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Topic

Early Detection of Keratoconus Through Astigmatism Monitoring

Defended on June 26, 2025, before the jury composed of:

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Dedication

We dedicate this work:

To our dear parents who have been our first teachers, our greatest supporters and our most constant source of love. Your endless sacrifices, your patience and your unwavering faith in us have guided us every step of the way. Without your encouragement and prayers, this work would not have been possible. This achievement is as much yours as it is ours.

To our beloved brothers and sisters who have shared our joys and challenges, always ready with a kind word, a helping hand or a smile that lifted our spirits. Your support has been a silent strength that has kept us going through difficult times.

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And without missing to thank ourselves for the dedication, perseverance, and teamwork that allowed us to complete this project successfully.

ABSTRACT

Introduction:

Astigmatism particularly when it progresses or changes axis, can be one of the earliest warning signs of developing keratoconus but only the monitoring of specific topographic indices allows for a reliable diagnostic confirmation.

Methods and Materials:

A retrospective-method study was conducted on 32 patients under the age of 25 in two ophthalmology clinics. The analysis included refraction and corneal imaging using Pentacam, with extraction of topographic indices to assess the accuracy of these parameters in detecting early keratoconus.

Results:

Myopic astigmatism was common and its progression was significant in keratoconic eyes. The topographic indices IVA, ISV, KI, IS, and IHA showed strong discriminative power (AUC > 0.83), with KI being the most effective. The CKI and IHD indices were less sensitive.

Conclusion:

Changes in astigmatism should raise suspicion of keratoconus but it is topographic indices that provide a reliable diagnostic confirmation. Integrating the monitoring of these indices into optometric practice enables earlier and more accurate screening.

Keywords:

Astigmatism, keratoconus, topographic indices, Pentacam, early detection, optometry.

RÉSUMÉ

Introduction :

L'astigmatisme notamment lorsqu'il évolue ou change d'axe, il peut être un des premiers signes d'alerte d'un kératocône débutant mais seul le suivi de certains indices topographiques permet une confirmation diagnostique fiable.

Méthodes et matériaux :

Une étude rétrospective a été menée sur 32 patients âgés de moins de 25 ans dans deux cliniques ophtalmologiques. L'analyse a inclus la réfraction, l'imagerie cornéenne Pentacam avec extraction d'indices topographiques, afin d'évaluer la précision de ces paramètres dans la détection du kératocône précoce.

Résultats :

L'astigmatisme myopique était fréquent et sa progression notable chez les yeux kératocôniques. Les indices topographiques IVA, ISV, KI, IS et IHA ont montré une forte capacité discriminative (AUC > 0,83), le KI étant le plus performant. Les indices CKI et IHD étaient moins sensibles.

Conclusion :

Les changements d'astigmatisme doivent alerter sur un risque de kératocône, mais ce sont les indices topographiques qui offrent une confirmation diagnostique fiable. L'intégration du suivi de ces indices dans la pratique optométrique permet un dépistage plus précoce et plus précis.

Mots-clés :

Astigmatisme, kératocône, indices topographiques, Pentacam, détection précoce, optométrie.

الملخّص

المقدمة

تعدّ اللابؤرية، خاصةً عند تطورها أو تغيّر محورها، من أولى العلامات المنذرة لاحتمال وجود قرنية مخروطية في مراحلها المبكرة إلا أن تأكيد التشخيص بشكل موثوق لا يتم إلا من خلال متابعة بعض المؤشرات الطوبوغرافية الخاصة

.

الطرق والمواد

اجريت دراسة استعادية على 32 مريضًا تقل أعمارهم عن 25 سنة في عيادتين لطب العيون. شملت التحاليل قياس الانكسار والتصوير الطوبوغرافي للقرنية باستخدام جهاز البنتاكام مع استخراج مؤشرات طوبوغرافية، وذلك لتقييم دقة هذه المؤشرات في الكشف المبكر عن القرنية المخروطية

النتائج

كانت اللابؤرية القصيرة شائعَة، وتبيّن أن تطورها ملحوظ في العيون المصابة بالقرنية المخروطية. أظهرت المؤشرات الطوبوغرافية IVA,IS,KI,ISV,I, قدرة تمييز عالية (AUC > 0,83) بينما كانت مؤشرات CKI,IHD اقل حساسية

الخاتمة

ينبغي أن يُثير تغيّر اللابؤرية الشك بوجود قرنية مخروطية، إلا أن المؤشرات الطوبوغرافية هي التي تقدم تأكيدًا تشخيصيًا موثوقًا. إن دمج مراقبة هذه المؤشرات ضمن الممارسة البصرية يسمح بالكشف المبكر والدقيق عن المرض.

الكلمات المفتاحية

اللابؤرية ،القرنية المخروطية، المؤشرات الطوبوغرافية، بنتاكام، الكشف المبكر، البصريات

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Abbreviations

A/

AS : Astigmatism

AB : Asymmetry Bowtie

AI : Artificial Intelligence

ATR : Against the rule astigmatism

ARC : Anterior Radius of Curvature

ACS : Anterior Corneal Surface

AUC : Area Under The Curve

Antk : Anterior Keratometry

ANNs : Artificial Neural Networks

AS-OCT : Anterior-Segment Optical Coherence Tomography

B/

BCS : Brittle Cornea Syndrome

BFS : Best Fit Sphere

BFTE : Best Fit Toric Ellipsoid

BOSS : Brillouin Optical Scanner System

BLS : Brillouin Light Scattering

BCVA : Best corrected visual Acuity

C/

CT : Corneal Topography

CL : Contact Lens

CH : Corneal Hysteresis

CI: Confidence Interval

CCT : Central Corneal Thickness

CRF : Corneal Resistance Factor

CXL : Cross Linking

CBI : Corvis Biomechanical Index

CKI : Center Keratoconus Index

CDVA : Corrected Distance Visual Acuity

CODES : Colombian Ocular Diseases Epidemiology study

D/

D : Diopter

DZ : Dizygotic

DS : Down Syndrome

DM: Diabetes Mellitus

DED : Dry Eye Disease

DALK: Deep Anterior Keratoplasty

E/

EDS : Ehlers Danos Syndrom

ECM : Extracellelure Matrix

F/

FM : Fine Mapping

FFKC : Forme Fruste Keratoconus

G/

GWLS : Genome-Wide Linking Study

GWAS : Genome-Wide Association Study

I/

IS: Inferior Steep

I-S: Inferior-Superior Index

ISV: Index of Surface Variance

IVA: Index of Vertical Asymmetry

IHA: Index of Height Asymmetry

IHD: Index of Height Decentration

IOLs : Intra Ocular Lenses

ICLs:

ICRS: Intrastromal Corneal Ring Segment

K/

KC : Keratoconus

Kmax : Maximum Keratometry

KSS : Keratoconus Severity Score

KPI : Keratoconus Prediction Index

KSI : Keratoconus Severity Index

KC AL : Keratoconus Allergic

KC NAL: Keratoconus Non Allergic

L/

LD: Linkage Disequilibrium

LCA : Leber's Congenital Amaurosis

LEDs : Light-Emitting Diodes

LASER : Light Amplification by Stimulated Emission of Radiation

LASEK : Laser-Assisted Subepithelial Keratectomy

LASIK : Laser_Assisted In Situ keratomileusis

M/

MZ : Monozygotic

MA : Meta-Analysis

MRSE : Manifeste Refraction Spherical Equivalent

MMPs: Matrix Metalloproteinases

N/

NCN : Nidek corneal Navigator

O/

OR: Odd Ratio

OZ : Optical Zone

OCT : Optical Coherence Tomography

ORA : Ocular Response Analyzer

P/

PK : Penetrating Keratoplasty

PKR : Photorefractive keratoctomy

PMD : Pellucid Marginal Degeneration

PLK : Pellucid Like Keratoconus

PRC : Posterior Radius of Curvature

PIOLs : phakic Intraocular Lenses

P-value : Probability value

PMMA : Polymethyl Methacrylate

R/

ROS : Reactive Oxygen

ROC : Receiver Operating Characteristic

RMS : Root Mean Square

RGP : Rigid Gas-Permeable Lens

S/

S : Sequencing

SS : Superior steep

SB : Symmetric Bowtie

SCK : Subclinical Keratoconus

SAI : Surface Asymmetry Index

SRI : Surface Regularity Index

SNPs : Single Nucleotide Polymorphism

SRAX : Skewed Radial Axis

SMILE : Incision Lenticule Extraction

T/

TG : Targeted Genotyping

TP : Thinnest Point

TGD : Theroid Dysfunction Subclinical Keratoconus

U/

UV : Ultra-Violet

US : United State

USA : United State of America

UDVA : Uncorrected Distance Visual Acuity

UCVA : Uncorrected Visual Acuity

V/

VIPA: Virtually Imaged Phased Array

W/

WTR : With The Rule Astigmatism

INTRODUCTION

Visual health is a vital component of overall well-being and early detection of ocular pathologies plays a role in preventing long-term visual impairment. Among the most common ametropia astigmatism affects a large segment of the population. While it is often benign and easily corrected, astigmatism can, in certain cases serve as an early clinical indicator of progressive corneal disease known as keratoconus.

Keratoconus (KC) is a non-inflammatory ectatic disorder of the cornea characterized by progressive thinning, protrusion, and distortion, leading to irregular astigmatism and visual deterioration. The disease often begins with the early stages presenting minimal symptoms and escaping detection during routine eye exams. However delayed diagnosis can cause permanent damage affecting both vision and the success of surgeries like refractive surgery.

In recent years, advances in corneal imaging including topography and tomography have improved our ability to detect early biomechanical and morphological changes in the cornea. Despite this progress, there remains a significant gap in clinical practice particularly in optometric settings regarding the standardized assessment of patients at risk. Monitoring the evolution of astigmatism particularly changes in axis orientation or power may provide meaningful observations for detecting early signs of keratoconus.

This thesis aims to investigate the role of astigmatism monitoring as a potential tool for the early detection of keratoconus specifically it evaluates the correlation between changes in refractive parameters and topographic indices across preliminary stages of the disease. Through retrospective analyses this study is designed to enable eye care professionals to suspect and manage early forms of this condition.

The structure of this work is divided into two main parts. The first is theoretical section consists of three chapters: the first addresses astigmatism, the second focuses on keratoconus and the third explores the concept of early detection, including clinical signs, topographic criteria, and indices for diagnosis. The second part presents the practical component in which clinical data is analyzed to assess the relationship between astigmatism evolution and early keratoconus.

Chapter 01: Astigmatism

Introduction

Eye health is an essential indicator of an individual’s overall health. Astigmatism is one of the most prevalent vision problems that a lot of people may not realize they have it, this refractive error can affect the clarity of vision, the lifestyle and the way of living if left uncorrected.

Therefore, the specialists in the vision health focused on understanding the mechanism of astigmatism, the causes, symptoms, diagnosis and treatments options of it.

Definition

Astigmatism, a refractive error (ametropia) caused by parallel rays of light entering the non accommoding eye not focusing on the retina, is derived from the Greek words "a" (absence) and "stigma" (point); When incident light rays fail to converge at a single focal point, astigmatism results. Because of its consistent curvature, the cornea of a healthy eye has an equal refracting power across its whole surface. In astigmatism, the cornea is not uniform, and one meridian (plane) has a larger curvature than another, like a football and a rugby ball.

Retinal images from both close and far objects are blurred and may appear extended or widened because light rays refracted by this cornea are not brought to a single point focus. Astigmatism is the term for this refractive defect.

There are two types of astigmatism, corneal (or keratometric) and lenticular. The majority of astigmatism originates in the cornea. Uneven curvature and varying refractive indices inside the crystalline lens cause lenticular astigmatism.

It is widely acknowledged that internal astigmatism and corneal astigmatism are somewhat related.

When any one of the human eye's refracting surfaces takes on a toric shape, astigmatism develops. Astigmatism is referred to as "regular astigmatism" when the two meridians are at a 90° “right angle”. In cases when these meridians are not perpendicular, "irregular astigmatism" occurs (1) .

