

Challenging the “No Rub, No Cone” Keratoconus Conjecture

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ABSTRACT

Eye rubbing has long been acknowledged as a risk factor for keratoconus (KC), but its role in the pathogenesis of KC may not have been accorded sufficient prominence. This article puts forth the conjecture that KC is not a dystrophy of unknown genetics and biomolecular substratum, but rather a syndrome caused by eye rubbing, i.e., what has been called “keratoconus” is the direct consequence of mechanical trauma to the cornea by chronic and incessant eye rubbing, resulting in the progressive deformation and thinning of the corneal wall, the hallmarks of the disease. The conjecture is challenged in this article to investigate its compatibility with what is currently known about KC. The conjecture does not contradict previous clinical or experimental findings about KC, all of which can be interpreted in light of this proposed mechanism. Rather, it is a synthetic approach that incorporates the results of previous genetic and biochemical perspectives for understanding the pathophysiology of KC. In fact, this mechanical disease proposition would appear *more* compatible with explaining the variability of KC expression between patients, between eyes, and the predominance of sporadic cases. As such, eye rubbing may not be solely a risk factor as often coined in medical literature, but the direct cause of the syndrome labeled “keratoconus.” In conclusion, this mechanical theory provides a better explanatory framework for what is currently known about KC and confirms the validity of the “no rub, no cone” conjecture.

Keywords: Ectasia, Eye rubbing, Keratoconus.

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INTRODUCTION

The word “keratoconus” originates from the Greek word “kéras,” meaning cornea and the Latin word “cōnus,” meaning cone. This denomination is purely descriptive, however, and does not suggest any mechanism to account for the corneal deformation which is the hallmark of the disease. The progressive structural deformation of corneal

shape leads to refractive instability and reduction in the optical quality of the keratoconic eye. The exact molecular or tissue abnormalities in KC are still unknown.

Eye rubbing is a common activity occurring at different times of the day: Most regularly upon waking, before sleep, during extended computer work, and throughout the day in response to ocular itch and irritation, fatigue, or emotional stress.^{1,2} It is usually benign but when performed too vigorously, too frequently, or over extended periods, rubbing becomes pathological and can be harmful to the cornea. Prolonged and repetitive forceful knuckle rubbing is often seen in KC.

In a previous paper, I defended a new theory where abnormal eye rubbing is not just a risk factor, but is the main and necessary causative factor of KC.³ Thus, in this postulate, the absence of rubbing would prevent KC from occurring and this conjecture may be condensed as: “no rub, no cone.” In mathematics, a conjecture is defined as a proposition which is consistent with known data. It has neither been verified nor shown to be false. While formal proof that eye rubbing is the indispensable causative factor for KC may be difficult, the “no rub, no cone” represents a valid conjecture for elucidating the mystery of the pathophysiology of KC, therefore, offering potential benefits to the management of what is considered the most frequent corneal “dystrophy.”

The blunt statement that “eye rubbing is a chronic mechanical injury necessary to trigger and accelerate the corneal deformation observed in keratoconic eyes” defies the widely adopted theory that KC is primarily a corneal dystrophy. However, it is entirely possible that KC is a primarily mechanical disease. In addition, the “no rub, no cone” conjecture suggests that there is a possibility of stopping the progression of existing KC by cessation of eye rubbing. Even more importantly, if the mechanical injury caused by chronic eye rubbing really is the necessary ingredient in the recipe of the KC disease, surely its suppression would make it possible to even eradicate it. As such, it should raise significant interest among the medical and ophthalmic community.

A conjecture is considered proven only when it has been shown that it is logically impossible for it to be false. While mathematicians would seek robust demonstrative proof to make it a theorem, in contrast, new theories in medicine can be supported by conjectural models relying

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on tangible evidence. In what follows, I will show why the “no rub, no cone” conjecture may be proven correct by existing logical data and evidence. The line of arguments developed here will hopefully receive enough consideration to be accepted as a viable theory and, if proven true, lead to new guidelines for managing and preventing KC.

KERATOCONUS IS NOT AN ECTASIA BUT A PERMANENT CORNEAL WARPAGE

The corneal deformation in KC is often referred to as “ectasia,” but this term is certainly not specific to KC and is also employed to describe the most dreaded complication of laser-assisted *in situ* keratomileusis (LASIK) surgery.

In medicine, an ectasia is defined by a permanent widening, distension, or ballooning of any tubular organ or part, or more specifically, “a dilation, expansion, or distension,”⁴ all of which invokes the notion of an increase in surface area by a process of stretching. Annuloaortic ectasia, for example, refers to a proximal dilatation of the aortic root at the level of the aortic annulus. The diagnosis is based on the increase in aortic wall diameter. It occurs with conditions, such as Marfan disease, Ehlers-Danlos syndrome, and other familial forms of connective tissue diseases.

In the ophthalmic context, the use of the term “corneal ectasia” is a misnomer because it is not a truly accurate description of the morphology of the keratoconic cornea. A truly “ectatic” bulge would necessarily incur an increase in surface area of the anterior corneal surface. However, Smolek and Klyce⁵ demonstrated that the surface area of the cornea does not, in fact, increase when KC develops. Except for the single case of keratoglobus, corneal surface area tended to be conserved near a value of 120 mm² for all groups in their study, including corneas with KC. The authors reported that the surface area is remarkably insensitive to curvature change near the vertex. Thus, they concluded that KC is not a true ectasia (unlike keratoglobus where the corneal surface expands), but rather a specialized type of warpage, at least in mild-to-moderate forms of the disease.

From a mathematical perspective, Gauss’ Theorema Egregium (Latin for “Remarkable Theorem”) is a foundational proof in differential geometry demonstrated by Gauss⁶ concerning the curvature of surfaces. His theorem states that the Gaussian curvature of a surface does not change if one bends the surface without stretching it. Hence, the flattening seen in the periphery of keratoconic corneas (increased prolateness) corresponds to a necessary coupling effect compensating for the increase in curvature in the cone region. These observations bluntly contradict the concept of KC being an ectasia in the strict medical sense and indicate that the deformation of

keratoconic corneas may be better described as an extreme but isometric form of distortion or warpage, which redistributes the corneal curvature without local protrusion.

The common perception that keratoconic corneas are “ectatic” may be partly due to subjective interpretation of curvature maps obtained from specular corneal topographs (Fig. 1). Using conventional topography scales, the increase in axial curvatures plotted in maps of keratoconic corneas results in islands of warmer colors surrounded by annuli of cooler hues. Our subjective visual perception tends to isolate any area colored in red from the surrounding zones of bluer colors, and this distinction may lead to a false impression of a local protrusion. The colors and scales used in corneal topography, however, are arbitrarily chosen and when their parameters are varied, may lead to variations in the plot of the same data. Hence, it makes no sense to delineate a “cone” by simply following the contours of an area of reddish colors. Moreover, one should not try to extrapolate the three-dimensional shape of the cornea from axial curvature plots and consider any “red zone” as equivalent to a local bulging.

