

# THE ROLE OF INFLAMMATION IN KERATOCONUS: AN UPDATED REVIEW OF CURRENT EVIDENCE

narrative review (ID: 1702)

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## ABSTRACT

**Background:** Keratoconus is a progressive corneal ectatic disorder characterized by stromal thinning, anterior corneal protrusion, irregular astigmatism, and gradual visual deterioration. Although it has traditionally been considered a non-inflammatory disease, increasing molecular, genetic, and clinical evidence suggests that chronic low-grade inflammation may contribute to its development and progression.

**Objective:** This narrative review aims to summarize current evidence on the role of inflammation in keratoconus, with emphasis on tear-film cytokines, matrix metalloproteinases, oxidative stress, genetic susceptibility, environmental triggers, inflammatory biomarkers, and emerging therapeutic implications.

**Methods:** A narrative literature review was conducted using relevant peer-reviewed articles from major scientific databases. Evidence was synthesized thematically to discuss inflammatory mechanisms, molecular pathways, ocular surface factors, clinical implications, and future directions in keratoconus research and management.

**Main Findings:** Current evidence indicates that patients with keratoconus may show increased levels of inflammatory mediators, including interleukin-1 $\beta$ , interleukin-6, tumor necrosis factor-alpha, high-mobility group box 1, and matrix metalloproteinases. These mediators may contribute to extracellular matrix degradation, keratocyte dysfunction, stromal thinning, and progressive corneal weakening. Oxidative stress, cellular senescence, allergy, atopy, dry eye disease, and habitual eye rubbing may further amplify inflammatory activity at the ocular surface. Recent genetic and molecular studies also suggest that keratoconus susceptibility may involve both biomechanical and atopy-inflammatory pathways. Corneal collagen cross-linking remains the established treatment for progressive disease, while anti-inflammatory, exosome-based, intense pulsed light, and nutritional approaches remain supportive or investigational.

**Conclusion:** Keratoconus should not be viewed as a purely biomechanical disorder. Current evidence supports a broader inflammatory-degenerative model in which inflammation, oxidative stress, genetic susceptibility, ocular surface disease, and environmental factors interact to influence disease progression. Further longitudinal studies, standardized biomarker validation, and controlled clinical trials are needed before inflammatory markers or emerging therapies can be incorporated into routine keratoconus care.

**Keywords:** Keratoconus; inflammation; tear-film biomarkers; cytokines; matrix metalloproteinases; oxidative stress; eye rubbing; corneal collagen cross-linking

## INTRODUCTION

Keratoconus is a progressive corneal ectatic disorder characterized by localized stromal thinning, anterior protrusion of the cornea, irregular astigmatism, and gradual deterioration of visual quality. The disease is usually bilateral, although the severity is often asymmetric between the two eyes (1,2). It most commonly becomes clinically apparent during adolescence or early adulthood, a period in which visual demands are increasing and disease progression may have a considerable impact on education, daily functioning, and quality of life (3). As the cornea becomes thinner and more conical, patients may develop increasing myopia, irregular astigmatism, higher-order aberrations, and reduced best-corrected visual acuity (4,5). Although keratoconus was previously considered an uncommon condition, recent epidemiological evidence suggests that it is more frequent than earlier estimates indicated. Improved diagnostic technologies, particularly corneal tomography and anterior segment imaging, have enabled earlier detection of mild and subclinical disease. Contemporary studies have reported higher prevalence rates, including estimates approaching 1.7% in the United States and a global prevalence of approximately 138 cases per 100,000 individuals (6). These findings suggest that keratoconus should not be regarded only as a rare corneal disorder, but as an important clinical condition requiring early recognition, appropriate monitoring, and timely intervention.

For many years, keratoconus was traditionally described as a non-inflammatory corneal disease. This view was largely based on the absence of classical inflammatory signs such as corneal neovascularization, marked leukocytic infiltration, and obvious immune-cell accumulation within the corneal stroma (7–9). As a result, the pathogenesis of keratoconus was mainly attributed to biomechanical weakening of the corneal tissue, structural abnormalities of the extracellular matrix, and progressive stromal degeneration. However, this concept has changed considerably over the last two decades. A growing body of molecular, biochemical, genetic, and clinical evidence now indicates that inflammation may play an important role in the development and progression of keratoconus (5,10). Current evidence suggests that keratoconus is better understood as a multifactorial disorder rather than a purely degenerative or biomechanical disease. Several interacting mechanisms appear to contribute to corneal weakening, including inflammatory signaling, extracellular matrix remodeling, oxidative stress, genetic susceptibility, allergic disease, and environmental triggers such as habitual eye rubbing (11–13). Studies have demonstrated increased levels of inflammatory mediators in the tear film, corneal tissue, and aqueous humor of patients with keratoconus. These include pro-inflammatory cytokines such as interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor- $\alpha$ , as well as chemokines, matrix metalloproteinases, and damage-associated molecular pattern molecules (5,10,14). Among these inflammatory mediators, matrix metalloproteinases have received particular attention because of their role in extracellular matrix degradation and stromal remodeling. Increased activity of enzymes such as MMP-9 may disturb the balance between collagen synthesis and degradation, thereby contributing to progressive thinning of the corneal stroma. In parallel, oxidative stress may further damage corneal cells and extracellular matrix components, while also stimulating inflammatory pathways and cellular senescence. This creates a self-sustaining cycle in which oxidative injury, inflammation, and tissue degradation reinforce one another and promote disease progression (13,15). The inflammatory perspective of keratoconus is also supported by its clinical association with allergic and atopic disorders. Many patients with keratoconus report ocular allergy, eye rubbing, asthma, eczema, or allergic rhinitis. These conditions are associated with chronic ocular surface inflammation and may increase mechanical and biochemical stress on the cornea. Eye rubbing, in particular, may act as an important modifiable factor by inducing epithelial trauma, increasing inflammatory mediator release, and accelerating structural weakening in susceptible individuals (12,13).

Recent genetic and molecular investigations have added further depth to this evolving understanding. Evidence suggests that keratoconus susceptibility may involve both structural and inflammatory pathways. Genetic factors related to extracellular matrix integrity may influence corneal biomechanical stability, whereas immune-related and atopic-inflammatory pathways may increase vulnerability to chronic low-grade inflammation. This dual contribution helps explain why keratoconus varies widely among individuals in terms of age of onset, rate of progression, clinical severity, and response to treatment (13,15). Recognition of inflammation as a contributing component in keratoconus has important clinical implications. Tear-film biomarkers may help identify early disease activity, predict progression, or monitor treatment response. Similarly, a better understanding of inflammatory and oxidative pathways may support the development of adjunctive therapies aimed at modifying the ocular surface environment, reducing inflammatory activity, and complementing established treatments such as corneal collagen cross-linking. However, much of the current evidence remains heterogeneous, and many proposed biomarkers and emerging therapies still require validation through well-designed longitudinal and clinical studies. Therefore, this narrative review aims to summarize and critically discuss the current evidence on the role of inflammation in keratoconus. Particular attention is given to tear-film cytokines, matrix metalloproteinases, oxidative stress, genetic susceptibility, environmental and atopic factors, and the potential clinical relevance of inflammatory biomarkers and emerging therapeutic approaches. By integrating evidence from molecular, genetic, and clinical studies, this review seeks to provide a balanced understanding of keratoconus as a disorder with both biomechanical and inflammatory-degenerative components.

## 2. METHODS / LITERATURE SEARCH STRATEGY

### 2.1 Review Design

This article was designed as an updated narrative review to summarize and discuss current evidence regarding the role of inflammation in the pathogenesis, progression, diagnosis, and management of keratoconus. A narrative review approach was considered appropriate

because the available literature includes a wide range of evidence, including clinical studies, laboratory investigations, genetic analyses, biomarker studies, systematic reviews, and emerging therapeutic reports. The aim was not to perform a formal meta-analysis, but to provide a balanced synthesis of the main biological and clinical concepts linking inflammation with keratoconus.

## 2.2 Search Sources and Time Frame

A literature search was conducted using major electronic databases, including PubMed/MEDLINE, Google Scholar, Scopus, Web of Science, ScienceDirect, SpringerLink, and relevant ophthalmology journals. The search focused mainly on articles published from January 2000 to June 2026, with greater emphasis on recent publications from the last ten years. Older studies were included when they provided important background information regarding keratoconus pathophysiology, inflammatory mediators, oxidative stress, or extracellular matrix remodeling.

## 2.3 Search Terms

The search strategy used combinations of the following keywords and Medical Subject Heading terms where applicable: “keratoconus,” “inflammation,” “ocular surface inflammation,” “tear film biomarkers,” “cytokines,” “interleukin,” “IL-1 $\beta$ ,” “IL-6,” “TNF-alpha,” “matrix metalloproteinases,” “MMP-9,” “oxidative stress,” “reactive oxygen species,” “cellular senescence,” “HMGB1,” “genetic susceptibility,” “Mendelian randomization,” “atopy,” “allergy,” “eye rubbing,” “dry eye,” “corneal collagen cross-linking,” “anti-inflammatory therapy,” “exosomes,” “intense pulsed light,” and “nutritional factors.” Boolean operators such as AND and OR were used to combine terms and refine the search.

## 2.4 Eligibility Criteria

Articles were considered eligible if they discussed keratoconus in relation to inflammatory pathways, tear-film or corneal biomarkers, cytokine expression, matrix metalloproteinase activity, oxidative stress, genetic or immune susceptibility, environmental risk factors, allergic disease, ocular surface disease, or treatment approaches with potential inflammatory relevance. Original research articles, systematic reviews, meta-analyses, narrative reviews, experimental studies, genetic studies, and clinically relevant observational studies were included. Studies were excluded if they were unrelated to keratoconus, did not address inflammatory or associated biological mechanisms, focused only on surgical technique without relevance to disease pathophysiology, or provided insufficient scientific detail. Non-peer-reviewed material, thesis-based work, and hypothesis-generating articles were considered only when they provided useful background or emerging concepts, and their findings were interpreted cautiously.