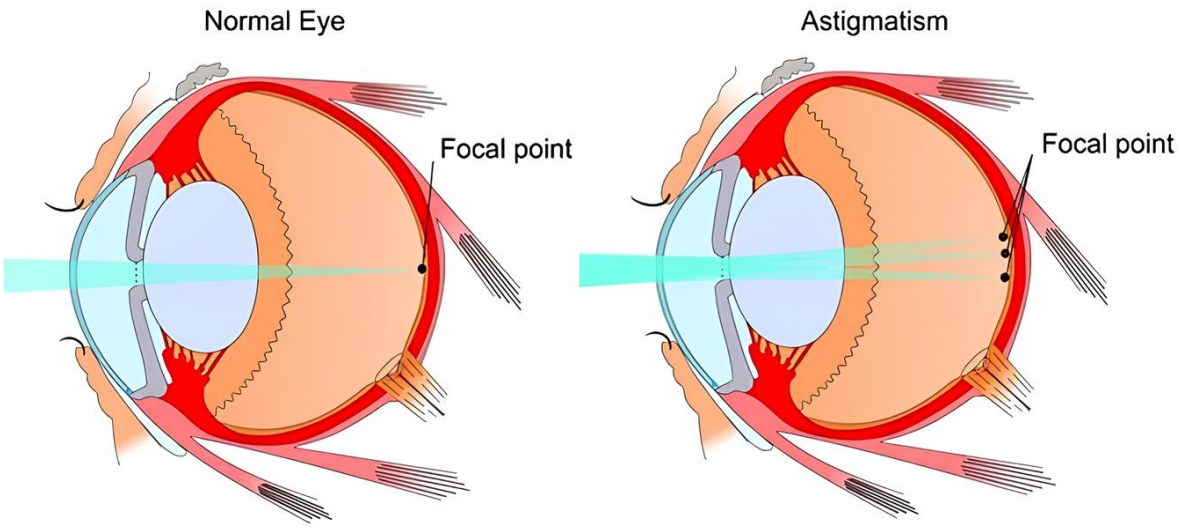


Figure 1 : Schematic of Astigmatic eye (2).

1. Epidemiology of astigmatism

Astigmatism is clinically significant due to its related symptoms including asthenopia (eye strain), hazy vision at different viewing distances, also spatial distortion of objects. It alerts emmetropization and linked to another eye problems such as myopia. therefore; understanding the distribution of astigmatism around the world will inform clinical treatment research, epidemiology in records and resource allocation (3).

1.1 Global prevalence:

- The astigmatism (more than 0.5 D) prevalence rates can range from 30% to more; depending the age or ethnic group. It accounts for 13% of the refractive errors of the human eye (1).
- Studies have found that the prevalence differs racially. it reaching 13.7% in black people, 49% in Asian people, 33.3% in Caucasian people (3).
- Other studies showing how common astigmatism is in the general population throughout different countries and regions. The reported prevalence was as follows (4):

Table 1 : The prevalence of astigmatism in general population (4).

Countries	South Korea	Germany	Spain	Japan	USA	Northern and western Europe	China
Prevalence %	31_58%	32%	54%	54%	46%	27%	8_62%

1.2 Age / Gender _Patterns:

1.2.1 Age:

Newborn and young children

Several studies have reported a high prevalence and notable degree of astigmatism (AS >1 D) in infants and young children (5); the prevalence changes from country to another (1).

Table 2 : The prevalence of astigmatism >1 D in young children around the world.

Countries	Native American	USA	Canada	Hong Kong	Sydney	Taiwan	Australia
Prevalence %	44%	28.4%	22%	21.1%	4.8%	11.4%	5%

In addition, the prevalent axis of astigmatism is still up for debate.one study found that **with_the_rule** astigmatism is more prevalent, while other study observed a preponderance of **against_the_rule.** these contradictory may stem from the difficulties of taking precise measurement in infants due to the variations in corneal shape during early childhood, but alongside emmetropization, the prevalence of high astigmatism declines with age (5).

School Aged children:

Studies (from 2000 to 2021) found that the prevalence of astigmatism (more than 0.5 D) in the age of 5_17 years old changes around the world (6); Its prevalence is reportedly lower in This age than in infants, these studies associated the prevalence of astigmatism to the progressive myopia (1).

Table 3: The prevalence of astigmatism in children in different studies worldwide (6).

Country	Age (years)	Power of astigmatism	Prevalence%
Europe			
Northern Ireland	6_7 12_13	>1 D	22.9% 18.4%
Poland Poland	6_18 6_14	>0.5 D >0.75 D >1 D	4.0% 7.3% 4.9%
North America			
USA	5_17	>1 D	28.4%
South America			
Chile	5_15	>0.75 D	27.0%
Asia			
China China (Hong Kong) China (Guangzhou) China (Southern) India(urban) India(rural) Iran (Dezful) Malaysia Nepal Singapore Taiwan	5_15 5_16 5_15 5_15 5_15 7_15 7_15 7_15 5_15 7_9 7_15	>0.75 D >0.75 D >1 D >0.75 D >0.75 D >0.75 D >0.75 D >0.75 D >0.75 D >0.75 D >0.5 D	1.0% 18.1% 42.7% 42.8% 14.6% 9.7% 18.7% 21.3% 3.5% 28.3% 42.5%(1995) 51.0%(2000)
Africa			
Marocco Nigeria Republic of South Africa Tunisia	6_16 5_15 5_15 6_14	>0.75 D >0.75 D >0.75 D >0.75 D	23.5% 2.3% 14.7% 6.7%
Australia			
Australia	12	>1 D	21.8%

Other studies found that the most common astigmatism is the against-the-rule astigmatism, it was about 48.7%, (44.7%) with-the-rule astigmatism and oblique astigmatism about (6.6%) (6).

Adults and elderly:

The prevalence of astigmatism in the young adults of 20 _ 30 years old is going more with WTR astigmatism, however the degree of astigmatism is generally minor (<1 D). the research has been reported that with advancing age , the prevalence of astigmatism increases, and axis shifts from a predominance of WTR in adults younger than 40 years old to a predominance of ATR astigmatism in adults older than 40 years old (5).

Although refractive astigmatism became more common with age after 50, while the cornea astigmatism remained stable until the age of 80 (5).

1.2.2 Gender:

Studies differed in presenting this topic, some recent studies concluded that Astigmatism was more prevalent in males (34 to 54%) than females(30 to 54%),but a reverse epidemiological studies observed in three other studies that astigmatism was higher in females (54 to 59%) compared with males (41 to 58 %) ,they also vary depending on the type of astigmatism (4).

- All sphero astigmatism were more known in females but it decreases with age (7).
- The ATR astigmatism was more frequent in males than in females at middle age and older age (8).

1.3 Risk factors:

1.3.1 Genetic factors:

Research has indicated that genetic factors may play a role in the development of astigmatism. There are many genes like PDGFRA, MTOR, VAX2, NRXN1 and others genes are associated with the corneal curvature, the patterning control of the dorsoventral axis of the eye and its development in general, which is associated with the onset of astigmatism (5).

1.3.2 Corneal biomechanics and aging:

Many reports have suggested that elasticity and rigidity of the cornea may be influenced by age-related changes in the physiology of the cornea. They revealed that people in older age (>65) had a higher mean collagen fibril radius, axial periods and intermolecular Bragg spacing compared to young

people.in addition the Descemet membrane became thick. These changes may impact the age-related changes in astigmatism (5).

1.3.3 Eyelid (pressure, morphology and pathology)/ extraocular muscles:

- One of the possible causes of corneal astigmatism has been determined as eyelid pressure on the cornea as a mechanic factor. Several studies have proposed that astigmatism is a result of the tightness of the eyelids and the cornea's stiffness, especially in the old people. Also; The angle of the eyelid fissure is correlated with the corneal cylinder axis. Other studies found an association between palpebral fissure width and corneal astigmatism. The eyelid pathologies have an impact on the corneal astigmatism too; like the chalazion, congenital ptosis,…etc (5).



Figure 2: Example of the association between the angle of the palpebral fissure and the angle of the corneal cylinder axis (5).

- Several studies have proposed that the change in the tension of the extraocular muscles may cause a corneal astigmatism (5).

1.3.4 Environmental and external factors:

- Studies related the high prevalence of astigmatism to the high level of education and the impact of prolonged near work (studying, reading, working, using digital screens,…etc.) on eye health and the changes of the cornea shapes (9).

- A poor socioeconomic status affect the astigmatism prevalence with the less developed health care services (9); people in rural areas can't have regular eye exams; they may not be aware to astigmatism symptoms; lack of optometrist; ophthalmologist and the poor nutrition may contribute to weaker corneal structures (10).

1.3.5 Ocular conditions and surgery:

Astigmatism can be developed from certain diseases situations, trauma or from eye surgeries (pterygium removal, cataract, extraction, PKR, LASIK,…) (1).

2. Regular astigmatism:

In regular astigmatism, the more prevalent type, the cornea resembles a football, akin to a rugby ball positioned on one end, on its side, or less frequently, tilted to one side. The two principal meridians are present, spaced 90 degrees apart; the optimal spectacle-corrected visual acuity is a minimum of 20/20, particularly in the case of corneal astigmatism. In regular astigmatism, the refractive power changes from one meridian to another, while each meridian maintains a constant curvature at every point across the entrance pupil (1).

3. Classifications of regular astigmatism:

3.1 Light refraction abnormalities:

3.1.1 Non-astigmatic eye:

a) The emmetropic eye (normal): parallel light rays converge sharply on the retina (1).

b) The myopic eye: parallel light rays converge before reaching the retina (1).

c) The hyperopic eye: in the unaccommodated eye parallel light rays converge behind the retina (1).

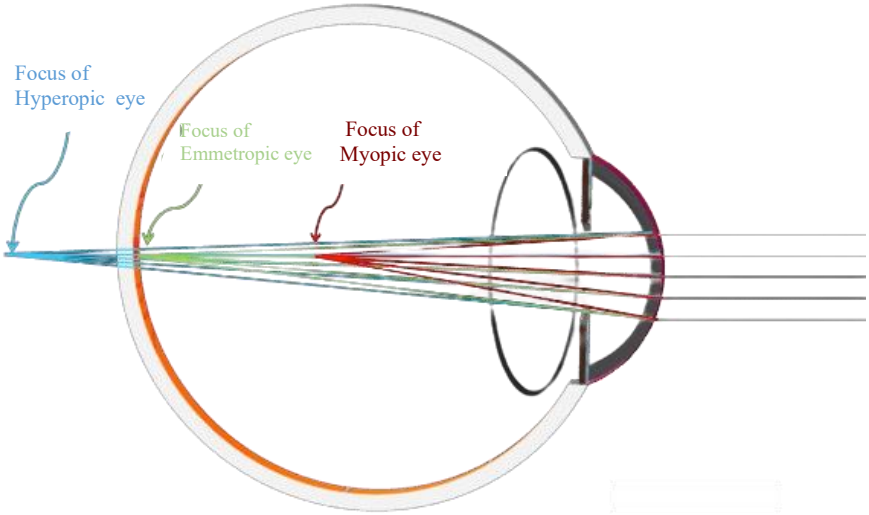


Figure 3 : Light refraction in non-astigmatic eye (11).

3.1.2 Astigmatic eye:

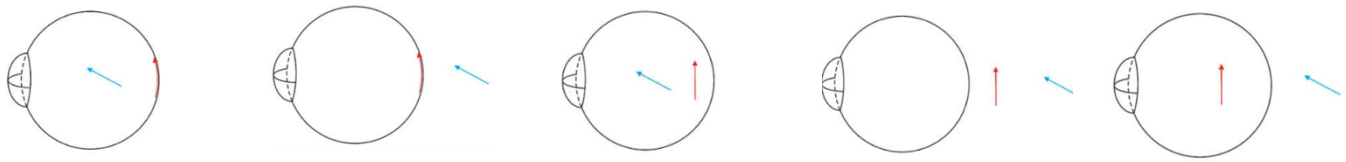
a) Simple myopic astigmatism: one meridian focuses light before the retina, while the other focuses it directly on the retina (1).

b) Simple hyperopic astigmatism: light is focused on the retina by one meridian, while the other focuses it theoretically behind the retina (1).

c) Compound myopic astigmatism: light is focused in front of the retina by both meridians (1).

d) Compound hyperopic astigmatism: in both meridians, light is focused theoretically behind the retina (1).

e) Mixed astigmatism: one meridian concentrates light before the retina, while the other does so behind the retina (1).



(a) (b) (c) (d) (e)

Figure 4 : Classes of regular astigmatism (12).

3.2 Types of astigmatism based on anatomical origin:

Total astigmatism is the sum of corneal astigmatism and internal astigmatism (12).

3.2.1 Corneal astigmatism:

Corneal astigmatism may result from unequal curvature along the two principal meridians of the anterior cornea, and it may also be influenced by the shape of the posterior cornea (1). Regular corneal deformation, or "toricity," is the geometric feature that causes regular corneal astigmatism. The curvature of a toric cornea varies from the steepest meridian to the flattest meridian (13) .

