



Refractive Challenges in Marfan's Syndrome: A Review of Non-Surgical Management Strategies

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Abstract

Marfan's syndrome is among the most common inherited connective tissue disorders with significant ocular manifestation. It is usually associated with a mutation in the FBN1 gene located at the 15q15-21 band, which makes the fibrillin-1 protein. It can affect several body systems, including skeletal, ocular, cardiovascular, and pulmonary systems, as well as the dura, skin, and integument. It affects all sexes and ethnicities equally. Fibrillin-1 provides structural support in most of the ocular structures. A mutation or other abnormalities of the fibrillin-1 protein result in zonule weakening, which allows subluxation or even dislocation of the lens. The ocular finding of Marfan's syndrome is only ectopic lentis (as a major) and myopia greater than 3 D (as a minor) included in the Ghent-2 criteria. In contrast, the other features of Marfan's syndrome (transillumination defect, abnormal flat cornea, increased axial length, corneal astigmatism, and retinal detachment) are not included in the Ghent-2 nosology. Refractive error is one of the common causes of visual impairment in Marfan's syndrome patients; however, the best approach for visual rehabilitation is still controversial. Proper refractive correction and visual rehabilitation, especially in children, pose significant challenges for the optometrist and pediatric ophthalmologist due to ongoing visual development and difficulty explaining their visual problems. Proper refractive correction with glasses and/or special contact lenses is the initial approach in mild cases of ectopic lentis. Early surgical intervention should be considered in advanced cases where conservative management fails to correct the refractive error or prevent functional amblyopia.

Keywords: Amblyopia; Conservative Management; Marfan's Syndrome; Refractive Challenges

Introduction

Marfan's syndrome is a multisystem disorder that principally affects the skeletal, cardiac, and ocular systems [1]. In the early 20th century, over 100 years after the initial observation, a French pediatrician named Antoine Bernard Jean Marfan documented a case involving a five-year-old girl with arachnodactyly. Later, this condition came to be known by his name [2]. Over the past few years, several epidemiological studies have been conducted for a better understanding of ocular and systemic manifestation of Marfan's syndrome.

The Berlin criteria first described Marfan's syndrome in 1986, [3] and the Ghent-1 nosology (revised Berlin criteria) redefined the diagnosis by identifying the connection between Marfan's syndrome and FBN1 gene mutation, which encodes the fibrillin-1 protein [4]. In 2010, the criteria were further updated, and ectopic

lentis and aortic root aneurysms were considered major diagnostic criteria [5]. Ocular features of Marfan's syndrome include ectopic lentis (displacement of the crystalline lens), abnormal flat cornea, and elongation of the globe [6-8]. All of these conditions often cause significant refractive errors such as high myopia, astigmatism, and anisometropia (unequal refractive error of the two eyes). All these impair vision and increase the risk of permanent vision loss due to amblyopia [9]. Frequent changes in lens position and axial elongation cause fluctuating and inconsistent refractive errors. Proper refraction and refractive correction is challenging for optometrists in these cases. Surgical options may be considered when non-surgical management is insufficient [10]. This review article aims to explore refractive challenges in Marfan's syndrome and highlights conservative management strategies like optical correction, laser therapy, and customized contact lenses.

Methodology

This article was a comprehensive review of the literatures on non-surgical management of Marfan's syndrome. The syndrome is categorized into the ocular features and refractive changes. The article analysed conservative therapy to identify the trendy and evidence-based recommendation for conservative planning. Literature was searched from online electronic databases (such as PubMed, Google Scholar, and Scopus) up to Dec 2024. The search terms "MARFAN'S SYNDROME", "pathophysiology", "epidemiology of Marfan's syndrome", "refractive challenges", and "visual rehabilitation" were used, and preference was given to recently published articles. References of included articles were reviewed for additional relevant studies and incorporated when appropriate.