The deformation of the keratoconic cornea is global and not confined to the central area, despite what the color renditions of axial curvature maps may incorrectly suggest. The inspection of the corresponding elevation map of such surfaces, which is a truer representation of

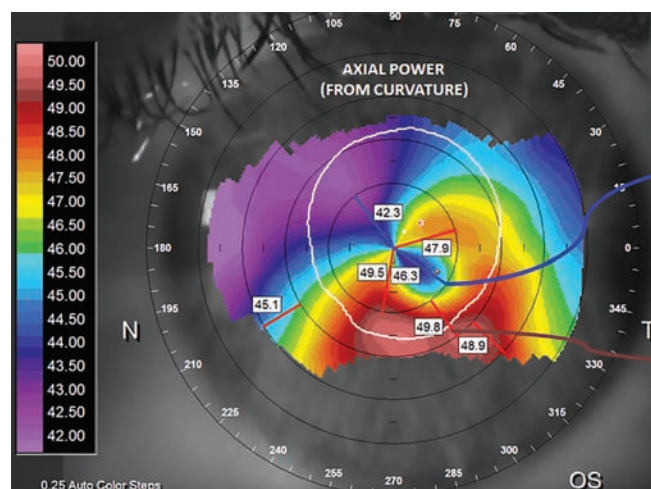


Fig. 1: Axial power map of a keratoconic cornea (*left eye*). The inferotemporal red zone can be interpreted by the inexperienced physician as an area of local protrusion. However, this map does not correspond to a plot of the shape of the cornea. Rather, it corresponds to the representation of the local axial curvature of the anterior corneal surface. Curvature is inversely proportional to the local axial radius of curvature (the shorter the radius, the steeper the surface). This inferior steepening does not mean that the corneal surface is bulging inferiorly. Rather, the deformation of the cornea incurs a predominant central flattening along an oblique direction, which is the result of the curvature coupling effect compensating for the inferior steepening. The mean Gaussian curvature within the central 8 mm diameter zone is balanced to 40 D (a value similar to what would be encountered in normal corneas), which is consistent with the Gauss’ *Theorema Egregium*

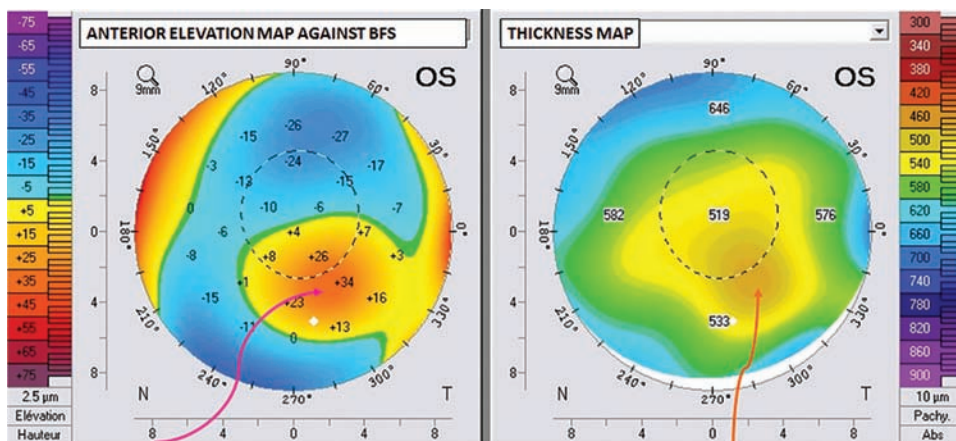


Fig. 2: *Left:* the anterior elevation map provides a better representation of the spatial properties of this anterior surface. The inferiorly decentered island of red colors corresponds to positive elevation against the sphere declivity. It is a consequence of global corneal deformation, and should not be interpreted as a local protrusion. *Right:* The thickness (pachymetry) map reveals the temporal inferior thinning of the cornea, which is accompanied by a vertical displacement of the thinnest point

the actual shape of the considered corneas, allows one to rectify this impression and reveals a more progressive gradient of colors (Fig. 2).

Elevation plots against a best-fit sphere (BFS) generally outlines an “island pattern” which reflects the increased prolateness of the keratoconic surface (decrease in the curvature from the corneal apex to the periphery).⁷ In KC, the corneal deformation is characterized by a warpage combining a central steepening with a concomitant compensatory peripheral flattening. The complete absence of any associated dilatation or expansion makes the term “ectasia” inappropriate in describing accurately the morphological changes at play in the keratoconic cornea (Figs 3 to 6).

In KC, the posterior corneal curvature is affected in addition to the anterior corneal surface. Moreover, early morphological changes in eyes with KC may develop on the posterior surface. In a theoretical study, we established that the representation in elevation of theoretical corneal models against a BFS may explain the differences in the elevation patterns of the anterior and posterior corneal surfaces.⁷ Given the geometry of the posterior corneal surface, which is naturally steeper and more aspheric than the anterior surface, any concomitant apical steepening and peripheral flattening of both corneal surfaces would result in a greater increase in the apical distance to the posterior surface’s BFS, and therefore, a warmer central color in the elevation plot (Fig. 7).

These theoretical predictions echo the clinical impression that early manifestations of KC are often characterized by an increase in the apical posterior elevation. Our results show that during the evolution of KC, the posterior surface of the cornea deforms concomitantly with the anterior surface of the cornea, but that the effects of these changes on elevation maps are more visible in the posterior surface of the cornea.

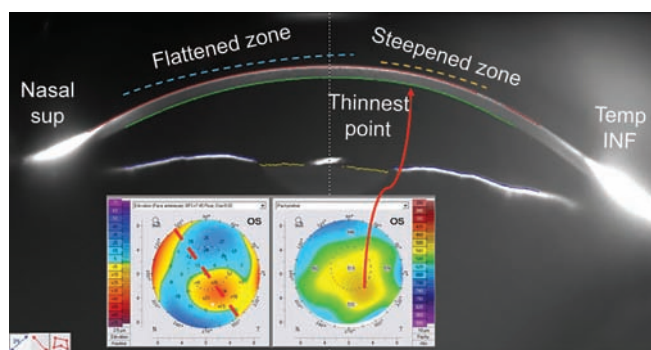


Fig. 3: This oblique cross-section of the Scheimpflug image provides a direct visualization of the cornea deformation and notably does not suggest any local “protrusion” or “ectasia.” Rather, the corneal deformation results in a different repartition of the curvature along this particular corneal meridian: The slight inferotemporal flexure of the cornea is adjacent to the thinnest part of the cornea, and is accompanied by a concomitant superonasal flattening. Many synergistic mechanisms brought about by pathological rubbing induces a permanent warpage. This isometric deformation is caused by a paracentral flexure of the corneal wall accompanied by a central thinning which is mainly caused by a displacement of the ground substance of the cornea during the initial phase of the disease and/or the release of proteolytic molecules in the tears triggered by eye rubbing

WHAT THEN CAUSES THE CORNEAL WARPAGE OF THE KERATOCONIC CORNEA?

While both environmental and genetic factors are thought to contribute to the development of the disease, the physiopathology of KC has not been elucidated until now. An exploration of the supportive and intertwining subtheories follows.

The Case Revisited—Are These Risk Factors Correlation or Causative?

Eye rubbing has been presented as a risk factor (by correlation) for KC, among others including ocular allergy, atopy, and Down syndrome.⁸⁻¹⁰ Keratoconus appears



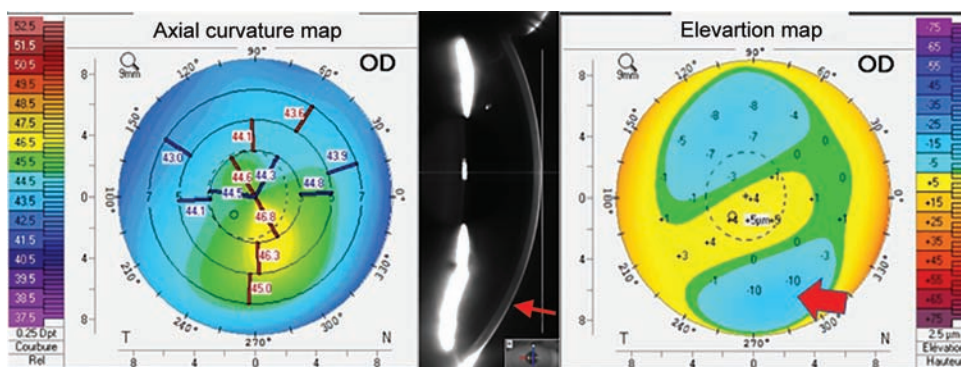
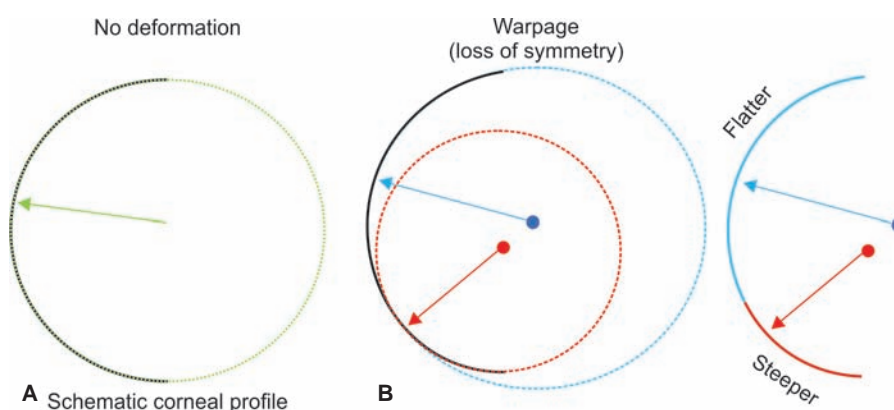