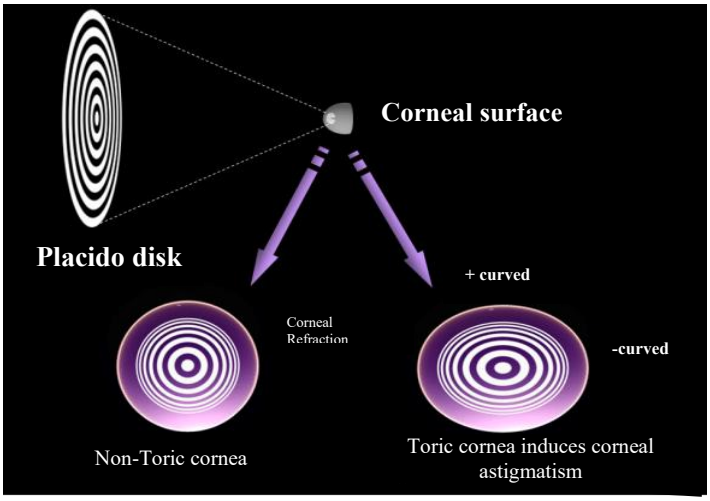


Figure 5 : Visualization of Corneal Astigmatism Due to Toric Cornea Using Specular Topography (13).

3.2.2 Non-corneal astigmatism:

Errors in the curvature of the anterior and posterior surfaces of the crystalline lens, irregularities in the lens's refractive index, or an eccentric position of the lens can contribute to non-corneal factors (1).

3.3 Orientation of astigmatism:

3.3.1 With the rule astigmatism:

If the meridian of maximum curvature is within 30 degrees of vertical alignment, regular astigmatism is termed "with the rule" (12), Which means that meridians (60° to 120°) are stronger than the horizontal meridians (0°/30° and 150°/180°).

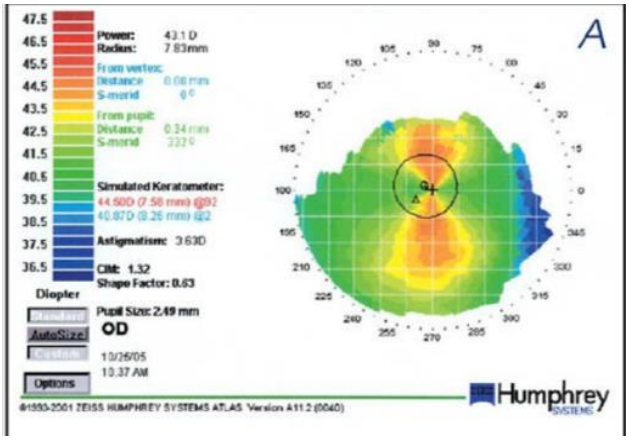


Figure 6 : with the rule astigmatism curvature map (12).

3.3.2 Against the rule astigmatism:

If the meridian of maximum curvature is less than or equal to 30 degrees from the horizontal orientation, regular astigmatism is referred to as “against the rule”.

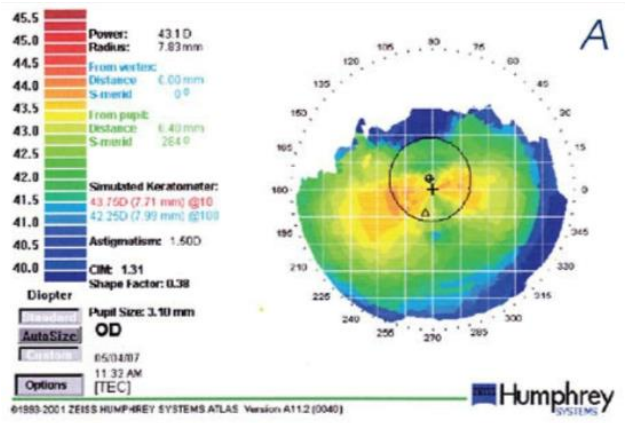


Figure 7: against the rule astigmatism curvature map (12).

3.3.3 Oblique astigmatism:

Oblique astigmatism, an important optical aberration in peripheral vision, arises from rays striking the refracting surfaces of the cornea and crystalline lens at oblique angles (14).

The meridians do not align with the standard horizontal or vertical axes; they are located in the oblique range, with one meridian between 30° and 60° and the other between 120° and 150° (15).

3.4 Severity of astigmatism:

3.4.1 Mild astigmatism:

Astigmatism ranges from “0.25 D to 1.5 D” in its initial or law stages (15).

3.4.2 Moderate astigmatism:

In the moderate stage, astigmatism ranges from above 1.5 D to below 3.0 D (15).

3.4.3 Severe astigmatism:

Severe astigmatism is defined as astigmatism greater than 3 diopters (15).

3.5 Congenital /acquired astigmatism:

Astigmatism can have both genetic and environmental influences, with some studies suggesting a hereditary component, while others emphasize external factors. Congenital astigmatism is often linked to genetic predisposition and developmental factors, whereas acquired astigmatism may result from disease, ocular surgery, trauma, or mechanical interactions affecting the eye's structure (1).

4. Irregular astigmatism:

Irregular astigmatism, which occurs less frequently, causes the corneal “rugby ball” to deviate from its usual shape and/or become bumpy. Irregular astigmatism is defined in various ways. A thorough definition characterizes it as a refractive state where “refraction in different meridians conforms to no

geometrical plan and the refracted rays have no planes of symmetry. It is an astigmatic condition that cannot be corrected with a sphero-cylindrical lens in the most of cases. the strength and the direction of astigmatism differ from one location to another within the entrance pupil (1)

5. Diagnosis of astigmatism:

Astigmatism assessment requires a history assessment and patient examination. Anamnesis should include elements of comprehensive medical eye assessment to take into account the patient's visual needs and all pathology of the eye (1).

5.1 Common diagnosis tools :

a) Corneal Topography: Corneal topography is often used to assess irregular astigmatism associated with keratoconus or corneal distortion. To assess the corneal surface after penetration of keratoplasty and to investigate the causes of visual loss of unknown etiology, three systems are currently being used Placido based, elevation based, and interferometric. Corneal topography helps to determine and document visual complications from corneal dystrophy, scars, pterygium, recurrent erosion, and chalazia (1).

b) Wavefront analysis: This novel approach assesses the refractive condition of the entire internal ocular light path at chosen corneal intercepts of incident light pencils [Harris, 1996]. It is possible to measure the refractive path taken by each beam and infer the specific spatial correction needed on each path by comparing the wavefront of a pattern of several small beams of coherent light projected through to the retina with the emerging reflected light wavefront (1).

c) Astigmatic fan diagram test: It consists of a number of lines with the same thickness, spreading out from a shared center, like the familiar Snellen fan. These lines need to be positioned at a distance that allows one or two running in the same direction to be seen clearly and distinctly. The placement of the direction at such a distance allows for one or two running in one direction to be seen clearly and distinctly. The orientation of one of the principal meridians will correspond to these lines, while the other will be perpendicular to it (16).

5.2 Refraction test:

a) Phoropter: The patient peer through a sizable device resembling binoculars and inform the physician of the letter that is easier to see. The doctor will write a prescription based on the answers to ensure that the patient achieve the clearest vision possible (2).

b) Autorefractor: This device also assists in measuring the astigmatism or other refractive errors automatically (12).

c) retinoscopy: Retinoscopy is the first step in refractive index. It is used to determine the approximate type and range of refractive errors and to estimate the type and performance of the lens required to correct the error. Retinoscopy is sometimes referred to as objective refractive index, as patients do not require participation or response. Typical patterns of irregular astigmatism are known to experienced retinoscopists and include "scoring" of reflexes and unpopular reflexes (1).

6. Treatment options for astigmatism :

6.1 Corrective lenses:

Astigmatism can be corrected most easily and safely with eyeglasses, so they should be the first option considered before contact lenses or refractive surgery. Whenever visual symptoms arise, a patient's eyeglasses and refraction should be assessed. Correction may not be necessary for patients with low refractive errors (low astigmatism); it is generally not recommended to make small adjustments to astigmatism corrections in asymptomatic patients. People who have regular astigmatism may not require full correction. Adults who have astigmatism might not accept complete cylindrical correction in their initial pair of glasses or in later pairs if their astigmatism has only been partially addressed. On the whole, axis or power changes of a substantial nature are not well tolerated (1).

6.2 Spherocylindrical lens:

A spherocylindrical lens, or toric lens, incorporates spherical and cylindrical elements, making it suitable for correcting astigmatism along with myopia or hyperopia. A spherocylinder (such as a rugby

ball) has different curvatures in two perpendicular meridians; one flat and one steep. unlike a spherical lens (like a basketball), which has equal curvature in all directions. This results in the focusing of light into two distinct focal lines rather than a single point. The clearest sight occurs between these lines, at the circle of least confusion. The lens offers tailored correction along each meridian, providing an accurate solution for complex refractive errors (1).

6.3 Contact lenses:

A comprehensive eye examination and thorough ocular history are necessary prior to fitting contact lenses. It is essential to inform patients about the risks, including microbial corneal ulcers, particularly associated with overnight lens wear. Irregular astigmatism, which is frequently the result of conditions such as keratoconus or corneal scars, does not respond well to glasses and necessitates rigid contact lenses for the best vision. Astigmatism that is severe can be treated with rigid gas-permeable, hybrid, bitoric, or custom soft toric lenses, which provide improved centration, comfort, and visual correction. For the sake of comfort and eye health, it is essential that lenses fit properly and move as they should (1).

6.4 Refractive surgeries:

Vision improvement and a decreased reliance on eyeglasses or contact lenses are benefits of refractive surgery. To correct the refractive error, an eye surgeon reshapes the cornea's curves with a laser beam. Prior to the operation, professionals will decide whether the patient qualify for refractive surgery.

6.4.1 LASIK (Laser assisted In Situ keratomileusis):

Laser-Assisted In Situ Keratomileusis (LASIK) is the most commonly performed corneal refractive surgery used to correct myopia, hyperopia, astigmatism, and presbyopia. The procedure involves three main steps: creation of a superficial stromal flap using a femtosecond laser, application of excimer laser photoablation to reshape the corneal stroma, and repositioning of the flap. It is often recommended to create an oval or elliptical flap that is wider along the less curved (flatter) meridians of the cornea, as the excimer laser impacts are more broadly distributed along these meridians, enhancing the effectiveness of the correction (17).

6.4.2 PRK (Photorefractive keratectomy) :

Photorefractive Keratectomy (PRK) involves applying a refractive correction to the surface of the cornea after the removal of the superficial corneal epithelium. Unlike LASIK, PRK does not require the creation of a corneal flap. There are two variants depending on how the epithelium is removed, In the manual technique, the epithelium is removed (peeled) using a sponge after applying a diluted solution. In the all-laser technique or transepithelial PRK, the epithelium is photo-ablated by the excimer laser (18).

6.4.3 LASEK (Laser-Assisted Subepithelial Keratectomy):

LASEK is a technique derived from PRK, sharing the same main procedural steps. The key difference is that, in LASEK, the epithelium is gently loosened using a diluted alcohol solution, then preserved and repositioned over the corneal surface after the excimer laser has been applied. Like PRK, LASEK is classified as a surface ablation technique, meaning it does not involve the creation of a stromal flap (19).

6.4.4 Smile (Incision Lenticule Extraction) :

The SMILE technique in refractive surgery involves the extraction of an intra-corneal lenticule created by a femtosecond laser for the correction of myopia and myopic astigmatism (20).

6.5 The intraocular lenses:

6.5.1 Toric intraocular lenses:

Toric intraocular lenses (IOLs) are regarded as the most reliable method for correcting corneal astigmatism in patients undergoing cataract surgery, as they can effectively treat astigmatism as low as 0.75 diopters. These lenses are available in both monofocal and multifocal designs, with the choice depending on the patient's visual needs and expectations. However, toric IOLs are not suitable for individuals with existing posterior segment disorders, zonular weakness, or irregular astigmatism (21).

6.5.2 Phakic toric IOL's:

There are three main types of phakic intraocular lenses (pIOL's) commonly used in clinical practice to correct ametropia among them astigmatism:

1. **Iris-fixated anterior chamber lenses**
2. **Angle-supported anterior chamber lenses**
3. **Posterior chamber lenses**

Each type differs in design and placement within the eye, offering specific advantages based on the patient's ocular anatomy and refractive needs (22). It preserves the eye's natural refractive elements such as the cornea and crystalline lens intact. Unlike corneal refractive surgeries, pIOL's do not alter or remove any ocular tissue, making them a reversible and less invasive option that maintains the eye's accommodative ability (23).

