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REVIEW

Systemic and ocular associations of Keratoconus

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ABSTRACT

Introduction: Keratoconus (KC) is the most prevalent corneal ectasia in the world, and its pathogenesis is influenced by both ocular and systemic factors. This review explores the multifaceted associations between keratoconus and systemic health conditions, ocular characteristics, and various other environmental/exogenous factors, aiming to illuminate how these relationships influence the pathophysiology of the disease.

Areas Covered: This review will summarize the fundamental attributes of KC, review and discuss the systemic and ocular association of KC including molecular biomarkers, and provide an organized overview of the parallel alterations occurring within various biological pathways in KC.

Expert Opinion: Despite the substantial volume of research on keratoconus, the precise etiology of the disease remains elusive. Further studies are necessary to deepen our understanding of this intricate disorder and improve its management.

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1. Introduction

Keratoconus (KC) is a progressive, sight-threatening disease and is the most common corneal ectasia in the world [1–3]. It is characterized by thinning and conical protrusion of the cornea [1–4] which often leads to legal blindness or significant visual impairment if left untreated [1]. KC typically onsets during adolescence and progresses into the third or fourth decade of life [1–3] before reaching a stable phase, although the rate of progression and severity varies among demographic and geographic regions [5–7].

The prevalence of KC is variable worldwide, with reported estimates ranging from 1:21 in a young adult population in Saudi Arabia [8,9] to about 1:5700 in an elderly US population [10]. The disease affects both the sexes and all ethnicities [1,11,12], and although male dominance has been reported in the Caucasian KC population [1], the male/female predominance is less clear in higher prevalence regions such as the Middle East. For example, Hashemi et al. reported a higher prevalence in males in Mashhad, Iran [9], but two other studies found a higher prevalence in females in Shahroud, Iran, and Saudi Arabia [8,13]. While it appears that the incidence of KC is increasing worldwide, particularly in developed countries, the higher reported incidences are also due in part to advancements in clinical and diagnostic technology that allow earlier and more accurate diagnoses [1].

KC is diagnosed using many modern techniques. One of the most common methods used is corneal tomography, most commonly the Oculus Pentacam (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany), which maps the anterior and posterior corneas and can allow early detection of the corneal steepening and thinning that occurs in KC [11,14–19]. Another useful tool is the spectral-domain optical coherence tomography (SD-OCT) which can delineate the corneal epithelium and stromal layers [20], unlike topography which only scans the surface of the cornea. Since epithelial thinning is one of the first signs of KC, this method may allow even earlier detection of the disease [21]. Furthermore, changes in corneal biomechanics (reduced corneal hysteresis and resistance factor [22–24]) may be another early and reliable sign of disease and could provide a method for early detection. Castro-Luna et al. have successfully classified subclinical KC using Random Forest, a machine learning model [25], and other techniques being investigated for diagnostics are biomarkers from tears [26], serum [27], saliva [28], and aqueous humor [29], although no distinct biomarkers have been detected for use yet. Genetic testing is also available to assess the risk for KC [11].

KC manifests with unique corneal findings and has been associated with a variety of biomechanical, proteomic, genetic, environmental, metabolic/hormonal, as well as systemic conditions. Precise pathophysiology continues to allude to researchers, with evidence pointing to a multifactorial etiology

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Article highlights

- Keratoconus (KC) is a sight-threatening disease that is multifactorial and shapes the cornea into a cone.
- Current KC research is investigating protein and cellular biomarkers as well as metabolic and hormonal biomarkers.
- KC may also be impacted by genetic and environmental influences.
- Other diseases may play a role in the development of KC such as sleep apnea and down syndrome.

[1,3,4]. In this review, the systemic and ocular associations of KC will be detailed and considered helping us understand the broader context of the disease.

1.1. Clinical manifestations of KC

KC manifests with varying signs and symptoms based on its severity. Early signs include blurred vision, increased light sensitivity, and increasing astigmatism that standard spherocylindrical spectacle lenses are insufficient to refractively neutralize [30]. In mild-to-moderate cases, localized corneal steepening, usually in the infero-temporal paracentral region, causes an increase in corneal aberrations (e.g. coma) [12,31] that cause the retinoscopy reflex to appear 'scissored' [32]. Rizzutti's sign, a conical reflection on the nasal cornea when light is shone temporally, becomes apparent [33]. Biomicroscopic examination reveals structural changes in KC corneas, such as ferritin deposits and a widening of intracellular epithelial spaces at the base of the cone (Fleisher's ring) [12,34], visible thinning of the stroma, and stress lines in the posterior stroma (Vogt's striae) [35–37]. Obvious protrusion of the cornea, displacing the lower eyelid in downgaze (i.e. Munson's sign) is also observed in severe disease [11,12]. Severe KC may lead to complications such as acute hydrops (occurring in about 1–3% of the cases) [38,39] and stromal scarring; in rare cases, corneal perforation or melt can occur [40,41]. The great visual impact of severe KC, often necessitating a corneal transplant when scarring is significant, highlights the importance of timely and effective management.

