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Collagen-Based Therapeutics in Ocular Regeneration and Repair: A Comprehensive Review of Corneal and Eyelid Applications

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Abstract

Corneal and eyelid disorders are major causes of ocular morbidity worldwide. These disorders lead to visual impairment, ocular surface dysfunction, and reduced quality of life. Conventional surgical and reconstructive techniques are limited due to complications such as immune rejection, donor tissue shortages, donor site morbidity, and functional limitations. These challenges have led to the development of collagen-based biomaterials as alternative strategies for ocular repair. Collagen, as the main structural protein of the extracellular matrix (ECM), demonstrates biodegradability, high biocompatibility, low toxicity, and structural similarity to native ocular tissues. These significant advantages make it an attractive material for regenerative corneal and eyelid applications.

This mini-review summarizes recent advances in collagen-based biomaterials for corneal and eyelid regeneration. It discusses the biological characteristics of collagen and reviews current evidence on corneal collagen cross-linking (CXL), collagen-based scaffolds, decellularized collagen matrices, acellular dermal matrices, and recombinant collagen. Experimental and clinical studies indicate that collagen promotes epithelial healing, supports cell adhesion, enhances extracellular matrix remodeling, improves tissue integration, and facilitates corneal stromal, conjunctival, and eyelid reconstruction.

Despite these substantial advances, several challenges, such as differences in collagen sources, fabrication methods, and study design, continue to limit direct comparisons between studies and complicate the development of standardized treatment strategies. Future research should focus on improving biomaterial consistency, strengthening clinical evidence through larger studies with longer follow-up, and optimizing long-term performance. Addressing these challenges will help define the clinical role of collagen-based biomaterials and expand the therapeutic options available for corneal and eyelid repair and reconstruction.

Keywords: Collagen, Corneal regeneration, Eyelid reconstruction, Collagen-based biomaterials.

Introduction

Corneal and eyelid disorders represent a major cause of ocular morbidity and visual impairment worldwide. Corneal disorders, including keratitis, keratoconus, and traumatic scarring, are responsible for millions of cases of vision loss worldwide. Owing to the limited regenerative capacity of the cornea, patients with advanced disease often require corneal transplantation (keratoplasty). However, its widespread use is limited by several challenges, including donor tissue shortage, the risk of immune rejection, and its unsuitability for some patients. Similarly, eyelid disorders, including lower eyelid retraction, blepharoptosis, eyelid tumors, dermatochalasis, ectropion, entropion, and conjunctival or posterior lamellar defects, are common causes of ocular surface dysfunction. These conditions compromise ocular surface protection, disrupt tear-film stability, and may impair visual function. These disorders also significantly affect the quality of life of the population by interfering with daily activities and work. The conventional treatments of eyelid disorders have several limitations, includ-

Collagen is the main structural protein of the extracellular matrix (ECM) and plays a fundamental role in maintaining the structure and mechanical properties of both the cornea and the eyelid. In the cornea, type I and type V collagens form the stromal collagen fibrils, whereas type IV collagen is primarily located in the epithelial and endothelial basement membranes (7). Collagen provides the strength, transparency, and structural support required for normal corneal function. Disorders in collagen synthesis, degradation, or cross-linking can directly contribute to the onset and progression of ocular diseases (8-10). In keratoconus, a corneal disorder, disruption of collagen architecture and weakening of stromal collagen fibrils lead to progressive corneal curvature and thinning (ectasia). Optical coherence tomography (OCT) studies have shown that both cellular and collagen contents decrease with increasing corneal depth in keratoconus, with collagen loss accompanying reductions in keratocyte density (16, 17). In the eyelid, collagen-rich connective tissues provide the mechanical strength, protection, elasticity, and flexibility required for normal eyelid function (11).

Ocular tissues present significant challenges for tissue replacement and repair due to their intricate structure and specialized functions. Collagen, a natural biomaterial, is widely used in ocular applications due to its structural and compositional similarity to the ocular ECM. Its excellent biocompatibility, biodegradability, and favorable mechanical properties have made it a promising material for the repair and regeneration of corneal and eyelid tissues (11-13). Compared with many synthetic biomaterials, collagen provides a more suitable microenvironment for cell attachment and tissue remodeling, making it one of the most widely used biomaterials for corneal and eyelid tissue engineering with promising results (14-16).

Advances in biomaterials engineering have led to the development of new collagen-based strategies for ocular regeneration. Corneal collagen cross-linking (CXL), decellularized grafts, acellular matrices, and recombinant collagen have been developed for the treatment of corneal and eyelid disorders. These biomaterials facilitate tissue repair by supporting cell adhesion, extracellular matrix remodeling, epithelial regeneration, angiogenesis, tissue integration, and biomechanical restoration (11, 14, 16, 17).

Although collagen is well suited for ocular regeneration, it still has some drawbacks. Its relatively low mechanical strength, rapid enzymatic degradation, and potential immunogenicity associated with xenogeneic sources remain important limitations that require further optimization (14, 15).

This mini-review highlights recent progress in the use of collagen-based biomaterials for corneal and eyelid regeneration. It summarizes collagen biology, recent advances in natural, decellularized, recombinant, and engineered collagen-based materials, current preclinical and clinical evidence, and the remaining challenges for clinical translation.

2. Literature Search Strategy

A literature search was performed using Web of Science, PubMed, Google Scholar, and Scopus to identify relevant studies published through 2026. This review mainly included original research articles, clinical studies, and recent publications on collagen-based biomaterials for corneal and eyelid repair and regeneration.