Results and Discussion

Ocular features

As previously stated, Marfan's syndrome is a multisystem disorder that primarily affects the musculoskeletal, cardiac, and ocular systems simultaneously. Early clinical diagnosis helps restore vision and increases the chance of saving lives by preventing serious complications like aortic root aneurysms [11]. More than half of those with Marfan's syndrome are diagnosed during an eye examination [12]. Previous studies have shown that the most prominent ocular features of Marfan's syndrome include ectopic lentis, myopia, transillumination defect, increased axial length, decreased corneal curvature, corneal astigmatism, secondary glaucoma, and retinal detachment. However, ectopic lentis, myopia, high corneal astigmatism, secondary glaucoma, and retinal detachment are the leading causes of vision loss in Marfan's syndrome [7,13,14]. In the early stages, patients may be asymptomatic, but in advanced cases, ectopic lentis, high myopia, irregular astigmatism, anisometropia, and amblyopia frequently result in severe visual impairment. Proper refractive correction and visual rehabilitation are often challenging for optometrists and ophthalmologists [12,15] Table 1.

Late diagnosis
Ectopic lentis
Fluctuating and blurry vision
High and irregular astigmatism
Difficulty in performing refraction
Diplopia (monocular or binocular)
Anisometropia and amblyopia
Visual rehabilitation
Follow-up

Table 1: Refractive Challenges in Marfan's syndrome.

Marfan's syndrome requires an integrative approach, and optometrists play a crucial role in ensuring the best quality of life.

Refractive error

Uneven refraction leads to focusing rays of light away from the retina, causing defocus of the retinal image and individual perceived as a blurred vision. Refractive error is the most common cause of visual impairment, and myopia is the second most common ocular feature of Marfan's syndrome, with prevalence ranging from 34% to 45% [6,16,17]. This prevalence is significantly higher in Marfan's syndrome patients compared to the general population [8,10]. One hospital-based observational and cross-sectional study in Western Nepal found that 82.35% had myopia greater than 3D [18]. Besides ectopic lentis, myopia >3D is the only ocular minor criterion in the revised Ghent-2 nosology for Marfan's syndrome [5].

Ocular components influence refraction; high axial length induces high myopia, [19] and corneal flattening is associated with hyperopia [20]. One study hypothesized that fibrillin-1 molecule alteration leads to an unwanted increase in length, a more common cause of high myopia than ectopic lentis [21]. Recent studies demonstrate that axial length is significantly higher in Marfan's syndrome patients than in controls, with a notable increase in adults. Additionally, eyes with ectopic lentis exhibit greater axial length than those without this condition [6,16,17,22].

Corneal astigmatism is another common ocular feature of Marfan's syndrome, [6,8] frequently associated with corneal flattening. Vertical steepening is the most common cause, often manifesting as "with-the-rule" astigmatism. Over time "with-the rule" converted into "against-the rule" and similarly into "oblique" astigmatism [18]. Alterations in fibrillin-1, similar to those in zonular defects, contribute to increased corneal astigmatism [8,23].

Asymmetric lens subluxation, axial elongation, and abnormal corneal flattening contribute to variation in refractive error between the eyes, resulting in anisometropia. Due to ongoing visual development, this condition causes amblyopia, especially in children. Children with anisometropia present with worsened binocularity, which affects various parts of the visual system, such as impairment in stereo acuity, contrast sensitivity, and grating acuity [24]. One study reported that approximately 50% of Marfan's syndrome patients develop permanent functional amblyopia even after best conservative management [9].

The multi-systemic nature of the disease makes early detection more difficult. Patients with Marfan's syndrome have symptoms that range from mild refractive error to severe cardiovascular complications. Several methods and modalities, including ocular examination, have been used for early diagnosis [25]. However, routine eye exams can miss mild refractive error and lens displacement. A comprehensive routine examination should include full pupillary dilation and fundus evaluation, necessitating extensive optometric and ophthalmic knowledge. According to one study, 83% of patients referred from the eye clinic had a confirmed Marfan's syndrome diagnosis [26].