1.2. Corneal biomechanics

The corneal tissue has a high tensile strength and elastic modulus, which allows it to maintain its shape and resist deformation under the various surrounding forces [42,43] such as intraocular pressure, blinking, and eye movements [44]. The stroma, normally composed of about 250 collagen lamellae [45], accounts for about 90% of the corneal thickness and likely has the greatest influence on corneal biomechanics [44]. In KC, the cornea appears more susceptible to deformation than normal, which contributes to the conical shape of the cornea (usually inferior) in the disease [46].

Biomechanical changes to the cornea appear early and consistently in KC. The Ocular Response Analyzer (ORA) can measure both corneal hysteresis and corneal resistance factor and is found to be decreased in the disease [22–24]. The newer Corvis ST Tonometer uses a high-speed Scheimpflug camera to capture detailed corneal responses, including parameters such as deformation amplitude, applanation lengths, and corneal velocities. These additional metrics offer deeper insights into the viscoelastic properties of the cornea providing vital information for diagnosing conditions like keratoconus [47–49]. The changes in the corneal deformation properties are potentially a direct result of stromal tissue remodeling [50], splitting of collagen fibrils [51], increased proteolytic activity [52], and/or redistribution of collagen through slippage between lamellae [50,52,53]. Specifically, a reduction in lamellae or the unraveling of lamellae can compromise the cornea's ability to resist various forces, leading to its increased susceptibility to deformation, as seen in KC. Furthermore, any disturbance in the intricate network of collagen fibrils, through breakdown or redistribution, can impact the cornea's tensile strength and elasticity [54].

Apoptosis can also lead to keratocyte death in KC and is associated with stromal thinning and degradation [55,56]. In addition, the breakdown of the anterior limiting lamina (i.e. Bowman's membrane) occurs and could also reduce corneal hysteresis [57]. Since these biomechanical changes are observed early in the disease, they could lead to early detection and more precise monitoring of KC.

1.3. Biomolecular associations in KC

Research over the past 20 years has in part focused on finding a biomarker for KC, assessing cytokines, proteases, cells, metabolites, hormones, and other analytes in KC tears, corneal sections, aqueous humor (AH), and blood. Although obtaining specimens from the cornea and AH is invasive and technically challenging, the tear film and blood provide more easily accessible routes to study biomarkers in the disease. These methods are not without their challenges, such as a small tear volume (as little as 10 µL) that is easily contaminated [26,58], or the somewhat invasive nature of venous blood collection, but much has been learnt about KC from studying these fluids (Figure 1).

1.3.1. Protein and cellular biomarkers

Several proteomic studies on KC tears have suggested that there is an imbalance of pro- to anti-inflammatory mediators that favor a pro-inflammatory tear phenotype in KC. It is well established that overall protein levels in KC tears are reduced [59–61], most likely due to lower levels of lactoferrin [62] and secretory immunoglobulin A (sIgA) [2,63], two of the largest and most abundant tear proteins. However, despite the reduction in total protein content, there appears to be an increase in inflammatory proteins and a dysregulated balance of pro- and anti-inflammatory proteins that favors a pro-inflammatory environment. For example, there is strong evidence of increases in proteolytic enzymes (i.e. cathepsins [2,64,65], matrix metalloproteinase (MMP)-1 [61,66–68], MMP-9 [2,67,69]) and pro-inflammatory cytokines (i.e. IL-6 and TNF-α), countered by decreases in the anti-inflammatory protease inhibitors (e.g. cystatin) and pro-collagen enzymes (e.g. Prolidase) [60,66,70]. In addition to this strong evidence (i.e. multiple confirming studies), there are other possible alterations in the tear fluid reported, such as an increase in