Fig. 4: The curvature map (*left*) shows a mild inferior steepening. One should not interpret this as an area of local protrusion. On the contrary, this area of the cornea is located in a more posterior plane than its superior counterpart, as shown on the vertical cross-sectional image taken by the Scheimpflug camera (*red arrow*), and also demonstrated on the elevation map, which reveals a more negative elevation relative to the BFS. This change in corneal curvature occurred in a patient after several years of vigorous eye rubbing



Figs 5A and B: Schematic representation of the change in the corneal profile caused by repeated trauma. The initial corneal profile is depicted by an arc of a circle (A). It has a constant curvature (the *green arrow* corresponds to the radius of curvature). Repeated trauma exerted on the corneal surface results in asymmetric curvature redistribution (B). This incurs not only an inferior steepening (decreased local radius of curvature: *red arrow*), but a concomitant superior flattening (extended local radius of curvature: *blue arrow*). This process should not be considered ectatic, as it is isometric (no change of the corneal surface area, as there is no distension of the corneal tissue), at least in its initial stages.

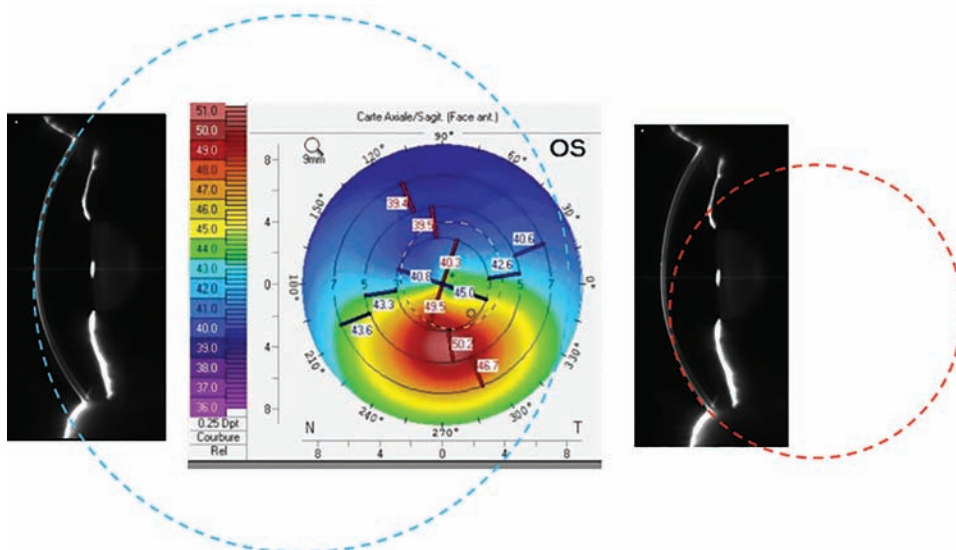


Fig. 6: This example shows the vertical cross-section of a keratoconic cornea, for which two different circles have been used to approximate the superior (flatter) and inferior (steeper) hemi-corneal profile

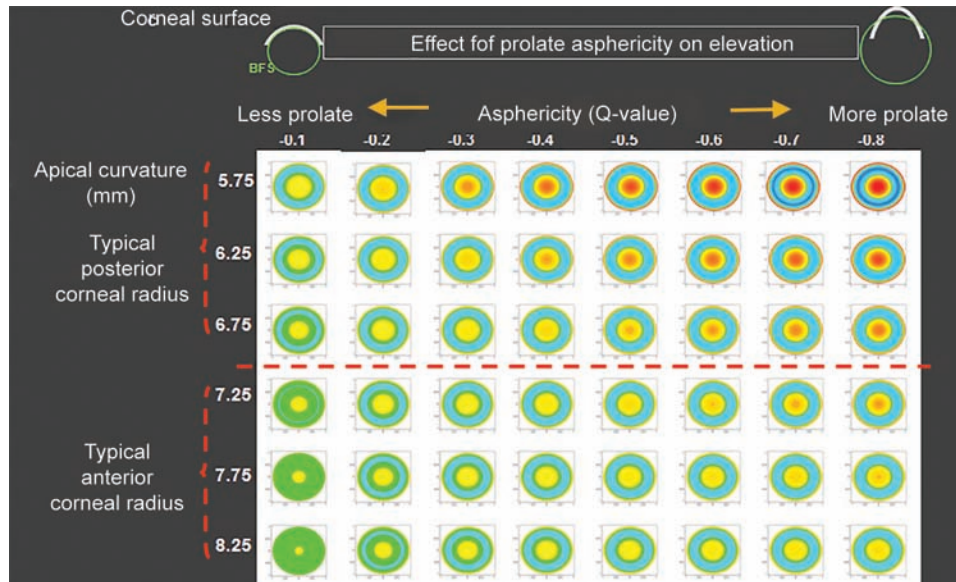


Fig. 7: This figure shows various theoretical corneal surfaces, which were modeled as aspheric surfaces of different elliptical profiles, all plotted in elevation against their BFS. The evolution of KC corresponds to an increase in corneal deformation characterized by apical steepening and an increase in negative asphericity (increased prolateness). For the same asphericity change, the steeper surface will have more central elevation against the BFS (and warmer colors on the elevation map). This is due to mathematical and scaling reasons. The keratoconic deformation does not start posteriorly in the cornea, but its concomitant effects on the anterior and posterior corneal surfaces elevation plots are not linear and more perceptible on the posterior map

more prevalent in certain ethnicities.^{11,12} It has also been reported that diabetes could be a protective factor against KC.⁹

Much of scientific evidence, however, is based upon a correlation of variables. It is therefore, necessary to point out that correlation does not necessarily mean causation. When two variables are found to be correlated, it is tempting to assume that this demonstrates that one variable causes the other. A similar fallacy would state that an event that followed another one was necessarily a consequence of the first event.

For instance, the well-established correlations between KC and atopy or Down syndrome may not mean that atopy or Down syndrome directly causes KC. A spurious relationship may explain both correlations, because in reality, eye rubbing may be the common and confounding variable. In the context of atopy, dry eye or Down syndrome, chronic eye rubbing may be the reason for increased risk for KC. In such a context, the correlation between chronic eye rubbing and KC corresponds to direct causative link, not just a statistical correlation.

The Case for Rubbing and Unilateral KC

Unilateral KC has been found to develop only in the eye that is subjected to frequent and abnormal (severe) episodes of rubbing trauma.¹³⁻¹⁶ These cases and others^{17,18} suggest the possibility that KC can develop in a normal

eye in response to a single etiological mechanism, such as eye rubbing-related trauma.

The Case for Rubbing and Contact Lenses

Patients with KC reported significantly more rubbing before and after wearing their contact lens as well as longer rubbing episodes compared with non-KC patients wearing contact lenses.¹⁹ During contact lenses wear, rubbing may induce lacrimal gland expression of more tears to relieve dry eye symptoms. Irritation, dryness, or itching after lens removal at the day's conclusion may trigger eye rubbing.

The Case from a Baropathic Perspective

That repeated and vigorous eye rubbing (primarily a mechanical force) may in fact be eventually causing the direct change in corneal shape (a permanent deformation) has the merit of being a straightforward concept.²⁰ Using an ophthalmodynamometer to applanate the inferior sclera through the lower lid, researchers have compared the effect of an elevation of intraocular pressure (IOP) to an average level of approximately double the baseline.²¹ An average response of 1.84 D of steepening in keratoconic subjects was observed when comparing corneal topography examinations before and after the pressure elevation. No significant topographic changes were observed for eyes with normal corneas. These findings suggest that keratoconic corneas are weakened and

unable to support the IOP, the effect of which causes the cornea to bend centrally and flatten peripherally. Hence, sharp elevations in IOP have the potential to contribute to progression of this condition and acute events, such as hydrops and perforation, may be dependent on acute IOP elevations.