Although not included in the revised Ghent-2 nosology, several studies strongly recommended that ocular components have mutual effects, such as an abnormally flat cornea counteracted by high myopia associated with increased axial length. So there is a higher chance of misdiagnosis of Marfan's syndrome without ectopic lentis, especially in children. Some previous studies strongly support ocular biometric components such as high axial length, abnormal flat corneal curvature, and high corneal astigmatism as potential diagnostic markers for Marfan's syndrome [8,18,23,27,28].

Patients with Marfan's syndrome present with unique refractive errors that need specialized attention from optometrists and ophthalmologists to improve visual outcomes and rehabilitation. Unstable refractive power makes spectacle correction more challenging. Over time, corneal irregularity leads to abnormal scissor reflexes, impairing precise refractive error determination and complicating management.

Refractive challenges

Ectopic lentis refers to the malposition of crystalline lenses within the globe due to zonular weakness. It is frequently bilateral and superotemporal orientation. Subtle iridodonesis and phacodonesis are typical signs. The condition is labeled subluxation when the lens remains within the pupillary axis. If it is misalignment, it is termed dislocation. Dislocation may occur in the anterior chamber, vitreous cavity, or rest on the retinal surface. Anterior dislocation into the pupillary area increases the risk of lens-induced glaucoma. Primary open-angle glaucoma is most commonly associated with Marfan's syndrome, while angle closure is rare due to pupillary block [28]. Posterior dislocation can induce vitreoretinal traction, chronic vitritis, and chorioretinal inflammation, and increase the risk of retinal detachment [29].

It may or may not be associated with systemic conditions [18]. Ectopic lentis is most frequently related to genetic disorders. According to the expert, even in the absence of an FBN1 mutation, the increased sensitivity and specificity of ectopic lentis are regarded as major Marfan's syndrome diagnosis criteria if clinical diagnostic criteria are met [5]. Ectopic lentis is more frequently seen in males than females and can occur at any age [29,30] The estimated prevalence of ectopic lentis varies from 4.6 to 6.81 per 100,000 [31,32]. Individuals with ectopic lentis pose typically feature when presented for the first time in the eye clinic [1,25] Table 2.

Visual impairment
Fluctuating blurry vision
Monocular/Binocular diplopia
Refractive error (myopia, hypermetropia, or astigmatism)
Amblyopia
Secondary glaucoma
Cataract
Retinal detachment
Aniridia
Pseudoexfoliation syndrome
Megalocornea
Persistent pupillary membrane

Table 2: Common Ocular Features of Ectopic Lentis.

The crystalline lens inside the eye helps to focus incoming rays onto the retina to achieve precise vision. In Marfan's syndrome, zonular weakness leads to ectopic lentis, disrupting optical function. This alters refractive status depending on head and eye movement, often manifesting as simple lenticular myopia, astigmatism, or aphakic hyperopia [6,10]. Subtle displacement allows patients to see through the phakic portion, resulting in unusual astigmatism. If the lens partially obstructs the pupil, patients alternately use phakic and aphakic portions, creating a pseudo-bifocal effect. Patients with ectopic lentis present unique refractive challenges due to crystalline lens instability, leading to fluctuating refractive error making precise determination difficult, particularly in children at high risk of amblyopia and visual impairment.

Luxation of the lens causes complete separation of the crystalline lens from the ciliary body, causing it to become smaller and spherical. This condition is known as microspherophakia [33]. This induces a high degree of myopia. Ectopic lentis pose significant

refractive error. Understanding the refractive implication and its management challenges is crucial for improving visual outcomes, especially in children, where normal visual development is at risk [34]. We could not find more articles that enhance and explore the position of the lens and level of visual impairment. In one study, the researcher highlighted the position of the lens and level of visual impairment in children; they reported that children probably have the most severe amblyopia if the lens obscures the visual axis, with the lens edge positioned at 1.3 mm from the center of the pupil, within a range of 0.3 to 2.3 mm [9]. Patients with ectopic lens present unique refractive error and challenges for the optometrist, primarily due to the instability of the crystalline lens. This results in fluctuating refractive error, complicating accurately determining the patient's refractive status due to difficulty ascertaining the actual refractive status, particularly in the pediatric population, where the risk of amblyopia and consequent visual impairment is significantly high. The dynamic nature of the refractive error can lead to long-term visual deficits and needs a more trivial approach to the optometrist examination and management [15].