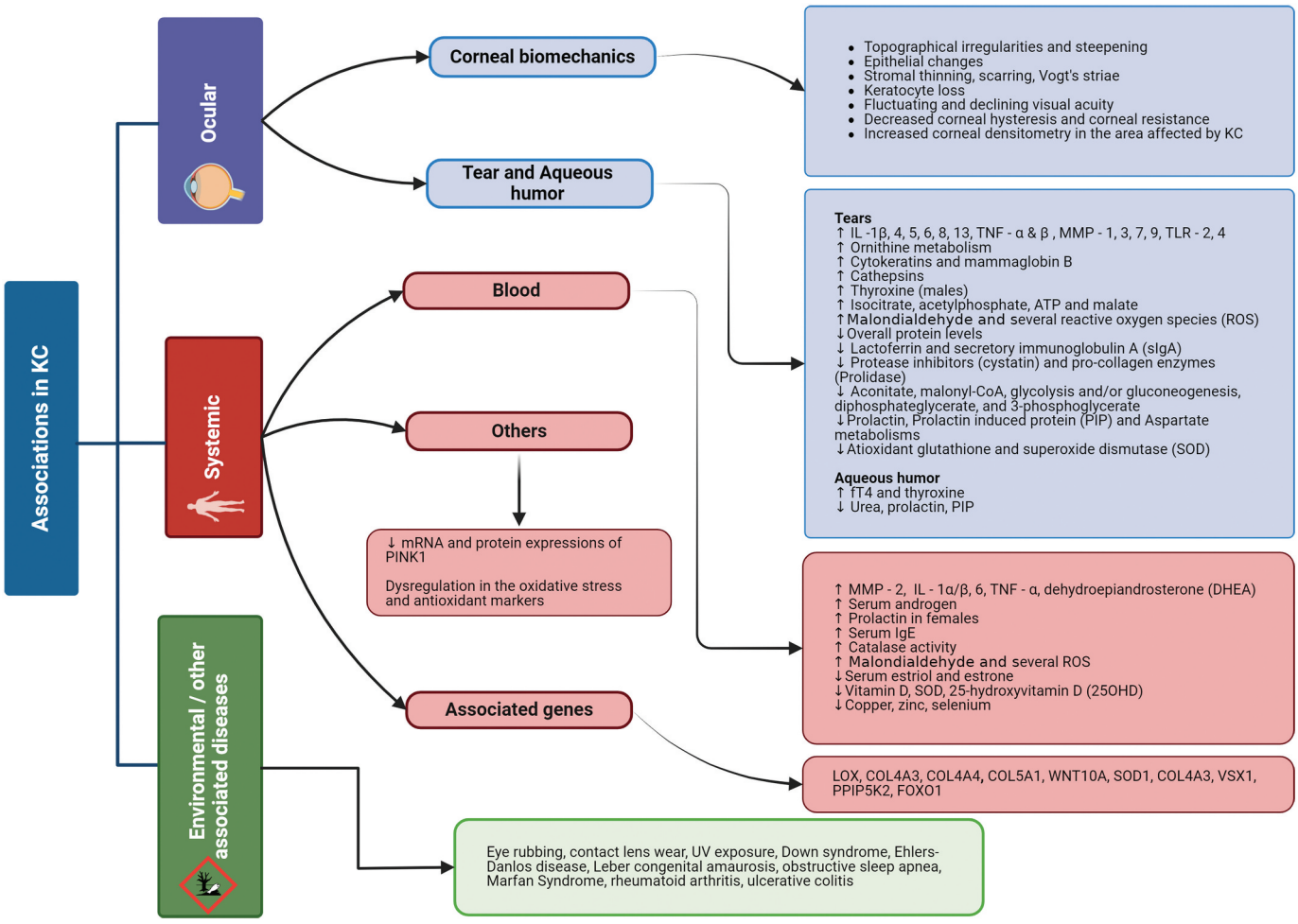

Figure 1. Overview of the various environmental, systemic and ocular associations of keratoconus (KC). Interleukin (IL), matrix metalloproteinase (MMP) Reactive oxygen species (ROS), Lysyl Oxidase (LOX), Collagen Type IV Alpha 3 (COL4A3), Wingless Type 10 A(WNT10A), Visual System Homeobox (VSX), Diphosphoinositol Pentakinase 2 (PPIP5K2), Forkhead Box Protein 01 (FOXO1).

cytokeratins and Mammaglobin B (MGB2) [59,68], as well as increased tear expression of cytokines IL-1β, −4, −5, −8, −13, MMP-3, MMP-7, and TNF-β [66,67], and toll-like receptors (TLR) 2 and 4 (in subclinical KC) [71]. Prolactin-Induced Protein (PIP) is present in many bodily fluids, including tears, where it performs several critical functions related to immune defense and cellular communication. Sharif et al. have demonstrated that PIP levels are notably diminished in the tears and saliva of patients suffering from KC. The reduction in PIP levels in these patients suggests a potential disruption in the protective and regulatory functions of the tear components, which could contribute to the pathophysiology of keratoconus by affecting the corneal surface's health, its ability to repair and defend against microbial invasion, and possibly influencing the progression of the disease [1,28]. Collectively, over 100 proteins have been assessed in tears in dozens of studies, which collectively support that there are elevated inflammatory cytokines and proteases and a reduction in anti-inflammatory cytokines that favor the classification of a pro-inflammatory tear proteome in KC.

In the blood, alterations have been found in serum proteins in KC, many of which are consistent with the changes seen in the tears, although fewer studies have been reported. Pro-inflammatory factors such as MMP-2, IL-1α/β, IL-6, and TNF-α were found to increase in KC serum in one study [2], and prolidase (enzyme essential for collagen remodeling) has been reported to be reduced [2,72]. Serum immunoglobulins have also been investigated in KC, and an increase in serum IgE levels with and without allergies could provide a molecular association between KC and allergic conditions [2]. In addition, cellular biomarkers such as the monocyte-to-HDL-cholesterol ratio (MHR) and neutrophil-to-lymphocyte ratio (NLR) may be of interest in KC, although one study found both inflammatory biomarkers to be increased [73] and another showed them unchanged [74]. Yet another recent study has found an increase in TLR2 and TLR4 receptors in the monocytes and neutrophils in the KC blood [75], complementing the same increased receptors that have been found in the tears in KC. Although still unclear and in need of additional studies with larger cohorts, these studies do provide evidence that there could be systemic factors that could help understand and diagnose KC.

