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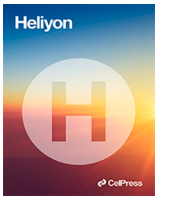

Review article

Collagen is crucial target protein for scleral remodeling and biomechanical change in myopia progression and control

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ABSTRACT

In recent decades, the prevalence of myopia has been on the rise globally, attributed to changes in living environments and lifestyles. This increase in myopia has become a significant public health concern. High myopia can result in thinning of the sclera and localized ectasia of the posterior sclera, which is the primary risk factor for various eye diseases and significantly impacts patients' quality of life. Therefore, it is essential to explore effective prevention strategies and programs for individuals with myopia. Collagen serves as the principal molecule in the extracellular matrix (ECM) of scleral tissue, consisting of irregular collagen fibrils. Collagen plays a crucial role in myopia progression and control. During the development of myopia, the sclera undergoes a thinning process which is primarily influenced by collagen expression decreased and remodeled, thus leading to a decrease in its biomechanical properties. Improving collagen expression and promoting collagen crosslinking can slow down the progression of myopia. In light of the above, improving collagen expression or enhancing the mechanical properties of collagen fibers via medication or surgery represents a promising approach to control myopia.

1. Introduction

The causes of myopia can be attributed to both environmental and genetic factors. However, recent evidence suggests that environmental factors have a more significant influence on the prevalence and severity of myopia [1]. These factors include prolonged periods of near work and excessive use of electronic devices. It is projected that by 2050, approximately 50 % of the global population will develop myopia [2]. Myopia is characterized by excessive elongation of the eye's axial axis beyond its focal point [3]. In myopia, various changes occur, such as thinning of the sclera, decreased biomechanical properties, localized ectasia of the posterior sclera, increased elasticity and creep rate, and thinning of collagen fibers [4–6].

Various strategies exist for the prevention and control of myopia. In recent years, corneal refractive surgery has been widely used in clinics as an effective means to restore vision and improve quality of life and has been demonstrated to be safe, and effective [7]. However, postoperative complications, such as degenerative changes in myopia and iatrogenic keratectasia, may impede surgical progress [8]. Active remodeling of the sclera, particularly its weakening, thinning, and dilation, is crucial in myopia development [9]. Sclera thinning is related to the decrease of collagen fiber diameter, collagen fiber formation defect, and collagen cross-linking, and

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reversing these abnormalities may make the sclera tougher and may be a treatment option for the progression of myopia [10]. Scleral collagen cross-linking involves the formation of bonds between polymer chains, including proteins, which lead to increased tissue hardness and resistance to mechanical degradation and deformation, subsequently reducing the risk of associated complications [11]. Rabbit experiments have further demonstrated that scleral collagen cross-linking can limit axial length growth in progressive myopia [12]. Although scleral collagen cross-linking is still in the animal and in vitro experimental stages, and its mechanism remains unclear, it holds significant potential for clinical use in the prevention and control of myopia development [13]. In this review, PubMed and Google academic databases were used for reference search, and 120 references related to scleral collagen in myopia were included. We focused specifically on collagen and examined the expression of scleral collagen in myopia, the collagen-related mechanisms of myopia, and strategies for myopia control. Regulating collagen expression or improving the structural properties of collagen, supports the prevention and control of myopia.

2. The human sclera

The sclera is a complex, highly viscoelastic, opaque, and load-bearing connective tissue [4]. Forming the outer layer of the eyeball, connected to the cornea, provides stable support during changes in intraocular pressure and eye movements, providing a stable base for the contraction of the ciliary muscle, in promoting accurate eye movements, by providing a stable base for extraocular muscle contractions and in allowing vascular and neural access to adjacent intraocular structures [14,15], as shown in Fig. 1. And plays a central role in the progression of myopia: Scleral thickness decreases significantly with the increase of axial length in myopia, which is scleral remodeling, a special mechanism. Study shows that the changes in scleral composition, ultrastructure, and biomechanics are closely related to scleral remodeling [16].

3. Collagen is the primary structural component of the sclera and determines its biomechanical properties

3.1. Physical and chemical properties of collagen

Collagen serves as the principal molecule in the ECM, capable of self-assembly into cross-striated fibrils that provide structural support for cell growth and contribute to the mechanical elasticity of connective tissues [17]. There are various types of collagen, including fibro-collagen, reticular collagen, fiber-associated triple helix interrupt collagen, membrane-associated triple helix interrupt collagen, and multiple triple helix domains interrupt collagen [18]. To date, over 20 different types of collagen have been identified [19], with types I, II, and III accounting for approximately 80–90 % of the total collagen in the human body [17]. Collagen is composed of three left-handed helical α chains, which intertwine to form a right-handed helix. Depending on the specific α chain composition, collagen can be categorized as homotrimers (e.g., type II collagen) or heterotrimers (e.g., type IV collagen) [18,20]. The discovery of collagen types followed a chronological order, from type I to type XXVIII [21]. The triple helical structure consists of a repeating Gly-X-Y sequence, where X and Y typically represent proline and 4-hydroxyproline, respectively. This supramolecular aggregation then forms collagen fibrils, which align parallelly and bundle together, ultimately being covalently cross-linked to create collagen fibers [20,21].