3. Structure of Collagen

Collagen is the most abundant structural protein in the mammalian body and the main component of the ECM. It is essential for maintaining the structure, strength, and function of both the cornea and the eyelid (13, 18). The collagen structure is characterized by a triple helix formed by three α-polypeptide chains linked by hydrogen bonds between hydroxylysine and l-hydroxyproline, as well as by covalent bonds, resulting in a highly organized 3D structure. Each polypeptide chain of collagen consists of repeating residues of glycine, proline, and hydroxyproline (Gly-X-Y). Currently, there are 29 different types of collagens, which vary in length, the shapes of their globular domains, and the structures of their

triple helices. Collagen types I, II, III, IV, and V are found in various human tissues, including bone, skin, eyes, cartilage, tendons, and others. Collagen is an ideal biomaterial for ocular tissue homeostasis, repair, and regeneration, constituting 71% of the corneal ECM and serving as the primary structural scaffold for corneal transparency and mechanical stability. Furthermore, collagen offers several benefits, including cost-effectiveness, greater availability, and low immunogenicity. Collagen, via integrin-mediated interactions, modulates critical cellular functions, including cell adhesion, migration, growth, and differentiation, which are essential for ocular tissue regeneration (11, 13, 15). Collagen is sourced from natural animal tissues, including bovine bone, porcine skin, rat, and human cadaveric tissues such as dermis and amniotic membrane. It is also derived from marine organisms (e.g., fish, starfish, jellyfish, and marine sponges) and recombinant sources, each of which offers specific advantages and limitations in availability, functionality, and sustainability (12, 19). Natural collagen, owing to its biocompatibility, biodegradability, and structural similarity to the native ECM of ocular tissues, shows great potential for treating various ocular diseases. Nevertheless, natural collagen exhibits several limitations, including the induction of immune responses, particularly when derived from different sources, rapid biodegradation, limited mechanical strength, inadequate light transmission, and vulnerability to enzymatic degradation (11, 12, 14). The following section delves into the functions of different collagen types (based on their sources). Figure 1 illustrates the major collagen sources, the different collagen-based biomaterial platforms, and their applications in corneal and eyelid repair and regeneration.

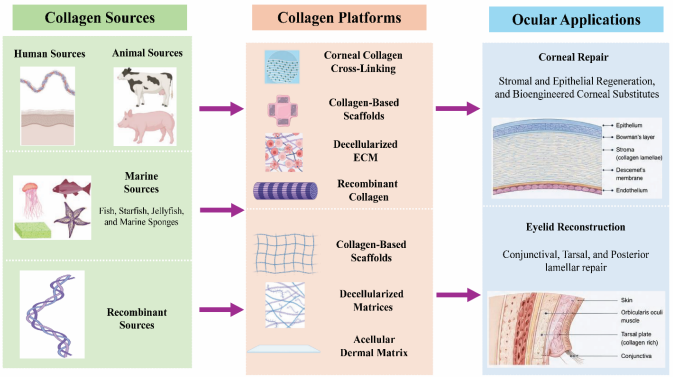

Figure 1. *Overview of collagen-based biomaterials for corneal and eyelid regeneration. Three principal collagen sources (natural animal/human tissue, marine organisms, and recombinant/genetically engineered collagen) are processed into five collagen-based biomaterial platforms: corneal collagen cross-linking (CXL), collagen-based scaffolds, decellularized collagen matrices, acellular dermal matrix (ADM) grafts, and recombinant collagen implants. These platforms are applied clinically and experimentally to two ocular targets discussed in this review: corneal repair (stromal and epithelial regeneration, and bioengineered corneal substitutes) and eyelid reconstruction (conjunctival, tarsal, and posterior lamellar repair).*

4. Applications of collagen in the treatment of eye disorders

4.1. Applications of collagen in corneal repair

The cornea is a transparent, colorless, avascular organ that constitutes approximately one-sixth of the eye's outer coat and is essential for normal vision. From anterior to posterior, the cornea consists of five layers, including epithelium (cellular layer), Bowman's layer (anterior limiting, acellular layer), stroma (cellular layer), Descemet's membrane (posterior limiting, acellular layer), and endothelium (cellular layer) (15). Among these layers, the stroma is a collagen-rich ECM composed mainly of collagen-I, which accounts for 80–90% of corneal thickness and is responsible for maintaining corneal transparency and mechanical strength and elasticity. Collagen V, VI, and XII, as minor collagens, play roles in regulating fibril diameter, spacing, and matrix interactions (11, 15). Globally, approximately 10 million people suffer from corneal blindness caused by corneal disorders and defects. Corneal diseases remain a major cause of visual impairment worldwide, and restoring damaged corneal tissue remains a significant clinical challenge. Although treatments such as corneal transplantation (keratoplasty), topical therapies, and artificial corneas have improved patient outcomes, they do not fully address the limitations of current care. Donor tissue shortage, the risk of immune rejection, and the cornea's limited regenerative capacity continue to limit long-term treatment success. These challenges have increased interest in regenerative approaches that aim to repair and regenerate the native cornea rather than simply replace damaged tissue. Because collagen is the main structural component of the corneal extra-

cellular matrix (ECM), collagen-based biomaterials have become a major focus in corneal tissue engineering. Based on their therapeutic approach, these biomaterials can be grouped into four main categories: (I) corneal collagen cross-linking (CXL), (II) collagen-based scaffolds, (III) decellularized corneal matrices, and (IV) recombinant and bioengineered collagen implants. The following sections summarize the current evidence for each of these approaches (15, 20, 21).