## 2.5 Evidence Selection and Synthesis

The identified literature was reviewed thematically rather than statistically. Evidence was grouped according to major biological and clinical domains, including tear-film cytokines, matrix metalloproteinases, damage-associated molecular patterns, genetic susceptibility, oxidative stress, environmental influences, ocular surface disease, inflammatory biomarkers, and therapeutic implications. Greater weight was given to recent peer-reviewed studies, systematic reviews, meta-analyses, and studies with direct relevance to keratoconus. The findings were synthesized in a descriptive manner to highlight areas of agreement, emerging evidence, and remaining uncertainty. Particular attention was given to whether inflammatory changes in keratoconus appear to be directly involved in disease progression or whether they may represent secondary responses to corneal stress and tissue damage. Because this was a narrative review, no formal risk-of-bias assessment or quantitative pooling of results was performed. However, limitations of the available evidence, including heterogeneity in study design, variability in tear-sampling methods, small sample sizes, and lack of validated clinical biomarker thresholds, were considered while interpreting the literature.

## 3. INFLAMMATORY MECHANISMS IN KERATOCONUS

Keratoconus has traditionally been described as a non-inflammatory ectatic disorder because affected corneas usually do not show the classical signs of inflammation, such as marked leukocyte infiltration, corneal neovascularization, or obvious immune-cell accumulation. However, this older view does not fully explain the molecular and biochemical changes now reported in the tear film, ocular surface, and corneal tissue of patients with keratoconus. Increasing evidence suggests that keratoconus is associated with a chronic, low-grade inflammatory state that may contribute to extracellular matrix disruption, keratocyte loss, stromal thinning, and progressive corneal weakening (5,7–10). Inflammation in keratoconus should not be understood in the same way as acute infectious or autoimmune keratitis. Instead, it appears to be a subtle and persistent biological process involving inflammatory cytokines, proteolytic enzymes, oxidative stress mediators, and damage-associated molecular signals. These changes may interact with genetic susceptibility, ocular allergy, eye rubbing, tear-film instability, and environmental stressors, creating a microenvironment that favors progressive ectatic change (11–13).

### 3.1 Tear-Film Cytokines

The tear film is an important source of information about the ocular surface environment because it can be collected non-invasively and reflects many biochemical changes occurring at the corneal surface. In keratoconus, several studies have reported altered tear-film cytokine profiles, with increased concentrations of pro-inflammatory mediators compared with healthy eyes (16). These findings support the concept that the ocular surface in keratoconus is not biologically inactive, even when there are no visible clinical signs of

inflammation. Interleukin-1 $\beta$  is one of the most frequently discussed cytokines in keratoconus. It may contribute to disease progression by promoting keratocyte apoptosis and stimulating enzymes involved in extracellular matrix degradation. Through these mechanisms, IL-1 $\beta$  can influence stromal remodeling and may play a role in progressive corneal thinning (5,17). Interleukin-6 has also been reported at increased levels in tear fluid and ocular surface tissues of patients with keratoconus. This cytokine is involved in inflammatory signaling and may encourage matrix metalloproteinase activity, thereby contributing to extracellular matrix breakdown (18).

Tumor necrosis factor-alpha is another important inflammatory mediator implicated in keratoconus. It can activate inflammatory pathways and promote proteolytic activity within corneal tissue. Increased TNF- $\alpha$  levels may therefore contribute to a tissue environment in which collagen degradation and stromal remodeling are favored (5). Other cytokines, including IL-8, IL-17, and transforming growth factor-beta, have also been discussed in relation to keratoconus, although their exact roles are not completely uniform across studies. Some mediators may be elevated in certain patient groups, while others may remain unchanged or show variable expression depending on disease stage, sample type, and laboratory methods (15,19). Recent genetic and Mendelian randomization studies have further strengthened interest in inflammatory pathways. Associations involving inflammatory mediators such as IL-12B, IL-13, and IL-17A suggest that immune-related pathways may influence keratoconus susceptibility, although these findings should be interpreted carefully because genetic association does not always translate directly into clinical disease activity (20). Overall, tear-film cytokine studies indicate that inflammation is likely to be part of the keratoconus disease process, but more standardized research is needed before these biomarkers can be used routinely in clinical practice.

### 3.2 Matrix Metalloproteinases

Matrix metalloproteinases are proteolytic enzymes responsible for the turnover and degradation of extracellular matrix components. In a healthy cornea, a balance exists between matrix synthesis, matrix degradation, and tissue repair. In keratoconus, this balance appears to be disturbed, with increased proteolytic activity contributing to stromal weakening and progressive thinning (5). Among the matrix metalloproteinases, MMP-9 has received particular attention because of its relationship with ocular surface inflammation and extracellular matrix remodeling. Increased MMP-9 activity may promote degradation of collagen and other stromal components, making the cornea more vulnerable to biomechanical deformation. This is clinically relevant because progressive weakening of the stromal architecture is a central feature of keratoconus (5,16).

The activity of MMPs is closely linked to inflammatory signaling. Cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  can stimulate the expression of matrix-degrading enzymes in corneal epithelial cells and stromal fibroblasts. As a result, inflammation and tissue degradation may reinforce each other. In this cycle, inflammatory mediators increase protease activity, protease activity damages the extracellular matrix, and tissue injury may further stimulate inflammatory responses (5,18). Other MMPs, including MMP-1, MMP-3, MMP-7, and MMP-13, have also been discussed in relation to keratoconus. Emerging genetic analyses suggest that some matrix metalloproteinases may be involved in disease susceptibility, but the strength and clinical relevance of these associations still require further confirmation (20). At present, MMPs are best understood as important contributors to the inflammatory-degenerative process of keratoconus rather than isolated causes of the disease.

### 3.3 HMGB1 and Damage-Associated Molecular Patterns

High-mobility group box 1 is a nuclear protein that can act as a damage-associated molecular pattern when released into the extracellular environment. Under normal conditions, HMGB1 helps regulate nuclear functions. However, when cells are stressed, injured, or undergoing damage-related changes, HMGB1 may be released outside the cell and can trigger inflammatory signaling (21,22). In keratoconus, increased HMGB1 levels have been reported in the tear film, suggesting that cellular stress and tissue injury may be present at the ocular surface. Once released, HMGB1 can interact with pattern-recognition receptors such as toll-like receptor 4 and receptor for advanced glycation end products. These interactions may activate downstream inflammatory pathways and promote the production of additional cytokines and matrix-degrading enzymes (18,22). The relevance of HMGB1 is that it links tissue damage with inflammation. In keratoconus, repeated epithelial stress, oxidative injury, eye rubbing, and tear-film instability may promote cellular damage. HMGB1 released from stressed or damaged cells may then help maintain a chronic inflammatory microenvironment. This process may partly explain how mechanical and environmental triggers can become connected with biochemical tissue degradation in susceptible corneas.

### 3.4 Ocular Surface Inflammation

The ocular surface plays an important role in the inflammatory profile of keratoconus. Many patients with keratoconus also have symptoms of ocular allergy, dry eye disease, meibomian gland dysfunction, or chronic irritation. These conditions may not only increase discomfort but may also contribute to disease progression by maintaining a pro-inflammatory tear-film environment (23,24). Allergic eye disease is particularly relevant because it is commonly associated with itching and habitual eye rubbing. Eye rubbing can produce direct mechanical stress on the cornea, but it may also stimulate epithelial trauma and inflammatory mediator release. When this occurs in a cornea that is already genetically or structurally vulnerable, repeated rubbing may accelerate stromal weakening and ectatic progression (22,23).

Dry eye disease and tear-film instability may further disturb the ocular surface environment. Reduced tear-film quality can increase friction, oxidative stress, and epithelial irritation. Inflammatory mediators such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and MMP-9 are shared between keratoconus and other ocular surface disorders, suggesting that these conditions may overlap biologically (25). Therefore, managing ocular allergy, dryness, and eye rubbing should be considered an important supportive part of keratoconus care. Taken together, the inflammatory mechanisms in keratoconus appear to involve several interconnected pathways rather than a single isolated mediator. Tear-film cytokines, matrix metalloproteinases, HMGB1, oxidative stress, ocular allergy, and tear-film instability may act together to promote extracellular matrix degradation and stromal thinning. Although inflammation may not be the only cause of keratoconus, current evidence strongly suggests that it contributes to the disease environment and may influence progression, severity, and future therapeutic strategies.

**Table 1. Inflammatory Biomarkers Implicated in Keratoconus**

<b>Biomarker / Mediator</b>	<b>Sample / Site Reported</b>	<b>Reported Change in Keratoconus</b>	<b>Proposed Role in Disease Process</b>	<b>Clinical Relevance</b>
IL-1 $\beta$	Tear film, corneal tissue	Increased	Promotes keratocyte apoptosis and stimulates extracellular matrix degradation	May indicate inflammatory activity and stromal remodeling (5,16,17).
IL-6	Tear film, ocular surface tissue	Increased	Enhances inflammatory signaling and may stimulate matrix metalloproteinase activity	Potential marker of ocular surface inflammation and disease activity (18).
TNF- $\alpha$	Tear film	Increased	Activates inflammatory and proteolytic pathways involved in tissue remodeling	May contribute to chronic low-grade inflammatory microenvironment (5).
IL-8	Tear film / ocular surface	Variable or increased	Supports inflammatory cell recruitment and ocular surface immune activation	Possible supportive biomarker, but not specific for keratoconus (15,19).
IL-17	Tear film / genetic evidence	Variable	May influence protease expression and inflammatory signaling	Requires further validation because findings are not fully consistent (15,20).
HMGB1	Tear film	Increased	Acts as a damage-associated molecular pattern and activates inflammatory pathways	May link cellular stress with persistent inflammation (18,22).
MMP-9	Tear film, corneal epithelium	Increased	Degrades extracellular matrix and contributes to stromal thinning	One of the most promising biomarkers, but clinical cutoffs are not standardized (5,16).
MMP-13	Genetic / molecular evidence	Possible association	May contribute to matrix degradation and disease susceptibility	Emerging marker requiring further clinical confirmation (20).

**Table 1.** Summary of inflammatory biomarkers implicated in keratoconus and their proposed biological and clinical relevance.