Many factors regulate the formation of collagen fibers. For instance, type V collagen is necessary for the nucleation of collagen fibers and is involved in regulating the diameter of the fibers [22]. Type IV collagen forms a fibrillar meshwork [17]. Additionally, small leucine-rich proteoglycans play a role in regulating collagen cross-linking [23]. Therefore, collagen fibers are considered to be macromolecular aggregates of collagen and non-collagen proteins or proteoglycans [20]. Collagen and proteoglycan work in synergy within the ECM to provide mechanical support for tissues, withstand tissue loads, and maintain tissue shape [24,25]. The N–H (Gly) O=C(Xaa) hydrogen bond formed in the triple helix structure has a high strength, which significantly contributes to the mechanical properties of collagen [18]. Pro hydroxylation at the Y position and ring pucker type at the Xaa position is also crucial for stabilizing the triple helix structure [18,26]. Given its diversity, collagen exhibits significant variation in molecular and supramolecular composition, tissue distribution, and function [27]. Studies have revealed that the overall level of collagen cross-linking in mouse tail tendons decreases with age [28]. However, it has been observed that in myopia scleral collagen cross-linking naturally accumulates

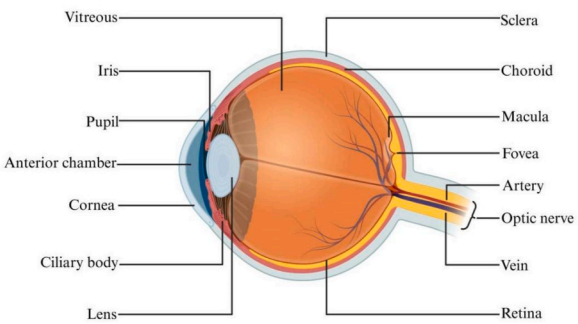

Fig. 1. Anatomy of the human eye.

with age, and can reduce scleral remodeling and susceptibility to myopia [29].

In conclusion, the structural characteristics of collagen determine its biomechanical properties, allowing it to provide mechanical support, maintain tissue shape, and play a vital role in the proper functioning of various tissues.

3.2. Collagen in the sclera

Cornea is a transparent tissue, containing small collagen fibers, uniform diameter, with a high degree of spatial organization; Sclera is an opaque tissue, containing sticky collagen fibers, arranged in parallel layers at right angles to each of the adjacent layers, the presence of elastin fibers increases the elasticity of the sclera [30]. The outer membrane of the eyeball is comprised of the cornea and the sclera, both of which play a crucial role in protecting the eye. The corneal tissue contributes significantly to the eye's refractive power, accounting for approximately two-thirds of it. And consists of the stroma, a central layer rich in type I collagen, which constitutes nearly 90 % of the corneal thickness [31–33].On the other hand, the sclera is a connective tissue abundant in collagen, wherein the collagen fibrils embedded in the proteoglycan-rich scleral ECM perform vital functions in vision [4,34]. The scleral tissue of mammals contains about 90 % collagen, predominantly of type I (by dry weight) [35]. The metabolism of type I collagen impacts the mechanical properties of the sclera, which subsequently influences the axial elongation of the sclera and the development of myopia [36]. Additionally, apart from type I collagen, the human sclera also contains type III, IV, V, VI, VIII, XII, and XIII collagens, notably, type II collagen is the main fibrous collagen of cartilaginous avian sclera, it has also been found in the sclera of embryonic mice, but it is absent in the human sclera [4]. Similar to other collagens, scleral collagen forms collagen fibers through various processes, providing the sclera with elasticity and maintaining the structural integrity and shape of the eyeball [37]. During this process, small and leucine-rich proteoglycans, along with several glycosaminoglycan chains, interact with type I collagen fibrils, where most ligands can directly influence the size and shape of collagen fibrils [38]. Type III is often mixed with type I collagen to form fibril [19]. Type V collagen interacts with type I collagen, and type I collagen synthesis is significantly reduced in the sclera of myopia, resulting in imbalance. The higher the ratio of type V collagen to type I collagen, the smaller the diameter of collagen fibrils [6,39]. Since the arrangement and microstructure of collagen fibers can impact the stress-strain behavior of the sclera, the diameter of collagen fibrils exhibits a linear correlation with the elastic modulus. Changes in mechanical properties are thus a significant factor contributing to axial elongation and even myopia. Therefore, the expression of collagen in the sclera plays a crucial role in its mechanical properties and remodeling [37].