Moreover, the IOP spikes occurring during regular rubbing episodes may not only aggravate but initiate corneal tissue weakening. The pressure exerted on the corneal wall during vigorous rubbing by patients with KC has been estimated to be 10 times more pronounced than in nonkeratoconic patients. It can reach 4 kg/cm^2 ,²² which is considerable; this in fact represents the internal pressure of a car tire!

Muller et al²⁴ showed that the tightly interwoven collagen fiber network in the anterior stroma is mainly responsible for the structural integrity of the cornea.²³ The interweaving appears maximal at the anterior surface and significantly reduces toward the posterior stroma.²⁴ Repeated shearing and torsional forces may induce the loosening of this network and reduce the shear modulus which measures the resistance of the corneal tissue to shearing strains. In addition, there may be additive complex effects related to chronic eye rubbing, as the corneal trauma may arise from a combination of possible mechanical effects: High hydrostatic tissue pressure, thixotropically reduced ground substance viscosity, temporary displacement of ground substance from the corneal apex, buckling and flexure of fibrils associated with waves of corneal indentation, and biomechanically coupled curvature transfer to the cone apex.

A mixture of these factors, like the displacement of ground substance from the corneal apex, may explain the central thinning which is not involved in typical warpage, but is instead a consistent finding in keratoconic corneas.

When a mechanical stress is removed from a viscoelastic material, there is an instantaneous recovery of the elastic deformation, followed by slow recovery of the viscous creep. One must realize that corneal tissue itself is viscoelastic: And all of the mechanisms evoked previously (all of which have been admirably detailed by the work of McMonnies²⁵) may therefore, alter the viscoelastic properties of the cornea. Abnormal rubbing with longer duration and/or greater force and/or greater frequency may induce permanent central buckling of the corneal tissue with compensatory peripheral flattening. Rubbing-related temperature spikes may also upregulate further collagenase activity and alter the ground substance viscosity.

These combined effects facilitate the bending response of the cornea to rubbing-mediated IOP distending stress via a reduction in its shear modulus²⁶ and the changes in extracellular matrix.²⁵

To better understand the genesis of KC deformation, Perone et al²⁷ created a laboratory model of a cornea that was subjected to various pressures and thermal and mechanical factors. The corneal anatomy was modeled as circular multilaminated patches of araldite (10 cm in diameter, 5 mm thick) and was subjected to pressure using compressed air. Three models were assessed: A fault-free model with no lesion and two models with a defect. The first of the defective models had an external crack-type lesion, whereas the second defective model had one quarter thinned down by 30 to 40% using abrasive sandpaper. For the healthy cornea, homogeneous modification was noted when examined under polarized light. There was no excessive deformation except for stress lines at the edge of the lesion for the first defective model. However, the second (thinned) model showed deformity under air compression, similar to keratoconic deformation. These findings suggest that the KC disease progresses under environmental stresses, especially when there is an initial thinning down defect. This thinning down defect may be induced by continual eye rubbing.

The Case from a Cellular Physiology Perspective

Repeated eye rubbing with great force over weeks or months may cause significant corneal tissue responses not limited to direct injury to the collagen fiber arrangement and extracellular matrix but also impacts the cellular composition of the corneal tissue. Cells of living organisms have a repertoire of strategies for dealing with mechanical stimuli. Several are relevant to the eye and to the way ocular cells respond to their physical environment in health and disease. This mechanosensitivity is relevant to the eye with respect to axial myopia and the pressure-related disease of glaucoma. When subjected to mechanical forces, such as compression, extension, torsion, and shearing, human cells can be damaged and become necrotic or apoptotic.²⁸ In addition, increased hydrostatic pressure caused by eye rubbing may increase the apoptotic rates for keratocytes. The subsequent reduced maintenance of collagen and ground substance may reduce further the biomechanical resistance of the cornea.

The Case from a Cellular Inflammation Perspective

Eye rubbing for 60 seconds has been demonstrated to increase the level of tear film matrix metalloproteinase-13, interleukin-6, and tumor necrosis factor- α in normal study subjects.²⁹ The increase in protease release, protease activity, and inflammatory mediator formation after eye rubbing may be exacerbated even further during the

persistent and forceful eye rubbing seen in people with KC. Sustained elevated levels of inflammatory mediators in the tears due to repeated rubbing episodes may be significant in KC development and progression.³⁰

It has been shown in both animal and human models that there exists a rubbing-related mechanical epithelial trauma which triggers the release of inflammatory mediators and a wound-healing response in keratocytes. Slight rubbing for 10 seconds using one finger and in a smooth circular movement repeated 30 times over a 30-minute period was shown to significantly reduce the keratocyte density in human corneas, and also leads to a greater concentration of inflammatory mediators in the tears.³¹ Rubbing-related epithelial thinning may include cell flattening, as well as displacement from the rubbed area of some cells, extracellular fluid, mucin, and cytoplasm from any burst cells. After an experimental fifteen seconds of rubbing in a circular pattern with use of light-to-moderate force and the finger pad of an index finger, the epithelial thickness of normal human corneas was found to be reduced by 18.4%, both centrally and midperipherally.³² Recovery to baseline thickness took 15 to 30 minutes centrally and 30 to 45 minutes midperipherally.

Patients with atopic dermatitis and mild blepharoconjunctivitis without any keratopathy may have an impaired ocular surface epithelial barrier.³³ This may facilitate cellular infiltration from tears or other corneal inflammatory processes.³⁴ Since eye rubbing can induce inflammatory events,^{28,35} any disease or wound-healing process with an inflammatory component has the potential to be exacerbated by rubbing trauma.

The Case from a Structural Microscopy Perspective

Cumulative tissue changes caused by repetitious rubbing episodes may also help link chronic rubbing-related trauma to cone formation. Cone deformation commences most often in the paracentral inferonasal cornea, which corresponds to the location where the most senile epithelial cells may be more vulnerable to mechanical forces.³⁶ The fine reticular scars of Bowman's membrane tears preceded by visible dehiscences is a classic characteristic feature of KC and are at this level.³⁷ These dehiscences followed by scarring may represent evidence of rubbing-related ruptures of Bowman's layer.

These mechanisms eloquently suggest that even in the absence of any primary ocular disease, KC can be self-induced as a manifestation of compulsive rubbing behavior. This makes pathological eye rubbing highly likely as the foundation on which to explain the pathophysiology of KC.

Can the Cornea deform without Repeated Focal Trauma?

The obligation of repeated local corneal mechanical trauma inducing a permanent corneal deformation is the core of the "no rub, no cone" conjecture. In order to refute this, it would suffice to demonstrate that corneal deformation could occur without any external force, through the reduction of corneal resistance secondary to a molecular alteration of its collagen fibrils.

There is a common assumption that alterations in corneal collagen make the cornea thin and less resistant to the gradient of pressure between the anterior chamber and the atmosphere. An unknown stromal collagen degeneration may indeed make the cornea less resistant, but the mechanisms by which the corneal deformation could occur progressively remain unclear. Although there is no identified genetic mutation nor clear biochemical cascade leading to such change in the corneal shape, would such corneal tissue "softening" due to a hypothetically altered molecular constitution lead to the evolution of KC, without the exertion of any other force against the cornea than that mediated by the difference between intraocular and atmospheric pressure?

The Case Study with Marfan Syndrome

Marfan syndrome, a disorder with an identifiable genetic mutation of the fibrillin-1 molecule, represents a perfect counterexample to explain the inconsistency of such theories on the pathogenesis of KC.³⁸ Keratoconus, like Marfan syndrome, is believed to result from abnormal collagen synthesis in association with genetic and cellular factors. However, unlike Marfan syndrome, this belief is but a theory, as no specific genetic mutation or biomolecular changes have been identified. If the classic genetic and biomolecular theories of KC genesis hold true, Marfan syndrome would be the archetype of a "softening and bulging phenomenon" involving the blood vessels and organs of the human body including the cornea. However, despite the reduction of collagen strength in the corneal stroma, no keratoconic pattern is found in the eyes of Marfan syndrome patients. Although these corneas are thinner, they actually tend to be flatter rather than steeper.³⁹

There is no paradox here: Because the force from the IOP is evenly distributed against the posterior surface of the cornea and the inner surface of the sclera, a softer eyeball will undergo a progressive distension of its shell, which causes the local corneal radii of curvature to increase (and the corneal curvature to decrease), with concomitant progressive thinning.

