the eye's principal optical component, contributing approximately two-thirds of the total refractive power of the visual system, so that even small changes in its structure or biomechanical properties can produce meaningful visual consequences. In normal individuals, corneal transparency and biomechanical stability are maintained through the orderly organization of stromal collagen lamellae (comprising approximately 90% of corneal thickness), proteoglycan interactions, and extracellular matrix balance.

Several studies have shown that the cornea in individuals with Down syndrome has distinct characteristics: it tends to be thinner, steeper, and shows a higher prevalence of optical aberrations and keratoconus (Little et al., 2009; Alió et al., 2018), indicating that these corneal changes are likely not incidental phenomena but part of a more fundamental biological disruption of connective tissue homeostasis (Table 4).

Trisomy 21 is known to be associated with altered gene regulation and extracellular matrix metabolism. Although a direct causal relationship is not yet fully understood, these changes likely produce a cornea with reduced biomechanical resistance to deformation, which over the long term facilitates changes in corneal curvature, increases astigmatism, and increases susceptibility to corneal ectasia.

A steeper cornea increases the eye's total refractive power and contributes to astigmatism, while a thinner cornea is associated with reduced biomechanical stability and an increased risk of ectasia. In addition to causing irregular astigmatism, altered corneal biomechanics can also produce increased higher-order aberrations, such as coma, trefoil, and spherical aberration, which cannot be fully corrected with conventional spherocylindrical lenses (Table 4). Visual quality in Down syndrome may therefore be determined by two components, namely the magnitude of refractive error and the optical quality of the retinal image, rather than by the degree of ametropia alone.

Keratoconus is the most characteristic corneal manifestation in Down syndrome, with a reported risk several-fold higher than in the general population (Kristianslund & Drolsum, 2021). This increased risk is likely multifactorial: altered corneal biomechanics and collagen organization produce a cornea more susceptible to progressive deformation; eye-rubbing behavior, more frequently observed in this population, increases biomechanical stress on the cornea (McMonnies, 2009); and an increased prevalence of atopic disease and ocular surface inflammation are thought to further contribute to keratoconus progression. The presence of keratoconus has important implications, as it can cause progressive irregular astigmatism, increase optical aberrations, and meaningfully reduce visual quality.

A more important question than simply describing keratoconus or corneal thickness changes is whether altered corneal biomechanics also contributes to emmetropization failure. Theoretically, changes in corneal curvature, irregular astigmatism, and increased higher-order aberrations can produce an unstable, low-quality retinal image, potentially disrupting the visual signals required to guide refractive growth. Altered corneal biomechanics may therefore function not only as an anatomical consequence of trisomy 21, but also as one of the components that sustains retinal blur and disrupts the emmetropization process (Figure 1).

Table 4. Corneal Biomechanical and Optical Characteristics: General Population vs. Down Syndrome

Parameter	General Population	Down Syndrome	Source
Central corneal thickness	Relatively thick and stable	Tends to be thinner	Little et al. (2009); Alió et al. (2018)
Corneal curvature	Relatively flat and stable	Tends to be steeper	Little et al. (2009); Alió et al. (2018)
Biomechanical stability (resistance to deformation)	High	Reduced, predisposing to ectasia	Alió et al. (2018); Kristianslund & Drolsum (2021)
Higher-order aberrations (coma, trefoil, spherical aberration)	Minimal	Increased, reducing retinal image quality	McCullough et al. (2013)
Keratoconus prevalence	Rare	Several-fold higher	Kristianslund & Drolsum (2021); McMonnies (2009)

Accommodative Dysfunction in Down Syndrome

Accommodation is the ability of the eye's optical system to increase its refractive power so that near objects can be focused precisely on the retina, involving a complex interaction among the retina, visual cortex, ciliary body, zonules, and crystalline lens. Under normal conditions, retinal blur from a near object triggers contraction of the ciliary muscle, which reduces zonular tension so that the lens becomes more convex.

A growing body of evidence indicates that accommodation is an important component of the visual feedback system that regulates refractive growth during childhood, so that accommodative dysfunction during the developmental period may produce persistent retinal blur that disrupts the homeostatic mechanism regulating refractive growth.