In conclusion, as shown in Table 1, the distribution of collagen is specific to different tissues. The scleral tissue mainly consists of type I collagen, which significantly affects the biomechanical properties of the sclera and vision. Other types of collagen are less abundant in the sclera and the effect is also very weak.

4. Scleral collagen expression decreased in myopia

Myopia is most prevalent among children and adolescents, with approximately 20 % of children under the age of 6 experiencing abnormal vision, often related to refractive abnormalities [40]. Moderate hyperopia at birth and an increase in the axial length of the vitreous body are significant factors for achieving normal vision [41]. However, myopia occurs due to excessive elongation of the eye's vitreous body, resulting in distant objects appearing in front of the retina. The sclera, a connective tissue primarily composed of fibrocytes and ECM, plays a vital role in the onset and progression of myopia. Studies have shown that the process of myopia development and recovery is active remodeling of scleral tissue, rather than passive redistribution [42]. One of the main structural changes observed in axial myopia is the thinning of the sclera and localized ectasia, particularly in the posterior pole [43]. In severe myopia, changes in the diameter of collagen fibrils begin to occur over time, with a more pronounced increase in the frequency of

Table 1
Physical and Chemical Properties of Collagen and its Roles in the Sclera.

Collagen typing	Physical and Chemical Properties of Collagen	The roles in the sclera
I	It is the most abundant [17], and increases with age [4]. Type I, II, and III collagen account for the vast majority, accounting for about 80–90 % of the total collagen in the human body [17]	The metabolism of type I collagen impacts the mechanical properties of the sclera, which subsequently influences the axial elongation of the sclera and the development of myopia [36]
II	Homotrimers [18]	It is the main fibrous collagen of cartilaginous avian sclera and has been found in embryonic mouse sclera, but not detected in human sclera [4]
III	Comparatively stable [4]	Interacts with type I collagen, and the synthesis of type I collagen in the sclera of myopia is significantly reduced, resulting in a higher ratio of type III to type I collagen producing smaller diameter collagen fibers [19]
IV	Heterotrimers [20], and decreases with age [4]. It forms a fibrous network structure [17]	The sclera contains type IV collagen, which like other types of collagen, makes the sclera very elastic and maintains the sclera structure and the shape of the eyeball [37]
V	Decreases with age [4], which is necessary for collagen fiber nucleation and is involved in the regulation of fibers diameter [22]	Consistent with type III [6,39]
Others	Constitutive fibril [35]	Other types of collagen are found in very little amounts in the sclera [35]

smaller diameter collagen fibrils observed in the outer area of the sclera [44]. The thickness of the sclera can reach half or even less than that of normal eyes [5]. In the early stage of myopia, the mitotic activity of scleral fibroblasts is decreased, and the production of collagen, especially type I collagen, is down-regulated. Other studies have proved that the decrease of scleral collagen accumulation in high myopia eyes is the result of the decrease of collagen synthesis and the increase of collagen degradation [6,45]. Thus, it can be concluded that the reduction of scleral ECM and scleral remodeling occur rapidly during the development of axial myopia, whereas the presence of small diameter collagen fibrils is only observed after a longer period, as a consequence rather than a cause of myopia.

Scleral remodeling primarily depends on the regulation of specific protein gene expression in the scleral ECM [43]. Proteoglycan, abundant in the scleral ECM, consists of numerous glycosaminoglycan (GAG) side chains. During myopia development, the protein levels of proteoglycan and GAG are reduced, and their effects are highly complex. They serve as regulatory factors for the assembly and arrangement of collagen fibers and are associated with increased scleral creep in myopia, influencing the biomechanical properties of the sclera and controlling the growth of myopia [44]. Studies have indicated that the decrease in collagen content and fibril diameter are two key factors leading to the thinning and weakening of the sclera [46]. Yang et al. suggested that myopia is a collagen disease, as they found a correlation between high myopia and reduced collagen accumulation in both human and animal models [45].