Hence, in the absence of a localized or focal additional force or trauma as in Marfan syndrome, the biomechanical

weakening of Marfan corneas results in a flatter corneal surface. This distension of the eyeball also contributes to its increase in axial length, and most Marfan patients indeed suffer from axial myopia. Abnormally flat corneas and axial myopia both give rise to the ocular diagnostic criteria for Marfan syndrome. This description better corresponds to what should be truly called an ectatic cornea (Fig. 8), since, as for the ectatic aorta, the progressive homogenous stretching and expansion of such a structure lead to an increase in its respective radius of curvature (meaning that the curvature logically decreases).

In Marfan syndrome, morphologic abnormalities resulting from fibrillin-1 mutations can produce the displacement of the crystalline lens but fails to produce any corneal changes other than flattening and thinning. This may sound counterintuitive to most ophthalmologists who would assume that the thinning and excessive weakening of the corneal stroma must result in a central steepening. In fact, the medical community has wrongly assumed that a softer cornea must bend and bulge (steepen). In Marfan corneas, the exact opposite happens: While it undertakes the effect of the IOP at its posterior surface, the softer cornea tends to gradually stretch and distend (flattens). This strongly suggests that, without an additional factor, altered biomechanics from collagen abnormalities alone are insufficient to account for the focal steepening and weakening seen in KC. Hence, the "no rub, no cone" conjecture is not contradicted.

On the contrary, it may be logically hypothesized that patients with Marfan syndrome or any other related connective tissue disease would be more prone to develop KC if they rub their eyes too frequently and vigorously, given the inherent structural weakness of the corneal wall.

The Case Study with Brillouin Optical Microscopy

The Brillouin optical microscopy is a technology that has been proposed to measure, *in vivo*, corneal biomechanics through the analysis of light scatter.^{40,41} In the case of KC, recent studies have demonstrated that the alteration of the corneal curvature and biomechanics are not evenly distributed throughout the corneal wall but are instead concentrated within the corneal apical area. Working with donor corneas, researchers demonstrated using Brillouin measurements that biomechanical alterations in the keratoconic corneas were primarily concentrated within the area of the cone. Outside the cone, the biomechanical properties evaluated with Brillouin measurements were comparable to that in normal corneas!⁴² This focal aspect does not favor the hypothesis of an unknown collagen dystrophy which would affect the stroma globally. Conversely, chronic eye rubbing (which is exerted in the vicinity of the corneal apex where the cascade of tissue changes described previously would predominate) is compatible with the focal nature of damage to the corneal stroma.

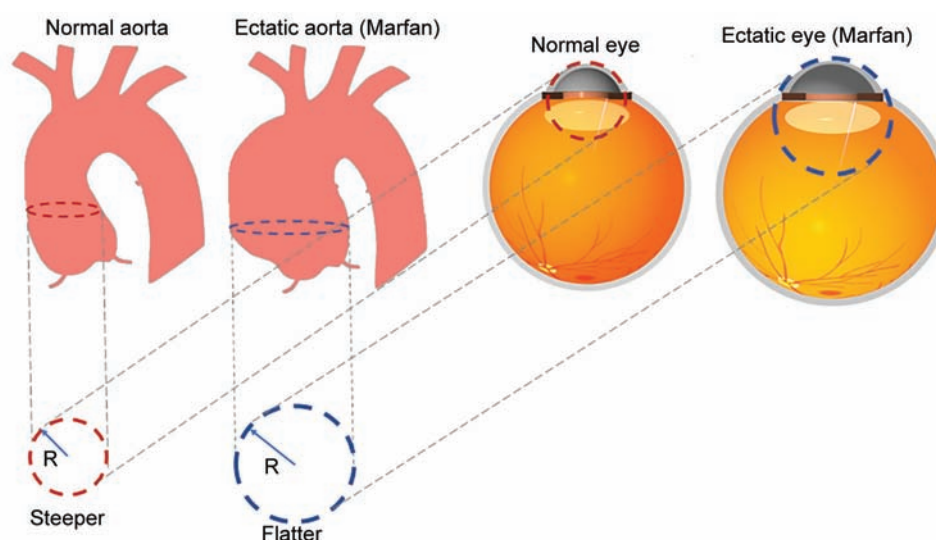


Fig. 8: The dilation of the ascending aorta in Marfan syndrome is characterized by fragmentation and loss of elastic and smooth muscle fibers in the vessel wall. When the aorta dilates, the radius of curvature of its wall increases, which means that its curvature decreases. This is consistent with the mechanisms involved at the ocular level. The progressive distension of the eyeball affects the sclera (myopic shift) and the cornea, which thins and flattens progressively. This comparison raises questions about defining KC as ectatic because truly ectatic corneas are thin and flat. In KC, the cornea is thin but steep, and this thinning and steepening is focal rather than global. The molecular mechanisms and the signaling pathways which would seemingly only select part of the corneal shell to thin and deform specifically and "spontaneously" under the sole influence IOP forces have never been defined. Rather, the influence of an external mechanical force like eye rubbing is better at accounting for these characteristics seen in keratoconic corneas

REEXAMINING THE “GENETICS” OF KC

Some familial cases and genetics research are still in favor of a genetic dimension to KC but as yet, no genetic mutations have been identified for any of the identified KC chromosome loci. Certain genes, such as VSX1, DOCK9, or TGFB1 may have a role in the disease.⁴³ Although a long list of genes has been reported to be associated with KC, the evidence for their pathogenic role remains limited. So far, the pattern of inheritance is estimated to be less than 20%. Discordance for KC in two pairs of monozygotic twins has been reported⁴⁴ which supports a pathogenetic role for environmental influences, such as eye rubbing. Concordance for KC has also been reported between monozygotic twins.⁴⁵ This concordance may also be due to being in similar environments and confounding variables, such as atopy leading to ocular itch and eye rubbing. Neither pathogenic mutations nor chromosomal deletions/duplications have been found to provide a complete explanation for isolated (sporadic) cases of keratoconic patients.⁴⁶ In essence, it is difficult to explain solely with genetics the inter-eye variability in the stage of KC and the different ages of onset. One must then ask—could eye rubbing be the necessary non-genetic variant or epigenetic factor to explain the disease etiology?

As alluded to above, genetic components could actually be related to the predisposition of conditions that lead to increased eye rubbing and to variations in corneal thickness and resistance, such as Down syndrome, Tourette syndrome, atopy, sleep apnea, sleep disorders, and pregnancy. A cornea that is genetically weaker or constitutionally thinner may be more vulnerable to any rubbing trauma as previously discussed. The central corneal thickness is one of the most highly heritable human traits. Ethnic-related differences in central corneal thickness may partly account for the increased prevalence of KC in some ethnicities.⁴⁷ Among the identified 16 new loci associated with central corneal thickness, two were found to confer relatively large risk for KC.⁴⁸ For the same rubbing pattern, thinner corneas may be at greater risk for KC.

Despite intensive research, no specific gene has been discovered and it is highly probable that none will ever be. Rather, efforts conducted in studying molecular genetics to identify people with native thinner or weaker corneas and who are prone to immune system disorders leading to allergy or atopy should be encouraged.

An analogy with sunburn may be a useful tool to better pinpoint the role played by eye rubbing in the genesis of keratoconus. Just as not all sunbathers will get a sunburn despite spending the same number of hours at the beach, not all eye rubbers would develop keratoconus.

For any one condition, risk factors predict the odds for developing that condition. In the case of keratoconus, these risk factors are akin to having a particular “keratotype”, which include corneal thickness and resistance determined by heterogeneous genetically inherited traits, and susceptibility of the immune system to develop allergies (which incite eye rubbing).

Just as sunburn would not occur in an individual even if they had various risk factors and phototypes predisposing them to a sunburn as long as their skin is adequately protected from ultraviolet light, no keratoconus would occur in an allergic patient with thin and soft corneas as long as they do not rub their eyes.