#### 4. GENETIC AND MOLECULAR BASIS OF INFLAMMATORY SUSCEPTIBILITY

Keratoconus is a complex disorder in which genetic, molecular, biomechanical, and environmental factors appear to interact rather than act independently. Although corneal thinning and ectasia are the most visible clinical features, these structural changes may be influenced by deeper biological pathways involving extracellular matrix regulation, immune signaling, oxidative stress, and inflammatory susceptibility. Recent genetic studies have therefore shifted attention from a purely mechanical model of keratoconus toward a broader disease concept in which inherited vulnerability may affect both corneal strength and inflammatory responsiveness (23,24).

##### 4.1 Genetic Susceptibility

The hereditary contribution to keratoconus has been recognized for many years, particularly because the disease may cluster in families and is more common among first-degree relatives of affected individuals. However, the genetic basis of keratoconus is not simple. Rather than being explained by a single gene defect, current evidence suggests that multiple genetic variants may contribute small but meaningful effects, influencing corneal structure, epithelial integrity, stromal remodeling, and immune regulation (23,25). Several genes associated with extracellular matrix stability have been investigated in relation to keratoconus. These genes are important because the corneal stroma depends on well-organized collagen fibers, appropriate cross-linking, and balanced matrix turnover to maintain its shape and biomechanical resistance. Variants affecting collagen organization or matrix regulation may weaken the cornea and make it more vulnerable to progressive deformation under normal ocular forces (23,24). At the same time, genetic susceptibility may also influence how the cornea responds to environmental stress. A genetically vulnerable cornea may be less able to tolerate chronic irritation, oxidative injury, allergic inflammation, or repeated mechanical trauma from eye rubbing. In this way, genetic risk may not directly “cause” keratoconus on its own, but may create a biological background in which inflammatory and environmental triggers become more damaging (26,27).

#### 4.2 Immune-Related Genes

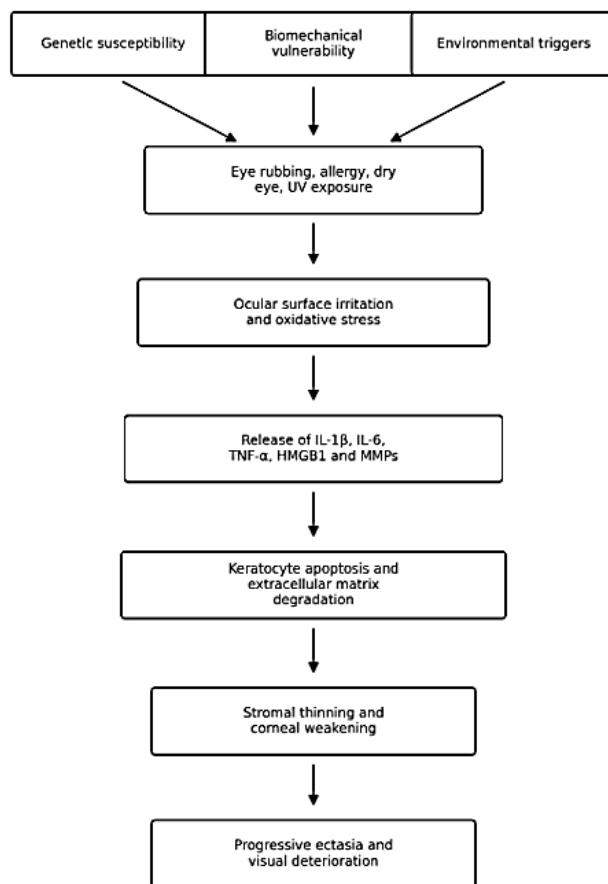
Growing evidence suggests that immune-related genes may also contribute to keratoconus susceptibility. This is important because it provides a possible explanation for the link between keratoconus, atopy, allergy, ocular surface inflammation, and inflammatory mediator expression. Immune-related genetic pathways may influence cytokine activity, inflammatory cell regulation, and the way corneal tissues respond to cellular stress (20,24). Among the candidate genes discussed in recent literature, COL1A1, LOXL2, and ITGA1 have been associated with protective effects, largely because of their roles in extracellular matrix organization and corneal structural stability. In contrast, SFRP1 has been described as a risk-associated gene with possible involvement in immune and inflammatory signaling pathways (23,24). This contrast is clinically meaningful because it supports the idea that keratoconus may involve two overlapping biological processes: one related to structural weakness of the cornea and another related to inflammatory or immune susceptibility.

Single-cell and molecular analyses have also suggested that different genes may influence different disease pathways. For example, disruption of genes involved in collagen organization may mainly affect tissue architecture, whereas genes linked with immune regulation may alter inflammatory signaling and cellular response to stress. These findings support a more integrated view of keratoconus, in which corneal weakening and inflammation are not separate explanations, but connected parts of the same disease process (24). The interleukin-1 gene cluster has also been discussed in relation to keratoconus. Interleukin-1 family cytokines are biologically relevant because they can influence keratocyte apoptosis, matrix metalloproteinase activity, and extracellular matrix degradation. Although the strength of genetic associations may vary between populations and study designs, the relationship between IL-1-related pathways and corneal tissue remodeling remains an important area for further investigation (25).

#### 4.3 Mendelian Randomization Evidence

Mendelian randomization studies have provided another way to explore whether inflammatory mediators and immune-cell traits may have a causal relationship with keratoconus. Unlike simple observational studies, Mendelian randomization uses genetic variants as instrumental variables to examine whether an exposure may contribute to disease risk. This approach can reduce some forms of confounding, although it still depends on the quality of available genetic data and the assumptions used in the analysis (20,24). Recent Mendelian randomization analyses have reported associations between keratoconus and several immune or inflammatory factors. These include inflammatory proteins such as IL-12B and IL-13, as well as possible involvement of IL-17A and matrix metalloproteinase-

**Figure 1. Proposed inflammatory-degenerative pathway in keratoconus**



related pathways (20). Some findings have also suggested potential relationships involving macrophage inflammatory protein-1 $\beta$  and MMP-13, supporting the possibility that immune signaling and matrix degradation may be biologically connected in keratoconus (20,24).

Immune-cell phenotypes have also been explored in relation to keratoconus risk. Reported associations involving B lymphocyte and T-cell populations suggest that immune regulation may influence disease susceptibility or progression in some individuals (26). However, these results should be interpreted carefully. Genetic association and Mendelian randomization findings can highlight possible biological pathways, but they do not automatically prove that a specific inflammatory mediator is clinically useful as a diagnostic marker or therapeutic target. Overall, Mendelian randomization evidence strengthens the argument that inflammation is not merely a secondary observation in keratoconus. It suggests that immune-related pathways may contribute to disease susceptibility. Still, these findings need confirmation through well-designed clinical studies, functional laboratory research, and longitudinal patient follow-up before they can be translated into routine clinical practice (20,24).

#### 4.4 Atopy–Inflammatory Liability Pathway

One of the more useful recent concepts in keratoconus genetics is the idea that disease risk may involve both structural and inflammatory liability. Genomic analyses have proposed two broad pathways: a corneal biomechanical stability pathway and an atopy–inflammatory liability pathway. The corneal biomechanical stability pathway appears to protect against ectatic change by supporting stromal strength and matrix organization, whereas the atopy–inflammatory liability pathway may increase susceptibility through immune and allergic mechanisms (20,24). This model is helpful because it fits well with clinical observations. Many patients with keratoconus have allergic conjunctivitis, atopic disease, ocular itching, or habitual eye rubbing. In such patients, inflammatory and mechanical factors may act together. Atopy may increase ocular surface inflammation and itching, eye rubbing may create repeated epithelial and stromal stress, and genetic susceptibility may reduce the ability of the cornea to resist these insults. Over time, these interacting factors may contribute to progressive stromal thinning and corneal protrusion (28).

The atopy–inflammatory liability pathway also helps explain why keratoconus does not behave in the same way in every patient. Some individuals may have stronger biomechanical vulnerability, while others may have more prominent allergic or inflammatory drivers. This variation may influence age of onset, speed of progression, severity, and response to treatment. It also supports the need for a more individualized approach to keratoconus management, where clinicians address not only corneal shape and thickness, but also ocular allergy, rubbing behavior, tear-film instability, and inflammatory risk factors. In summary, genetic and molecular evidence supports the view that keratoconus is not only a disease of corneal shape, but also a disorder influenced by inherited structural weakness and inflammatory susceptibility. The interaction between extracellular matrix genes, immune-related pathways, oxidative stress, allergy, and environmental triggers may create a vulnerable corneal microenvironment. Recognizing these pathways may improve future risk stratification, biomarker development, and the design of targeted therapies for patients at higher risk of progression (20,23,24,27).

### 5. OXIDATIVE STRESS AND INFLAMMATION

Oxidative stress is increasingly recognized as an important contributor to the biological changes seen in keratoconus. The cornea is continuously exposed to ultraviolet radiation, atmospheric oxygen, environmental pollutants, and mechanical stress from blinking or eye rubbing. Under normal conditions, corneal cells are protected by antioxidant defense systems that help maintain a stable balance between oxidant production and antioxidant activity. In keratoconus, this balance appears to be disturbed, allowing reactive oxygen species and reactive nitrogen species to accumulate and damage corneal tissues (28,29). The relationship between oxidative stress and inflammation is particularly relevant because these two processes can strengthen each other. Oxidative injury may activate inflammatory signaling pathways, while inflammation itself can increase oxidative burden through cytokine release, cellular stress, and proteolytic enzyme activity. This interaction may contribute to epithelial dysfunction, keratocyte apoptosis, extracellular matrix degradation, and progressive stromal thinning in keratoconus (29,30).