MMPs and TIMPs play a role in the dynamic process of scleral ECM remodeling, particularly in relation to ECM protein degradation. MMPs, a family of zinc-dependent proteases, degrade ECM proteins, while TIMPs inhibit MMP activity [47]. During myopia, the expression of MMP-2 is upregulated [48], while the expression of TIMP-2 is downregulated [49]. Different subtypes of proteases mediate the degradation of various ECM components, resulting in scleral thinning [50]. Experiments conducted on tree shrews, guinea pigs, and mice have demonstrated the upregulation of MMP-2 in myopia. During minus-lens treatment, there is selective regulation of MMP-2, TIMP-2, and TIMP-3 mRNA levels [47]. Fei Zhao et al. found that the knockdown of MMP-2 significantly inhibits the reduction of collagen Iα1 chain accumulation in the sclera during myopia, while exogenous supplementation of TIMP-2 delays the development of myopia. It was also observed that the increase in MMP-2 expression precedes the increase in form deprivation myopia (FDM), and it was speculated that the rise in FDM might be attributable to collagen degradation and ECM remodeling [48] The interaction among these macromolecular components determines the biomechanical properties of the sclera. Consequently, in myopia, there is a disorganized assembly of scleral fibers, resulting in a thinner sclera and weakened scleral biomechanics [5,43]. Because the changes in the amount of MMPs and TIMPs ultimately result in changes in collagen and proteoglycan, which are less abundant in ECM, the main change in the course of myopia is the change of the collagen in ECM.

However, as shown in Table 2, the mechanism that affects the expression of collagen is very complex. For example, with FDM, the Wnt3/β-catenin signaling pathway is activated in guinea pig scleral fibroblasts. This pathway reduces the expression of type I collagen by reducing TGF-β1 and is ultimately involved in scleral remodeling during myopia development [51]. Overexpression of Hsa-miR-142-3p can reduce type I collagen and TGF-β1 expression in human fetal scleral fibroblasts [52]. In vitro experiments using primary scleral fibroblasts from tree shrews showed that TGF-β1, TGF-β2, and TGF-β3 can all increase collagen production dose-dependently [53]. Nearly one-third of human myopia risk genes interact with the genes in the HIF-1α signaling pathway. Experimental myopia selectively induces HIF-1α up-regulation in the sclera of mice and guinea pigs, and hypoxia exposure (5 % O2) promotes the transdifferentiation of myofibroblasts and down-regulates type I collagen, which eventually leads to scleral remodeling [54]. In recent years, in the mouse and human sclera fibroblasts, it has been found that HIF-2α can induce myopia by up-regulating MMP-2 and promoting scleral collagen degradation. At the same time, HIF-1α up-regulation can only reduce the accumulation of COL1-α1, but cannot upregulate MMP-2 in the sclera [50]. In the development of myopia in chickens, collagen degradation of the scleral fiber layer was increased, but inhibition of collagen degradation activity by TIMP-2 did not affect the development of refractive errors [55]. In guinea pigs, the expression of scleral BMP-2 was significantly reduced in lens-induced myopia, and ECM such as collagen was increased in human scleral fibroblasts treated with BMP-2. Therefore, BMP-2 is involved in scleral remodeling during myopia occurrence and recovery [56]. There's also research that shows after siRNA silencing PDE4B in human scleral fibroblasts, COL1A1 expression was down-regulated [57]. The increase in cAMP accumulation promoted myopia progression, and the gene

Table 2
Effects of Different Genes and Pathways on collagen expression in myopic sclera.

Species	Effect on scleral collagen expression in myopia
Human	Overexpression of Hsa-miR-142-3p can decrease the expression of TGF-β1 in HFSFs and thus decrease the expression of type I collagen [52]; HIF-2α can induce myopia by promoting scleral collagen degradation through up-regulation of MMP-2, while HIF-1α up-regulation can only reduce the accumulation of COL1-α1 [50]; ECM such as collagen was increased in human scleral fibroblasts treated with BMP-2 [56]; After siRNA silencing PDE4B in human scleral fibroblasts, COL1A1 expression was down-regulated [57]; The effect of miR-29a on human scleral remodeling may be mediated by targeting Hsp47 and inhibiting Smad3 pathway [61]
Guinea pig	Activate the Wnt3/β-catenin signaling pathway can reduce TGF-β1 and thus reduce the type I collagen [51]; HIF-1α up-regulation in the sclera of myopia guinea pigs, and hypoxia exposure down-regulates type I collagen, which eventually leads to scleral remodeling [54]; The expression of scleral BMP-2 was significantly reduced in myopia guinea pigs [56]; In FDM guinea pigs, cAMP level was selectively increased and collagen expression decreased [59]; HSP47 promotes the synthesis and secretion of collagen I, and inhibits the degradation [60]
Tree shrew	TGF-β1, TGF-β2, and TGF-β3 can all increase collagen production dose-dependently [53]
Mouse	HIF-1α up-regulation in the sclera of myopia mice, and hypoxia exposure down-regulates type I collagen, which eventually leads to scleral remodeling [54]; HIF-2α can induce myopia by promoting scleral collagen degradation through up-regulation of MMP-2, while, HIF-1α up-regulation can only reduce the accumulation of COL1-α1 [50]; The cAMP hydrolase PDE4B in the FDM was down-regulated, cAMP was increased, and collagen expression was decreased [58]
Chicken	Inhibition of this collagen-lysis activity with TIMP-2 had no effect on the development of refractive errors [55]