THE ROLE OF ACQUIRED RISK FACTORS FOR EYE RUBBING AND KC

Over the last few decades, acquired risk factors for eye rubbing and corneal weakening have come to the fore.

Allergy and atopy may be the most commonly addressed provocative factors for abnormal eye rubbing.⁴⁹ Many epidemiological surveys among which repeated cross-sectional surveys have most validity have demonstrated a twofold increase in the prevalence of allergy and asthma during the past two decades.^{50,51} Among allergens, house-dust mites have been advocated to be responsible for the increasing trend in the prevalence of allergic diseases.⁵² In a sample of 82 consecutive cases of vernal keratoconjunctivitis which is characterized by intense itching, computer-assisted videokeratographic maps indicated that 27% of eyes showed at least early signs of KC.⁵³

While air pollutants from industrial sources have been drastically reduced in the last decades, air pollutants from vehicle exhausts (nitrogen dioxide, diesel exhaust particulates, ozone) show an increase in concentration in some urban areas. Experiments have shown a synergy between air pollutants and allergens.⁵⁴ The risk of developing a sensitization to an allergen is boosted when the exposure to air pollutants has been performed prior to the exposure to the allergen.

The tremendous increase in computer usage has led to the development of computer vision syndrome in many individuals. Episodes of rubbing during extended computer use are frequently admitted by patients once properly informed about it. Ocular fatigue and eye strain are the main components of computer vision syndrome, and may elicit pathological eye rubbing.⁵⁵ Associated evaporative dry eye from reduced blink frequency can also elicit eye rubbing and account in part for the recent increase in the prevalence of KC in the young population.

Contact lens wearers often disclose that they periodically rub their eyes after contact lens removal. Eye rubbing after contact lens removal (“removal-relief” rubbing) was

found to be significantly more prevalent among contact lens-wearing keratoconic patients compared with contact lens-wearing nonkeratoconic patients.¹⁹

Post-LASIK ectasia may be the consequence of the stromal flap cut and laser photoablation on corneas already weakened by chronic eye rubbing. The LASIK-induced dry eye exacerbation may encourage rubbing behavior which dramatically increases the risk of corneal ectasia. It is therefore logical that eye rubbing avoidance may reduce the incidence of post-refractive corneal ectasia.

The recent increase in prevalence of these acquired risk factors for eye rubbing may account for the increase in the prevalence and annual incidence of KC.⁵⁶

FORME FRUSTE KC (FFKC)—FORME FRUSTE RUBBING—THE MISSING LINK?

In the surgical field, the identification of subclinical KC is a primary concern when screening patients for refractive surgery because performing LASIK on undiagnosed KC has been identified as the leading cause of ectasia after refractive surgery. Several terms have also been used to describe this condition, including subclinical KC, KC suspect, and FFKC. These diagnostic subtleties are always, however, very dependent on arbitrary thresholds and definitions. It is quite difficult to draw a line between what is "normal" and what is "abnormal" within corneal topography maps. Some practitioners or automated diagnostic algorithms restrict their interpretation to the anterior surface of the cornea, while others consider the posterior surface and variations of the corneal thickness in their analysis. Algorithms and thresholds may vary between topographic instruments of various manufacturers. Hence, there may be discrepancies in subjective and objective analysis of the same cornea when analyzed by different instruments and/or interpreted by automated diagnostic algorithms or physicians.

Beyond any semantic debate, what these entities have in common in terms of topography is that they share the subtle features of corneas which we diagnose as having KC. In the light of the conjecture, they would correspond to the missing links between corneas that are strictly normal (never or rarely rubbed), and corneas that are very distorted (by repeated and pathological rubbing) which correspond to established KC.

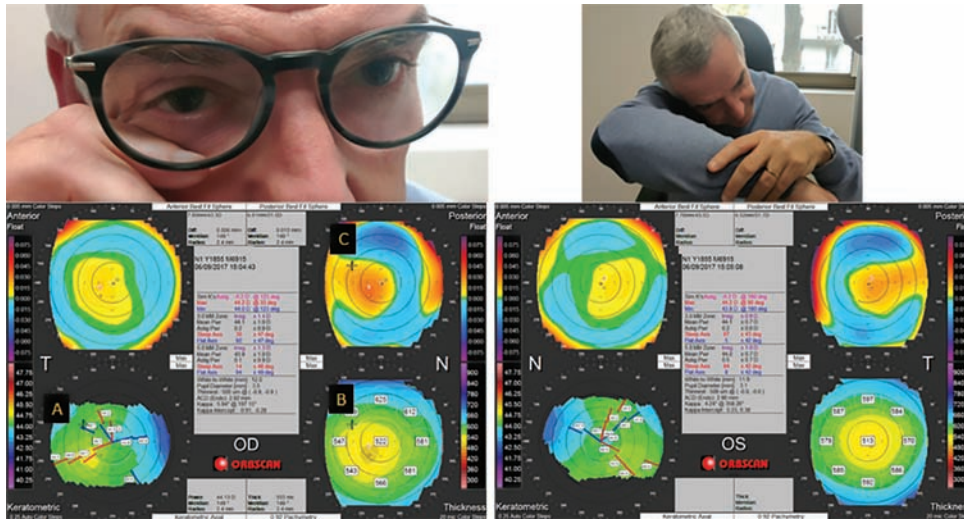
In our practice, there is indeed a remarkable clinical parallelism between these slightly deformed corneas which cause diagnostic problems where the practice of eye rubbing is not very intense or less frequent. For example, some women remove their eye make-up every night and rub their eyes vigorously on this occasion. This habit may cause moderate corneal deformations which

cause the apparition of topographic patterns, such as an isolated inferior steepening. Due to the risk of smearing eye cosmetics, these women tend to avoid rubbing their eyes during the day, which prevents the corneal deformation from becoming more severe more rapidly. They use their finger pulps to rub and soft pads to remove eye make-up, which may not be as detrimental as the effect of the pressure exerted by the knuckles on the corneal dome. In contrast, men are more likely to develop frank KC.

There is a continuous spectrum of topographic features from corneas judged "very normal" to corneas that are obviously showing topographic abnormalities. While this variability in the amount of corneal deformation (between patients and between eyes of the same patient) may be difficult to explain if KC would be an acquired or genetically inherited disease, our experience reveals that the variable techniques of eye rubbing (in type, duration, intensity, and frequency) may explain this broad topographic spectrum. In light of this, the following hypothesis on FFKC could be proposed: That FFKC is the consequence of "forme fruste rubbing": A less pronounced form of KC due to less frequent and less pronounced eye rubbing (Fig. 9). The large variations in rubbing intensity, frequency, and duration among patients and their effects on corneas of variable native resistance may be reflected in the broad topographic spectrum of warpage and thinning; from minor topographic abnormalities to advanced KC, encompassing all shades of subclinical KC in between.

The displacement of the thinnest corneal area may occur early in the pathologic process. In a previous study,⁵⁷ we showed that the thinnest corneal thickness position and the vertical decentration of the thinnest corneal thickness was statistically different between normal corneas and FFKC (the FFKC group was composed of corneas appearing normal based on a specular artificial intelligence system, while the fellow eye had frank KC). However, we also found in another study that there was no inter-eye difference regarding either the thinnest corneal thickness position or the vertical decentration of the thinnest corneal thickness between keratoconic eyes of various stages.⁵⁸

These findings support the hypothesis that thinnest corneal thickness decentration occurs early in the keratoconic pathologic process. The downward displacement of the thinnest point may be caused by two synergistic mechanisms. The first may be the consequence of upward and outward movement of the eye when the eyes close (this palpebral oculogyric reflex corresponds to Bell's phenomenon which is thought to be a defensive phenomenon).⁵⁹ This may preferentially expose the inferior part of the cornea to the rubbing forces, which are exerted on closed eyes. The displacement of ground substance



Figs 9A to C: This 55-year-old patient was referred for refractive surgery evaluation (correction of hyperopia). Minor topographic abnormalities are seen on the right eye: a slight inferotemporal steepening (A), and a paracentral inferior thinning (B). The posterior surface prolateness is increased (C). The left eye topography is unremarkable. The topographic features in the right eye are commonly found in FFKC. When asked about possible chronic rubbing habits, the patient admits that he rubs his right eye often during the day, because this eye feels irritated and watery. When questioned about his sleeping habits, the patient declares that he constantly sleeps on the stomach with the head rotated to the left, causing the right orbit to be compressed on the right forearm. In our experience, there is a striking correlation between the side on which patients sleep, and the side where the most pronounced topographic abnormalities are evident. Compression, heating, and local contamination may all contribute to ocular irritation at night, leading to itching sensations during the day. The itch in turn triggers repeated eye rubbing leading to various levels of deformation depending on native corneal properties and the duration, frequency, type, and intensity of eye rubbing

may be maximal near but inferior to the corneal apex. The second mechanism may be related to the downward direction of the gravity force: One may also hypothesize that this force may induce some asymmetry in the flexure of the weakened corneal wall, which would also incur a more inferiorly pronounced steepening. Even without any spatial redistribution of the corneal thickness, this would cause an apparent slight inferior displacement of the thinnest point from its initial location due to the vertical “sag” of the corneal dome.