6.5.2.1 Toric implantable collamer lenses (ICL's) :

Toric implantable collamer lenses (ICL's), a kind of phakic intraocular lens implanted in the posterior chamber, are extremely successful at correcting moderate to severe myopia astigmatism, particularly in individuals who are unsuitable for corneal refractive operations. These lenses deliver great visual results, stability, and safety while retaining the native crystalline lens. It improved refractive results in eyes with high astigmatism (≥2D to ≤4D), with a high efficacy index and low complication rates (23).

6.5.3 Piggy back-toric IOL's :

It is the process of implanting an artificial lens in the same position as the eye's natural lens. After that, the vision must be corrected. The easiest approach to accomplish this is to implant a piggyback or add-on lens. This lens is extremely thin and is intended to sit immediately in front of the first lens. That is the secondary or piggyback lens, which is located in the sulcus of the eye, immediately in front of the capsular bag (24). The toric monofocal piggyback IOL produced excellent visual and refractive results while demonstrating adequate rotational stability. This IOL seems to be a successful treatment for residual astigmatic refractive error in pseudophakic eyes (24).

Conclusion

Astigmatism is a frequent refractive error caused by an uneven curvature of the cornea or lens, causes distorted or blurred vision. There are two principal categories of astigmatism; one is called regular astigmatism which contain four types, the other called irregular astigmatism; each with distinct clinical implications. accurate diagnosis, using technologies like keratometry and corneal topography is important and essential for the optimal correction and monitoring. Understanding these distinctions ensures effective correction and aids in detecting issues that may necessitate more complex therapies.

Chapter 02: Keratoconus

Introduction

For more than three centuries, keratoconus has fascinated and perplexed medical professionals (25)(26). It was first identified in the 1700s and while its etiology is still unclear and frustrating, its therapeutic has evolved significantly over the past century, improving the lives of people who are impacted. Although there are several ways to treat KC, including surgical techniques and optical correction, the underlying cause of the condition is still unclear. The fact that molecular genetics techniques have identified single nucleotides as the cause of many diseases, including several linked to KC, the condition is thought to have both genetic and environmental roots and cannot be ascribed to a single, persistent genetic defect (27).

Definition:

Keratoconus (KC) is a condition in which the cornea becomes conical and the stroma thins. This process causes irregular astigmatism, myopia, and protrusion, resulting in mild to severe visual impairment (28). KC is a degenerative condition that normally affects both eyes but disease presentation can be severely asymmetric, with just one eye affected clinically (29). Symptoms vary greatly and are partially determined by the stage of illness progression. Early in the disease, there may be no specific symptoms, and the ophthalmologist may diagnose KC solely because the patient cannot be refracted to a clean 10/10 corrected vision. In serious condition, there is significant vision distortion, as well as profound vision loss.

Although the standard description of KC is that it is a non-inflammatory condition, there is enough evidence to suggest that inflammation is a substantial component of KC's pathophysiology. The inflammation seen in KC is more like the chronic inflammation associated with systemic illnesses than acute inflammation (30). More recently, with the use of Scheimpflug imaging analysis and anterior segment optical coherence tomography, early illness diagnosis has been obtained using information such as pachymetry, epithelium, elevation, and aberrometry data (31)(32). Many terminology have been coined as a result of these new instruments' including subclinical keratoconus (SCK) and forme fruste keratoconus (FFKC) (33).

1. Epidemiology:

1.1 Incidence & prevalence:

Incidence and prevalence are basic epidemiological tools that quantify the impact of a disease on a certain community. In the case of KC, these variables are critical for understanding diseases development and directing therapeutic options.

Estimate of the prevalence and annual incidence of keratoconus have been suggested by several studies. The most cited is a 48-year registration study performed in the United States which report a prevalence of 54.5 cases per 100,000 individuals and an annual incidence of two cases per 100,000 individuals (34). However, reported prevalence and incidence rates vary widely among different studies. In South Korea, the prevalence was 13,343 cases per 100,000 people and the incidence was 5.56 cases per 100,000 person over a five-year period (35), while Sweden shows a prevalence of 169.5 per 100,000 and incidence of 11.8 per 100,000, peaking in young adults over 10 years (36).

The prevalence of KC varies across the world. It has been recorded as 0.0003% in Russia(37), 0.086% in Denmark (38), 0.249% in Iran (39), and 2.3% in Lebanon and India (40). Beyond geographic differences, prevalence also depends on the method of data collection. With an improved understanding of the disease as well as new imaging modalities and the advent of refractive surgery, keratoconus is being diagnosed more frequently and at earlier stages than in the past (41).

1.2 Environmental & genetic factors:

Recent research have revealed that the prevalence of KC varies throughout the world contrary to what was previously considered (42). For instance KC is less prevalent in Northern Europe, the Urals, and the United States (43)(37)(34), while higher prevalence is observed in the Middle East (44)(39), India (40), and China (45).

Figure 8 compares the KC prevalence and humidity in the regions under study. There seems to be a correlation between humidity and KC prevalence; for example, the US and Scandinavia have high humidity and prevalence, but Iran has high prevalence and low humidity (46) . This variance, with peaks in certain places, supports the idea that environmental factors like UV exposure and humidity affect the development of KC.

Previously it was believed that KC affect all ethnic groups equally (42). However, it has now been demonstrated that there are differences. An incidence 4.4 times higher has been observed in Asians than in whites (47). This was confirmed in two other investigations where the difference in incidence was 7.5/1 and 9.2/1 (48)(49) .

Beyond ethnic variations, genetic and family history also plays an essential role, where many studies have reported the presence of large number of familial KC. The rate ranges from 5% to 27.9% (50) .Wang et al noted that the prevalence of KC in first-degree relatives was 15 to 67 times higher (51). Another research compared dizygotic (DZ) and monozygotic (MZ) twins and found that MZ had much higher concordance, which means that there is a genetic link to the condition (52) (50).

In summary. Both environmental and genetic factors contribute to the pathogenesis of KC and notable achievements have been made in the understanding of its epidemiology.

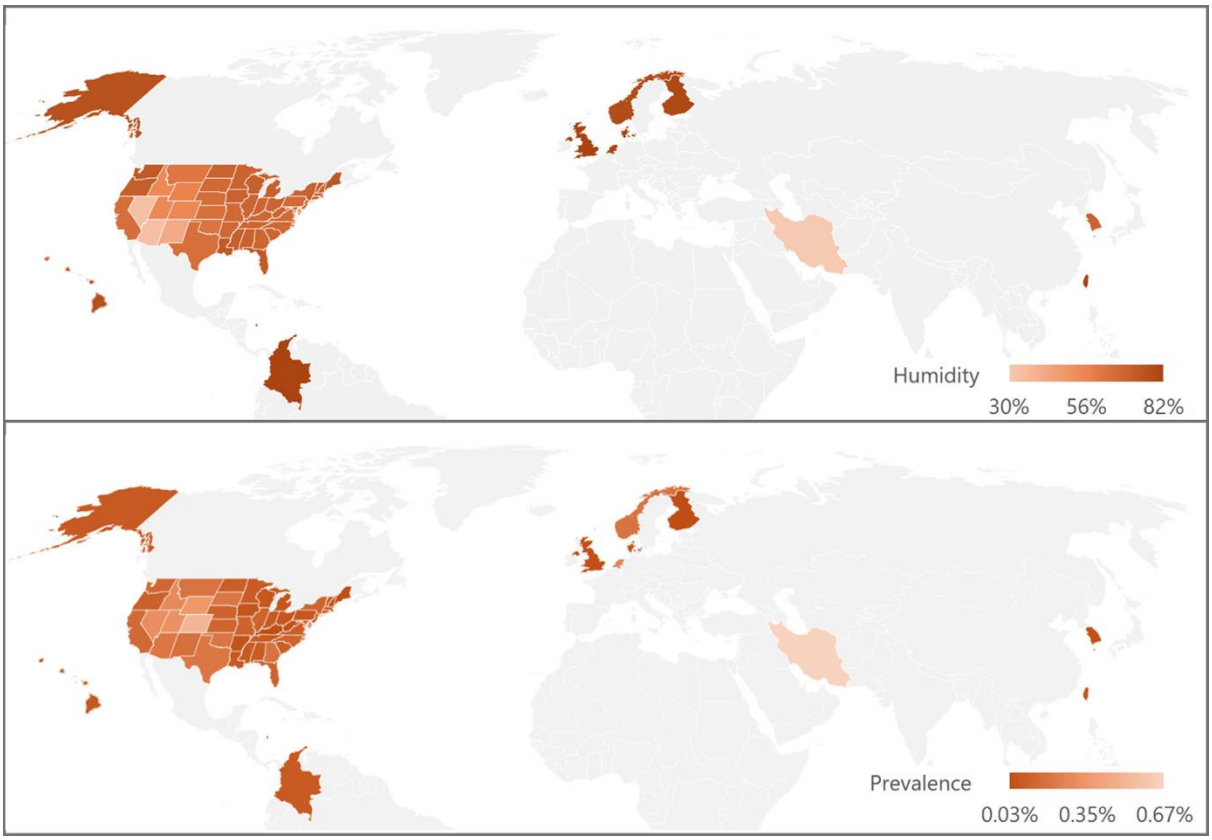


Figure 8 **:** Distribution of humidity (top) and prevalence (bottom) across the included study regions. The maps were created using Microsoft Excel 365. The entire state or country was shaded uniformly, even when data were derived from a smaller subregion. Hawaii was manually enlarged and repositioned to improve visibility. In the United Kingdom, two prevalence estimates were available; this graph displays data from the study that directly reported prevalence values (46).

1.3 Eye rubbing & allergy:

Eye rubbing is also regarded as another major risk factor in the development of KC. The mechanical stress caused by repeated rubbing weakens the cornea, increasing disease risk ($p = 0.002$) (53).

A case of an 11-year-old boy who stopped episodes of rapid heart rate by rubbing his left eye, activating the oculo-cardiac reflex up to 20 times a day. His initial eye examination was normal but four years later he was diagnosed with KC in one eye (54).

The association with eye rubbing and allergic eye disease is now accepted (50). Hilgartner identified the link between ocular allergies and KC in 1937. While early study showed a correlations ranging from 7% to 35%, more recent studies establish a direct association between allergens and KC (55). Ocular allergies cause inflammation and can make the effects of eye rubbing last longer.

As Figure 9 suggests, DED might be a mediator in this relationship, as low humidity is directly associated with DED and a history of DED is a known risk factor for keratoconus. Other possible mediators of the association between keratoconus and low humidity include eczema and ocular allergy. These two conditions seem more frequent under low humidity conditions (46).

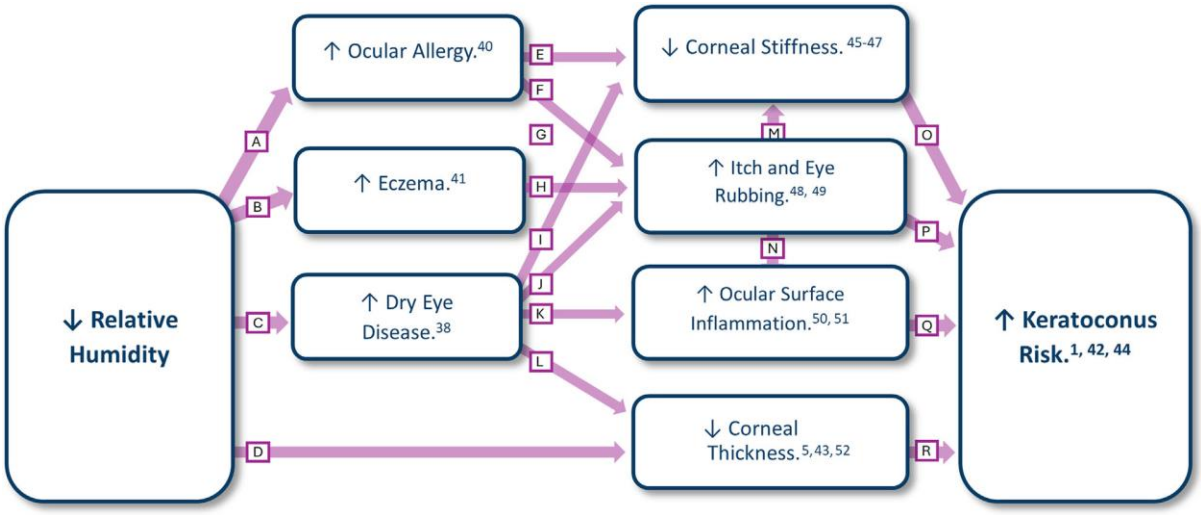


Figure 9 **:** Suggested pathways for the relationship between low humidity and keratoconus. The letter on each arrow describes relevant findings from studies (46).