#### 5.1 Oxidative Stress in Keratoconus

The cornea is especially vulnerable to oxidative damage because it is directly exposed to external environmental stressors. Ultraviolet radiation can generate reactive oxygen species within corneal cells, while air pollutants, tear-film instability, and chronic ocular surface irritation may further increase oxidative stress. In healthy corneal tissue, antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase help neutralize these reactive molecules. However, several studies suggest that antioxidant defense mechanisms may be altered or insufficient in patients with keratoconus (28,29). Excessive oxidative stress can affect the cornea in several ways. It may damage cellular proteins, lipids, mitochondrial function, and extracellular matrix components. In keratoconus, these changes are clinically important because the strength and transparency of the cornea depend on healthy keratocytes and a well-organized stromal matrix. When oxidative injury becomes persistent, corneal cells may lose their ability to maintain normal matrix repair, leading to progressive weakening of the stromal architecture (29). Oxidative stress may also promote keratocyte apoptosis, which has been reported as one of the histopathological features of keratoconus. Loss of keratocytes can reduce the capacity of the stroma to repair and maintain collagen organization. At the same time, oxidative injury may increase the expression of inflammatory cytokines and matrix-degrading enzymes, thereby linking cellular stress with inflammatory tissue damage (14,29).

## 5.2 Cellular Senescence

Cellular senescence is another mechanism that may connect oxidative stress with chronic inflammation in keratoconus. Senescence refers to a state in which cells permanently stop dividing but remain metabolically active. These cells are not simply inactive; instead, they may release a range of inflammatory cytokines, chemokines, growth factors, and matrix metalloproteinases. This secretory pattern is known as the senescence-associated secretory phenotype (30). In the cornea, oxidative stress may induce senescence in epithelial cells and keratocytes. Once senescent cells accumulate, they may alter the local tissue environment by producing inflammatory mediators and proteolytic enzymes. This can disturb extracellular matrix homeostasis and may contribute to progressive stromal remodeling. In this way, senescence may serve as a bridge between repeated cellular injury and long-term corneal degeneration (29,30). The senescence-associated secretory phenotype is particularly important because many of its components overlap with the inflammatory mediators already implicated in keratoconus. These include cytokines, chemokines, and matrix metalloproteinases that can promote tissue degradation and maintain low-grade inflammation. Therefore, cellular senescence may help explain why keratoconus can continue to progress even in the absence of visible classical inflammation (30).

## 5.3 Oxidative Stress–Inflammation Cycle

The interaction between oxidative stress and inflammation in keratoconus may be understood as a self-reinforcing cycle. Environmental stressors such as ultraviolet exposure, air pollution, allergy, dry eye, and eye rubbing can increase oxidative burden at the ocular surface. This oxidative damage may injure epithelial cells and keratocytes, leading to the release of inflammatory mediators and damage-associated signals (28,31). These inflammatory mediators can then stimulate matrix metalloproteinase activity and extracellular matrix breakdown. As the stromal matrix becomes damaged, the cornea becomes biomechanically weaker and more susceptible to further deformation. Tissue injury may also generate additional oxidative stress, creating a repeated cycle of cellular damage, inflammation, proteolysis, and stromal thinning (29,30).

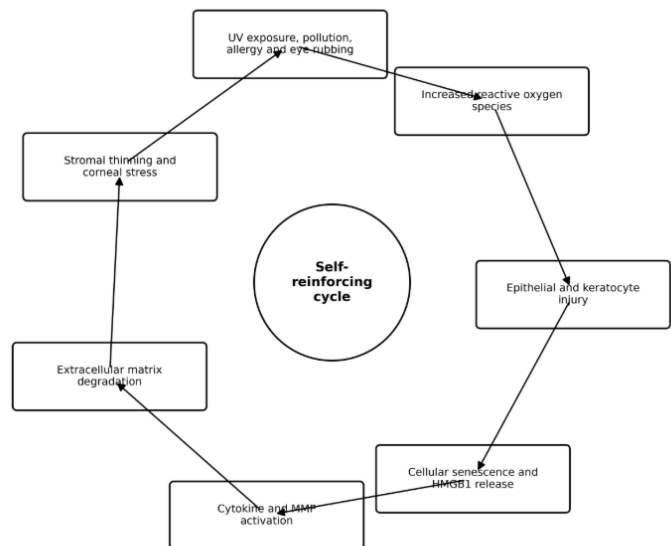
This cycle is clinically important because it suggests that keratoconus progression may not be driven by mechanical weakness alone. Instead, corneal weakening may be amplified by ongoing biochemical stress within the ocular surface and stromal microenvironment. It also supports the need to address modifiable factors that increase oxidative and inflammatory stress, including allergic eye disease, dry eye, tear-film instability, and habitual eye rubbing (31–34). Although oxidative stress is strongly implicated in keratoconus pathophysiology, important uncertainties remain. Many studies are cross-sectional, and methods for measuring oxidative markers vary between laboratories. It is also unclear whether oxidative stress is a primary driver of keratoconus or a secondary response to corneal tissue injury. Future longitudinal studies are needed to clarify whether oxidative markers can predict disease progression, guide treatment decisions, or serve as therapeutic targets. Overall, oxidative stress appears to be closely linked with inflammatory activity in keratoconus. Persistent oxidative injury may promote cellular senescence, cytokine release, matrix metalloproteinase activity, and stromal degradation. Recognizing this oxidative stress–inflammation cycle provides a broader understanding of keratoconus as an inflammatory-degenerative condition and may help guide future research into preventive and adjunctive treatment strategies (29–31).

## 6. ENVIRONMENTAL AND CLINICAL RISK FACTORS

Environmental and clinical factors appear to play an important role in the development and progression of keratoconus, especially when they act on a genetically or biomechanically vulnerable cornea. These factors do not usually work in isolation. Instead, they may interact with inflammatory signaling, oxidative stress, tear-film instability, and mechanical trauma to create a corneal microenvironment that favors stromal weakening and ectatic change. Among these factors, eye rubbing, allergic and atopic disease, dry eye, ocular surface inflammation, ultraviolet exposure, and environmental stressors have received particular attention (31–34).

### 6.1 Eye Rubbing

Figure 2. Oxidative stress–inflammation cycle in keratoconus



Eye rubbing is one of the most consistently recognized modifiable risk factors associated with keratoconus. It is commonly reported in patients with ocular allergy, itching, dry eye symptoms, or chronic ocular irritation. Although eye rubbing may appear to be a simple behavioral habit, repeated mechanical stress on the cornea can have important biological consequences, particularly in eyes that are already predisposed to corneal thinning or biomechanical weakness (32). The harmful effect of eye rubbing is likely related to both mechanical and inflammatory pathways. Repeated rubbing can produce microtrauma to the corneal epithelium and anterior stroma. This mechanical stress may stimulate epithelial cells and keratocytes to release inflammatory mediators, proteolytic enzymes, and damage-associated signals. Over time, these changes may contribute to extracellular matrix degradation, keratocyte loss, and progressive stromal thinning (32,33). Eye rubbing may also increase local temperature and transiently raise intraocular pressure, both of which may place additional stress on the corneal structure. When this occurs repeatedly, especially in younger patients with active disease, the cornea may become more susceptible to progressive deformation. For this reason, counseling patients to avoid eye rubbing is an important part of keratoconus management and should be emphasized early, particularly in children and adolescents with allergic eye disease (32,33).

## 6.2 Allergy and Atopy

Allergic and atopic conditions are frequently associated with keratoconus. Patients may report allergic conjunctivitis, vernal keratoconjunctivitis, atopic dermatitis, asthma, eczema, or seasonal allergic rhinitis. These conditions share a tendency toward chronic immune activation, ocular itching, and persistent surface inflammation. In many patients, allergy and eye rubbing are closely linked, making it difficult to separate the mechanical effects of rubbing from the inflammatory effects of allergy itself (33). Atopic inflammation may contribute to keratoconus through several mechanisms. Allergic eye disease is often associated with mast cell activation, increased immunoglobulin E levels, and Th2-dominant immune responses. These immune changes may increase the release of cytokines and inflammatory mediators at the ocular surface. In a susceptible cornea, this inflammatory environment may promote matrix metalloproteinase activity and extracellular matrix breakdown, thereby contributing to stromal weakening (33). Clinically, the association between keratoconus and atopy has important implications. Patients with persistent ocular allergy, especially those who rub their eyes frequently, should be assessed carefully for early signs of corneal ectasia. Periodic corneal topography or tomography may be useful in high-risk individuals, particularly when there is reduced visual quality, increasing astigmatism, frequent prescription changes, or a family history of keratoconus. Early identification allows timely intervention before advanced corneal distortion develops (33).

## 6.3 Dry Eye and Ocular Surface Disease

Dry eye disease and ocular surface abnormalities are commonly reported in patients with keratoconus. These conditions may contribute to discomfort, fluctuating vision, contact lens intolerance, and persistent ocular irritation. Although dry eye may not directly cause keratoconus, it can worsen the ocular surface environment and may indirectly promote rubbing, inflammation, and tear-film instability (34). The inflammatory profile of dry eye disease overlaps with several mechanisms described in keratoconus. Increased levels of cytokines such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and MMP-9 have been reported in ocular surface disorders and are also discussed in relation to keratoconus. This overlap suggests that tear-film instability and ocular surface inflammation may contribute to a shared inflammatory microenvironment in some patients (34). Meibomian gland dysfunction may further aggravate the problem by reducing tear-film quality and increasing evaporative stress. A poor-quality tear film can increase friction between the eyelid and corneal surface, leading to epithelial irritation and discomfort. This may encourage eye rubbing and further stimulate inflammatory mediator release. Therefore, treatment of dry eye, meibomian gland dysfunction, and ocular surface irritation should be considered a supportive component of keratoconus care, especially in symptomatic patients (34).

## 6.4 UV Exposure and Environmental Stressors

The cornea is directly exposed to ultraviolet radiation, atmospheric oxygen, air pollutants, allergens, and other environmental stressors. These exposures may increase the production of reactive oxygen species and reactive nitrogen species within corneal tissues. Under normal conditions, antioxidant defense mechanisms help protect the cornea from oxidative injury. In keratoconus, however, several studies suggest that antioxidant protection may be reduced or insufficient, allowing oxidative stress to contribute to tissue damage (28,29). Ultraviolet exposure is particularly relevant because it can promote oxidative injury in corneal epithelial cells and keratocytes. Persistent oxidative stress may damage cellular proteins, lipids, DNA, and extracellular matrix components. It may also activate inflammatory pathways and increase matrix-degrading enzyme activity. These changes can weaken the stromal structure and may contribute to the chronic inflammatory-degenerative process observed in keratoconus (28,29). Other environmental factors, including air pollution, chronic ocular irritation, poor tear-film stability, and allergen exposure, may further increase oxidative and inflammatory stress at the ocular surface. Although the direct causal role of these factors in keratoconus is not fully established, they may act as aggravating influences in susceptible individuals. Their effects are likely stronger when combined with allergy, dry eye, and habitual eye rubbing (31,34).