EYE RUBBING IS THE ROOT CAUSE OF KC

Bringing all of these elements together, a new model to explain KC formation emerges. Based on these findings, eye rubbing is detrimental to corneal biomechanical stability through two main pathways, which are synergistic as both reduce corneal resistance (Fig. 10). The first pathway outlines the mechanical impact of rubbing on tissue structures, such as collagen fibrils. Rubbing-related buckling and flexure of these fibrils may facilitate cone formation, associated with fibrillar slippage in the cone region. The second pathway corresponds to the impact of eye rubbing on cellular structures, which may undergo changes and apoptosis, further compromising corneal structural properties.

DOES A KERATOCONIC EYE ALWAYS HAVE A RUBBING HISTORY?

Finding a counter-example to the conjecture would suffice to invalidate it. Conversely, for this theory to be valid, it should be demonstrated that every patient presenting with KC has a history of chronic eye rubbing. Although such a systematic approach may be difficult to establish, our experience at the Rothschild Foundation is amazingly conclusive.

While most patients disclose a rubbing history (often associated with a chronic ocular allergy history) on their first visit, some patients are not conscious of their rubbing habit and when first interviewed will reply in the negative to the question, “Are you rubbing your eyes frequently?” (Fig. 11). If asked too bluntly, this question may sometime destabilize the patient–doctor relationship and elicit some falsely negative answers. Some patients may mistakenly believe that their physician is trying to blame the visual problems on the patient, and be reluctant to disclose their rubbing habit. The patient’s denial of a history of rubbing could also be based on guilty feelings about potentially inflicting injury to oneself. Undisclosed rubbing may occur during sleep or without awareness. The presence of close relatives accompanying the patient offers the possibility to confirm or confront the patient’s



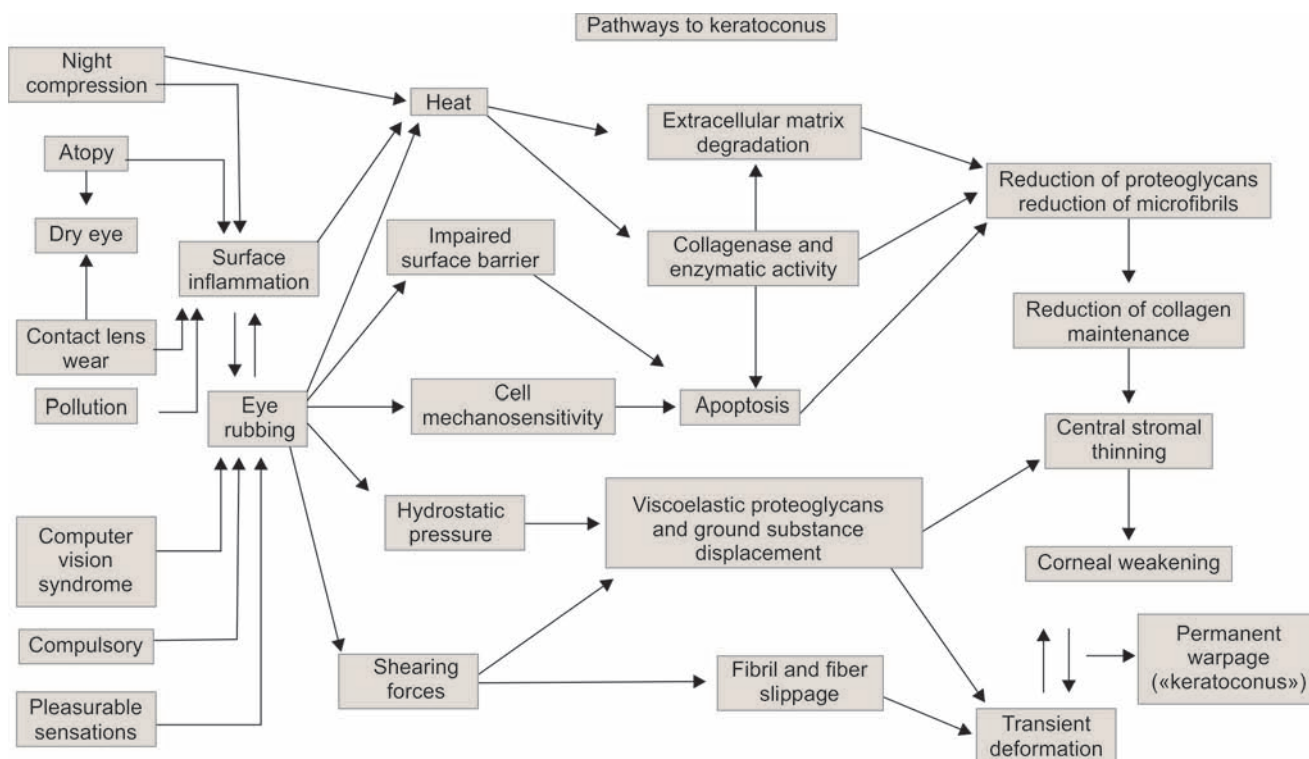


Fig. 10: Eye rubbing is a central and obligatory habit that induces the permanent warpage of the cornea referred to "KC." Without eye rubbing, the absence of increased hydrostatic pressure and shearing forces will not result in significant corneal deformation (no KC), since the case of Marfan syndrome teaches that weaker corneas do not become steeper and irregular. Interestingly, inflammatory processes in the cornea usually result in localized topographic flattening. The imbalance caused by the reduced corneal resistance and abnormal rubbing eventually causes a permanent warpage of the cornea

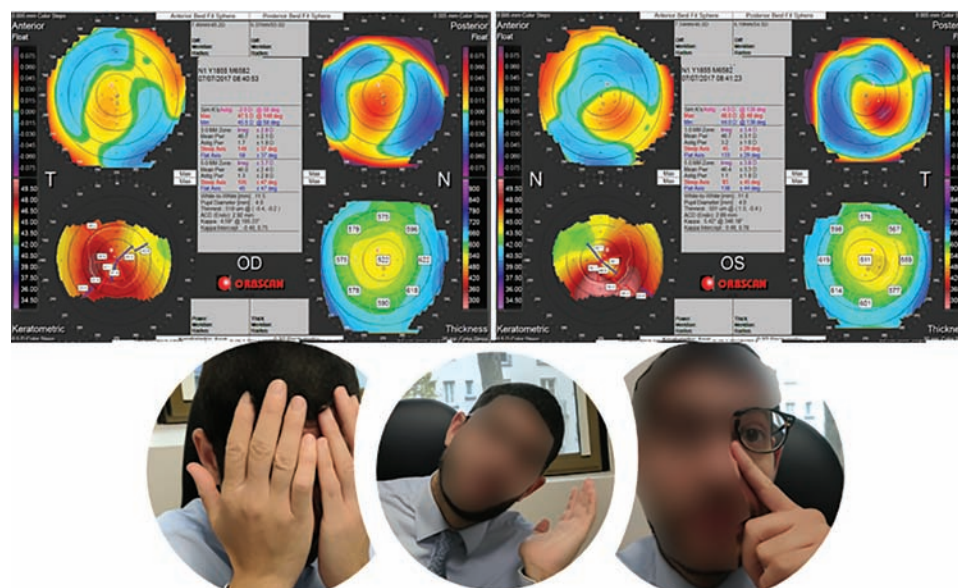


Fig. 11: *Top:* corneal topographies of the right (OD) and left (OS) of a 40-year-old myopic patient referred for refractive surgery preoperative evaluation. These maps, obtained with the Orbscan topograph, reveal the presence of a previously unknown bilateral KC pattern, slightly more pronounced on the left eye. During this first visit, the patient did not acknowledge any particular eye rubbing habit. We explained to this patient that eye rubbing could occur without self-awareness, and asked him to pay attention to possible unknown rubbing episodes in the coming days. *Bottom:* At his second visit, 1 month later, the patient admitted to realizing that that he rubbed his eyes many times a day, using his palms, the pulp of his index finger and knuckles. He spontaneously rubbed his left eye to demonstrate his rubbing technique. He also declared that he was always sleeping on the left side, with his head buried in the pillow. He attributed this rubbing habit to fatigue and long hours on the computer. His sleeping habit may also explain the preferential rubbing of the left eye