1.4 Age & gender:

Keratoconus begins around puberty and progressively develops, with the most common age range for KC is between 20 and 30 years old, it tends to stabilize around the age of 35 (28)(56).Some studies show no difference between genders, while others report variations.

In younger, middle-aged, and older age groups, the distribution ratios of KC were 17.2%, 75.3%, and 7.5% , in the same study the ratios of patients by gender were 62.2% for males , while 37.8% were females (57).

Similarly, the Colombian Ocular Diseases Epidemiology Study (CODES) reported gender-related variations (58) :

- Incidence peak in males occurs in their early 20s.
- Incidence peak in females occurs in their late 20s.
- Male-to-female incidence rate ratio of 1.60.

Contrary to these findings, a longitudinal study of keratoconus progression found no significant difference between genders (61% vs. 62% male subjects) (59).In the same vein , a recent study found that sex have no correlation with KC (60).

In conclusion, men and women are equally affected by keratoconus, which is usually diagnosed in late adolescence or early adulthood.

1.5 Association with other diseases:

- **Down Syndrome:** The prevalence of KC in individuals with DS varies across studies, Mathan et al. reported that the prevalence of KC in athletes with DS ranges from 30.6% to 38.8% (61), while Haseeb et al found that KC is 6 to 30 times higher than in the general population (62). in line with this, Table 4 shows that the prevalence varies widely, ranging from 0% to 71% (61).
- **Diabetes:** Some studies found no relationship while others suggest that lower glucose level increase KC risk. Epidemiological studies suggest that diabetes decreases the chance of having

KC by 20–52% depending on DM severity (63). Lower proinsulin levels were related to a higher risk of keratoconus (64).

- **Leber's Congenital Amaurosis** : KC is frequently associated with LCA with reported incidence rate between 30% and 100% in small studies (65). In one study, 10 of 35 children (28.6%) with LCA had KC, which highlights a strong association between both conditions.(65)

- **Thyroid Dysfunction:** According to Said et al 7.5% of individuals with TGD had KC compared to 0.5% in control group ($p < 0.0001$). with 95% of TGD cases were hyperthyroidism, while only 5% were hypothyroidism (66).
  According to a nationwide population-based cohort study between 2009–2018 among individuals with TGD, the incidence was 6.019 per 100,000 in hypothyroidism and 8.287 per 100,000 in hyperthyroidism (67). In conclusion, Hyperthyroidism appears to be potential risk factor for KC while hypothyroidism does not show a significant association.

Table 4 : Proportions with Keratoconus in Persons with Down Syndrome (studies identified by literature review) (61)

Reference	n DS	n (%) KC	Location	CT	Patient group and age
Walsh	91	7 (8%)	Sweden	No	Institutionalized mentally retarded persons (5–60 years)
Wong & Ho	140	0 (0%)	Hong Kong	No	Children (3 months–13 years) in hospital
Van Allen et al	38	6 (15.8%)	USA	No	Adults (30–68 years old) in residential center
Haugen et al	47	5 (10.6%)	Norway	Yes	Case-control study (all ages)
Kim et al	123	0 (0%)	Korea	Yes	Children (6 months–14 years), non-institutionalized
Van Splunder et al	409	36 (9%)	Netherlands	No	Cross-sectional survey. Adults (≥18 years)
Liza-Sharmini et al	60	0 (0%)	Malaysia	No*	Children (1 month–17 years) in hospital
Fimiani et al	157	0 (0%)	Italy	No	Children (1 month–18 years) in hospital
Karlica et al	153	2 (1.3%)	Split-Dalmatia	No	Children (0–18 years)
Fong et al	91	1 (1%)	Hong Kong	No†	Cross-sectional survey. Adults (≥18 years)
Aslan et al	27	21.1% (11 eyes)	Helsinki	Yes	Children (5–12 years). Clinical trial. Identified

					early subclinical keratoconus
Li et al	20	36.3% (12 eyes)	Hong Kong	Yes‡	Adult patients scheduled for cataract surgery (tertiary eye hospital)
Real de Asua et al	144	10 (7%)	Spain	Unknown	Retrospective review of medical records. Adults (17–65 years)
Alio et al	59§	42 (71.3%)	Spain and Egypt	Yes	Multicenter case–control study. Age 3 months–60 years
Marsack et al	140	11.8%–20.8%¶ (26–46 eyes)	USA	Yes	Case–control study. Age 8–55 years
Hashemi et al	226	28 (12.4%)	Iran	Yes	Population-based cohort study. Age 10–30 years
Imbornoni et al	31	10 (32%)	USA	Yes	Children/young adults (4–24 years) in hospital
Mathan et al	98	30 (30.6%) **	New Zealand	Yes	Screening of Paralympics athletes (ages 15–53 years)
Bermudez et al	1207	331 (27.2%)	Brazil	Yes‡	Retrospective review of medical records. Adults (all ages)
Kristianslund & Drolsum	4342	238 (5.5%)	Norway	Yes††	Population-based register study. All ages

Notes:

- *Placido disc used to detect keratoconus.
- †Corneal thickness measured.
- ‡When KC was suspected and the patient cooperated.
- §Number of patients that cooperated with eye examination.
- ¶Proportion above threshold on detection metric (two types used).
- **Small sample numbers.
- ††Performed in many cases when indicated and the patient cooperated, however, proportion unknown.
- CT, corneal topography/tomography; DS, Down Syndrome; KC, keratoconus; n, number.

2. Etiology & risk factors of keratoconus

The etiology of KC has been the subject of numerous studies. Several of these studies have provided strong indications that genetic and environmental risk factors play a major role in its development.

2.1 The genetics of keratoconus:

Genetic linkage studies have identify at least 17 gene loci showing the existence of several genes in KC (68).Studies on CCT and corneal biomechanical discovered of numerous loci impacting corneal curvature and rigidity such as such as COL5A1 (9q34.2.3) (69) (70), FNDC3B (3q26.31) (69)(71) and FOXO1 (13q1.1)(69)(71)(72) validate the concept of a genetic-environmental relation (73).

However, no one gene has been identified as the main cause and several genetic mutations have been studied for their potential involvement in the disease (74).

Genetic advances, especially through genome-wide association studies (GWAS) and exome sequencing have led to the identification of novel loci connected to KC and a better understanding of its pathophysiology (75).

2.1.1 Genes for familial keratoconus:

LOX:

Many SNPs in LOX gene were identified as related with KC, some in the intron ,others in the exon (76) , with Variation in intron may affect gene regulation while in the exon may modify the action of the lysyl oxidase enzyme which is required for collagen stiffness (77).

DOCK9:

In many Ecuadorian families with KC, the rs191047852 mutation in the DOCK9 gene was identified suggesting a hereditary transmission (78).This mutation was almost absent in controls but present in many affected individuals reinforcing a dominant familial genetic factor, which leads to disrupted corneal wound healing (78) (79).

PPIP5K2:

PPIP5K2 has been identified in multigenerational families (four-generation), and mapped to a chromosomal region linked to KC suggesting that is a key gene in certain familial forms of KC (80)(81). Studies on mouse models shown that mutations in this gene lead to corneal abnormalities similar to human KC , which reinforce the genetic link (82) .

2.1.2 Genes associated with keratoconus and related syndromes:

COL5A1:

Mutation in these gene are present in 50% of patients with EDS (83). The COL5A1 and COL5A2 encode the chains of type V collagen which are fundamental for the stability of connective tissues. In addition, a Modification in COL5A1 lead to abnormal protein translation in a three-generation KC family which reinforce the gene role in keratoconus (70).

ZNF469:

The ZNF469 gene is linked to BCS which is an autosomal disorder that cause severe corneal thinning and high rupture risk (84).While some studies report a higher frequency of pathogenic ZNF469 in KC patients others found no real association (85).

TGFBI:

TGFBI gene encodes TGF beta-induced protein (TGFBIP) which play a key role in cell adhesion to collagen, proteoglycans and maintain corneal structure (86).

Mutations in it are associated with epithelial-stromal corneal dystrophies which are a group of disorder characterized by progressive corneal opacification and vision impairment (87).

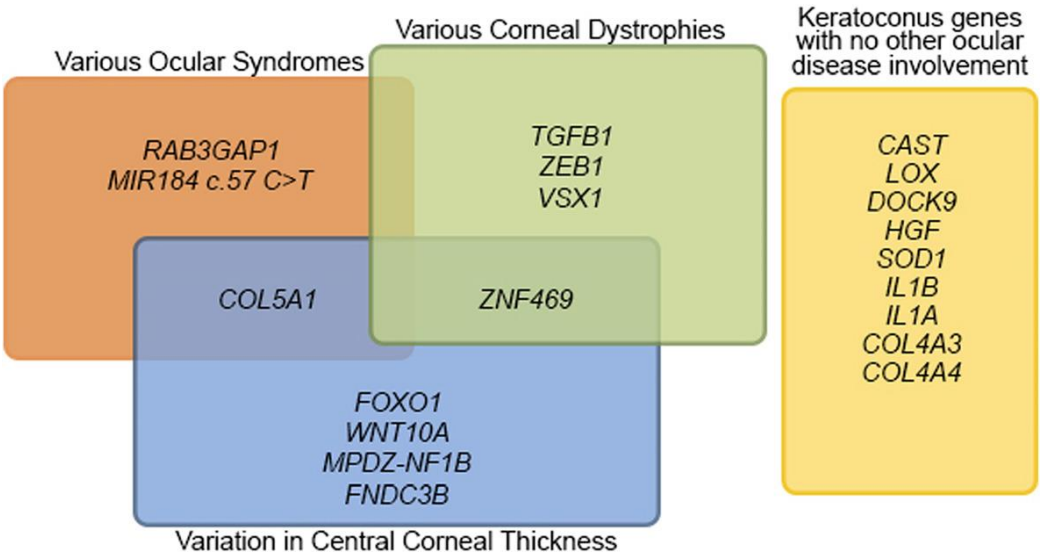


Figure 10 **:** Keratoconus genes and their involvement in other ocular diseases (88).

2.2 Environmental risk factors:

In 1854, Dr. John Nottingham opened the ‘conical cornea’ chapter in his treatise, which has remained an enigma for many years. In an effort to better understand its etiology, recent research has identified many environmental risk factors associated with KC, including eye rubbing, comorbidities, contact lens wear, asthma and allergy with atopy, and UV exposure.

2.2.1 Eye rubbing:

As many studies show, eye rubbing is associated with KC. Some consider it as contributing factor to its development, while others believe it is the main cause.

Gunes et al. reported the case of the youngest patient with bilateral KC secondary to chronic persistent eye rubbing. Their study suggests that trauma from eye rubbing could be a causing factor from an early age (89) .A Case-Control Study of KC Risk Factors showed a strong correlation between eye rubbing and KC particularly when it is with the knuckles (90).

In 2009 ,McMonnies reported that responses and possible causal link to eye rubbing may contain increased corneal temperature, epithelial thinning, increased inflammatory mediators (IL6, TNFa, MMP9) in the precorneal tears, abnormal enzyme activity, large intraocular pressure spikes, high hydrostatic tissue pressure, thixotropically reduced ground substance viscosity, temporary displacement of ground substance from the corneal apex, buckling and bending of fibrils associated with waves of corneal recession, biomechanically coupled curvature transfer to the cone apex, slippage between collagen fibrils at the cone and changes to keratocytes due to mechanical trauma and/or high hydrostatic pressure, in addition to scar formation (91).

2.2.2 Comorbidities:

More than 49 comorbidities and syndromes have been identified in association with KC, including both of ocular and systemic health.

Keratoconus is associated with Down syndrome (61) , LCA (65), osteogenesis imperfecta (92), certain pigmentary retinopathies, mitral valve prolapse , vascular collagen diseases, Marfan

syndrome, Ehlers-Danlos syndrome (93) and other non-inflammatory connective tissue disorders such as joint hypermobility (94).

KC therefore can be divided into three broad categories: (a) KC associated with genetic disorders such as Down syndrome, LCA…etc.; (b) KC associated with eye rubbing, mitral valve prolapse, atopy, contact lens use, LCA, and a positive family history; and (c) isolated KC without any associations (94).