expression level of cAMP hydrolase PDE4B was down-regulated in the eyes of FDM mice [58]. The level of cAMP in the sclera of FDM guinea pigs was selectively increased [59]. HSP47 promoted the synthesis and secretion of collagen I in guinea pigs' scleral fibroblasts and inhibited its degradation [60]. The effect of miR-29a on human scleral remodeling may be mediated by targeting Hsp47 and inhibiting the Smad3 pathway [61].

In conclusion, during myopia, multiple gene changes, the synthesized collagen, proteoglycan, and its GAG side chains are reduced, and the degradation of existing collagen and proteoglycan are increased, ultimately leading to the reduction of scleral collagen and proteoglycan. All of the above mechanisms affect scleral remodeling by affecting collagen accumulation, which eventually manifests as the thinning of the scleral thickness in terms of structure and the reduction of biomechanical properties in terms of function.

5. Prevent and control myopia

There are many factors that lead to myopia, including outdoor activity time [62], education attainment [63], and near work [64]. Increasing outdoor activities and reducing the amount of near work have been found to be effective in delaying the onset of myopia [65]. In recent years, there has been a shift towards focusing on ways to slow down the progression of myopia in children and adolescents rather than solely correcting it [66]. There are many strategies to prevent and control myopia.

Concave lenses can clear vision by redirecting distant objects onto the retina. Randomized clinical trials have demonstrated that the use of progressive or bifocal lenses (eyeglasses or contact lenses) can slow down myopia progression in children, possibly due to their influence on the adaptive capacity of the eye [67,68]. Contact lenses are a widely used form of vision correction that is generally well tolerated and can occasionally cause corneal infections, with an annual incidence of about 2–20 per 10,000 wearers [69]. While Tideman et al. showed that visual impairment was related to axial length and equivalent spherical lens [70]. If early myopia is not treated, the development of high myopia can lead to a series of complications and even blindness. So, the risk of keratitis caused by contact lenses is less than the risk caused by no treatment. Exploration of soft multifocal contact lenses has shown an average reduction of 36.4 % in myopia progression and 37.9 % in axial growth, but the question of how to minimize myopia progression without affecting vision remains [71]. Recent reviews have shown that defocus incorporated multiple segments spectacle lenses control myopia can affect peripheral diopter and slow the progression of central myopia [72]. Orthokeratology lenses are approved in many countries worldwide for the temporary reduction of myopia, the axial elongation of the eye decreases by 0.25 mm over two years, however, questions remain about the sustainability of these benefits and the potential acceleration of myopia after discontinuation [73]. Atropine combined with orthokeratology improved myopia in children aged 8–12 years compared with monotherapy [74].

Currently, there is widespread recognition among experts and scholars internationally regarding the correlation between light exposure and myopia in children. However, implementing outdoor interventions in real-life situations for children and adolescents is challenging. In recent years, RLRL has been employed to control myopia progression in school-age children [75]. And the duration of