Overall, environmental and clinical risk factors should be viewed as important contributors to the keratoconus disease environment rather than isolated causes. Eye rubbing, allergy, atopy, dry eye, and oxidative stress may interact with genetic and biomechanical susceptibility to accelerate corneal weakening. Recognizing and managing these modifiable factors may help reduce inflammatory burden, improve ocular comfort, and support strategies aimed at slowing disease progression (32–34).

**Table 2. Environmental and Clinical Risk Factors Related to Inflammation in Keratoconus**

Risk Factor	Mechanism Linking It to Keratoconus	Inflammatory / Biological Effect	Practical Clinical Implication
Eye rubbing	Repeated mechanical trauma to corneal epithelium and stroma	Stimulates inflammatory mediator release, epithelial injury, and matrix degradation	Patients should be counseled strongly to avoid eye rubbing (32).
Allergic conjunctivitis	Chronic ocular itching and immune activation	Increases cytokines, mast cell activity, and rubbing behavior	Allergy control should be part of keratoconus management (33).
Atopy	Systemic allergic tendency involving asthma, eczema, rhinitis, or dermatitis	Associated with Th2-mediated inflammation and increased ocular surface irritation	High-risk atopic patients may need corneal screening (33).
Dry eye disease	Tear-film instability and increased ocular surface friction	Promotes irritation, inflammation, and rubbing tendency	Lubrication and ocular surface treatment may reduce inflammatory burden (34).
Meibomian gland dysfunction	Poor tear-film lipid layer and evaporative stress	Increases ocular discomfort and tear-film instability	Lid hygiene and tear-film optimization may improve comfort (34).
UV exposure	Direct oxidative stress to epithelial cells and keratocytes	Promotes reactive oxygen species and cellular injury	Oxidative stress may contribute to inflammatory-degenerative progression (28,29).
Air pollution / environmental irritants	Chronic ocular surface irritation	May increase oxidative stress and inflammatory mediator release	Environmental protection and ocular surface care may be supportive (31).

**Table 2.** Environmental and clinical risk factors that may contribute to inflammatory and oxidative stress pathways in keratoconus.

## 7. CLINICAL IMPLICATIONS

The growing evidence of inflammatory involvement in keratoconus has important clinical implications. Traditionally, clinical decision-making in keratoconus has relied mainly on refraction, visual acuity, slit-lamp findings, corneal topography, tomography, pachymetry, and evidence of progression. These tools remain central to diagnosis and management. However, they mainly describe structural and optical changes that may already be established. Inflammatory biomarkers may provide additional biological information about disease activity, especially in early or progressive cases where clinical changes are subtle (5,16). Understanding keratoconus as a condition with inflammatory, oxidative, genetic, and biomechanical components may help clinicians take a broader approach to patient care. This includes not only detecting corneal shape changes, but also identifying modifiable contributors such as ocular allergy, dry eye disease, tear-film instability, and habitual eye rubbing. Such an approach may support earlier intervention, better patient counseling, and more individualized monitoring strategies (32–34).

### 7.1 Inflammatory Biomarkers

Tear-film biomarkers have received considerable attention because tears can be collected in a relatively simple and non-invasive way. Several inflammatory mediators have been reported at increased levels in patients with keratoconus, including IL-1 $\beta$ , IL-6, TNF- $\alpha$ , HMGB1, and MMP-9. These biomarkers may reflect inflammatory activity at the ocular surface and may help explain the link between inflammation, extracellular matrix degradation, and progressive stromal thinning (5,16,18). Among the proposed biomarkers, MMP-9 is one of the most clinically relevant because it is closely related to extracellular matrix remodeling. Increased MMP-9 activity may indicate an active proteolytic environment in which stromal collagen and other matrix components are being degraded. This makes it a potentially useful marker for disease activity, although it should not yet be considered a stand-alone diagnostic test for keratoconus (5,16).

Cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  may also have clinical value because they represent inflammatory signaling pathways that can influence keratocyte apoptosis, matrix metalloproteinase expression, and tissue remodeling. HMGB1 may provide additional information about cellular stress and damage-associated inflammatory activation. Together, these mediators suggest that the tear film may carry useful biological signals related to disease behavior (18,22). Despite this promise, inflammatory biomarkers are not yet ready for routine clinical use in most keratoconus patients. Studies vary in their tear collection techniques, laboratory assays, patient selection criteria, disease severity grading, and control groups. As a result, reliable cut-off values have not been established. Larger longitudinal

studies are needed to determine whether these biomarkers can consistently predict progression, distinguish active from stable disease, or guide treatment decisions (5,16).

## 7.2 Diagnostic Potential

The diagnostic potential of inflammatory biomarkers is greatest in early or subclinical keratoconus, where structural changes may be mild and visual symptoms may be limited. In such cases, corneal tomography remains the main diagnostic tool, but tear-film markers could eventually provide supportive biological evidence of disease activity. This may be particularly useful in young patients, patients with allergic eye disease, and individuals with a family history of keratoconus (5,33). Inflammatory biomarkers may also help identify patients whose corneas are biologically active even when clinical findings appear relatively stable. For example, a patient may have mild topographic changes but persistent ocular allergy, eye rubbing, increased tear-film inflammation, and subtle progression over time. In this context, inflammatory assessment could theoretically help clinicians recognize a higher-risk disease profile before advanced ectatic changes occur (16,18).

However, biomarker testing should be interpreted with caution. Many inflammatory mediators are not specific to keratoconus and may also be elevated in dry eye disease, allergic conjunctivitis, meibomian gland dysfunction, contact lens-related irritation, and other ocular surface disorders. Therefore, inflammatory biomarkers should not be viewed as replacements for clinical examination or corneal imaging. Their most realistic future role may be as adjunctive tools used alongside tomography, pachymetry, clinical history, and assessment of ocular surface disease (34). At present, the diagnostic use of inflammatory biomarkers remains largely investigational. Before these markers can be incorporated into routine practice, future research must standardize sample collection, define normal and abnormal ranges, clarify disease-stage differences, and determine whether biomarker levels change meaningfully with treatment or disease progression (5,16).

## 7.3 Disease Monitoring and Risk Stratification

Inflammatory mechanisms may also be useful for disease monitoring and risk stratification. Keratoconus progression is not uniform; some patients remain stable for years, while others progress rapidly, particularly during adolescence and early adulthood. Current monitoring depends mainly on serial corneal imaging, changes in refraction, visual acuity, pachymetry, and clinical judgment. Inflammatory biomarkers may eventually add another layer of information by identifying patients with a more active biological disease environment (3,5). Patients with persistent ocular allergy, frequent eye rubbing, dry eye symptoms, or tear-film instability may require closer follow-up because these factors can increase inflammatory and mechanical stress on the cornea. In such patients, management should include treatment of allergic conjunctivitis or dry eye, counseling to avoid eye rubbing, optimization of contact lens tolerance where relevant, and timely consideration of corneal collagen cross-linking when progression is documented (32–34).

Risk stratification may also benefit from integrating genetic and molecular findings. Recent studies suggest that some individuals may have stronger inflammatory or atopic susceptibility, while others may have greater biomechanical vulnerability. Although this information is not yet routinely used in clinical practice, it supports the future possibility of more personalized keratoconus care. Patients with combined risk factors, such as young age, family history, atopy, eye rubbing, progressive tomography changes, and inflammatory ocular surface disease, may need more frequent monitoring and earlier intervention (20,24,33). Inflammatory assessment may also help evaluate response to treatment in future research settings. For example, reductions in MMP-9 or other inflammatory mediators after corneal collagen cross-linking or ocular surface treatment may provide insight into how therapies affect the disease microenvironment. However, such findings should be considered supportive rather than definitive until validated by larger prospective studies (31). Overall, the clinical implication of inflammatory research is not that keratoconus should be managed as a classical inflammatory disease. Rather, it suggests that inflammation is one important part of a wider disease process. A practical clinical approach should combine structural assessment, progression monitoring, control of ocular surface inflammation, prevention of eye rubbing, and timely biomechanical stabilization when indicated. This broader approach may improve early detection, reduce modifiable risk factors, and support more individualized care for patients with keratoconus (5,31–34).

## 8. THERAPEUTIC IMPLICATIONS AND EMERGING TREATMENTS

The recognition of inflammatory activity in keratoconus has widened the way this disease is understood and managed. Traditionally, treatment has focused on optical correction and biomechanical stabilization of the cornea. These approaches remain essential, particularly because progressive stromal thinning and ectasia are the main clinical problems in keratoconus. However, increasing evidence suggests that ocular surface inflammation, oxidative stress, allergic disease, tear-film instability, and eye rubbing may influence disease activity and progression. Therefore, management should not be limited only to correcting refractive error or strengthening the cornea, but should also include attention to the inflammatory and environmental factors that may worsen the disease course (31–34). At present, most anti-inflammatory and biologically targeted strategies should be considered adjunctive or investigational rather than replacements for established treatment. Corneal collagen cross-linking remains the main evidence-based treatment for halting documented progression. Other approaches, including anti-inflammatory therapy, exosome-based treatment, intense pulsed light, and nutritional support, are promising but require stronger clinical validation before they can be recommended as standard therapy for keratoconus (31,35–37).