2.2.3 Contact lens wear:

Wearing CL with polymethyl methacrylate (PMMA) lead to endothelial function loss characterized by increased polymegathism and pleomorphism, with reduced level of cell density causing a stromal edema developing from the posterior to the anterior surface. Hypoxic stress also plays a significant role in the endothelial alterations (95).

Building on these, an increase epithelial cell surface area (polymegathism) and decreased keratocyte density observed in CL wearers with lower keratocyte density in keratoconic patients who wear CLs compared to non-wearers. This loss may be result of the mechanical stimulation from lenses and the production of inflammatory substances. While the progression of KC itself is the primary cause of keratocyte loss, Although wearing CL just exacerbates the condition, depending on the type of lenses and the duration of use (96). Contrary to Patel et al., who found no decrease in keratocyte density, P. Kallinikos et al. observed an immediate reduction within just 2 hours (97) (98).

Table 5 : Strongly Associated Risk Factors with Keratoconus (99)

Authors	Year	Country	Study design	Total study participants (n)	Risk factor(s) analyzed
Macsai et al.	1990	USA	Retrospective cohort	199	Contact lens
Donnenfeld et al.	1991	USA	Case report	5	Floppy eyelid syndrome
Bawazeer et al.	2000	Canada	Case-control study	120	Atopy, eye rubbing
Owens et al.	2003	New Zealand	Survey questionnaire	673	Age, gender, consanguinity,

					allergy, and asthma
Moon et al.	2006	South Korea	Cross-sectional study	42	Contact lens wear
Naderan et al.	2017	Iran	Case-control study	2411	Allergy
Moran et al.	2020	France	Case-control study	557	Eye rubbing, pattern of eye rubbing, dominant hand, allergies, history of dry eye, screen time, sleep position, and night-time work
Sorbara et al.	2021	Canada	Cross-sectional study	56	Contact lens wear
Sahebjada et al.	2021	Australia	Cross-sectional study	260	All known environmental risk factors including asthma, BMI, smoking, diabetes, rheumatoid arthritis, eczema

2.2.4 Allergy:

The relationship between KC and allergy was focus of numerous studies with accord on the correlation between them two.

An Italian study found that the KC AL group showed higher percentage of patients tested positive for MMP-9 than in the KC NAL group (81% of KC AL & 4% of KC NAL) and the Kmax value increased from 50.2 D to 55.2 D after 12 months indicating worsening corneal distortion (100). Another study looked at the connection between keratometry and eye itching found that the most curved corneas were present in the eyes with frequent and intense pruritus (101).

The ocular response begins when the conjunctiva exposed to an environmental allergen and binds with specific IgE (102). Sharma et al confirme that ocular allergy has an important role in disease progression (55).

2.2.5 Atopy:

The incidence of Atopic disease ranges from 2-20 % of the general population, which is a high rate. This has made it the subject of many studies to investigate its potential as a cause or factor in the development of KC since the beginning of the 20th century.

In 1989, Harrison found that the presence of atopic disease or predisposition history in KC patients where more than half of total study group. The cases were more likely to have bilateral KC (103). Similarly, a Turkish study showed that atopic KC eyes have steeper cone which is thinner centrally and more peripherally located (104). Although atopy may contribute the early development of KC possibly through immune response & increased eye rubbing, it does not directly affect the corneal structure (105).

"This is what Igor Kaiserman and Sara Sella wrote in Chapter 2, Chronic Ocular Inflammation and Keratoconus, of the book Controversies in the Management of Keratoconus: 'Not surprisingly, the anterior cornea, which is most affected by ocular surface atopy, is also the most damaged layer in KC, with changes to the basal epithelial cell layer, thinning of the epithelial layer, breaks in the Bowman layer, and a thickened sub-basal nerve plexus."

2.2.6 UV Exposure:

The cornea is the first structure to face the UV radiation it blocks most of UVB contrary to UVA, which penetrate the cornea and reach the anterior lens as shown in the picture below.

The UV exposure contributes to (106) (107):

- The generation of reactive oxygen species (ROS).
- Oxidative stress in the corneal tissue.

- Potential localized damage in the interpalpebral zone (cornea).
- Chronic inflammation due to the induction of pro-inflammatory cytokines.
- Activation of MMPs due to UVB and degradation of ECM.

Gordon-Shaag et al. reported that reduce or limiting time in the sun was not associated with KC, this is why UV radiations may provide a positive effect to the cornea by getting collagen cross-linking (108).

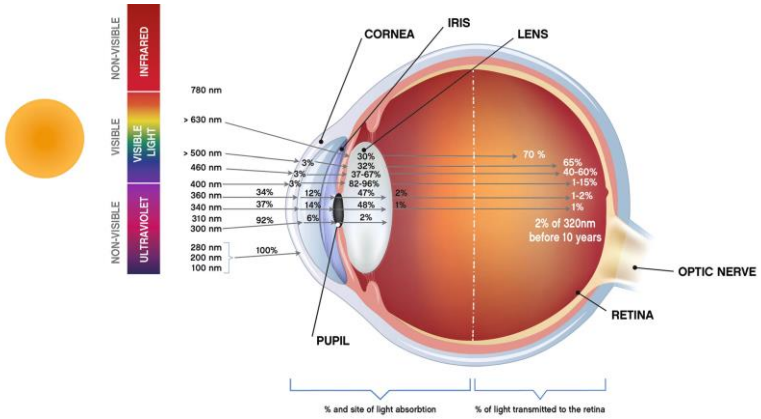


Figure 11 : Solar radiation and filtration by the structures of the eye (109)

Taken together, the current evidence suggests that KC is heterogeneous in nature and more studies are needed to investigate the detailed relationship of eye rubbing and its initiation, ongoing progression, and severity of KC.

3. Biomechanics of keratoconus:

An optimal cornea is optically transparent, positive and prolate that bend light into retina. Even small changes in the macro or microstructures can lead to dysfunction.

3.1 Background:

The cornea is composed of multiple layers of which the stroma constitutes approximately 90% of its thickness. This layer compact and mostly acellular primally made of (110):

- Type I collagen fibrils

- Fibronectin
- Organized into lamellae by proteoglycans.
- Elastins (for plasticity) and glycosaminoglycans (for viscosity).

The viscoelastic of stroma offer resistance to and tensile forces contributing to the biomechanical properties of the cornea. The strength is influenced by collagen fibrils orientation which changes from the anterior to the posterior (the anterior 40% is more interwoven) making it mechanically stronger (111).

3.2 Biomechanical changes:

Each layer including tear film (viscoelastic), Bowman's layer, stroma, and Descemet's membrane have high elastic moduli. with specific spatiotemporal pattern. Many supraocular and ocular variables affect corneal hysteresis with the cornea's viscous and elastic properties vary linearly with age (111).

The corneal stiffness increases while viscosity decreases; as result of changes in biomechanics due to non-enzymatic cross-links in the stroma same thing for hyperglycemia case with thyroid hormone concentrations and ethnicity affects corneal biomechanics.

Many Studies have reported many differences between KC and healthy eyes. The KC corneas have significant lower CCT,CH, CR, this may be explained by distorsion of lamellar matrix in stroma and other microstructural changes associated as shown in **Table** (110).

Table 6: Summary of corneal microstructural changes associated with keratoconus.

Structure	Change with KCN
Whole cornea	• Changes in expression of laminin (Tuori et al., 1997), collagen VII (Tuori et al., 1997) • Increased enzyme activity (Shetty et al., 2015)
Tear film	• Various biomarkers (Lema et al., 2010; Balasubramanian et al., 2012)
Epithelium	• Thinning (Roy et al., 2013) • Apoptotic cells (Sherwin and Brookes, 2004) • Focal thinning over cone and peripheral thickening (Reinstein et al., 2009)
Epithelial basement membrane	• Increase in collagen IV (1/2) (Tuori et al., 1997) • Decrease in collagen IV (5/6) (Tuori et al., 1997) • Changes in fibronectin, collagen IV (3/5), laminin (Kenney et

	al., 1997) • Decrease in fibrin (Millin et al., 1986)
Bowman's layer	• Discontinuities and defects (Scroggs and Proia, 1992; Tuori et al., 1997) • Fibrotic regions (Kenney et al., 1997) • Deposits of collagen VIII, fibrillin, collagen V (1/2) (Kenney et al., 1997)
Stroma	• No significant change in collagen types (Newsome et al., 1981; Tsuchiya et al., 1986) • Disorganized lamellae (Meek et al., 2005) • Altered fiber alignment (Akhtar et al., 2008) • Thinning (Scroggs and Proia, 1992; Tuori et al., 1997) • Increased fibril density, reduced diameter, increased proteoglycans (Akhtar et al., 2008) • Fewer keratocytes (Sherwin and Brookes, 2004)
Pre-Descemet's (Dua's) layer	• No known changes
Descemet's membrane	• No immunohistochemical change (Kenney et al., 1997) • Ruptures, folds (Sherwin and Brookes, 2004)
Endothelium	• Apoptotic cells (Sherwin and Brookes, 2004)

4. Pathophysiology & histopathology of keratoconus:

4.1 Pathophysiology of keratoconus:

To understand KC pathophysiology where inflammation is considered as the chief pathway in the development and progression of KC. Galvis et al (112) proposed that there is five major events supporting inflammation theory: (a) changes in the composition of corneal stroma, (b) inflammation at the molecular level, (c) imbalance of proteolytic enzymes, (d) oxidative stresses, and (e) cellular hypersensitivity.

Cornea is mainly composed of collagen. Any alteration in size shape or volume cause corneal structure changes. Type I collagen makes up over 75% of the cornea's collagen content .The lamellae are interlaced with collagen types III, V, and VI, whereas the basement membrane epithelium and subepithelial stroma are interwoven with collagen type XII .Consequently, stromal thinning is due to reduction in both the number of collagen lamellae and the decrease in the quantity of collagen types and other proteins (113).

In addition to structural alterations, inflammation promotes keratocyte death in the cornea and tear film by over activating inflammatory mediators (TGF-β, IL-1, IL-6, TNF-α, MMP-9, etc.). Tissue degeneration is caused by an imbalance between pro- and anti-inflammatory cytokines. an

imbalance of proteolytic enzymes particularly the overactivity of MMPs such as MMP-1, MMP-2, and MMP-3 contribute in KC progression by excessive degradation of corneal extracellular matrix and stopping the regulation of these enzymes (113).

In combination with oxidative stress and cellular hypersensitivity, KC corneas show reduced antioxidant defenses and increased ROS which damage keratocytes and collagen structure, accelerating tissue degeneration. Keratocytes in KC are more sensitive to apoptosis leading to accelerated cell loss. This contributes further to stromal thinning and structural instability, both of them contribute to KC by damaging stromal keratocytes and accelerating cell loss (113).

4.2 Histopathology of keratoconus:

In KC the histopathological changes go from mild to severe to affect all corneal layers where the changes start in the anterior stroma, bowman's layer and epithelium in early stages with normal posterior stroma. The complete histopathological findings are noted using specimens from penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK).

- **Epithelial Changes:** This layer shows many irregularities as said earlier, where many corneas show a central epithelium thinning .However, researchers found that epithelial cells might vary in the number of layers ranging from 2-3 layers in some areas to more specially in the apex (more than 10 layers) (113).

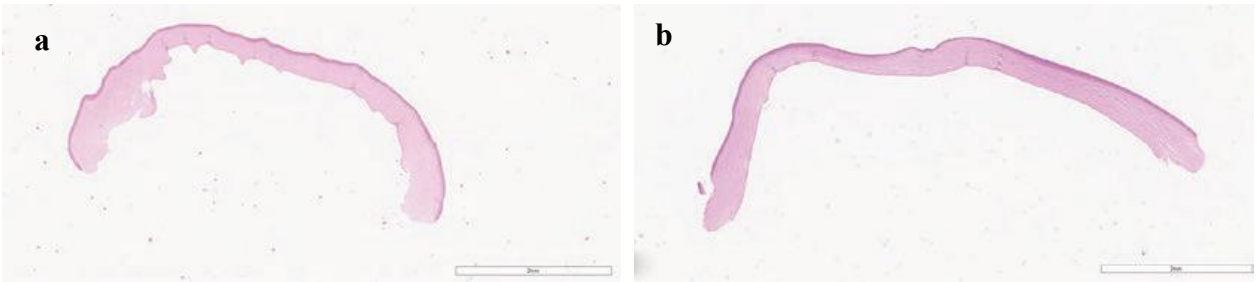


Figure 12 **:** Penetrating keratoplasty specimens: (a) histopathology of the entire section of a KC cornea shows a bow-shaped cornea with diffuse thinning throughout except for the peripheral parts of the section (b) Prominent thinning of the central stroma as compared to the periphery (113).