1.3.2. Metabolic and hormonal biomarkers

The metabolome in KC has been increasingly investigated. A study by Karamichos et al. included 45 subjects in 3 clinically

defined groups (healthy, KC patients without corrective lenses, and KC patients wearing Rigid Gas Permeable (RGP) lenses). Analysis by liquid chromatography-mass spectrometry (LCMS) revealed 296 different metabolites and more than 40 of those metabolites showed significant changes in the glycolysis, gluconeogenesis, and urea cycles of KC patients [76,77]. In the urea cycle, there was an upregulation of ornithine and a downregulation of aspartate metabolisms [26]. The study also identified different metabolites belonging to the tricarboxylic acid cycle to be upregulated (isocitrate, acetylphosphate, ATP, and malate) and downregulated (aconitate, malonyl-CoA, glycolysis and/or gluconeogenesis, diphosphateglycerate, and 3-phosphoglycerate) [26]. The upregulation and downregulation of the above metabolites may indicate that the cornea is attempting to maintain homeostasis while experiencing oxidative stress.

Hormones have also been investigated in KC and have shown alterations in the disease. Prolactin and PIP have both been shown to be decreased in the tears and aqueous humor of KC patients [2,28,29], and prolactin has been found to be reduced in KC blood and saliva [2,28]. However, this finding has been challenged by another study that found that prolactin was increased in female KC patients [27], possibly indicating that there are sex differences to be considered. Thyroxine, a hormone involved in metabolism, was found to be elevated in one KC study, and more so in males with the disease [78]. The aqueous humor, located on the opposite side of the cornea, has been found to have increased fT4 and thyroxine concentrations in KC [2,29]. Furthermore, systemic studies have shown a greater incidence of thyroid gland dysfunction in a KC population [79–81], and reductions of serum estriol [2], estrone [2], Vitamin D [2,82,83], and riboflavin levels [84]; dehydroepiandrosterone (DHEA) sulfate [2] and androgen levels [27] were increased in KC serum. These hormonal differences seen in KC compared to normal, while not well defined at this time, could provide insight into how sex and age contribute to KC development and progression.

1.3.3. Evidence of oxidative stress in KC

Several studies have shown altered markers of oxidative stress and an imbalanced redox homeostasis in the blood, cornea, aqueous humor, and tears in KC. A 2021 systematic review and meta-analysis comprehensively summarized the changes in many oxidative and antioxidant stress markers in KC [85]. Notably, there appears to be a consistent increase in several reactive oxygen species (ROS) (e.g. superoxide and nitric oxide) in the tears, cornea, blood, and aqueous humor in KC with an imbalance of antioxidants (e.g. catalase and superoxide dismutase) that are important to reduce ROS-mediated cell damage [65,85–92]. Specifically, decreased blood, tear, and corneal levels of antioxidant glutathione and superoxide dismutase (SOD) have been observed in KC as well as reduced enzymatic activity of lysyl oxidase (LOX) in the tear fluid [2,92–95]. One ROS, malondialdehyde, a reactive aldehyde formed during lipid peroxidation, shows potentially the greatest evidence of consistent increases in the KC cohorts in blood, tear, and cornea samples [86,88,90,92]. In the blood, the total oxidant and antioxidant status have suggested an increase in systemic oxidative stress [92,96–98], and metal ions that are cofactors of enzymes involved in antioxidant activity, cross-linking, and collagen synthesis (i.e. 25-hydroxyvitamin D (25OHD), copper, selenium, iron, and zinc) are lower in KC serum [2,90,99–101], which suggest lowered antioxidative activity in KC patients [99,100]. Furthermore, one group has shown a hyper-response of corneal fibroblasts to oxidative stress in KC cell cultures, including more production of ROS [56,102]. Collectively, it appears that there is an altered oxidative stress response in KC at the local and systemic levels, which could contribute to, or be a sequela of the disease process.

Complementary to the altered ROS response in KC, there may be an irregular response to the degradation of damaged mitochondria. Mitophagy, a conserved, self-degradation process of damaged mitochondria, is reduced at both the mRNA and protein level (gene: *PINK1*) in the KC corneal epithelium [103]. Shetty et al. reported a difference in the autophagy markers Microtubule-associated protein 1A/1B-light chain 3 (LC3) and ubiquitin-binding protein (p62) in KC corneas when compared to healthy corneas [104,105]. They also saw a clear decrease in the expression of LC3 in the different grades of severity [104,105], ultimately providing evidence that a defective autophagy mechanism could be a consequence of oxidative damage and play a role in KC pathogenesis.