## 8.1 Corneal Collagen Cross-Linking

Corneal collagen cross-linking is currently the established standard treatment for progressive keratoconus. Its main therapeutic purpose is to increase corneal biomechanical strength by inducing additional covalent bonds between stromal collagen fibers. This helps stabilize the corneal structure and reduce the risk of further ectatic progression. For this reason, cross-linking is particularly important in younger patients and in those with documented progression on serial corneal imaging (31). Although cross-linking is primarily understood as a biomechanical treatment, recent studies have suggested that it may also influence the inflammatory microenvironment of the cornea and tear film. Reductions in tear-film inflammatory mediators, including matrix metalloproteinases, have been reported after cross-linking in some studies. These findings raise the possibility that part of the clinical benefit of cross-linking may be related not only to mechanical stabilization but also to modification of proteolytic and inflammatory activity at the ocular surface (31). However, this anti-inflammatory effect should be interpreted carefully. Cross-linking should not be described mainly as an anti-inflammatory treatment, because its proven clinical role remains biomechanical stabilization. The reported changes in inflammatory mediators are better understood as additional biological effects that may support corneal stability, rather than as the primary mechanism of action. Further longitudinal studies are needed to clarify whether changes in tear-film biomarkers after cross-linking can predict treatment response or long-term disease stability (31).

## 8.2 Anti-Inflammatory Approaches

Because keratoconus is associated with low-grade inflammatory activity, anti-inflammatory management may have a supportive role, especially in patients with ocular allergy, dry eye disease, meibomian gland dysfunction, or persistent eye rubbing. In clinical practice, this means that associated ocular surface disease should be actively identified and treated. Reducing itching, irritation, and inflammation may decrease the urge to rub the eyes and may help reduce additional mechanical stress on the cornea (32–34). Topical anti-allergic medications, lubricants, lid hygiene, and treatment of meibomian gland dysfunction may be useful in selected patients, particularly when symptoms of itching, dryness, or ocular surface irritation are present. These treatments are not expected to reverse established corneal ectasia, but they may improve ocular comfort, reduce inflammatory burden, and support overall disease control. Patient education is equally important, because avoiding habitual eye rubbing remains one of the most practical and modifiable interventions in keratoconus care (32–34). Targeted anti-inflammatory therapies are also being explored as possible adjuncts to conventional treatment. Advanced molecular techniques, including transcriptomic and single-cell analyses, have identified inflammatory activity in corneal tissues, which may help guide future therapeutic targets. Nevertheless, there is still insufficient clinical evidence to recommend any specific anti-inflammatory drug as a disease-modifying treatment for keratoconus. Future studies should determine whether controlling inflammatory pathways can slow progression when used alongside established approaches such as cross-linking (23,31).

## 8.3 Exosome-Based Therapies

Mesenchymal stem cell-derived exosomes have attracted interest as a possible cell-free regenerative therapy for corneal diseases. Exosomes are small extracellular vesicles that can carry proteins, lipids, and nucleic acids involved in cell signaling. In experimental models, mesenchymal stem cell-derived exosomes have shown regenerative, anti-inflammatory, and immunomodulatory properties. These effects may be relevant to keratoconus because the disease involves stromal remodeling, keratocyte dysfunction, oxidative stress, and inflammatory mediator activity (35). The potential value of exosome-based therapy lies in its ability to influence several biological processes at the same time. Experimental evidence suggests that these vesicles may support corneal epithelial repair, regulate extracellular matrix remodeling, reduce fibrotic responses, and modulate inflammatory signaling. In theory, such effects could help improve the corneal microenvironment and protect against progressive tissue degradation (35). Despite this promise, exosome-based therapy remains experimental in the context of keratoconus. There is currently not enough high-quality clinical evidence to support its routine use for patients with keratoconus. Important questions remain regarding the ideal exosome source, dosage, delivery method, safety, long-term effect, and whether the treatment can truly alter disease progression. Therefore, exosome-based therapies should be presented as an emerging research direction rather than an established treatment option (35).

## 8.4 Intense Pulsed Light

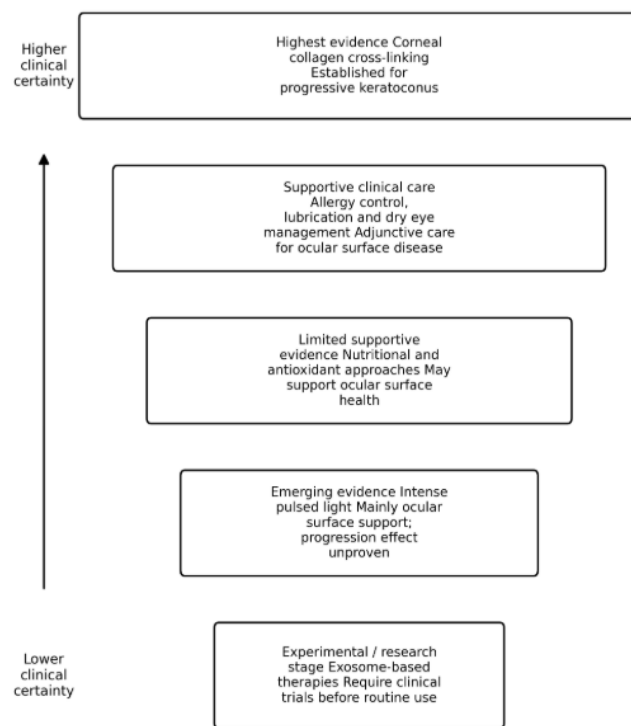
Intense pulsed light has been used mainly in the management of meibomian gland dysfunction and evaporative dry eye disease. Its possible relevance to keratoconus is related to the close relationship between tear-film instability, ocular surface inflammation, itching, and eye rubbing. By improving the ocular surface environment, intense pulsed light may theoretically reduce inflammatory activity and decrease symptoms that encourage rubbing behavior (36). Some studies and hypotheses suggest that intense pulsed light may reduce inflammatory cytokine levels, oxidative stress, and tear-film protease activity. It may also improve meibomian gland function and tear-film quality, which could reduce ocular irritation. In patients with keratoconus who also have significant dry eye symptoms or meibomian gland dysfunction, improvement in ocular surface comfort may be clinically helpful (36). However, the role of intense pulsed light in keratoconus remains uncertain. It should not be described as a proven treatment for halting keratoconus progression. Its current potential is best understood as supportive management for associated ocular surface disease rather than direct treatment of corneal ectasia. Well-designed clinical studies are needed to determine whether intense pulsed light has any measurable effect on inflammatory biomarkers, eye rubbing frequency, or keratoconus progression over time (36).

### 8.5 Nutritional and Supportive Approaches

Nutritional factors may also influence corneal health through their effects on oxidative stress, inflammation, and tissue repair. Omega-3 polyunsaturated fatty acids have well-recognized anti-inflammatory properties and may help support the ocular surface, particularly in patients with dry eye symptoms or tear-film instability. Antioxidant-rich nutrition may also be biologically relevant because oxidative stress is considered an important contributor to keratoconus pathophysiology (28,29,37). Although nutritional support may improve the general ocular surface environment, it should not be presented as a primary treatment for keratoconus. There is currently limited evidence that dietary modification or supplementation alone can prevent progression or reverse corneal ectasia. Nutritional approaches are better viewed as supportive measures that may complement standard care, especially in patients with ocular surface disease, poor tear-film quality, or increased oxidative stress (37).

Supportive care should also include patient counseling, allergy control, lubrication, avoidance of eye rubbing, and regular follow-up with corneal imaging. In progressive cases, timely corneal collagen cross-linking remains essential. A combined approach that addresses both biomechanical instability and modifiable inflammatory triggers may provide the most practical framework for keratoconus management (31–34). Overall, therapeutic implications of inflammation in keratoconus are promising but should be interpreted with caution. The strongest evidence remains in favor of corneal collagen cross-linking for progressive disease. Anti-inflammatory, exosome-based, intense pulsed light, and nutritional strategies may have adjunctive or future roles, but they require further validation through well-designed clinical trials. Until stronger evidence is available, these approaches should be considered supportive or investigational rather than standard disease-modifying treatments (31,35–37).

**Figure 3. Evidence hierarchy of inflammation-related treatments**



**Table 3. Therapeutic Implications and Emerging Treatment Approaches**

Therapy Approach	Main Proposed Mechanism	Evidence Status	Role in Current Practice	Key Limitation
Corneal collagen cross-linking	Strengthens stromal collagen and stabilizes corneal biomechanics	Established for progressive keratoconus	Standard treatment for documented progression	Anti-inflammatory effects are possible but not the main proven mechanism (31).
Allergy control	Reduces itching, inflammation, and eye rubbing	Clinically supportive	Important adjunctive care in allergic patients	Does not reverse established ectasia (33).
Lubricants / dry eye treatment	Improves tear-film stability and reduces irritation	Supportive	Useful in patients with dry eye or ocular surface symptoms	Not disease-modifying alone (34).
Anti-inflammatory therapy	May reduce ocular surface inflammatory activity	Investigational / adjunctive	May be considered when ocular surface inflammation is present	No specific drug is proven to halt keratoconus progression (23,31).
MSC-derived exosomes	Regenerative, anti-inflammatory, and immunomodulatory effects	Experimental	Research-stage therapy	Needs proper clinical trials; not standard treatment (35).
Intense pulsed light	May improve meibomian gland function and reduce ocular surface inflammation	Emerging hypothesis-generating	Possible supportive role in selected ocular surface disease	Not proven to stop keratoconus progression (36).

Omega-3 nutritional support	/	Anti-inflammatory antioxidant support	and	Supportive / limited evidence	May help ocular surface health	Should not be presented as primary keratoconus treatment (37).
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**Table 3.** Established, supportive, and emerging treatment approaches related to the inflammatory component of keratoconus.

## 9. LIMITATIONS OF CURRENT EVIDENCE

Although increasing evidence supports an inflammatory component in keratoconus, several limitations should be considered when interpreting the current literature. Much of the available evidence comes from cross-sectional studies, retrospective analyses, biomarker comparisons, laboratory investigations, and genetic association studies. These designs are useful for identifying possible relationships, but they cannot always confirm whether inflammation is a primary cause of keratoconus or a secondary response to corneal stress and tissue damage (5,16). Another important limitation is the relatively small sample size in many biomarker studies. Tear-film and corneal tissue studies often include limited patient numbers, and the findings may be influenced by disease severity, age, contact lens use, allergic eye disease, dry eye status, previous treatment, and sampling technique. Because of these differences, results are not always consistent across studies, and the same inflammatory mediator may be reported as elevated, unchanged, or variable depending on the population and methodology used (15,16,34).