Conservative management

Amblyopia, also known as lazy eye, is the most common cause of irreversible vision loss in individuals with Marfan's syndrome [34]. Various ocular conditions, such as refractive errors (myopia, hyperopia, astigmatism), anisometropia, ectopia lentis, keratoconus, strabismus, and retinal pathologies, increase the risk of amblyopia, particularly in children during critical visual development. Previously, due to a higher risk of intraoperative and post-operative complications, surgery was not considered the first option. However, with the advancement of microsurgical techniques and instruments, there is renewed interest in surgical intervention to improve visual function. Despite this, conservative approaches like spectacles and contact lenses remain effective with fewer risks [35]. Mild refractive errors from subtle lens tilt, axial elongation, and a flat cornea can be managed with spectacles. However, for lens displacement affecting the visual axis and abnormal corneal curvature, options include partially occlusive customized contact lenses (scleral, one-fit) and laser therapy.

- **Spectacle:** Spectacles are the primary method for correcting refractive errors [28]. They are effective for mild lens displacement or low refractive error. If the lens crosses the pupillary axis, the optometrist or ophthalmologist must decide whether the phakic (with lens) or aphakic (without lens) portion provides better vision. This depends on lens positioning. Depending on the patient's age, vision requirements, and preference, we can recommend a variety of spectacles such as:

- **Single-Vision Glasses:** Single-vision glasses are best suited to those individuals who require separate prescriptions for distance and near vision. Depending on the position of the lens, we should determine the type and extent of correction needed. In aphakic patients, separate glasses may be needed for optimal correction.
- Bifocal glasses are recommended for those requiring distance and near power. They have two distinct optical zones: distance and near. These glasses are best suited for presbyopic and/or younger patients with aphakia. However, they have some drawbacks, such as a visible line of demarcation and the potential for image jump when viewed near distance after the distance.
- **Progressive addition lens (PALs):** PALs have three distinct power zones that gradually correct distance, intermediate, and near vision. These lenses provide natural vision like young, although they may not be good for those with high anisometropia.

Even though glass is the safest method for visual rehabilitation, patients with higher refractive error and younger aphakic children do not tolerate it well due to its weight, prismatic effect, visual field constriction, and cosmetic intolerance [36].

Contact lens

Contact lenses can be a better alternative for refractive error correction and visual rehabilitation. Recent studies highlighted that contact lenses provide better outcomes. They are suitable for long-term refractive error correction and visual rehabilitation. Such lenses are beneficial in younger aphakic children [37]. They provide a wider field of view and aesthetic cosmetics compared to traditional glasses. The various designs available are mentioned below:

- **Partially occlusive contact lens:** These lenses are used to manage issues like monocular diplopia and glare resulting from lens edge. The optometrist or ophthalmologist will determine which part of the lens should be occluded depending on the lens orientation. Such lenses may or may not contain refractive power to correct the refractive error.
- **Scleral contact lens:** Scleral contact lenses are a large-diameter, rigid, gas-permeable optical device that partially or entirely rests on the sclera. They are designed to vault over the entire cornea. This design allows for the creation of a tear-filled reservoir between the anterior surface of the cornea and the posterior surface of the contact lens, which facilitates optimal visual correction. Even though not considered a first option, over the last decades, scleral contact lenses have obtained renewed concern.