1.4. Genetic associations in KC

Over 20 genes have been linked to KC, and it appears that there may be a genetic cause or predisposition to the disease in certain populations [106,107]. KC shows no Mendelian inheritance patterns, but it can follow an autosomal dominant/recessive inheritance mode in some families [12]. A few case studies indicate strong genetic links in KC although monozygotic twin studies have shown that the twins developed different severities of KC, which suggests a combined environmental and genetic etiology [1,3]. Several studies comparing different ethnicities at the same geographical location also provide evidence of a genetic link. For example, Pearson et al. found that Asians in the UK had a four-times greater prevalence compared to Caucasians living in the same area [1,108] and a positive family history for keratoconus in 5% of Caucasians and 25% of a small Asian subgroup in the Dundee University Scottish Keratoconus study [108,109]. Georgiou et al. also noticed an increase in prevalence in the Asian population compared to Caucasians [110]. Different populations may be predisposed to different genetic expressions based on their environments or inherited genes [111]. In this section, several of the most implicated genes associated with KC are discussed.

1.4.1. Lysyl oxidase (LOX)

The most investigated gene in the KC disease is lysyl oxidase (*LOX*) [112,113], which has been considered a potential biomarker in keratoconus. This gene plays a role in extracellular matrix maintenance by promoting covalent cross-links of collagens and elastins as well as oxidizing lysine residues which makes them insoluble to the extracellular matrix environment [112,113]. *LOX* is expressed in different parts of the eye

including the cornea [112,113]. Genotyping has shown that *LOX* affects the Iranian [112], European, and Chinese populations [113]. Mok et al. have observed that Koreans have an exceptionally high odds ratio of *LOX* in KC patients [113]. Lopes et al. found an absence of mutations in *LOX* in Brazilian patients that were diagnosed with KC [114].

1.4.2. Collagen Type IV Alpha 3 (COL4A3), Collagen Type IV Alpha 4 (COL4A4), Collagen Type V Alpha 1 (COL5A1)

Research has revealed significant insights into the roles of specific collagen types in KC development. Saravani et al. found that the presence of the *COL4A3* gene might reduce the risk of developing KC, suggesting a protective effect [115]. On the other hand, *COL4A4*, important for structural integrity, has been identified as a potential risk factor among Caucasian populations [116,117]. Furthermore, *COL5A1*, which contributes to the structure of corneal collagen fibrils, is implicated in the process of central corneal thinning observed in KC [118]. Studies document its role across different ethnic groups, with a specific risk allele linked to a reduced central corneal thickness in both Caucasian and Asian populations [119]. This highlights the gene's universal relevance to KC pathogenesis, particularly in regard to corneal thinning [120].

1.4.3. Transforming growth factor beta (TGF-β)

The secretion and assembly of the extracellular matrix (ECM), vital for corneal structural integrity, is regulated by TGF-β signaling [121]. In KC, the altered regulation of TGF-β signaling in KC progression has been shown [121], as well as an increase in markers associated with the TGF-β pathway in severe KC patients that suggest greater *TGF-β* activity may be correlated with disease severity [122].

1.4.4. Wingless type 10 a (WNT10A)

WNT10A, a gene expressed in the central corneal epithelium, plays a significant role in corneal health and integrity [123]. Foster et al. revealed that the protein levels of *WNT10A* were reduced in both the epithelium and Bowman's layer in individuals with KC [123], and their study suggested a correlation between *WNT10A* transcript levels and increased keratometry readings [123]. Adding to the understanding of *WNT10A*'s role in KC, Cuellar-Partida et al. discovered that a specific variant of *WNT10A* doubled the risk of developing KC in a population in Western Australia [124].

1.4.5. Superoxide dismutase 1 (SOD1)

SOD1 plays a critical role in converting superoxide radicals into molecular oxygen and hydrogen peroxide, acting as a key antioxidant defense mechanism [125,126]. Its role in KC is still being debated. A study by Moschos et al. suggests a potential causative link between *SOD1* and the pathogenesis of keratoconus in Greek patients [127], but studies in the Middle Eastern (mostly from Saudi Arabia and Iran) and Brazilian patients have found no mutation in the *SOD1* gene in KC [114,128,129]. These studies indicate that the role of *SOD1* in KC may vary among different populations.

1.4.6. Visual system homeobox 1 (VSX1)

In the cornea, *VSX1* is thought to play a significant role in maintaining cellular differentiation and transparency. Mok et al. discovered two novel missense mutations in the *VSX1* gene among Korean patients with KC, suggesting a possible genetic link to the disease in this population [130]. However, this potential connection does not appear to be universal. Studies by Lopes et al. in Brazil [114] and Al-Muammar et al. in southern Iran [128] did not identify any mutations in the *VSX1* gene in their respective KC cohorts, indicating variability in the gene's role across different ethnic groups. Similarly, Moschos et al. investigated a cohort of Greek patients and found no significant association between polymorphisms in the *VSX1* gene and keratoconus, further complicating the genetic associations with KC [127].

1.4.7. Diphosphoinositol pentakinase 2 (PPIP5K2)

PPIP5K2 is a bi-functional kinase/phosphatase pyrophosphate [131] that plays a key role in regulating the synthesis and degradation of inositol pyrophosphates, a group of molecules involved in a wide range of cell-signaling pathways. *PPIP5K2*'s regulation of inositol pyrophosphates suggests a significant role in controlling cellular activities crucial for maintaining corneal health, transparency, and function [131]. Khaled et al. conducted a four-generational family genetic study that identified potential mutations in the phosphatase domain in *PPIP5K2* [7,131]. Such mutations could impact the enzyme's function, potentially leading to dysregulation of cellular signaling in the cornea.