4.1.1. CXL

Corneal collagen cross-linking (CXL) is currently the standard collagen-based treatment for progressive corneal ectatic disorders, particularly keratoconus and post-refractive surgery ectasia. The procedure combines topical riboflavin (vitamin B2) with ultraviolet-A (UVA) irradiation to create additional covalent cross-links between collagen fibrils in the corneal stroma. These cross-links increase corneal biomechanical strength, improve resistance to enzymatic degradation, and help stabilize the weakened cornea, thereby slowing or halting disease progression (22-24). Numerous clinical studies have shown that CXL effectively stabilizes keratoconus, reduces maximum keratometry (Kmax), preserves visual acuity, and has a favorable long-term safety profile, including in pediatric patients (25, 26). For example, S. Hersh et al. conducted a multicenter clinical trial in the United States to treat 179 patients with corneal ectasia after laser refractive surgery with CXL. They reported that CXL is safe and effective, leading to a reduced Kmax value and improved both corrected and uncorrected distance visual acuity in eyes with corneal ectasia 1 year after treatment. CXL is the first approved procedure to reduce the progression of this ectatic corneal process (27). Likewise, Derakhshan et al. reported favorable long-term outcomes in 32 eyes of 22 patients with early keratoconus, demonstrating sustained disease stabilization and an acceptable safety profile after a 9-year follow-up period (28). Furthermore, Fernandes-Cunha et al. reported that type I bovine telocollagen, crosslinked with riboflavin as a photosensitizer under ultraviolet-A (UV-A) irradiation, can be used as a biomaterial for corneal wound repair. They demonstrated that this gel provides high transparency, supports corneal epithelial regeneration, promotes the proliferation of human corneal epithelial cells, and effectively seals corneal perforations in ex vivo models. These results suggest that this gel can be a promising approach for repairing deep corneal defects and perforations (29).

Although CXL has become the standard treatment for progressive keratoconus, it is not without limitations. The procedure is generally recommended only for corneas with sufficient stromal thickness and may cause postoperative pain, delayed epithelial healing, transient stromal haze, infectious keratitis, or endothelial damage in very thin corneas. In addition, CXL strengthens the existing collagen network but does not replace damaged stromal tissue or restore the normal corneal architecture. As a result, patients with advanced keratoconus or extensive corneal scarring may still require corneal transplantation, even when disease progression has been successfully stabilized (30, 31).

These limitations have encouraged the development of regenerative strategies that combine corneal strengthening with tissue repair. Collagen-based scaffolds, bioengineered collagen implants, stem cell therapies, and 3D bioprinting are among the most promising approaches.

4.1.2. Collagen-Based Scaffolds

Collagen-based scaffolds have emerged as a promising strategy for corneal regeneration because they closely mimic the native corneal ECM. Owing to their favorable biocompatibility, cell-adhesion promotion, biodegradability, and low immunogenicity, collagen-based scaffolds offer stromal remodeling, high optical transparency, and high biomechanical resistance, making them attractive alternatives to donor corneal transplantation. Recent advances in scaffold fabrication and cross-linking technologies have further improved their mechanical stability and integration with host tissue (11, 21). Recent studies have developed a variety of collagen-based scaffold

platforms with enhanced regenerative properties. For example, Goodarzi et al. reported that a biocompatible collagen-I-gelatin-based hydrogel crosslinked with an EDC/NHS agent exhibits enhanced mechanical strength, hydrophilicity, and optical properties and promises to be used as an artificial corneal substitute (32). Similarly, Wang et al. demonstrated that natural collagen-I, extracted from bovine tendon and crosslinked using double EDC/NHS and polyrotaxane multiple aldehydes (PRAs), exhibits enhanced mechanical strength, suture resistance, optical clarity, and enzyme tolerance. In addition, they suggested that collagen-EDC-PRA-based membranes in a rabbit model facilitated remodeling of the corneal epithelium and stroma and are a promising approach for treating anterior corneal lamellar injuries (33).

Additionally, Wu et al. developed a glycerol-modulated collagen scaffold (Col-Gly-OX) that promoted the formation of biomimetic collagen lamellae while improving optical transparency, mechanical strength, cytocompatibility, and permeability. In a rabbit lamellar keratectomy model, the scaffold integrated well with the host tissue, promoted epithelial healing, and supported stromal remodeling, demonstrating its promise for corneal tissue regeneration (34). Furthermore, Liu et al. showed that using a novel collagen-I-taurine (COL-I-Tau) film in corneal defects promoted corneal nerve cell growth and corneal epithelialization. They also suggested that the COL-I-Tau film could be a promising approach for treating corneal defects in the future (35).

Another study developed a hydrophilic, porous, fiber-reinforced collagen membrane with improved mechanical strength and suture retention. The scaffold maintained high optical transparency, supported epithelial and stromal regeneration, and integrated well with the host cornea, suggesting its potential for corneal repair (36). Despite promising results, several challenges remain, such as improvements in mechanical strength, degradation control, manufacturing standardization, and long-term clinical validation. The combination of collagen scaffolds with stem cells, growth factors, or 3D bioprinting represents a promising approach for improving corneal regeneration (11, 21).