These lenses indicate various ocular conditions, like corneal ectasia (such as keratoconus and keratoglobus), post-surgical refractive errors (such as corneal transplant), aphakia (absence of crystalline lens), and high myopia [38]. These lenses not only correct higher refractive error but also help to maintain binocularity in anisometropic children [39]. Several recently published articles highlighted that patients with Marfan's syndrome often present with significantly high refractive errors and irregular astigmatism (either lens or corneal origin). Scleral contact lenses are more beneficial for patients with irregular astigmatism, as their shape and special design of the lens can effectively neutralize refractive errors resulting from corneal or lenticular. However, these lenses directly rest on the ocular surfaces so they cause significant ocular problems like infectious keratitis, corneal ulcers, bacterial keratitis, and microbial keratitis [39].

Laser therapy

Researchers have shown that aphakic correction results in better visual outcomes compared to phakic [15,40,41]. The success of aphakia correction in optimizing visual outcomes largely depends on lens placement and pupillary space. Scientists have investigated different ways to increase pupillary space, with pharmacological mydriasis being a popular method [42].

Historically, more aggressive approaches, such as laser iridectomy and iris photocoagulation, were used to manipulate the iris to obtain similar results. Laser was used to increase the pupillary space to perform refraction well. However, these invasive techniques have become less favored due to potential complications such as iritis, hyphema, corneal edema, and inflammation associated with laser procedures [40,43].

Another method that has been investigated is Nd:YAG laser zonulolysis, which aims to create an optimized area for aphakic refraction. While this intervention can improve visual acuity, it may also lead to symptoms such as glare and photophobia, particularly in cases where significant pupillary dilation is necessary [44].

Similarly unpredictable nature of the refractive error and the associated risk of postoperative complications, including keratoconus, staphyloma, and the chance of Globe perforation, the role of Laser refractive therapy in Marfan's syndrome patients remains controversial [45]. Previous studies strongly demonstrated that Marfan's syndrome patients exhibit higher myopia, greater astigmatism, and thinner corneas compared to the general population, [28] so refractive laser surgery is not considered for refractive management. Which may also affect the intraocular lens (IOL) power calculation.

However, Sandvik, *et al.* [22], reported that Marfan's syndrome patients have stable refractive errors, with no significant changes in other ocular structures including corneal thickness or evidence of keratoconus. Based on this stability, mild refractive error in Marfan's syndrome patients, especially in the absence of lens subluxation, can be managed using laser refractive surgery [45]. However, in the case of lens subluxation laser surgery may have contraindications due to the increased risk of lens dislocation.

Orthoptic exercise and rehabilitation

Long-term follow-up and post-operative visual rehabilitation remain unresolved clinical issues, particularly in young children [29]. Previous research has shown that delayed clinical presentation is frequently associated with poor visual outcomes due to the development of amblyopia and other secondary complications (such as glaucoma) [46].

Several anti-suppression therapies have been investigated, including patching, and occlusion therapy [46]. Each sought to improve binocular function by reducing suppression and increasing the use of the amblyopic eye. However, previous research indicates that traditional anti-suppression therapies such as occlusion and patching have limited efficacy in treating amblyopia [47]. Similarly, a variety of orthoptic exercises, including the Hart chart and Brock string, are used to align the eyes and restore fusion and binocular vision. Studies have shown that such therapies are effective in managing strabismus and amblyopia to achieve optimal results. For example, a study by Z. Lv, *et al.* [48] and S. Ingle, *et al.* [49] found that orthoptic exercise improved binocular vision significantly. They stated that orthoptic exercise improved ocular alignment, binocular coordination, and fusion. These findings highlight the potential for orthoptic and visual rehabilitation techniques to be effective non-surgical management strategies for improving binocular vision in patients with amblyopia and other refractive challenges associated with Marfan's syndrome.

Conclusion

This analysis emphasized the importance of a multidisciplinary approach, involving eye care professionals and other specialists, to manage the unique refractive challenges associated with Marfan's syndrome. Ongoing advancements in surgical and non-surgical management techniques contribute to improved visual prognoses. Nevertheless, future studies should focus on exploring non-invasive and minimally invasive therapies, as well as refining management strategies to achieve optimal results.

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Conflicts of Interest

There are no conflicts of interest.

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