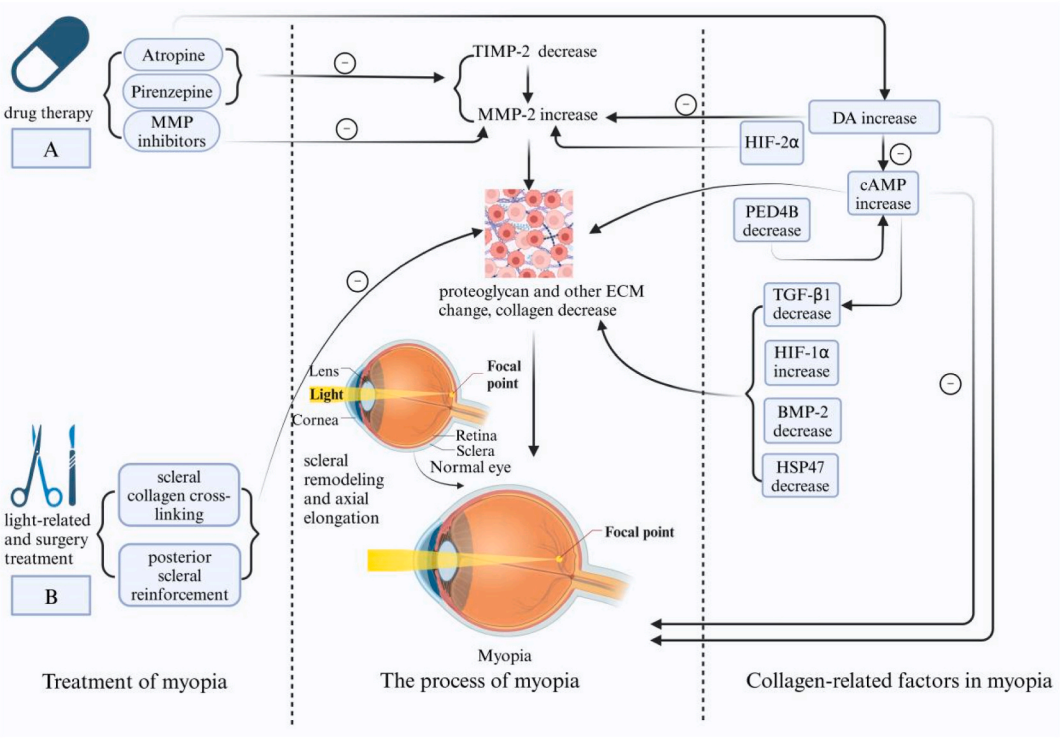

Fig. 2. The role of collagen-related factors in the myopia process and myopia correction.

use and the toxicity of the energy level to the choroid and retina should be carefully considered [76]. Combining RLRL therapy with orthokeratology may be a promising approach to control axial elongation in children with myopia [77].

High myopia is characterized by elongation of the eye axis, thinning of the sclera, and weakened scleral biomechanical properties [16]. Focuses on myopia and scleral collagen, posterior scleral reinforcement (PSR) associated with scleral collagen is commonly used, and scleral collagen cross-linking has shown promise in limiting the rate of axial elongation and with some progress being made [12].

5.1. Up-regulated collagen expression to prevent myopia

As shown in Fig. 2A and Table 3, drug therapy primarily involves muscarinic receptor antagonists (M receptor antagonists). There are five types of M receptors: M1-M5 [78]. Pirenzepine, a selective M receptor antagonist, primarily targets M1 receptors [79]. Pirenzepine delays the progression of myopia by inhibiting the expression of MMP-2 in the scleral fiber layer, promoting the expression of TIMP-2, reducing the degradation of collagen and proteoglycan in the ECM of the posterior pole, facilitating scleral remodeling, and improving the biomechanical properties of the sclera [79], due to its greater side effects, Pirenzepine is not marketed. Atropine, a non-selective M receptor antagonist [80], can increase the thickness of the sclera fibroblast layer, increase type I collagen and fibronectin [80,81], and decrease MMP-2 mRNA expression and MMP-2 protein activity in mice [82]. It can also increase dopamine levels, enhance scleral ECM, continuously inhibit refractive changes, and impede myopia progression, although it has a limited effect on axial elongation [81,83]. High-dose atropine (0.5%–1%) has been found to be the most effective, but myopia rebounds after discontinuation, and significant side effects may occur [84]. 0.01 % atropine was not significantly different from placebo, reduced spherical equivalent changes in myopic, but did not slow the increase in axial length [85,86]. A recent study conducted in China found that a concentration of 0.05 % atropine remains the optimal choice for children over three years old in terms of myopia prevention [87]. Therefore, it is crucial to continue researching the optimal strategy for utilizing atropine in preventing myopia development. Additionally, several MMP inhibitors have shown potential in reducing collagen and ECM degradation by inhibiting MMP activity. Batimastat (5 μM) and marimastat (50 μM) exhibit strong protective effects against FDM, but they may have corneal toxicity. Doxycycline (200 μM) indirectly inhibits MMP activity, although its effect is not as significant as the previous two drugs. However, it has demonstrated equivalent efficacy to 1 % atropine in delaying myopia progression in FDM rodents. These drugs can alleviate scleral thinning caused by FDM, reduce the percentage of small-diameter collagen fibrils, and maintain the regularity of collagen fibrils [82]. We still don't know the impact of combination therapy on the metabolic cascade from the retina to the choroid to the sclera. Various other medications are being explored for myopia treatment, including nicotinic receptor antagonists (N-receptor antagonists) [88], dopamine receptor activators [89], anti-VEGF [90], vasoactive peptides [91], and melatonin [92], among others. It is important to note that drug treatment strategies for myopia are still evolving, and further clinical trials are necessary to ensure the safety and efficacy of these drugs.