Methodological heterogeneity is also a major challenge. Studies differ in tear collection methods, storage conditions, laboratory assays, diagnostic criteria, grading systems, control groups, and statistical approaches. These variations make it difficult to compare results directly or to define reliable biomarker thresholds. At present, inflammatory markers such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , HMGB1, and MMP-9 remain promising, but they are not sufficiently standardized for routine clinical use in diagnosing keratoconus or predicting progression (5,16,18). The specificity of inflammatory biomarkers is another concern. Many of the inflammatory mediators reported in keratoconus are also elevated in other ocular surface conditions, including allergic conjunctivitis, dry eye disease, meibomian gland dysfunction, and contact lens-related irritation. Therefore, these markers may reflect ocular surface inflammation in general rather than keratoconus-specific disease activity. This limits their current diagnostic value unless they are interpreted alongside clinical examination, corneal tomography, pachymetry, refraction, and patient history (33,34).

The evidence regarding emerging therapies is also limited. Corneal collagen cross-linking is well established for progressive keratoconus, but its possible anti-inflammatory effects require further confirmation. Other approaches, including exosome-based therapies, intense pulsed light, targeted anti-inflammatory treatments, and nutritional interventions, remain investigational or supportive at this stage. These therapies should not be presented as proven disease-modifying treatments until stronger evidence from controlled clinical trials becomes available (31,35–37). Genetic and Mendelian randomization studies have added useful insight into inflammatory susceptibility, but their clinical translation remains incomplete. These studies can suggest possible biological pathways, yet they do not automatically prove that a specific immune factor can be used as a treatment target or clinical biomarker. Functional studies and long-term clinical validation are still required to understand how these genetic findings relate to real-world disease onset, progression, and treatment response (20,24). Overall, the current evidence supports a meaningful association between inflammation and keratoconus, but important uncertainties remain. Larger, standardized, longitudinal, and clinically focused studies are needed to clarify whether inflammatory markers can reliably predict progression, guide treatment timing, or identify patients who may benefit from adjunctive anti-inflammatory strategies.

## 10. FUTURE DIRECTIONS

Future research should focus on moving the inflammatory concept of keratoconus from observational evidence toward clinically useful tools. One of the most important priorities is biomarker validation. Tear-film cytokines, matrix metalloproteinases, HMGB1, oxidative stress markers, and immune-related proteins should be studied using standardized sampling methods, uniform laboratory protocols, and clearly defined disease stages. Without standardization, it will remain difficult to determine whether these biomarkers are reliable enough for routine clinical practice (5,16,18). Longitudinal studies are particularly needed. Most current studies provide a snapshot of inflammatory activity at a single time point, but keratoconus is a progressive disease. Future research should follow patients over time to determine whether inflammatory biomarkers can predict progression before significant topographic or tomographic change occurs. Such studies may help identify patients who require closer monitoring or earlier intervention, especially children, adolescents, patients with allergy, and individuals with a family history of keratoconus (3,32,33).

Another important direction is the integration of biomarker data with clinical imaging. Corneal tomography, epithelial thickness mapping, pachymetry, biomechanical assessment, and tear-film biomarker analysis may provide complementary information. A combined model may be more useful than any single test alone. For example, a patient with mild tomographic changes, increased inflammatory markers, active allergy, and frequent eye rubbing may represent a higher-risk profile than a patient with similar corneal shape but no inflammatory or clinical risk factors (5,31–34). Personalized treatment is also an important future goal. Keratoconus does not behave the same way in every patient. Some patients may have dominant biomechanical weakness, while others may have stronger

inflammatory, allergic, or oxidative stress-related contributors. A better understanding of these differences may allow clinicians to tailor management according to individual risk. This could include earlier cross-linking in high-risk progressive cases, stronger control of ocular allergy and dry eye, behavioral counseling to prevent eye rubbing, and possible adjunctive therapies when supported by evidence (20,24,31).

Clinical trials are needed to evaluate whether controlling inflammation can alter the course of keratoconus. Future studies should assess anti-allergic therapy, ocular surface optimization, targeted anti-inflammatory treatment, antioxidant strategies, nutritional support, intense pulsed light, and regenerative approaches such as exosome-based therapies. These trials should include objective outcomes such as keratometric progression, corneal thickness, visual acuity, biomechanical parameters, tear-film biomarkers, patient symptoms, and long-term safety (31,35–37). Further research is also needed to clarify the relationship between inflammation, oxidative stress, and cellular senescence. These pathways may form a self-sustaining cycle that contributes to stromal degradation and disease progression. Understanding this cycle may open new therapeutic possibilities aimed at protecting keratocytes, reducing oxidative injury, modulating inflammatory signaling, and preserving extracellular matrix integrity (28–30). In future, the most practical approach may involve combining structural, molecular, and clinical risk assessment. This would allow keratoconus to be managed not only as a corneal shape disorder, but as a complex disease influenced by biomechanical instability, inflammatory activity, ocular surface health, environmental exposure, and genetic susceptibility.

## 11. CONCLUSION

Keratoconus should no longer be viewed as a purely biomechanical or degenerative corneal disorder. Current evidence suggests that corneal structural weakness interacts with inflammatory signaling, oxidative stress, genetic susceptibility, allergic disease, ocular surface dysfunction, and environmental triggers such as eye rubbing (5,13,20,31–34). Inflammatory mediators, including IL-1 $\beta$ , IL-6, TNF- $\alpha$ , HMGB1, and matrix metalloproteinases, may contribute to extracellular matrix degradation, keratocyte dysfunction, stromal thinning, and progressive corneal deformation (18,20,24,28–30). Although corneal collagen cross-linking remains the main evidence-based treatment for progressive disease, associated factors such as allergy, dry eye, tear-film instability, and eye rubbing should also be addressed as part of comprehensive care (31–34). Inflammatory biomarkers and emerging therapies are promising, but further longitudinal studies and clinical trials are needed before they can be used routinely in practice (5,16,35–37).

## REFERENCES

1. Claessens JL, Godefrooij DA, Vink G, Frank LE, Wisse RP. Nationwide epidemiological approach to identify associations between keratoconus and immune-mediated diseases. *British Journal of Ophthalmology* [Internet]. BMJ Publishing Group Ltd; 2022 [cited 2026 June 26];106(10):1350–4. Available from: <https://bj.o.bmj.com/content/106/10/1350.abstract>
2. Hafezi F, Gomes JÁP, Hillen M, Ambrósio Jr R. The Global Consensus on Keratoconus 2: From Definitions to Decision Making. [Internet]. Vol. 45, *Cornea* LWW; 2026 [cited 2026 June 26]. p. 909–10.
3. Singh RB, Koh S, Sharma N, Woreta FA, Hafezi F, Dua HS, et al. Keratoconus. *Nature Reviews Disease Primers* [Internet]. Nature Publishing Group UK London; 2024 [cited 2026 June 26];10(1):81. Available from: <https://www.nature.com/articles/s41572-024-00565-3>
4. Santodomingo-Rubido J, Carracedo G, Suzaki A, Villa-Collar C, Vincent SJ, Wolffsohn JS. Keratoconus: an updated review. *Contact Lens and Anterior Eye* [Internet]. Elsevier; 2022 [cited 2026 June 26];45(3):101559. Available from: <https://www.sciencedirect.com/science/article/pii/S1367048421002058>
5. Doroodgar F, Alizadeh F, Niazi S, Razavi SM, Jalilian N, Azarnezhad A, et al. Inflammatory and genomic interactions within keratoconus susceptible patients: a nationwide registered case–control study. *Eye and Vis.* 2024;11(1):40. DOI: 10.1186/s40662-024-00407-z
6. Singh RB, Parmar UPS, Jhanji V. Prevalence and economic burden of keratoconus in the United States. *American journal of ophthalmology* [Internet]. Elsevier; 2024 [cited 2026 June 26];259:71–8. Available from: <https://www.sciencedirect.com/science/article/pii/S0002939423004646>
7. Gatzioufas Z, d PANOS G, Hamada S. Keratoconus: is it a Non-inflammatory Disease? *Medical Hypothesis, Discovery and Innovation in Ophthalmology* [Internet]. 2017 [cited 2026 June 26];6(1):1. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5392225/>
8. Murthy SI, Mishra DK, Rathi VM. Pathophysiology and Histopathology of Keratoconus. In: Das S, editor. *Keratoconus*. Singapore: Springer Nature Singapore; 2022. DOI: 10.1007/978-981-19-4262-4\_4
9. Chen X, Liu C, Cui Z, Huang Y, Luo Q, Chen S, et al. Integrative transcriptomics analysis and experimental validation reveal immunomodulatory patterns in keratoconus. *Experimental Eye Research* [Internet]. Elsevier; 2023 [cited 2026 June 26];230:109460. Available from: <https://www.sciencedirect.com/science/article/pii/S0014483523000817>
10. Meng F, Ren S. Identification of hub genes and molecular pathways in keratoconus by integrating bioinformatics and literature mining at the RNA level. *Int Ophthalmol.* 2024;44(1):244. DOI: 10.1007/s10792-024-03071-3
11. Santos A, José Filho APM, Cenedeze MA, Hiyane MI, Amano MT, Cruz MC, et al. Increased inflammatory mediators in the ocular surface tissue in keratoconus. *Molecular Vision* [Internet]. 2024 [cited 2026 June 26];30:279. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11575844/>