4.1.3. Decellularized Corneal Matrices

Decellularized corneal matrices have emerged as ideal scaffolds for treating corneal blindness by preserving the native extracellular matrix (ECM) architecture while removing cellular and immunogenic components. These matrices support cell attachment, tissue integration, and corneal regeneration by preserving the cornea's organized collagen structure and biomechanical properties, making them promising biomaterials for corneal tissue engineering (37-39).

Kim et al. reported a decellularized porcine corneal extracellular matrix (dECM) scaffold that supported human corneal endothelial cell adhesion and proliferation, restored corneal transparency, and significantly improved corneal thickness in a rabbit model of endothelial dysfunction. The dECM scaffold demonstrates its potential as a bioengineered corneal substitute (37). Similarly, Li et al. demonstrated that acellular porcine corneal stroma, used after therapeutic keratoplasty in patients, can serve as an effective alternative to human corneal tissue for lamellar keratoplasty (40). Another study reported that the use of acellular human amniotic membrane in a rabbit model did not result in neovascularization, opacity, rejection, or infection. This study showed that this matrix is stable, compatible, and safe within the corneal stroma, making it a promising candidate for corneal stromal regeneration (41). Although decellularized corneal matrices have shown considerable potential, further studies are required to optimize decellularization protocols, maintain long-term optical and biomechanical properties, and establish their long-term safety and clinical efficacy (37, 39).

4.1.4. Recombinant and Bioengineered Collagen Corneal Implants

Recombinant collagen is produced using genetic engineering and recombinant DNA technology, unlike natural sources. Recombinant collagen is produced from human- or animal-

derived gene fragments using various heterologous expression systems, including prokaryotic, mammalian, insect, and yeast cultures, as well as plant-based platforms, yielding high -purity, pathogen-free collagen. Additionally, recombinant human collagens have properties and stability similar to those of natural human collagens. However, recombinant collagen has limitations, including high production cost, low yield, and limited protein expression (12, 42). Recent studies have demonstrated substantial progress in this field. Zhao et al. developed a stromal structure-replicating corneal patch (SRCP) composed of recombinant human collagen, a decellularized cornea-templated nanotubular skeleton, and methacrylated gelatin. The implant demonstrated excellent biomechanical properties, enhanced resistance to degradation, promoted corneal epithelial and stromal cell migration, accelerated epithelial healing, maintained structural stability, and inhibited stromal scarring following transplantation, supporting its potential as a humanized corneal equivalent for sutureless clinical applications (43). In another approach, Liu et al. demonstrated that the recombinant human collagen-I and collagen-III produced in yeast-based hydrogels crosslinked with an EDC (N-ethyl-N'-[3-dimethylaminopropyl] carbodiimide), NHS (N-hydroxysuccinimide) combination are biocompatible, possess adequate tensile strength and elasticity, and have potential for future clinical applications as corneal substitutes for transplantation (44).

Additionally, Xeroudaki et al. demonstrated that transparent, porous bioengineered porcine collagen (BPC) hydrogels implanted with suitable mechanical properties promoted host stromal cell repopulation and the regeneration of the corneal epithelium and nerves. The study suggested that these hydrogels, together with a novel implantation technique, could be used as a promising treatment for corneal stromal regeneration and sustained local drug delivery (45).

Although recombinant collagen has demonstrated favorable findings, challenges, including variable large-scale manufacturing, long-term safety, regulatory approval, and clinical validation, remain. Future research combining recombinant collagen with bioactive molecules and advanced biofabrication approaches may further improve the performance of bioengineered corneal implants and facilitate their progression toward clinical application (46).

Table 1 provides an overview of the available clinical evidence on collagen-based biomaterials for corneal regeneration, including their therapeutic applications, clinical outcomes, and current limitations.

4.2. Applications of Collagen in Eyelid Repair and Reconstruction

The eyelid is a specialized soft-tissue structure anatomically divided into two lamellae. The anterior lamella consists of the skin, subcutaneous tissue, and the orbicularis oculi muscle (a striated muscle), while the posterior lamella is composed of the tarsal plate and conjunctiva. The eyelid plays a crucial role in protecting the ocular surface, maintaining facial structure, and supporting tear-film stability. However, eyelid defects caused by trauma, tumor excision, congenital disorders, or cicatricial diseases remain challenging to repair due to the complex anatomy and functional requirements of this structure.

Conventional reconstructive techniques, including grafts or transposition and flaps, often require additional donor tissue and may be associated with donor-site morbidity, limited availability of autologous tissue, graft contraction, and suboptimal functional outcomes.

In recent years, collagen-based biomaterials have become an attractive option for eyelid repair and reconstruction, offering a regenerative approach that addresses some of the limitations of conventional techniques. Their strong biocompatibility, low immunogenicity, tunable biodegradability, and close resemblance to the native extracellular matrix (ECM) make them well suited for supporting tissue healing. Additionally, collagen serves as a structural scaffold and a functional platform that facilitates cell migration, tissue integration,

angiogenesis, and drug delivery in the eyelid. Collagen-based biomaterials provide an appropriate microenvironment for tissue regeneration rather than simple defect replacement (11, 47-49). Current collagen-based strategies for eyelid repair and reconstruction can be categorized into three main groups based on their therapeutic characteristics and clinical use: (I) collagen-based scaffolds, (II) decellularized collagen matrices, and (III) acellular dermal matrices. The following sections provide an overview of each approach and their potential roles in eyelid regeneration.