1.4.8. Forkhead box protein O1 (FOXO1)

FOXO1 is part of the Forkhead box (FOX) transcription family and is an important regulator of cellular oxidative stress [117]. Genetic studies have highlighted the association of *FOXO1* with KC. *FOXO1* is one of the three genes that showed a genome-wide significant association with KC [117] underscoring its potential involvement in the disease's pathogenesis. Research examining *FOXO1* in diverse populations, including Caucasian and Asian groups, has identified several Single Nucleotide Polymorphisms (SNPs) in patients with KC, pointing to genetic variations that may influence susceptibility to the disease. However, studies in Chinese and Arab populations have not found a significant association, indicating that the relationship between *FOXO1* and KC may vary among different ethnic groups.

1.5. Environmental/exogenous associations in KC

KC is a multifactorial disease, and environmental factors may play a role in its progression. Chronic eye rubbing is the greatest independent behavioral risk factor in the development of KC [132]. A study conducted by Hassan et al. found that eye rubbing was associated with a 3.09 odds ratio, indicating a significant link between this behavior and the development or progression of KC [133]. The impact of eye rubbing on KC may vary depending on the duration and intensity of the rubbing, as some studies have shown that gentle rubbing may not have the same effect as a more vigorous rubbing

[109,134]. A case was reported of a 4-year-old girl who developed bilateral KC secondary to chronic eye rubbing [135], and other research suggests that individuals with KC tend to rub their eyes for a longer duration (between 10 and 180 seconds) compared to those with allergic or infective ocular disorders, whose eye rubbing usually lasts for less than 15 seconds [108,136]. Similarly, there have been multiple case studies of asymmetric KC development and worsening of the corneal curvature attributed to this behavior [119,137–139].

Contact lens wear is another environmental factor that has been linked to the possible progression of KC [140]. It is postulated that contact lens wear causes micro-trauma, potentially leading to keratocyte apoptosis and potentially triggering remodeling of the stromal matrix [141]' which may increase the likelihood of developing or worsening KC [142]. It has been demonstrated that both soft hydrogel and RGP contact lenses induce the release of MMP-9 and other inflammatory molecules in the tear film of normal subjects [141], and Lema et al. noted that RGP lenses caused greater increases in IL-6, TNF-alpha, ICAM-1, and VCAM-1 in the tears of patients with KC compared to normal myopic lens wearers [67]. In a study conducted by Bitirgen et al., it was revealed that KC patients who wore contact lenses experienced a significant reduction in basal epithelial cell density compared to those who did not wear them [143]. Additionally, contact lens wear is known to exacerbate dry eye symptoms, which could lead to increased eye rubbing among KC patients [144].

External environmental factors such as UV exposure and pollution have been found to have associations with KC [108,145]. However, further research is needed to establish a conclusive link particularly in the case of UV light [108]. While the precise mechanism by which pollution influences KC remains uncertain, there is speculation that particulate matter in highly polluted areas might aggravate ocular allergy symptoms and the propensity for eye rubbing, thereby increasing the prevalence of KC [145]. Preliminary studies suggest a potential correlation between exposure to certain airborne pollutants and increased KC prevalence. Jurkiewicz and Marty showed that fine particulate matter may be a possible risk factor for KC although more extensive research in diverse populations is necessary [145]. Interestingly, two independent studies have found a negative correlation or no association between cigarette smoking and KC [146,147]. The authors proposed that the by-products of cigarette smoke could potentially induce a beneficial cross-linking effect in the cornea [147].

1.6. Systemic conditions associated with KC

In understanding the ocular and systemic biomarkers that have been linked to KC, it may also be useful to consider them in the context of the several associated comorbidities such as Down syndrome [148], Ehlers–Danlos disease [149], Leber congenital amaurosis [150], obstructive sleep apnea [151–153], as well as several inflammatory-based diseases. KC can also be influenced by transient systemic conditions such as pregnancy, which can contribute to the progression of KC [154–158]. Many of these disease associations are thought to be genetically and/or behaviorally linked to KC, but the associations are challenging to delineate.

Down syndrome (DS) is the most common chromosomal anomaly [159] that has been reported to frequently present with ophthalmic manifestations [160]. Current literature suggests that 75% of the patients with DS tend to have corneal morphological features indicative of KC [161]. However, the prevalence of KC in DS patients has been reported to vary greatly between 0% and 71% [148]. It has been suggested that this association occurs as a result of central corneal thickness, genetics, and vigorous eye rubbing clinically described in DS patients [7]. Central corneal thickness (CCT) is decreased in patients with KC [162], and Evereklioglu et al. reported that the mean CCT in DS was significantly less (488.39 ± 39.87 µm) than that in the healthy control subjects (536.25 ± 20.70 µm) [163]. Several chromosomal regions have been linked with CCT variations and the potential risk of KC development [164]. *COL6A1* and *COL6A2*, which encode for type VI collagen [165], are on chromosome 21 and may play a role in the pathological connection between KC and DS [166].