Accommodative deficit is one of the most consistently reported visual abnormalities in Down syndrome. Woodhouse et al. (1993) were the first to document a reduced accommodative response in children with Down syndrome, and this finding was reinforced by quantitative measurements from Anderson et al. (2011), who reported a mean accommodation lag of 1.81 ± 1.30 diopters in individuals with Down syndrome, considerably greater than in the population without Down syndrome.

The principal characteristic of this dysfunction is accommodation lag, a condition in which the accommodative response generated is smaller than the accommodative demand actually required, so that the retinal image remains focused behind the retina and produces persistent retinal blur (Table 3). This finding is important because children with Down syndrome spend much of their learning activity at near distances, such as reading, drawing, and recognizing symbols, so that continuous retinal blur may have a broad impact on visual and cognitive development (Cregg et al., 2001; Al-Bagdady et al., 2009).

The mechanism underlying the accommodative deficit in Down syndrome is not yet fully understood. Several hypotheses have been proposed: a neurodevelopmental difference, given that accommodation is a complex sensorimotor process requiring integration of multiple neurological pathways; a primary sensory deficit, in which retinal image quality is already degraded by astigmatism, optical aberrations, or corneal abnormalities, thereby reducing the accuracy of the signal that triggers the accommodative response; and accommodative effector

dysfunction, namely possible differences in the response of the ciliary body, crystalline lens, or neuromuscular mechanism (Table 3). To date, there is insufficient evidence to determine which mechanism predominates, and it is quite possible that the accommodative deficit in Down syndrome results from the interaction of several of these factors.

The most intriguing aspect of the accommodative deficit in Down syndrome is its possible link to emmetropization failure. In the normal population, an adequate accommodative response helps maintain retinal image quality during near-vision activities; in contrast, in Down syndrome, accommodation lag produces persistent retinal blur, which could theoretically disrupt the visual signals required to regulate refractive growth (Figure 1). This hypothesis is compelling because it can account for two phenomena frequently found together in Down syndrome, namely a high prevalence of accommodation lag and a low proportion of emmetropia, although a direct causal relationship still requires further research.

Chronic retinal blur due to accommodative deficit has broader implications for visual development. The development of visual acuity and maturation of the visual cortex are highly dependent on the quality of visual input during the critical period of development, so that persistent retinal blur can increase the risk of amblyopia.

In Down syndrome, the risk of amblyopia is further increased because accommodative deficits frequently co-occur with high ametropia, anisometropia, strabismus, astigmatism, and suboptimal corneal optical quality, such that multiple factors independently capable of causing amblyopia occur simultaneously in this population (Table 6). Accommodative dysfunction is therefore likely one of the central components linking neurodevelopmental differences in Down syndrome with emmetropization failure and long-term impairment of visual function.

Integrative Model of Refractive Error Pathogenesis in Down Syndrome

Based on the synthesis of evidence presented above, refractive error in Down syndrome is likely not the consequence of a single anatomical abnormality, but rather the result of a dynamic interaction among altered connective tissue, disrupted neurological development, altered corneal biomechanics, and accommodative deficits. Trisomy 21 causes the expression of additional genes that affect tissue development, extracellular matrix metabolism, cell proliferation, oxidative stress, and neurological development, producing multisystem consequences that are not confined to a single organ (Catalano, 1990).

In the eye, this dysregulation produces differences in neuro-ocular development, altered corneal biomechanics, impaired accommodative function, and degraded visual input quality, which appear to interact to form a pathophysiological cycle that sustains ametropia throughout growth (Table 5, Figure 1).

Although the biological changes observed in Down syndrome are highly diverse, most of these mechanisms appear to converge on a single common consequence, namely retinal image degradation. Altered corneal biomechanics can produce astigmatism, irregular astigmatism, higher-order aberrations, and reduced contrast sensitivity, while accommodative dysfunction produces accommodation lag, chronic retinal blur, and reduced focus quality during near vision.

Both pathways converge on persistently suboptimal visual input. This concept is important because the retina not only receives light but also provides the biological signal that guides refractive growth; if visual input quality is chronically disrupted, the signal required to guide emmetropization may also be disrupted. Retinal image degradation is therefore likely the convergence point linking the various abnormalities of Down syndrome with emmetropization failure.