12. Zhang X, Cui F, Wang Q, Zhang C. Inflammation and keratoconus: A comprehensive bidirectional Mendelian randomization analysis. *Medicine* [Internet]. LWW; 2024 [cited 2026 June 26];103(30):e39067. Available from: [https://journals.lww.com/md-journal/fulltext/2024/07260/inflammation\\_and\\_keratoconus\\_\\_a\\_comprehensive.75.aspx?context=latestarticles](https://journals.lww.com/md-journal/fulltext/2024/07260/inflammation_and_keratoconus__a_comprehensive.75.aspx?context=latestarticles)
13. Nichani PAH, Solomon B, Trinh T, Mimouni M, Rootman D, Singal N, et al. Investigating the role of inflammation in keratoconus: A retrospective analysis of 551 eyes. *European Journal of Ophthalmology*. 2023;33(1):35–43. DOI: 10.1177/11206721221125013
14. Kempuraj D, Mohan RR. Autophagy in extracellular matrix and wound healing modulation in the cornea. *Biomedicines* [Internet]. MDPI; 2022 [cited 2026 June 26];10(2):339. Available from: <https://www.mdpi.com/2227-9059/10/2/339>
15. Pinheiro-Costa J, Lima Fontes M, Luís C, Martins S, Soares R, Madeira D, et al. Serum inflammatory biomarkers are associated with increased choroidal thickness in keratoconus. *Scientific Reports* [Internet]. Nature Publishing Group UK London; 2023 [cited 2026 June 26];13(1):10862. Available from: <https://www.nature.com/articles/s41598-023-37472-8>
16. Wisse RP, Kuiper JJ, Gans R, Imhof S, Radstake TR, Van der Lelij A. Cytokine expression in keratoconus and its corneal microenvironment: a systematic review. *The ocular surface* [Internet]. Elsevier; 2015 [cited 2026 Jan 14];13(4):272–83. Available from: <https://www.sciencedirect.com/science/article/pii/S1542012415000531>
17. Kaiserman I, Sella S. Chronic Ocular Inflammation and Keratoconus. In: Barbara A, editor. *Controversies in the Management of Keratoconus*. Cham: Springer International Publishing; 2019. DOI: 10.1007/978-3-319-98032-4\_2
18. Gil P, Gil JQ, Cruz N, Costa C, Rodrigues-Santos P, Sousa LM, et al. Persistent Proinflammatory Cytokine Profile in the Tear Fluid of Stable Keratoconus: Rethinking Clinical Quiescence. *Translational Vision Science & Technology* [Internet]. The Association for Research in Vision and Ophthalmology; 2025 [cited 2026 June 26];14(9):31–31. Available from: <https://iovs.arvojournals.org/article.aspx?articleid=2810859>
19. Elbeyli A, Kurtul BE. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio levels are associated with keratoconus. *Indian journal of ophthalmology* [Internet]. Medknow; 2021 [cited 2026 June 26];69(7):1725–9. Available from: [https://journals.lww.com/ijo/fulltext/2021/07000/systemic\\_immune\\_inflammation\\_index.18.aspx](https://journals.lww.com/ijo/fulltext/2021/07000/systemic_immune_inflammation_index.18.aspx)
20. Chen J, Jia Y, Qi X. Mendelian randomization and genetic analyses reveal causal roles of immune cells and inflammatory proteins in keratoconus. *Scientific Reports* [Internet]. Nature Publishing Group UK London; 2025 [cited 2026 June 26];15(1):25846. Available from: <https://www.nature.com/articles/s41598-025-10759-8>
21. Prause O, Bozinovski S, Anderson GP, Linden A. Increased matrix metalloproteinase-9 concentration and activity after stimulation with interleukin-17 in mouse airways. *Thorax* [Internet]. BMJ Publishing Group Ltd; 2004 [cited 2026 June 26];59(4):313–7. Available from: <https://thorax.bmj.com/content/59/4/313.short>
22. Nichani PAH, Solomon B, Trinh T, Mimouni M, Rootman D, Singal N, et al. Investigating the role of inflammation in keratoconus: A retrospective analysis of 551 eyes. *European Journal of Ophthalmology*. 2023;33(1):35–43. DOI: 10.1177/11206721221125013
23. Akoto T. Biomechanical and Genetic Factors Contributing to Keratoconus Pathogenesis [PhD Thesis internet]. Augusta University; 2023 [cited 2026 Jan 3]. Available from: <https://search.proquest.com/openview/ab12bfb1fe4945ff8f54e372260f493d/1?pq-origsite=gscholar&cbl=18750&diss=y>
24. Yu Y, Liu Q, Zhou C, Jiang J, Li Y. Genetic and immune landscape of keratoconus: insights from Mendelian randomization analysis. *Mamm Genome*. 2025;36(3):859–71. DOI: 10.1007/s00335-025-10135-x
25. Chiou GCY, Xuan B, Liu Q, Yamasaki T, Okawara T. Inhibition of Interleukin-1-Induced Uveitis and Corneal Fibroblast Proliferation by Interleukin-1 Blockers. *Journal of Ocular Pharmacology and Therapeutics*. 2000;16(5):407–18. DOI: 10.1089/jop.2000.16.407
26. Hao X-D, Chen P, Chen Z-L, Li S-X, Wang Y. Evaluating the Association between Keratoconus and Reported Genetic Loci in a Han Chinese Population. *Ophthalmic Genetics*. 2015;36(2):132–6. DOI: 10.3109/13816810.2015.1005317
27. Tur VM, MacGregor C, Jayaswal R, O’Brart D, Maycock N. A review of keratoconus: diagnosis, pathophysiology, and genetics. *Survey of ophthalmology* [Internet]. Elsevier; 2017 [cited 2025 Mar 25];62(6):770–83. Available from: <https://www.sciencedirect.com/science/article/pii/S0039625717300462>
28. Cejka C, Cejkova J. Oxidative Stress to the Cornea, Changes in Corneal Optical Properties, and Advances in Treatment of Corneal Oxidative Injuries. *Oxidative Medicine and Cellular Longevity*. Wiley; 2015;2015:1–10. DOI: 10.1155/2015/591530
29. Abdul-Maksoud RS, Fouad RA, Elsayed TG, Ibrahim RA, Badawi AE. The impact of catalase and glutathione peroxidase-1 genetic polymorphisms on their enzyme activities among Egyptian patients with keratoconus. *The Journal of Gene Medicine*. 2020;22(8):e3192. DOI: 10.1002/jgm.3192
30. Gu C, Wang L, Jiang Q, Gu Z, Li X, Yao Y, et al. Exploring the oxidative stress-related molecular clusters in the cornea of patients with keratoconus. *Experimental Eye Research* [Internet]. Elsevier; 2025 [cited 2026 June 26];110516. Available from: <https://www.sciencedirect.com/science/article/pii/S0014483525002878>
31. Huang RS, Mihalache A, Popovic MM, Chan CC. Evaluating Changes in Pro-and Anti-Inflammatory Mediators in Keratoconus Following Corneal Collagen Cross-linking: A Systematic Review: Pro-and Anti-Inflammatory Mediators Following Corneal CXL. *AJO International* [Internet]. Elsevier; 2025 [cited 2026 June 26];100185. Available from: <https://www.sciencedirect.com/science/article/pii/S2950253525000899>

32. Sahebjada S, Al-Mahrouqi HH, Moshegov S, Panchatcharam SM, Chan E, Daniell M, et al. Eye rubbing in the aetiology of keratoconus: a systematic review and meta-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology* [Internet]. Springer; 2021 [cited 2026 June 26];259(8):2057–67. Available from: [https://idp.springer.com/authorize/casa?redirect\\_uri=https://link.springer.com/article/10.1007/s00417-021-05081-8&casa\\_token=\\_eBl\\_lh3Az4AAAAA:dAjJ0ZC-yU1NYR\\_VpFN59bECeD2GCJFPG58D7EcMVOLHQ44W30U-Igntzuwob0LAEM6IEJo6tK0ZVGAe1g](https://idp.springer.com/authorize/casa?redirect_uri=https://link.springer.com/article/10.1007/s00417-021-05081-8&casa_token=_eBl_lh3Az4AAAAA:dAjJ0ZC-yU1NYR_VpFN59bECeD2GCJFPG58D7EcMVOLHQ44W30U-Igntzuwob0LAEM6IEJo6tK0ZVGAe1g)
33. Ahuja P, Dadachanji Z, Shetty R, Nagarajan SA, Khamar P, Sethu S, et al. Relevance of IgE, allergy and eye rubbing in the pathogenesis and management of Keratoconus. *Indian journal of ophthalmology* [Internet]. Medknow; 2020 [cited 2026 June 26];68(10):2067–74. Available from: [https://journals.lww.com/ijo/fulltext/2020/68100/Relevance\\_of\\_IgE,\\_allergy\\_and\\_eye\\_rubbing\\_in\\_the.6.aspx](https://journals.lww.com/ijo/fulltext/2020/68100/Relevance_of_IgE,_allergy_and_eye_rubbing_in_the.6.aspx)
34. Mirza E, Oltulu R, Oltulu P, Mirza GD, Okka M. Dry eye disease and ocular surface characteristics in patients with keratoconus. *Saudi Journal of Ophthalmology* [Internet]. Medknow; 2022 [cited 2026 June 26];36(1):117–21. Available from: [https://journals.lww.com/sjop/fulltext/2022/36010/Dry\\_eye\\_disease\\_and\\_ocular\\_surface\\_characteristics.19.aspx](https://journals.lww.com/sjop/fulltext/2022/36010/Dry_eye_disease_and_ocular_surface_characteristics.19.aspx)
35. Ambrósio R, Caiado ALC, Guerra FP, Louzada R, Roy AS, Luz A, et al. Novel Pachymetric Parameters Based on Corneal Tomography for Diagnosing Keratoconus. *J Refract Surg*. 2011;27(10):753–8. DOI: 10.3928/1081597X-20110721-01
36. Zhao Z, Liu Y, Zou Y, Liu Y, Yu M. Intense pulsed light alleviates keratoconus by improving the local corneal microenvironment. *Medical Hypotheses* [Internet]. Elsevier; 2025 [cited 2026 June 26];194:111526. Available from: <https://www.sciencedirect.com/science/article/pii/S030698772400269X>
37. Lasagni Vitar RM, Bonelli F, Rama P, Ferrari G. Nutritional and metabolic imbalance in keratoconus. *Nutrients* [Internet]. MDPI; 2022 [cited 2026 June 26];14(4):913. Available from: <https://www.mdpi.com/2072-6643/14/4/913>

#### AUTHOR CONTRIBUTION

Author	Contribution
Dr. Muhammad Kashif	The author contributed to the conception of the review topic, literature searching, evidence synthesis, manuscript drafting, critical revision, and approval of the final manuscript.