- **Bowman's Layer:** Is an acellular collagen matrix situated between epithelium and stroma .In KC cellular components have been observed which is abnormal and may indicate structural alteration or reaction .Some studies show the coexistence of

proliferative collagenous tissue which means that a reparative response is activated (114).

- **Stroma:** In KC lamellae are bigger with smaller angle .which alters the normal shape of cornea .The collagen lamellae split into bundles of collagen fibrils with down regulated of ACTB gene encoding β-actin which is responsible of the structure and stability of cytoskeleton (114).
- **Descemet's Membrane:** Ruptures of it have been observed in KC with the common morphological folds and irregularities and do not show any alteration in its extracellular matrix. However ,Descemet's folds is associated with pleomorphism and polymegethism of endothelial cells .The rupture in Descemet's membrane is a serious complication which is known as acute corneal hydrops (114).
- **Endothelial Cells:** This layer is a monolayer with regularly sized polygonal cells, which regulate the water content of corneal stroma. In some studies, this layer does not exhibit any changes during KC progression. In other it reported increase in endothelial cell density in KC, while others have shown significant decrease in moderate to severe KC (92).

5. Patterns &clinical grading:

Identifying KC patterns or grading is the first step in approaching the disease because severity and stage at which the patient diagnosed affect treatment results so KC classification depend on the morphology of cone and topographic patterns.

5.1 Morphological patterns:

The cones morphology is determined according to their size on corneal topography. Best seen in tangential maps where KC has three types of cones:

5.1.1 Nipple cone:

Are characterized by their small size (≤5 mm) with steep curvature, the cone is commonly central or paracentral (most common inferonasal) (115).

5.1.2 Oval cone:

Are larger than nipple cones (6-7 mm) ellipsoid and the cone displaced inferotemporal (115).

5.1.3 Globus cone:

Are the largest (>7 mm), involve 75% of the cornea (115).

5.2 Curvature based patterns:

There are many corneal patterns (curvature), some are accepted others are considered as risk factor for Lasik and may lead to ectatic diseases such as KC.

5.2.1 Symmetrical shapes:

Abnormal if Km> 47.2 D in Placido-based topography and 48 D in Scheimpflug-based tomography (94).

- **Round:** The steepest part of the cornea is round (hot spot), usually decentered (minimal anterior astigmatism) (116).
- **Oval:** The hot spot is oval centred or decentred as Fig (15) shows (116).
- **Symmetrical bowtie:** This pattern can be either vertical ‘WTR’ or horizontal ‘ATR’ or oblique this pattern can be normal astigmatism or symmetric type of KC (116).

5.2.2 Asymmetrical shapes:

- **Superior steep:** SS; the steepest part of the cornea is localised in the upper part (116).
- **Inferior steep:** IS; the steepest part is an isolated hot spot inferiorly (116).

5.2.3 Skwed shapes:

- **SYMMETRICAL BOWTIE:** With SRAX > 22 °
- **Asymmetrical bowtie:** With SRAX > 22 °

5.2.4 Irregular shapes:

- **Irregular:** The corneal surface take no regular shape; steep areas are mixed with flat one (116).
- **Crab claw:** Or kissing birds, this pattern is encountered in PMD, PLK (116).
- **Vortex pattern:** Also known as 'Nazi logo'.
- **Butterfly pattern:** The bowtie is horizontal with lobes inferiorly angulated (not necessarily equal in size).

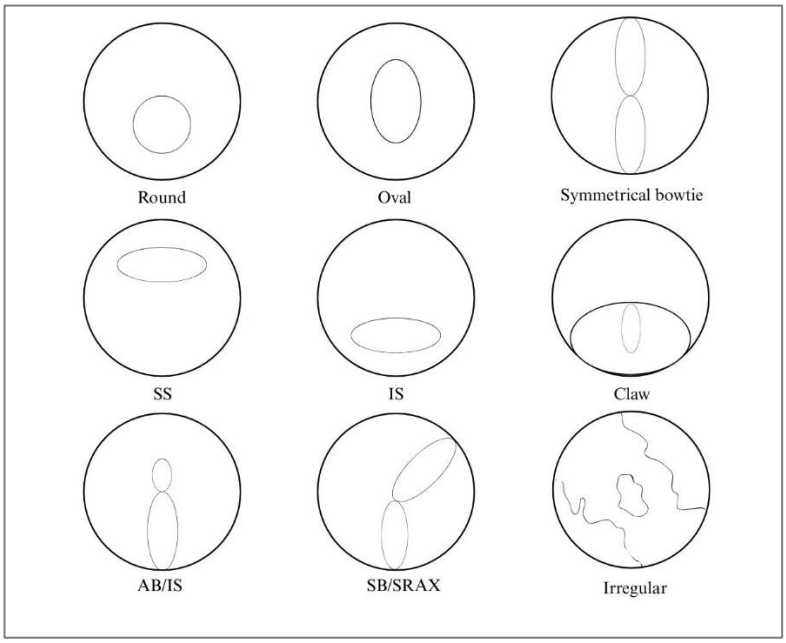


Figure 13 :Different Topographic Patterns.

5.3 Elevation based patterns:

Elevation maps are typically related to the change from corneal elevations and depressions in comparison with a computer-generated reference surface. Those maps are more accurate at detecting abnormal corneas, as the elevation is independent of the axis, or orientation, of the corneal curvature, false-positive results are not seen with. The most important references to qualifies and quantifies surface are:

5.3.1 Best-fit sphere float mode 8 mm reference (BFS):

According to D.Gatinel et al, The best fit sphere was approximated as the sphere minimizing the sum of the squared residuals with the tested corneal surface modeled by a biconic (117).

- Central when apex is in the 3 mm zone.

- Paracentral if the apex is in the 3-5 mm zone.
- Peripheral when it is outside 5 mm zone

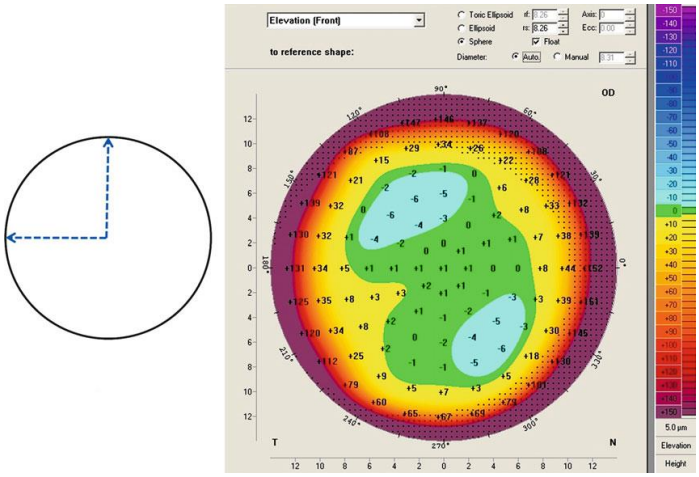


Figure 14**:** The elevation map displayed in the best fi t sphere float mode (115).

5.3.2 Best-fit toric ellipsoid float mode 8 mm reference (BFTE):

BFTE is the best reference to identify true cone elevations in irregular astigmatism (118).

- Any points superior than 12 µm on the anterior map is abnormal (116).
- All points >15 µm on the posterior map also abnormal (116).

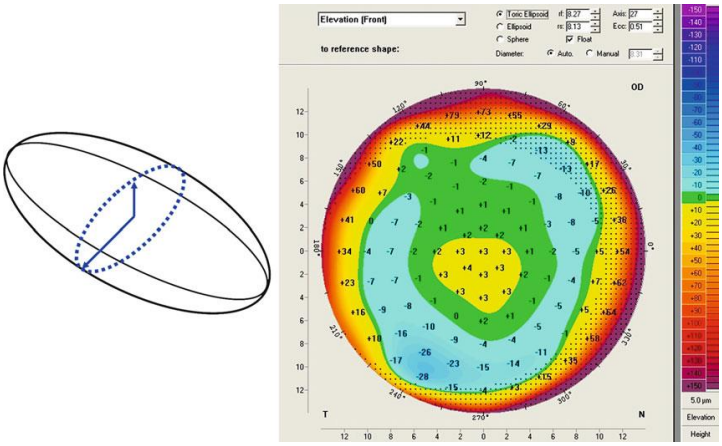


Figure 15**:** The elevation map displayed in the best fit toric ellipsoid float mode (115)

5.4 Pachymetry based patterns:

Corneal thickness becomes an important variable in disease detection or process. Where the thinnest part of a normal cornea is within 5 degrees and increase in periphery. The normal central

range between 520-540 µm, if the thinnest part is decentered or asymmetric it may suggest a corneal disease like KC.

Based on what Dr Moataz mentioned in his book 'KERATOCONUS THE WHOLE STORY', KC patterns can be divided into:

- Normal shape: is concentric
- Abnormal may be:
    - Oblique displacement of the thinnest location (dome shape)
    - Inferior thinning (bell sign)
    - Generalized thinning (keratoglobus).

5.5 Clinical grading:

KC therapeutic strategies must be based on many criteria; most commonly, clinical grading which depends on the corneal apex location, thickness, curvatures, elevation, and progression.

To date; there is no clinically adequate classification.

5.5.1 Amsler-Krumeich classification (1998):

The Amsler-Krumeich system is a combination of two classification approaches: the Amsler classification was based on semiology and Javal's measurements, while Krumeich classification, incorporates astigmatism dioptric power and K reading, central corneal thickness (CCT) measurement , with clinical signs such as Vogt's straie and corneal opacities as shown in Table 04 (119).

Table 7 : Amsler-Krumeich classification in 1998 (116).

Grade	Mean Central Keratometry	CCT	Spherical Equivalent	Cornea
1	< 48 D	> 500 µm	< -5 D	Clear
2	48 D to < 53 D	> 400 µm - 500 µm	- 5 D to < - 8 D	Clear
3	53 D to < 55 D	> 300 µm - 400 µm	> - 8 D	Clear
4	> 55 D	< 300 µm	Not Measurable	Scar

5.5.2 Alio - Shabayek classification (2006):

Alio and Shabayek proposed a modification of the Amsler-Krumeich classification after clinically detecting KC and confirming the diagnosis through videokeratography .Their approach takes into account the mean central K readings, the root mean square (RMS) of coma-like aberrations, as well as the presence of corneal scarring in advanced cases (120).The classification is structured in this way (120):

Stage I

- Mean central K readings <48.00 D.
- RMS of coma-like aberration from 1.50 to 2.50 µm.
- Absence of scarring.

Stage II

- Mean central K readings >48.00 to <53.00 D.
- RMS of coma-like aberration from >2.50 to <3.50 µm.
- Absence of scarring.
- Minimum corneal thickness >400 µm.

Stage III

- Mean central K readings >53.00 to <55.00 D.
- RMS of coma-like aberration from >3.50 to <4.50 µm.
- Absence of scarring.
- Minimum corneal thickness 300 to 400 µm.

Stage IV

- Mean central K readings >55.00 D.
- RMS of coma-like aberration >4.50 µm.
- Central corneal scarring.
- Minimum corneal thickness 200 µm.

5.5.3 RETICS Classification Jorge L. Alio et.al, (2011):

The RETICS classification proposed by Jorge L. Alio et al. (2011) is based on many criteria like BCVA, internal astigmatism, corneal asphericity or Q-value at 8 mm zone.

Table 8 : RETICS Classification Jorge L. Alio et.al, in 2011 (116).

Grade	BCVA	Internal Astigmatism	Q-Value	Coma (RMS)	Mean Central K	CCT
1	> 0.9	1.59 - 2.14	- 0.05 to - 0.22	1.16 µm - 1.52 µm	44.75 D - 45.4 D	495 µm - 510 µm
2	> 0.6 - ≤ 0.9	2.18 - 2.79	- 0.22 to - 0.48	1.82 µm - 2.31 µm	46 D - 46.93 D	475 µm - 493 µm
3	> 0.4 - ≤ 0.6	3.04 - 4.17	- 0.58 to - 0.95	2.65 µm - 3.32 µm	48.21 D - 49.27 D	451 µm - 470 µm
4	≤ 0.4	3.68 - 4.58	- 0.83 to - 1.21	3.45 µm - 4.42 µm	51.42 D - 53.12 D	433 µm - 454 µm
4 plus	≤ 0.2	> 5.5	< -1.5	> 5.5 µm	> 57 D	361 - 420 µm

5.5.4 Ishii and Associates Classification (2012):

The following table summarizes this classification by correlating clinical signs, visual acuity, and elevation-based indices to better define KC severity across five progressive stages.