4.2.1. Collagen-Based Scaffolds

Collagen-based scaffolds have become an attractive approach for eyelid repair because they mimic the native extracellular matrix and provide structural support for tissue regeneration. They promote epithelial cell adhesion, tissue integration, and neovascularization, while recent advances in scaffold design have improved their mechanical properties and regenerative potential for conjunctival and tarsal reconstruction (11, 50, 51). Xu et al. developed a biomimetic collagen/chitosan-based biphasic scaffold that mimicked the posterior eyelid lamella and promoted conjunctival re-epithelialization and functional tissue regeneration in a rabbit model, demonstrating its potential for tarso-conjunctival reconstruction (51).

Similarly, Witt et al. studied the effect of a new, biocompatible, and surgically usable plastic-compressed collagen-I (PCC) scaffold for conjunctival repair in a rabbit model. They reported that this scaffold, owing to its favorable biocompatibility, stability, surgical applicability, and tissue-integration properties, promoted conjunctival healing, supported epithelial cell growth, and integrated well with surrounding tissues without causing severe inflammation or rejection. Overall, this scaffold represents a new conjunctival substitute with promising potential for conjunctival repair (52).

4.2.2. Decellularized Collagen Matrices

Decellularized collagen matrices are cell-free biological scaffolds that preserve the native extracellular matrix while minimizing immunogenicity through the removal of cellular components. These collagen-rich biomaterials provide structural support and facilitate cell mobility and differentiation, making them promising alternatives for eyelid reconstruction (11, 48). In recent years, decellularized collagen-rich grafts derived from different tissue origins have gained attention as valuable biomaterials for ocular surface and eyelid reconstruction. McGrath et al. evaluated Permacol™, a decellularized porcine acellular dermal matrix, as a spacer graft for the management of lower eyelid retraction. In this retrospective case series involving 12 patients (16 eyelids), the graft significantly improved lower eyelid position and reduced inferior scleral show. They suggested that Permacol is a safe and effective alternative to autologous spacer grafts for lower eyelid reconstruction (53). Similarly, Guo et al. demonstrated that a decellularized porcine small intestinal submucosa (DSIS) scaffold preserved the native extracellular matrix architecture while exhibiting good biocompatibility and favorable mechanical properties. In addition, they reported that this scaffold promoted rapid conjunctival epithelialization, enhanced goblet cell regeneration, and accelerated wound healing compared with amniotic membrane in a mouse model. This biological scaffold has promising potential for conjunctival reconstruction (54).

4.2.3. Acellular Dermal Matrices

Acellular dermal matrix (ADM), derived from decellularized human or animal dermis and preserving basal membrane tissue and collagen fiber bundles, has become a widely used biologic spacer graft in eyelid reconstruction. It provides structural support, restores vertical eyelid height, promotes neovascularization and soft tissue remodeling, and reduces scar formation. Due to its low immunogenicity, strong biocompatibility, and favorable mechanical properties, ADM is particularly suitable for periorbital reconstruction (49, 55). The clinical application of ADM has also expanded to eyelid reconstruction. For example, ADM was used in 20 patients to reconstruct the posterior lamella after malignant eyelid tumor excision. The majority of patients experienced favorable functional and cosmetic results, without significant visual com-

plications or tumor recurrence. These outcomes suggest that ADM can serve as an effective biomaterial for reconstruction of the tarsal plate and conjunctiva in full-thickness eyelid defects (55). Similarly, Kim et al. prospectively evaluated human acellular dermal matrix (WITHderm®) in 20 patients undergoing orbital wall or zygomaticomaxillary complex fracture repair via a subciliary approach. The ADM spacer graft was placed between the orbital septum and orbicularis oculi muscle to prevent postoperative lower eyelid ectropion. No cases of ectropion were observed during the 1-month follow-up, and scar quality improved significantly at 3 and 6 months. These findings suggest that WITHderm® is a safe and effective adjunct for preventing postoperative lower eyelid malposition (49). In another clinical study, Dailey et al. evaluated porcine acellular dermal collagen matrix implants in 100 patients (160 eyelids) with lower eyelid retraction caused by thyroid eye disease, midface descent, facial nerve palsy, and other etiologies. The implants significantly reduced marginal reflex distance and inferior scleral show, providing durable structural support and favorable functional outcomes over a mean follow-up of 14 months, supporting their use as effective biological spacer grafts for lower eyelid reconstruction (56). Although ADMs have demonstrated favorable clinical outcomes, challenges including variable graft resorption, increased cost, and limited long-term comparative clinical evidence remain (49). Further prospective multicenter studies are needed to optimize graft selection and evaluate long-term functional and cosmetic outcomes.

Table 2 provides an overview of the available clinical evidence on collagen-based biomaterials for eyelid reconstruction, including their therapeutic applications, clinical outcomes, and current limitations. Also, experimental studies investigating emerging collagen-based biomaterials for corneal and eyelid tissue engineering are summarized in Table 3.

5. Current Challenges and Clinical Translation of Collagen-Based Biomaterials

Collagen-based biomaterials have shown promising results in both corneal and eyelid repair. However, several challenges still limit their routine clinical use. Although collagen offers strong biocompatibility and closely resembles the native extracellular matrix, its properties can vary depending on the collagen source, processing method, cross-linking technique, and scaffold design. These differences may affect mechanical strength, degradation rate, transparency, and cell behavior, making it difficult to directly compare results from different studies or establish standardized treatment protocols (11).