In the myopia process and its correction, collagen-related factors play a crucial role. Fig. 2 illustrates how myopic stimulation signals can decrease collagen expression, resulting in scleral remodeling and axial growth. Both drugs (A) and light-related and surgery (B) act by collagen to influence scleral remodeling and control axial growth.

5.2. Improve the scleral biomechanical properties to prevent myopia

As depicted in Fig. 2B, include posterior scleral reinforcement, and collagen cross-linking. These methods aim to induce scleral remodeling, enhance the biomechanical properties of the sclera, and delay the progression of myopia.

5.2.1. Posterior scleral reinforcement

PSR is a surgical procedure designed to mitigate the progression of myopia, particularly high myopia, by strengthening the

Table 3
Scleral collagen-related drugs for myopia.

Drugs	Variety	Mechanism	Advantages	Disadvantages
Pirenzepine	Muscarinic receptor antagonists	A selective M receptor antagonist primarily targets M1 receptors [79]	Delays the progression of myopia [79]	The mechanism is unclear [83]
Atropine	Muscarinic receptor antagonists	A non-selective M receptor antagonist [80]	Increase the thickness of the sclera fibroblast layer, increase type I collagen and fibronectin [80,81], and decreases MMP-2 mRNA expression and MMP-2 protein activity in mice [82]. It can also increase dopamine levels, enhance scleral ECM, continuously inhibit refractive changes, and impede myopia progression [81]	The mechanism is unclear [80], and has a limited effect on axial elongation [83]. High dose rebound [84], low dose dose-dependent [84]
Doxycycline	MMP inhibitors	Inhibition of MMP activity [82]	Alleviate scleral thinning caused by FDM, reduce the percentage of small-diameter collagen fibrils, and maintain the regularity of collagen fibrils [82]	Has some corneal toxicity [82]

weakened area of the sclera in the posterior pole using biological or synthetic materials. It can also involve remodeling and increasing the scleral thickness through non-specific inflammatory reactions between the posterior sclera and the reinforcement strip, thereby inhibiting axial elongation and slowing down changes in diopter [93–95].

Experimental studies conducted on rabbits have demonstrated that PSR can increase the elastic modulus of the sclera and elevate the hydroxyproline content, which is associated with the arrangement of collagen fibers. These findings highlight the biomechanical effectiveness of posterior scleral reinforcement [96]. However, this surgical procedure requires a considerable amount of time for graft fusion with the recipient's sclera during the reconstruction phase. The stretching of collagen fibers during graft integration can help slow down changes in diopter and axial elongation. Furthermore, PSR can remodel the sclera, increase its thickness and hardness, and achieve mechanical reinforcement to delay the progression of myopia [95].

In 2018, some researchers utilized Genipin(GP)-crosslinked scleral strips for PSR surgeries in patients, resulting in safe and effective inhibition of axial elongation during a follow-up period of 2–3 years [97]. Recent studies investigated robust regenerated silk fibroin (RSF) hydrogels showed good biocompatibility in vivo and promoted the formation of posterior scleral fibrosis, enhancing the biomechanics of the sclera [98]. However, it is important to note that surgical scleral reinforcement is typically suitable for severe and progressive myopia [67]. The efficacy of PSR remains a topic of debate due to variations in surgical materials and techniques, as well as potential severe surgical complications. Concerns about frequent surgical complications also persist, highlighting the need for well-designed studies to ascertain its long-term safety and efficacy [99].

5.2.2. Scleral collagen cross-linking

The sclera has a very complex ECM structure with highly anisotropic collagen and elastin fibrils. Human sclera becomes thinner and stiffer with aging, accumulation of non-enzymatic interfiber cross-linking and fiber diameter change provide a potential explanation for the age-dependent differences in stiffness [100]. In recent years, ophthalmology has made significant advancements in the development of collagen cross-linking techniques, which have proven to substantially enhance the mechanical strength of collagen fibers. Initially, corneal collagen cross-linking was clinically applied to treat conditions involving abnormal corneal remodeling. Later, Observations using Raman spectrometry and atomic force microscopy after riboflavin-ultravioletA (UVA) collagen cross-linking revealed that the arrangement of collagen fibers in the sclera was not as regular as in standard scleral fibers, indicating that collagen cross-linking can induce changes in the scleral structure [100] Now, scleral collagen cross-linking has emerged as a focal point for preventing myopia progression by improving the mechanical properties of collagen fibers, enhancing scleral rigidity, and inhibiting axial elongation [101].

Collagen cross-linking can be achieved through the use of chemical cross-linking agents or photosensitizers combined with light of different wavelengths, thereby dividing the technique into physical and chemical cross-linking methods [9,102].