In the normal population, retinal blur in early life triggers a cascade of biological responses that guide the refractive system toward emmetropia. In Down syndrome, by contrast, the various factors that produce retinal blur appear to occur chronically and

simultaneously, so that the refractive regulation system likely does not receive a visual signal accurate enough to drive compensatory growth. In this context, persistent ametropia is no longer viewed merely as a refractive abnormality, but as a manifestation of the failure of a homeostatic system that regulates visual development.

If this condition persists over the long term during the critical period of visual maturation, the consequences extend beyond persistent ametropia to include an increased risk of amblyopia, impaired binocular vision, delayed visual development, disrupted learning, and reduced quality of life (Table 5).

Table 5. Integrative Model of Refractive Error Pathogenesis in Down Syndrome: Stages and Mechanisms

Stage	Mechanism/Consequence	Source
Trisomy 21	Expression of additional genes affects tissue development, extracellular matrix metabolism, cell proliferation, and oxidative stress	Catalano (1990)
Dysregulation of extracellular matrix and collagen	Reduced biomechanical stability of the cornea and ocular connective tissue	Little et al. (2009); Alió et al. (2018)
Corneal abnormalities and accommodative dysfunction	Astigmatism, higher-order aberrations, and accommodation lag occur concurrently	Anderson et al. (2011); Kristianslund & Drolsum (2021)
Retinal image degradation	Persistent retinal blur that disrupts the biological signal for refractive growth regulation	Troilo et al. (2019); Tkatchenko et al. (2018)
Emmetropization failure	Low proportion of emmetropia; persistent and heterogeneous ametropia	Haugen et al. (2001); Cregg et al. (2003)
Long-term consequences	Increased risk of amblyopia, impaired binocular vision, learning difficulties, and reduced quality of life	McCullough et al. (2013); Haseeb (2022)

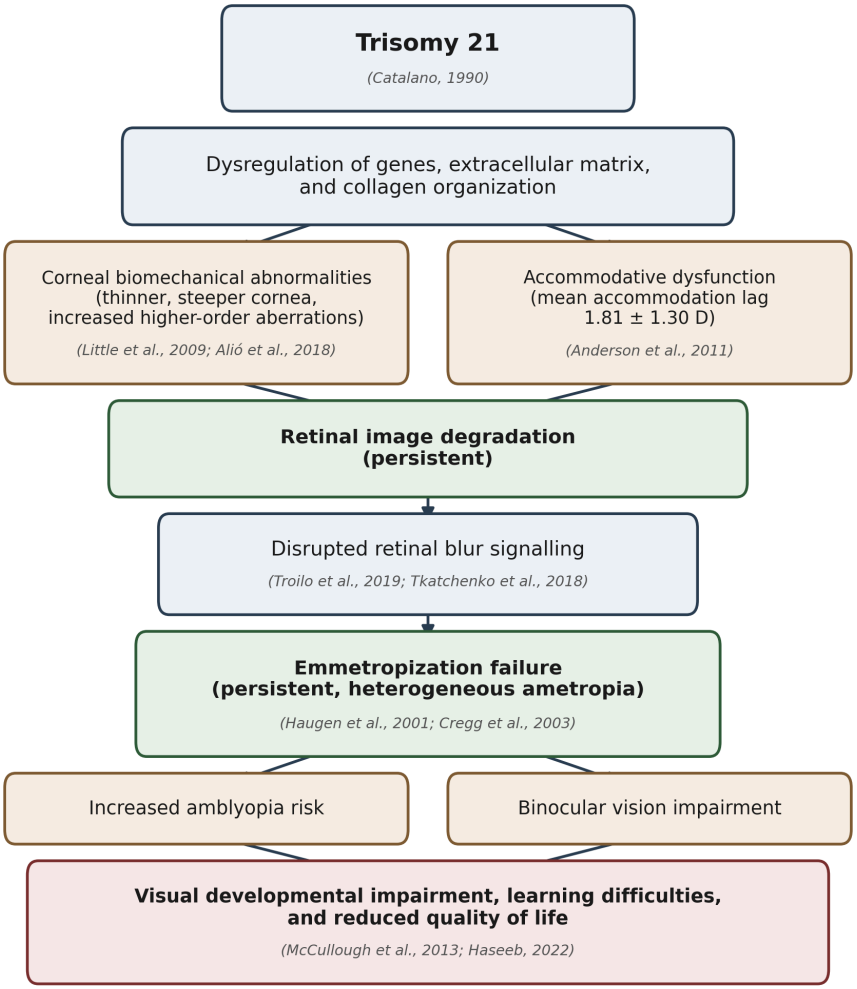

Figure 1. Integrative model of refractive error pathogenesis in Down syndrome, depicting the pathway from trisomy 21 through dysregulation of the extracellular matrix and collagen, branching into corneal biomechanical abnormalities and accommodative dysfunction, converging on retinal image degradation, disrupted retinal blur signalling, and emmetropization failure, leading to long-term consequences including increased amblyopia risk, impaired binocular vision, and visual developmental impairment.