The challenges also differ between corneal and eyelid applications. In corneal repair, biomaterials must remain transparent while providing sufficient mechanical strength and allowing normal diffusion of oxygen and nutrients to support tissue regeneration. Maintaining these properties over time without inducing inflammation, fibrosis, or loss of transparency remains a major challenge. In eyelid reconstruction, collagen-based biomaterials should provide stable structural support, integrate with the surrounding tissues, and preserve normal eyelid function while achieving acceptable cosmetic outcomes. Although acellular dermal matrices and collagen-based spacer grafts have shown encouraging clinical results, differences in graft remodeling, resorption, surgical techniques, and follow-up periods make it difficult to compare studies and assess their long-term clinical performance. Another major challenge is the absence of standardized manufacturing protocols. Differences in collagen extraction, decellularization, sterilization, and scaffold fabrication methods can substantially influence the characteristics of the final constructs, making it difficult to reproduce results across different studies. In addition, challenges associated with large-scale manufacturing, regulatory approval, and treatment costs continue to restrict their widespread clinical application. Compared with synthetic biomaterials, collagen generally provides better biocompatibility and supports tissue regeneration more effectively. However, synthetic materials often have greater mechanical strength, slower degradation, and more

consistent manufacturing. Therefore, recent research has increasingly focused on combining collagen with synthetic polymers or other bioactive components to overcome these limitations and improve the performance of collagen-based biomaterials (11, 14, 16, 17, 45, 48, 57-61).

Overall, current evidence suggests that collagen-based biomaterials have considerable potential to promote tissue repair in both corneal and eyelid applications. However, the available studies remain heterogeneous, with substantial variations in biomaterial composition, study design, patient characteristics, and outcome assessment methods. These variations make it difficult to directly compare findings across studies and emphasize the need for more consistent research approaches. Addressing these challenges will help define the specific clinical applications of collagen-based biomaterials and support their broader use in ophthalmic regenerative medicine.

6. Future Perspectives

Recent advances have expanded the role of collagen beyond its conventional use as a passive structural scaffold. Current research is increasingly focused on designing collagen-based platforms with improved biological activity, tunable mechanical properties, and enhanced long-term stability. These advances have contributed to the development of recombinant collagen, composite materials, and bioactive scaffolds that can better support tissue repair and regeneration.

An important direction in this field is the combination of collagen with other regenerative technologies. The incorporation of growth factors, stem cells, extracellular vesicles, and drug-delivery systems into collagen-based materials has shown encouraging results in preclinical studies by promoting cellular activity and improving tissue healing. At the same time, advances in three-dimensional bioprinting are allowing researchers to create more organized collagen-based constructs with controlled structures that more closely resemble native corneal and eyelid tissues.

Despite these advances, the clinical application of collagen-based biomaterials is still limited. Most available studies have been performed in animal models or small clinical groups, and relatively short follow-up periods make it difficult to fully evaluate their long-term safety, stability, and therapeutic benefits. Future clinical studies should therefore focus on larger patient populations, standardized evaluation methods, and longer follow-up periods to better determine the clinical value of these approaches.

Future progress in this field will depend on matching the right collagen-based biomaterial to the right clinical indication. Because corneal and eyelid disorders differ in their biological and mechanical requirements, no single collagen platform is likely to be suitable for every application. A better understanding of how different collagen-based biomaterials perform in specific clinical settings will help guide treatment decisions and support their wider use in ocular regenerative medicine.

7. Conclusion

Collagen-based biomaterials are playing an increasingly important role in corneal and eyelid regeneration. Their favorable biological properties and close resemblance to the native extracellular matrix make them well suited for ocular tissue repair. The studies reviewed here show that collagen-based scaffolds, decellularized collagen matrices, recombinant collagen, and acellular dermal matrices can support tissue regeneration and improve clinical outcomes across a wide range of experimental and clinical settings.

In corneal diseases, collagen-based biomaterials have shown favorable outcomes in stromal regeneration, epithelial healing, drug delivery, and the development of bioengineered corneal substitutes. In eyelid reconstruction, they have provided effective alternatives to conventional grafting techniques by improving posterior lamellar repair, conjunctival reconstruction, and lower eyelid support while reducing the need for autologous donor tissue. Although clinical evidence

is currently more extensive for corneal applications, recent studies suggest that collagen-based biomaterials are also becoming increasingly valuable in eyelid reconstruction.

The role of collagen in ocular regeneration has expanded considerably in recent years. Rather than acting only as a structural scaffold, collagen-based biomaterials provide a supportive environment for tissue repair and regeneration. Although additional clinical evidence is still needed, the studies reviewed here suggest that these biomaterials will play an increasingly important role in the future management of corneal and eyelid disorders.