KC has been associated with other congenital connective tissue disorders and collagen abnormalities, such as Ehlers–Danlos syndrome (EDS) [167]. There are several subtypes of this condition, many of which are associated with mutations in genes that produce fibrillar collagens or enzymes that modify these proteins [168]. A study done by Fransen et al. was the first to demonstrate a consistent role of genetic variants in Ehlers –Danlos genes in the etiology of KC [149]. The study identified significant associations between KC and variations in the *COL5A1* and *ZNF469* genes, as well as in two other genes related to EDS – *COL12A1* and *TNXB* – and also in the *COL2A1* gene, which codes for a component of type II collagen [149].

Leber congenital amaurosis (LCA) has been reported to be associated with KC. LCA is a family of congenital retinal dystrophy that leads to visual imparity [169]. A common manifestation of LCA is Franceschetti's oculo-digital sign, which is a result of repeated poking, pressing, and rubbing of the eyes [170] observed in up to 30% of the patients with KC [171]. Varying results have been reported on the association of LCA patients with *AIPL1* mutations and KC. Dharmaraj et al. reported that 26% of the 19 LCA patients presented with the mutation and KC and cataracts [172]. Whereas McMahon et al. found no association between *AIPL1* and KC [150]. The study did suggest that patients with LCA with a CRB1 mutation may have susceptibility to develop KC [150].

Obstructive Sleep Apnea (OSA) is a common sleep disorder marked by repeated interruptions in breathing due to upper airway collapse during sleep [173]. The relationship between OSA and KC has been in question for decades. In a late 1990s investigation, Mojon et al. found that 2.3% of the patients with OSA were also diagnosed with KC [174]. Since then, there have been many inquiries into the relationship between OSA and KC. In two separate studies, Gupta et al. and Saidel et al. found that the prevalence of OSA in patients with KC was 18% [151] and 19.6% [175], respectively. A 2020 meta-analysis concluded that there is an association with OSD and KC [152], but there is no clear pathophysiologic connection. The underlying connection between KC and OSA is likely complex, and both are also

associated with highly prevalent developed world conditions such as obesity [151,175]. In a prospective case–control study of 50 patients with KC, Pihlblad and Schaefer found almost 25% had OSA (12/50) and that over 50% (26/50) were obese [153]. There could also be a common factor in sleep position; it has been suggested that people who sleep with their hands near their face could be at greater risk of both KC and sleep apnea [151,176]. Proposed theories including chronic intermittent hypoxia (a hallmark of OSA) may influence corneal collagen structure and metabolism, potentially contributing to KC. Additionally, OSA can cause oxidative stress, which is believed to play a role in KC development. Also, individuals with OSA may often rub their eyes at night, a known risk factor for KC [134,177]. It has also been suggested that a common (dysregulated) MMP pathway could be the connection between KC and OSA [153]. Researchers continue to investigate the link between these two diseases.

Although controversial, one factor that may protect from this disease is diabetes. The hypothesis is that chronic high blood glucose levels lead to the glycosylation of the corneal stromal fibrils, providing natural collagen crosslinking (CXL), strengthening the corneal tissue, and thus reducing the risk of developing KC [1,178,179]. Kuo et al. performed two different studies investigating diabetes in KC. The first study focused on evaluating diabetes mellitus (DM) prevalence in patients with and without KC. This study found that there was no difference in the prevalence of DM in patients with or without KC. Study 2 focused on evaluating KC severity in patients with and without DM. This study found that the severity of KC was negatively associated with the presence of DM [180]. The relationship between Type 2 Diabetes Mellitus (T2DM) and KC is the subject of extensive discussion and debate. Some studies have stated that T2DM provides a protective effect against KC [180–183], while other studies have stated that T2DM has a positive association with KC [184,185].

The association of KC with several inflammatory diseases has been documented but is not well understood. A retrospective study in Israel found increased odds for the following diseases in KC: rheumatoid arthritis (OR: 8.1), ulcerative colitis (OR: 12.1), autoimmune chronic active hepatitis (OR: 6), and irritable bowel syndrome (OR: 5) [186]; other associated inflammatory diseases include Hashimoto's thyroiditis, asthma, vernal keratoconjunctivitis, environmental allergies, and atopy [187–190]. However, there is controversy [109,191] and some indication that the behavior of eye rubbing may drive the associations, particularly with allergic conditions [186]. In less obvious correlations, such as those with rheumatoid arthritis and ulcerative colitis, an underlying autoimmune link is suspected, though its specific nature remains to be clarified. These associated diseases might also lead to heightened inflammation on the ocular surface, potentially predisposing a patient to the development of KC [186]. It has been suggested that atopy may be a common factor underlying both KC and certain inflammatory conditions, such as irritable bowel syndrome [207]. However, research in some populations has not established a clear link between atopy and the development of KC [186]. Moreover, conditions like leukocytoclastic vasculitis (LVC) characterized histopathologically by immune complex-mediated vasculitis of the dermal capillaries and venules have been occasionally associated with KC, indicating a potential interplay of vascular inflammation in its pathogenesis [192]. However, a direct causative relationship between KC and LCV has not been established [193]. While direct causality between systemic inflammatory diseases and KC remains an area of ongoing investigation, reported associations between KC and autoimmune systemic diseases lend support to the current understanding of multifactorial etiology in KC that exists with several genetic and environmental contributing factors.