Clinical Implications and Screening Recommendations

Refractive error in Down syndrome is often regarded as a relatively simple ophthalmologic comorbidity that is easily managed through optical correction. This approach likely oversimplifies the problem, as ametropia in Down syndrome is not only more frequent, but also emerges at an earlier age, tends to persist, is frequently accompanied by high astigmatism and accommodative dysfunction, is frequently accompanied by amblyopia and strabismus, and has the potential to cause more extensive impairment of visual development.

The human visual system undergoes a critical period of development during the first years of life, so that chronic retinal blur occurring during this period can cause permanent changes in visual development; this risk is likely greater in Down syndrome because multiple sources of retinal blur (ametropia, astigmatism, accommodation lag, optical aberrations, strabismus) frequently occur together.

Several practical implications can be drawn from the pathogenesis model above. First, cycloplegic refraction should be regarded as an essential examination performed at regular intervals, given that non-cycloplegic refraction may yield less accurate estimates, particularly in children (American Academy of Ophthalmology, 2023). Second, evaluation of

accommodative function should be considered a routine component of ophthalmologic examination, given that accommodation lag is one of the most consistently reported visual abnormalities in Down syndrome yet is still rarely evaluated routinely in everyday clinical practice (Anderson et al., 2011).

Third, corneal topography allows early detection of corneal ectasia, which is often difficult to identify through slit-lamp examination alone at an early stage, making it increasingly important given the elevated risk of keratoconus in this population (Kristianslund & Drolsum, 2021). Fourth, given that multiple risk factors for amblyopia in Down syndrome (high ametropia, anisometropia, strabismus, accommodation lag, keratoconus, suboptimal retinal optical quality) frequently occur simultaneously, an approach to amblyopia prevention requires a more comprehensive strategy than in the general population (Table 6).

Given that ocular manifestations in Down syndrome are dynamic and may change throughout growth, the approach to ophthalmologic evaluation needs to be longitudinal and tailored to age group (Table 7; Down Syndrome Medical Interest Group, 2024). The goal of ophthalmologic management in Down syndrome is therefore not merely to correct refractive values or visual acuity, but also to optimize visual development and everyday learning function, given that children with Down syndrome rely heavily on visual information for learning and social interaction.

Table 6. Risk Factors for Amblyopia in Down Syndrome and Their Mechanisms

Risk Factor	Mechanism of Contribution to Amblyopia	Source
High ametropia (particularly hyperopia)	Chronic retinal blur due to inadequate focus	Woodhouse et al. (1997)
Anisometropia	Asymmetric visual input between the two eyes	Al-Bagdady et al. (2011)
Strabismus (particularly esotropia)	Binocular suppression and cortical competition	Roizen et al. (1994)
Accommodation lag	Persistent retinal blur during near-vision activity	Anderson et al. (2011); Cregg et al. (2001)
High/irregular astigmatism and corneal HOA	Degradation of retinal image optical quality	Little et al. (2009); Alió et al. (2018)
Keratoconus	Progressive irregular astigmatism	Kristianslund & Drolsum (2021)

Table 7. Ophthalmologic Screening Framework for Down Syndrome by Age Group

Age Group	Recommended Examination	Purpose
Neonate-<6 months	Red reflex, evaluation for congenital cataract, anterior segment	Early detection of vision-threatening structural abnormalities
<1 year	Initial cycloplegic refraction, alignment evaluation	Early detection of high ametropia and strabismus
Preschool age (1-5 years)	Periodic cycloplegic refraction, accommodative evaluation, amblyopia screening	Amblyopia prevention during the critical period of visual development
School age (6-12 years)	Cycloplegic refraction, corneal topography, accommodative function evaluation	Early detection of keratoconus and persistent accommodation lag
Adolescents and young adults	Periodic refraction, corneal topography, binocular evaluation	Monitoring of keratoconus progression and refractive stability

Source: synthesized from American Academy of Ophthalmology (2023); Down Syndrome Medical Interest Group (2024).