(1) Physical cross-linking:

This approach offers good safety as it avoids introducing exogenous chemical substances into the eyes. Riboflavin has the ability to absorb both blue and UV light. Combining riboflavin with blue light promotes cross-linking, with blue light penetrating scleral tissue more effectively than UVA light, resulting in better cross-linking effects [102]. However, it can cause transient retinal damage, necessitating further investigation into the long-term intraocular safety of this technique [103].

Currently, the most commonly used method is riboflavin-UVA cross-linking. While it is still in the experimental stage involving animal and in vitro studies, its mechanism remains unclear. Nonetheless, riboflavin and UVA light interact to activate oxidative and enzyme-induced glycosylation pathways, leading to collagen cross-linking formation. This technique holds great promise in clinical myopia management [13]. In rhesus monkey experiments, riboflavin-UVA scleral collagen cross-linking has been found to affect scleral remodeling, enhance the biomechanical properties of scleral tissue, and maintain scleral tissue stability for up to 12 months after surgery, demonstrating its effectiveness and safety in rhesus monkey sclera [104]. Rong et al. improved the riboflavin-UVA scleral collagen cross-linking procedure by using a rapid ionophoresis-assisted drug delivery system. They accelerated UVA irradiation (10 mW/cm2, 9 min), which effectively prevented myopia progression and significantly increased the strength of the sclera in New Zealand white rabbits [105]. Although riboflavin-UVA scleral collagen cross-linking is a non-invasive surgical method that reduces complications such as infection and rejection, direct application in human eyes has not yet been implemented [13]. Therefore, experimental studies involving human eyes are necessary to guide future clinical applications. The main target of scleral collagen cross-linking is the scleral equator, and the accidental linkage of the extraocular muscles may have a destructive effect on eye movement. The current challenge is to selectively deliver light to the equatorial sclera in a complete orbit through optimized photoconduction [106].

(2) Chemical cross-linking:

Chemical cross-linking methods, while effective, involve the use of substances such as glutaraldehyde, GP, and glyceraldehyde. These drugs can increase the hardness of the sclera, thereby preventing the progression of myopia [107], without the need for UVA exposure.

It is important to note that glutaraldehyde, despite increasing scleral hardness, has been shown to be toxic to humans and animals [108,109]. On the other hand, GP is considered to have superior biocompatibility compared to conventional cross-linking agents, demonstrating low inflammatory response, minimal long-term toxicity release, and high cross-linking activity. In scleral collagen cross-linking, GP has demonstrated effectiveness in blocking FDM in guinea pigs, with no observed histological damage to the retina or

choroid in treated eyes [110]. Glyceraldehyde has been utilized in human [111], rat [107], porcine [112], guinea pigs [113], and rabbit [114,115] models, and glyceraldehyde scleral collagen cross-linking has been found to increase biomechanical stiffness and thermodynamic stability of the sclera.

In summary, various forms of scleral collagen cross-linking have shown the ability to impact scleral remodeling in myopia, enhance the biomechanical properties of the sclera, and prevent the progression of myopia. However, it is essential to recognize the existence of potential side effects, and it should be noted that all current experiments involving scleral collagen cross-linking are conducted in animal or in vitro settings. Therefore, further research is needed to evaluate safety, effectiveness, and long-term persistence, and to determine the optimal approach for clinical implementation.

Prospects

Myopia has emerged as a global epidemic and has garnered significant attention. It is crucial to identify the causes of myopia and develop a safe, effective, and long-lasting method for its prevention and control. Myopia is influenced by multiple factors, and its underlying mechanism is complex. Collagen is a key component of the sclera. Current research suggests that myopia affects collagen expression and scleral remodeling through certain factors in the signaling pathway, then sclera thinning, and a decline in biomechanical properties. As depicted in Fig. 2, this review paper explores the causes of myopia and examines the safety, stability, and feasibility of various methods employed to prevent and control myopia.

In conclusion, all kinds of myopia prevention and control methods have certain side effects while achieving the effect of myopia control. The focus of this article is scleral collagen cross-linking, which has not yet been considered a standard treatment, and many aspects associated with this approach remain unresolved. Therefore, the long-term benefits and risks associated with this approach must be balanced. Finding good myopia prevention and control strategies also need further efforts.

Data availability statement

No data was used for the research described in the article.

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CRediT authorship contribution statement

Yun Sun: Writing – original draft, Investigation, Data curation. **Yaru Sha:** Investigation, Data curation. **Jing Yang:** Investigation, Data curation. **Hong Fu:** Investigation, Data curation. **Xinyu Hou:** Investigation, Data curation. **Zhuozheng Li:** Investigation, Data curation. **Yongfang Xie:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **Guohui Wang:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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