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Author (Year)	Disease	Collagen-Based Strategy	Study Design	Sample Size	Follow-Up
Islam et al. (2018)	Advanced corneal disease	Cell-free recombinant human collagen type III–phosphorylcholine (RHCIII-MPC) corneal implant	Open-label clinical study	7 patients (6 completed)	Mean 24 months
El-Massry et al. (2021)	Keratoconus/ post-LASIK ectasia	Decellularized porcine corneal lenticular implant	Retrospective clinical study	6 patients (7 eyes)	12 months
Hu et al. (2025)	Infectious corneal ulcers	Acellular porcine corneal stroma (APCS) for lamellar keratoplasty	Prospective interventional case series	14 patients (14 eyes)	12 months
Jabarvand et al. (2026)	Keratoconus	Double-crosslinked bioengineered porcine collagen implant (BPCDX)	Prospective interventional case series	17 patients (17 eyes)	12 months
Deshmukh et al. (2025)	Keratoconus	Xenia® porcine collagen stromal implant	Prospective interventional case series	9patients (9 eyes)	12 months

Table 1. *Clinical Studies of Collagen-Based Biomaterials for Corneal Regeneration (62-66).*

Author (Year)	Disease	Collagen-Based Strategy	Study Design	Sample Size	Follow-Up	Level of Evidence	Key Findings	Major Limitations
Islam et al. (2018)	Advanced corneal disease	Cell-free recombinant human collagen type III–phosphorylcholine (RHCIII-MPC) corneal implant	Open-label clinical study	7 patients (6 completed)	Mean 24 months	IV	Promoted corneal tissue and nerve regeneration, restored ocular surface integrity, improved visual acuity, and was well tolerated without long-term immunosuppression	-Small sample size -Heterogeneous population -No control group
El-Massry et al. (2021)	Keratoconus/ post-LASIK ectasia	Decellularized porcine corneal lenticular implant	Retrospective clinical study	6 patients (7 eyes)	12 months	IV	Improved visual acuity, increased central corneal thickness, reduced Kmax and higher-order aberrations, with excellent biocompatibility.	-Small sample size -Absence of a control group -Limited follow-up
Hu et al. (2025)	Infectious corneal ulcers	Acellular porcine corneal stroma (APCS) for lamellar keratoplasty	Prospective interventional case series	14 patients (14 eyes)	12 months	IV	Preserved globe integrity, accelerated epithelial healing, improved visual acuity, and showed a low graft rejection rate (1 patient)	-Small sample size -Heterogeneous ulcer etiologies -Postoperative corneal nerve data were unavailable due to equipment shortage
Jabarvand et al. (2026)	Keratoconus	Double-crosslinked bioengineered porcine collagen implant (BPCDX)	Prospective interventional case series	17 patients (17 eyes)	12 months	IV	Improved visual acuity, reduced Kmax, increased corneal thickness, and maintained graft transparency without serious complications.	-Small sample size -Limited follow-up -Lack of comparison with standard corneal transplantation procedures.
Deshmukh et al. (2025)	Keratoconus	Xenia® porcine collagen stromal implant	Prospective interventional case series	9patients (9 eyes)	12 months	IV	Significant improvement in UDVA, CDVA, and keratometric parameters (K1, K2, Kmean, and Kmax), with no graft rejection, suggesting Xenia® implantation as a potential alternative to keratoplasty in selected patients with advanced keratoconus	-Small sample size, -1-year follow-up -Two eyes had stromal melt within 3 months postoperatively, requiring lenticule explanation

Table 2. *Clinical Studies of Collagen-Based Biomaterials for Eyelid Reconstruction (58-61, 67, 68).*

Author (Year)	Disease	Collagen-Based Strategy	Study Design	Sample Dize	Follow-Up	Level of Evidence	Key Findings	Major Limitations
Kim et al. (2017)	Lower eyelid retraction (Graves' orbitopathy)	Acellular human dermis (AlloDerm ®) spacer graft	Retrospective comparative study	54 patients (95 eyes)	4-6 months	III	Simultaneous placement of an acellular human dermis spacer graft during orbital decompression significantly improved lower eyelid position (MRD2), reduced inferior scleral show, and achieved better functional and cosmetic outcomes than conventional surgery alone without increasing complications.	-Limited follow-up -Retrospective non-randomized design -Single-center study
Kavya et al. (2026)	Symblepharon	Collagen matrix implant (CMI)	Pilot study	9 patients (10 eyes)	6 months	IV	Improved forniceal depth, reduced recurrence, restored ocular surface anatomy, and showed excellent implant safety.	-Noncomparative pilot study -Limited sample size, -short follow-up -The implant used is costly and small in size.
Parker et al. (2024)	Lower eyelid retraction	Porcine collagen bioengineered acellular dermal matrix (Mucograft ® BADM) spacer graft	Retrospective case series	6 patients (12 eyes)	Mean period of 9.16 months	IV	Mucograft® BADM effectively corrected lower eyelid retraction, significantly improved eyelid position and cosmetic appearance, demonstrated good graft integration, and showed no serious graft-related complications or need for graft removal during follow-up.	-Limited follow-up -Small sample size -Short follow-up -Lack of long-term prospective comparative studies.
Barmettler & Heo (2018)	Lower eyelid retraction	Bovine acellular dermal matrix (SurgiMend®) and porcine acellular dermal matrix (ENDURAGen®) spacer grafts compared with autologous auricular cartilage	Prospective, randomized clinical trial	49 randomized lower eyelids (39 patients), 42 eyelids (32 patients) were completed.	6 months	II	All three spacer grafts significantly improved lower eyelid position (mean MRD2 improvement: 2.3 mm; $P < 0.0001$) and ocular symptoms, with no statistically significant differences in surgical outcomes, complication rates, or reoperation rates among porcine acellular dermal matrix, bovine acellular dermal matrix, and autologous auricular cartilage	-Limited statistical power due to small sample size -Short follow-up -Unmatched baseline characteristics (etiology, age, and sex) among the study groups.
Xie et al. (2025)	Full-thickness eyelid defect	Xenogeneic acellular dermal matrix combined with full-thickness skin graft	Retrospective observational study	21 patients (21 eyes)	6 months	IV	XADM combined with a full-thickness skin graft achieved successful reconstruction of full-thickness eyelid defects, with complete graft survival, satisfactory functional and cosmetic outcomes, and good tissue integration.	-Prolonged eyelid fusion with potential visual and functional limitations -Small sample size -Insufficient follow-up for long-term functional and aesthetic evaluation
Borrelli et al. (2012)	Lower eyelid retraction (facial nerve palsy)	Decellularized porcine-derived membrane (Tarsys®) spacer graft	Case report	1 patient (1 eye)	3 months	V	Successfully corrected lower eyelid retraction and resolved lagophthalmos without implant-related complications.	-Single case report with limited generalizability -Limited follow-up