Novelty

The novelty of this integrative review lies in the proposed unifying pathogenesis model that explicitly links two mechanisms previously examined largely in isolation, corneal biomechanical instability and accommodative dysfunction, as converging contributors to a single downstream pathway of persistent retinal image degradation and emmetropization failure in Down syndrome.

Whereas prior literature has predominantly characterized these domains through separate epidemiological or mechanistic lenses, this review synthesizes them into a single conceptual framework (Table 5, Figure 1) that reframes refractive error in Down syndrome not as an isolated optical finding, but as the clinical expression of a disrupted visual homeostatic system.

This integrative perspective has not, to our knowledge, been articulated as a unified model in the existing Down syndrome ophthalmology literature, and it provides a mechanistic rationale for the longitudinal, multidomain screening approach proposed in this review.

CONCLUSIONS AND RECOMMENDATIONS

Conclusion

Refractive error in Down syndrome is one of the most frequently observed ocular manifestations, with a prevalence consistently higher than in the general population. However, this phenomenon likely cannot be explained merely as an increased frequency of myopia, hyperopia, or astigmatism.

The available evidence suggests that refractive error in Down syndrome may represent disruption of a complex biological system: trisomy 21 is thought to cause alterations in neuro-ocular development and the extracellular matrix that produce corneal biomechanical abnormalities and accommodative dysfunction, and both mechanisms have the potential to produce persistent degradation of retinal image quality that disrupts the visual signals required for the regulation of refractive growth.

This disruption of the emmetropization process likely contributes to the low proportion of emmetropia and the high persistence of ametropia throughout growth in Down syndrome. Its long-term consequences extend beyond mere optical error to include an increased risk of amblyopia, impaired visual development, learning difficulties, and reduced quality of life.

Refractive error in Down syndrome should therefore be viewed as part of a broader disruption of visual development, rather than as an isolated optical error. A comprehensive, longitudinal clinical approach, encompassing early detection of ametropia through periodic cycloplegic refraction, routine evaluation of accommodative function, early identification of corneal biomechanical changes through topography, and amblyopia prevention, has the potential to provide greater benefit in optimizing visual development in the Down syndrome population.

Limitations

This review has several limitations. First, most of the available evidence comes from cross-sectional observational studies with relatively small sample sizes, so that causal relationships among the proposed mechanisms cannot yet be established and can only describe associations. Second, heterogeneity in examination methods, definitions of ametropia, subject age ranges, and the use of cycloplegic refraction makes direct comparison across studies difficult.

Third, data on axial growth, corneal biomechanics (corneal hysteresis, corneal resistance factor), and accommodative function remain relatively limited compared with epidemiological data on refraction. Fourth, most studies originate from Europe and North America, so that representation of Asian populations, including Indonesia, remains inadequate. Fifth, the pathogenesis model proposed in this review is a conceptual framework derived from a synthesis of available evidence and still requires validation through future longitudinal and multimodal research.

Recommendations

Several future research priorities can be drawn from these limitations: large-scale longitudinal studies evaluating axial length, corneal curvature and biomechanics, accommodative function, retinal optical quality, and refractive development simultaneously from infancy through adolescence, to understand when emmetropization failure begins and how the pattern of refractive change unfolds throughout growth; research clarifying the causal relationship between accommodation lag and emmetropization failure; evaluation of the role of higher-order aberrations and wavefront aberrometry in the formation of chronic retinal blur; and research from Southeast Asian populations, including Indonesia, which remain very limited to date.

Nonetheless, the integrative approach used in this review is expected to provide a more comprehensive perspective on the mechanisms underlying refractive error in Down syndrome and to serve as a foundation for future research.

Author Contributions

Conceptualization, literature search, and original draft preparation: Mohammad Aulia Molid Ogest Putra Calisanie; Supervision and writing (review and editing): Ramzi Amin; Supervision and writing (review and editing): Rusdianto. All authors have read and agreed to the published version of the manuscript.

Acknowledgment

The authors gratefully acknowledge the Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia, for their academic support and guidance throughout the preparation of this review.

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