declaration. Frequently, parents often vehemently declare that they have witnessed their child rubbing their eyes repeatedly in the past.

In a pioneer study published in 1976, 40 out of 55 (72%) patients with KC closely questioned about eye rubbing gave a positive response.⁶⁰ This study reports that some of these denied any personal knowledge of eye rubbing but remembered mothers or others reprimanding them for it. The article also cites the example of a patient with eczema who denied eye rubbing or skin scratching, yet there were obvious scratch marks on facial eczematous lesions. A study of the prevalence of eye rubbing found that it was reported in 80% of patients with KC, and in 58% of control subjects, with the difference being significant ($p < 0.001$).⁶¹ Based on these numbers, it is not unreasonable to postulate that about 20 to 28% of patients with KC would not be aware, or would not voluntarily disclose a chronic rubbing habit at the first glance. This denial would account for the several studies indicating “no history of abnormal rubbing” for some patients with KC,⁶² leading to the possibly erroneous conclusion that the causal rubbing hypothesis may be appropriate for only some forms of KC.

SEARCHING FOR EYE RUBBING

Every patient evaluated for KC should receive information to increase their awareness of unconscious rubbing episodes, which typically occur during awakening, under the shower, during extensive computer work (or video game playing), after contact lens removal, and before falling asleep. Patients should be advised to refrain from any vigorous rubbing when this is understood. The propensity to chronic eye rubbing should be reevaluated at the second visit as patients who at first denied eye rubbing may not be aware that they were eye rubbers or may downplay their habit. Some movements exerted against the eyes are sometimes not considered as “eye rubbing” by the patients. For example, prolonged hand palm compression or circular movements are considered as relaxing massage techniques by some patients. These may, however, contribute to mechanical fatigue of the cornea due to repetitive shear stress.

THE IMPORTANCE OF THE SLEEPING HABIT

As others have observed,⁶³ we have noticed that patients are more susceptible to KC when sleeping on their stomach or on their side. Because of the constrained lateral head position, they typically exert an extended pressure against one or both orbits while they sleep. Some patients favor the right or the left side when they fall asleep. The strong correlation between the side which is

more compressed on the pillow/arm/hand at night and the side of the most advanced KC suggests that even the sleeping habit may play a significant role in the genesis of KC. In this context, asymmetrical eye rubbing may be again the confounding variable. The direct and prolonged contact of the eyelids against the linen may increase the contamination of the ocular surface by irritants and allergens, such as dust mites, contributing to increased local pruritus and subsequently increased eye rubbing of the involved eye. In my practice, the correlation between KC and such sleeping habits is striking and even superior to the correlation with the dominant hand which has been previously reported only in severe KC.⁶⁴

THE CONJECTURE IMPLIES THAT THE CESSATION OF EYE RUBBING SUFFICES TO HALT PROGRESSION

The fact that KC appears after the deliberate realization of repeated rubbing does not formally prove that some cases of the disease cannot occur without rubbing. Designing a prospective study including patients randomly assigned to rub (or not) their eyes for extended periods of time may be contraindicated for ethical reasons. However, if the conjecture is correct, then the cessation of eye rubbing must, at least in the early and moderate forms, stop the progression of KC. We have studied a large number of patients with KC monitored at our institution to evaluate the impact of eye rubbing on not only the disease genesis but also on its progression. So far, all the adult patients who completely stopped rubbing their eyes have stopped their KC progression. With an average follow-up of 2 years, the complete cessation of eye rubbing has resulted in stabilization of the corneal deformation. This is a very encouraging finding for patients with KC. Furthermore, in our studies, KC progression has only been observed in patients who admit to being unable to abandon their eye rubbing habit. This is strong indirect evidence that eye rubbing is the root cause of KC. We have made the documentation of each of these cases accessible through the following website: <https://defeatkeratoconus.com/>. For each of the presented cases, the results of the follow-up are presented and include the realization of consecutive topographic difference maps.

Hence, these observations, which are carefully collected and will be the subject of a dedicated publication, have a significant evidence-based function in assessing the causal hypothesis of eye rubbing being the root and therefore, necessary cause of KC.

CONCLUSION

In this article, I have presented many bodies of evidence which strongly support the conjecture that chronic eye

rubbing and its mechanical influence on corneal tissue appear to be the only necessary inciting event for the permanent corneal warpage clinically designated as "keratoconus."

Chronic eye rubbing elicits structural changes to the cornea via the forces applied against the corneal stroma, and triggers molecular cascades and cellular activation leading to a reduction of stromal resistance. The "no rub, no cone" conjecture suggests that KC is not an inherited stromal dystrophy and the corneal deformation is not ectatic but isometric and corresponds to a permanent corneal warpage induced by excessive eye rubbing.

Accepting this conjecture contradicts the widely accepted idea that this disease is rooted in hidden genetic mechanisms. However, this conjecture provides a better explanatory framework to the genesis and clinical presentation of KC. Marfan syndrome should perfectly support the theories that attempt to explain KC as an ectatic process; on the contrary, it represents a perfect counterexample to explain the irrelevance of current theories on the pathogenesis of KC. Without any other particular condition, there is ample evidence that pathological eye rubbing alone can induce permanent corneal deformation via various but synergistic mechanisms and can account for the focal nature of the biomechanical impairment of the keratoconic cornea. Eye rubbing is the common denominator of many conditions predisposing to KC; while some patients may be predisposed to KC via a constitutively thinner or softer cornea, it is important to realize that only when a repeated mechanical force is applied against the cornea will the latter undergo permanent focal deformation, leading to the classic presentation of KC.

That every patient presenting with KC has rubbed one (unilateral presentation) or both eyes seems a challenging assertion which is equally difficult to approve or refute. However, the accumulated body of evidence and the compelling clinical investigations speak vehemently to consider eye rubbing as a necessary ingredient in the "KC recipe."

In our experience, patients who cease to rub their eyes do not show any progression. The cessation of eye rubbing brings about the stabilization of the cornea: Beyond the offered clinical benefit, it is another strong argument in favor of the "no rub, no cone" conjecture. As I am not involved in the management of pediatric KC, my keratoconic patients are all of adult age 16 years and older. A recent meta-analysis has shown that pediatric KC is more aggressive than adult KC, with high documented rates of progression in pediatric populations.⁶⁵ In addition, the literature overwhelmingly shows higher rates of failure and progression of keratoconus following corneal collagen cross-linking,

intra-corneal ring segments and penetrating keratoplasties as compared to adults. While this could be explained by structural differences in the cornea between the two populations, the reduced compliance and the persistence of irrepressible eye rubbing in children could also account for the aggressiveness of pediatric KC. However, considering that eye rubbing is the indispensable trigger precipitating the cascade of events leading to permanent corneal warpage paves the pathway toward KC prevention in children and young adults.

This primarily mechanical theory unifies most of what is observed and is coherent with the results of recent clinical and experimental investigations; thus the "no rub, no cone" conjecture should be regarded as an important milestone in our understanding of the KC physiopathology.

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