Table 3. *Experimental Studies of Collagen-Based Biomaterials for Corneal and Eyelid Tissue Engineering (69-79).*

Author (Year)	Disease Model	Collagen-Based Biomaterial	Model	Observation Time	Major Findings	Translational Potential
Ahn et al. (2013)	Corneal stromal defect	Crosslinked porcine type I atelocollagen and recombinant human type III collagen hydrogels	Mouse	22 days	Transparent collagen implants supported stromal regeneration with excellent biocompatibility, minimal inflammation, and stable integration.	Promising artificial corneal substitute for stromal replacement.
Hong et al. (2019)	Corneal stromal defect	Compressed Rat-tail type I collagen hydrogel combined with cornea (bovine eyeballs)-derived decellularized extracellular matrix (dECM)	*In vitro* (human corneal stromal cells)	7 days	Improved mechanical strength, keratocyte viability, ECM secretion, and expression of corneal stromal markers.	Biomimetic scaffold for corneal stromal tissue engineering and biofabrication.
Chang et al. (2020)	Infectious keratitis	Liposomal dexamethasone-moxifloxacin nanoparticle combinations with collagen (type I)/gelatin/alginate hydrogel	*In vitro* and Mouse	3 days	Sustained drug release, inhibit pathogen microorganism growth, enhanced corneal wound healing, and excellent biocompatibility.	Promising collagen-based drug-delivery scaffold for infectious keratitis and corneal wound repair; potential alternative to conventional eye drops
Ye et al. (2025)	Corneal epithelial defect	Porcine Atelocollagen I -based hydrogel loaded with acidic fibroblast growth factor (aFGF)	Mouse	14 days	Accelerated epithelial wound healing, reduced inflammation, promoted corneal nerve regeneration, and provided sustained aFGF release.	Therapeutic collagen contact lens for ocular surface regeneration and drug delivery.
Xu et al. (2025)	Corneal stromal defect	3D bioprinted Gelatin methacrylate (GelMA)/ collagen type I hydrogel	Rabbit	42 days	Enhanced stromal regeneration, collagen organization, corneal transparency, and biomechanical properties.	Bioengineered corneal substitute for stromal regeneration.
Timmerman et al. (2025)	Corneal stromal defect	Biosynthetic collagen-analog hydrogel (liquid and solid forms)	New Zealand rabbit	16 weeks	Promoted stromal regeneration, rapid re-epithelialization, and faster corneal nerve regeneration than allografts, with good transparency and biocompatibility	Promising biosynthetic corneal substitute for stromal repair and corneal regeneration
Inanlou et al. (2024)	Corneal stromal defect	In situ-forming nanocluster-reinforced collagen/hyaluronic acid hydrogel (NCColHA)	Rabbits	56 days	Promoted rapid re-epithelialization, suppressed inflammation, maintained hydrogel integrity for 14 days, and remodeled into a transparent corneal stroma by 56 days	Injectable regenerative hydrogel for corneal repair
Krivolapova et al. (2026)	Bulbar conjunctival defect	Collagen membrane	Chinchilla rabbit	6 months	Faster epithelialization, reduced inflammation, and complete conjunctival regeneration without fibrosis	Promising collagen membrane for clinical conjunctival reconstruction
Yao et al. (2017)	Conjunctival defects/ conjunctival epithelial coloboma	Type I collagen combined with poly (L-lactic acid-co-ε-caprolactone) (PLCL) nanofibrous scaffold	*In vitro*	14 days	Promoted epithelial cell adhesion, proliferation, and maintenance of conjunctival phenotype with good biocompatibility.	Scaffold for conjunctival tissue engineering and ocular surface reconstruction.
Krivolapova et al. (2025)	Conjunctival defects	Porcine tendons native type I collagen membranes (CM)	*In vitro*	13 days	Demonstrated excellent biocompatibility, favorable biomechanical properties, and supported conjunctival cell growth and phenotype maintenance.	Potential bioengineered conjunctival substitute for ocular surface reconstruction.
Yan et al. (2024)	Posterior lamellar eyelid defect	Tissue-engineered cartilage (TEC) grafts generated from rabbit auricular chondrocytes and a commercialized type I collagen sponge	Rabbits	24 days in Rabbits and 6 months post-implantation in immunodeficient mice	Successfully restored eyelid contour and movement, preserved conjunctival epithelium, and promoted regeneration of the posterior lamella	Promising substitute for posterior lamellar eyelid reconstruction