2. Considering the multi-factorial influences on KC

The pathophysiology of KC is certainly complex, but there can be important insight provided when the various associations of the disease are discussed and considered together. Certainly, it is widely agreed that genetics plays a role and can pre-dispose an individual to developing KC, but it seems for most populations that there are other factors, environmental or otherwise external to the genome, that can drive KC development. Based on the wide multifactorial associations with KC, we propose that patients who develop KC likely have a genetic predisposition toward faulty mechanisms related to ocular surface stress and collagen remodeling, which in the presence of certain hormonal, environmental, and inflammatory settings provide the perfect storm to develop KC. The cornea is the most anterior structure of the anterior chamber and is particularly vulnerable to external influences such as pollution or UV light, and also to behavioral influences like eye rubbing. These factors can trigger ocular surface inflammation including oxidative stress, and in KC, there appears to be a faulty mechanism for responding to stress. Indeed, many of the altered genes in KC (i.e. *SOD1*, *LOX*, and *gen*) are involved in managing oxidative stress on the ocular surface. Oxidative stress can also lead to apoptosis of keratocytes and reduced collagen in KC. The role of hormones and metabolites is intertwined in all physiological processes for example, in oxidative stress responses (estradiol, vitamin D), and while it is not well understood how they contribute to KC, important changes have been discovered. Another imperative variable to consider is that the onset of the disease in most patients occurs at the end of puberty, which could be related to changing hormones that could trigger a susceptible patient to develop KC.

3. Conclusion

KC is a multifaceted disease with a complex interplay of biomechanical, genetic, and environmental factors contributing to its onset and progression. The relationships between KC, oxidative stress, and other systemic diseases are intricate and warrant further research to elucidate the underlying mechanisms and potential therapeutic targets.

4. Expert Opinion

KC is widely accepted as a complex, multifactorial, and challenging disease of the human cornea, especially as it relates to its early detection and treatment. The types of symptoms, and how severe they are, can differ widely from person to person and from geographical region to region.

Many different factors can affect the course the disease runs, including the age of diagnosis. KC is also known to affect both males and females, and its sex-specific impact is just emerging as a key piece to the disease's manifestations and could provide details on systemic mechanisms. KC can have numerous comorbidities; however, the reason for those is largely unexplored. Future studies could eventually lead us to targeted therapies that can better treat and relieve the population of this debilitating disease. As it relates to early diagnosis/detection, technological advancements and the development of more sensitive clinical equipment could significantly help these efforts. Patient compliance can also be refined by improving the clinical examinations and specimen collection techniques to be more comfortable for patients. Available treatments need to be developed further. The primary treatments available are collagen crosslinking (CXL) and corneal transplantation, the latter of which introduces an entirely new condition to manage in its post-surgical state. CXL is the most effective and aims to arrest progressive KC, although continued progression has been reported in some cases and there are minor risks associated with the surgical procedure. It is therefore clear that clinical and lab-based research holds a great many promises in advancing our current knowledge and developing future tools and therapies, with the ultimate goal of preventing this disease from occurring in people all across the globe. By understanding KC at a molecular level, we can expect to have a better understanding of the disease and how it progresses before physical manifestations occur. Such information can then be used by ophthalmologists who will have the tools necessary to diagnose the disease earlier and provide effective treatments to slow the progression of KC. A promising research area to explore is the world of extracellular vesicles (EVs). These vesicles may hold clues to the progression of the disease, given their ability to travel far within the body and reach target organs and cells with great precision. Their surface proteins and our ability to detect and analyze them could provide clues about KC pathobiology. It is very possible that this field of research will not reach a definitive end-point due to the imaginative curiosity that scientists hold. Scientists will still be researching KC for many years to come, but hopefully, we will make some advancements in discoveries. Maybe the gene list will be narrowed down to a few candidate genes, and genetics will be once again at the forefront. Artificial Intelligence (AI) may help guide the field with pattern recognition software that can spot patterns that humans do not see when investigating KC. Perhaps, novel biomarkers unique to KC will be able to distinguish KC manifestations among different ethnic and racial groups. As more discoveries are made, we will better understand this disease and develop more effective tools to slow the progression of the disease and maybe one day, stop the progression all together. It has been the 'dream' in the KC field, as well as others, that a simple blood test or a drop of tears may hold the clues necessary for early diagnosis. We still have a long road ahead, but if we continue being passionate about this disease, anything is possible.

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