Table 9 : Ishii and Associates Classification in 2012 (116).

Grade	BCVA	ISV	KI	Other 4 Indices	R-min of ACS (mm)	Retinoscopy	Cornea
Early	1	< 30	1.04 – 1.07	Normal	7.8 – 6.7	Normal	Clear
1	0.8 – 1	30 – 55	1.07 – 1.15	Sometimes 1 value abnormal	7.5 – 6.5	Distorted red reflex, mild scissor reflex	Clear, Fleischer ring
2	0.3 – 1	55 – 90	1.10 – 1.25	Often 1 value abnormal	6.9 – 5.3	Difficult retinoscopy, clear scissor reflex	May be clear, Fleischer ring, Vogt striae
3	0.16 – 0.6	90 – 150	1.15 – 1.45	At least 1 value abnormal	6.6 – 4.8	Difficult retinoscopy, clear scissor reflex	May be clear, thinning, FR, VS
4	< 0.05 – 0.2	> 150	> 1.5	At least 1 value abnormal	< 5.00	Difficult retinoscopy, clear scissor reflex	Scarred, Munson sign

5.5.5 Belin ABCD Classification (2016):

This new classification system conveys both functional and anatomical data missed in Amsler-Krumeich classification. It defines stages from 0 to 4 based on anterior /posterior radius of curvature (ARC/PRC); thinnest pachymetry and BCVA (121).

Table 10 : Belin ABCD Classification in 2016 (121).

ABCD Criteria	A ARC	B PRC	C Thinnest Pachymetry	D BCVA (Snellen / decimal)	Scarring
Stage 0	> 7.25 mm (< 46.5 D)	> 5.9 mm	> 490 µm	≥ 20/20 (≥ 1.0)	–
Stage 1	> 7.05 mm (< 48 D)	> 5.7 mm	> 450 µm	≤ 20/20 (≤ 1.0)	–,+,++
Stage 2	> 6.35 mm (< 53 D)	> 5.15 mm	> 400 µm	< 20/40 (< 0.5)	–,+,++
Stage 3	> 6.15 mm (< 55 D)	> 4.95 mm	> 300 µm	< 20/100 (< 0.2)	–,+,++
Stage 4	< 6.15 mm (> 55 D)	< 4.95 mm	≤ 300 µm	< 20/400 (< 0.05)	–,+,++

Scarring – clear, no scarring (–), scarring, iris details visible (+), scarring, iris obscured (++); Diopters also shown for anterior radius of curvE.

6. Progression Criteria in Keratoconus:

Detecting the ecstatic state at the beginning or in the early stages is as important as the diagnosis and treatment itself. However, identifying or defining the disease progression remains to be challenging. Another difficulty lies in the lack of standardized quantitative data, which are likely to be specific to each imaging device (122).

Despite the development of several keratoconus classification systems, none of them are currently validated for monitoring disease progression. To date, none of the available criteria have achieved the required level to be considered as the gold standard (116). So several authors have attempted to establish reliable parameters that would indicate unfavorable evolution of the disease, as summarized in Table (122).

Table 11 : Diversity of the criteria used in the literature for defining the progressive state of the ectatic disease (122) .

Author	Kmax (AntK)	Corneal Thickness (TP)	Cylinder	Visual Acuity (UDVA/CDVA)	MRSE	Other Criteria
Raiskup-Wolf et al. (2008)	>1 D in 1 year	–	–	Subjective loss of BCVA	–	Dresden Protocol
Vinciguerra et al. (2009)	>1.5 D in 6 months	TP thinning > 5% in 6 months	>3 D in 6 months	–	Myopia >3 D in 6 months	–
Hersh et al. (2011)	>1 D in 2 years	>1 D in 2 years	–	–	SE >0.5 D in 2 years	–
Choi et al. (2012)	>1.5 D in 1 year	–	–	–	–	–
O'Brart et al. (2011)	>0.75 D in 18 months	>0.75 D in 18 months	–	Worsening >1 line in 18 months	–	–
Wittig-Silva et al. (2008)	>1 D over 6–12 months	>1 D over 6–12 months	–	–	SE >0.5 D in 6–12 months	–
Chatzis et al. (2012)	>1 D in 1 year	–	–	–	–	–
Hashemi et al. (2013)	>1 D in 1 year	>1 D in 1 year	–	Worsening >2 lines CDVA in 12 months	SE >1 D in 1 year	–
Mazzotta et al. (2014)	>1 D in 6 months	TP thinning >10 µm in 6 months	–	Worsening >0.5 line UDVA/CDVA in 6 months	SE >0.5 D in 6 months	SAI or IS >0.5 D in 6 months
Stojanovic et al. (2014)	>1.5 D in 12 months	>1 D in 12 months	–	–	Myopia >1 D in 12 months	–
Shetty et al. (2015)	>1 D in 6 months	TP thinning >5% in 6 months	–	–	SE >1 D in 6 months	–
Poli et al. (2015)	>0.75 D in 6 months	TP thinning >10 µm in 6 months	–	Worsening >1 line UDVA/CDVA in 6 months	SE >0.5 D in 6 months	–
Godefrooij et al. (2016)	>1 D in 6–12 months	–	–	–	–	–

Legends: AntK Anterior keratometry, D diopters, MRSE Manifest refractive spherical equivalent,OZ Optical Zone, TP Thinnest point, SAI Surface Asymmetry Index, IS Inferior -superior index,UDVA Uncorrected Distance visual acuity, CDVA Corrected distance visual acuity.

7. Diagnostic tools in Keratoconus:

Over the past decades, diagnostic tools have evolved going from basic anterior curvature assessment to highly sophisticated imaging and biomechanical analysis.

Modern KC diagnostics can be categorized into corneal shape analysis (topography and tomography), structural segmentation (such as epithelial thickness mapping) biomechanical evaluation and high-resolution imaging. Moreover, advanced technologies such as wavefront aberrometry, in vivo confocal microscopy and spectral microscopy, artificial intelligence (AI) and artificial neural networks (ANNs) are emerging as powerful tools in enhancing diagnostic precision and predictive modeling.

7.1 Topography & Tomography:

Corneal topography is defined as a non-invasive exploratory technique to analyze the morphology of the cornea granting its geometric characterization and differentiating standard patterns. Current corneal topographers are based on one of these technologies: 1) Systems based on the light reflection on the cornea, 2) Systems based on the projection of a slit light on to the cornea, and 3) Systems based on the asymmetric reflexion of multicolor light-emitting diodes (LEDs). This tool provides various maps including curvature and elevation maps where curvature maps may be sagittal, which give a spherical shape and offer smoothed, easier-to-read visuals or tangential, which offer higher sensitivity in detecting changes and require more advanced interpretation. Elevation maps, on the other hand, compare the corneal surface to a reference model, such as a best-fit sphere or ellipsoid, to detect protrusions or depressions (123).

The primary purpose of corneal topography is the indices generation that quantify the degree of corneal irregularity either local or global. From these data clinical studies have aimed to establish cut-off values to differentiate between normal and pathological corneas, as well as to define various stages of KC severity (123).

Therefore, to improve the diagnosis precision, tomography is used to eliminate the problem noted with centrally located technology cameras and captures both anterior and posterior surfaces plus corneal thickness profile (pachymetry) across the entire corneal surface. Which make it necessary to detect SCK and for intraocular lens calculations in irregular corneas (124).

7.2 Segmental Tomography with Epithelial Thickness:

Optical coherence tomography (OCT) is a high-resolution cross-sectional imaging modality initially developed for retinal imaging. Izatt et al first described anterior segment OCT (AS-OCT) imaging in 1994, using the same wavelength of light as retinal OCT, namely 830nm (125).

Segmental tomography using AS-OCT gives detailed image of the anterior chamber including corneal epithelium that measures 50-60 µm in normal situation (Figure 31a), and typically thicker inferiorly and nasally due to anatomy and blinking mechanics. The epithelium mask irregularity by thinning or thickening in the considered areas. In KC patterns like focal thinning or "doughnut" shape, can be present (Figure 31b) but are not diagnostic unless they coincide with posterior elevation. Epithelial thickening alone without posterior elevation may be reason of curvature changes without indicating KC. It is therefore a case of epithelial masking or optical effect not ectatic disease (116).

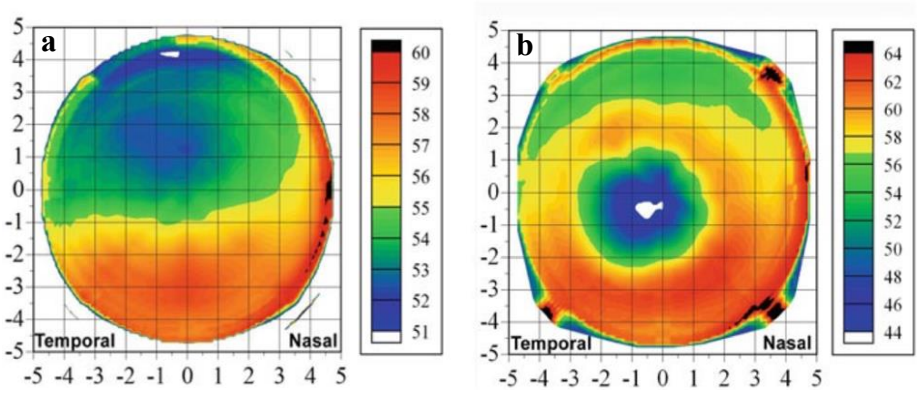


Figure 16**:** a) normal distribution of epithelial thickness b) doughnut pattern of epithelium (116).

7.3 Biomechanics of Cornea:

In his chapter on the early diagnosis of keratoconus, Tojar et al, states that there is a strong consensus that biomechanical changes are related to the onset of corneal ecstatic disease. Studies propose that there is a focal biomechanical change. The abnormality starts a pathology cycle, with secondary thinning and deformation (126).

The equipment that normally analyzes that aspect consists of:

7.3.1 Ex-Vivo Flap Extensiometry:

Is a biomechanical technique used to evaluate mechanical properties of corneal tissue, it compromises the corneal structure leading to collagen fibers destruction which makes it suitable only for ex vivo application and not for in vivo use. By analyzing the corneal flap response to stress this method helps in understanding the structural integrity and stability of the cornea post-surgery which makes it the gold standard to evaluate the risk of complications like ectasia (116).

Tensile loading can be one, two, or three-dimensional. In one dimensional tests force is applied in a single direction measuring strain but not reflecting the natural stress distribution. Two dimensional loading involves bi-directional forces on a circular flap and the three dimensional includes forces in multiple directions simulating more realistic corneal stress conditions (116).

7.3.2 Air Puff Deformation:

The equipment that normally analyzes that aspect consists of noncontact tonometers, the first of which is:

The **Ocular Response Analyzer (ORA)** It uses a collimated air beam that deforms an area of 5–6 mm and use two indices: the corneal hysteresis (CH) index and the corneal resistance factor (CRF) index. The second is the **Corvis ST** which is a noncontact tonometer system that uses an ultrahigh-speed Scheimpflug camera to monitor the corneal deformation over a 5- to 6-mm area during an air pulse application (126).

7.3.3 Brillouin optical scanner system (BOSS ™):

Brillouin microscopy is a non-contact label-free optical technique that characterize local micromechanical properties of biological tissue by measuring Brillouin light scattering (BLS) these light hits acoustic waves inside tissues and the way the light changes tells us how stiff or soft the tissue is (127).

N.B.BOSS™ is a combination of Confocal LASER scanning microscopy +VIPA +Brillouin spectroscopy (116).

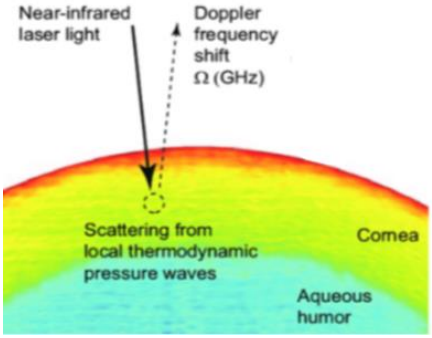


Figure 17**:** schematic diagram showing the idea of brilloiun scatter (116).

7.4 Wave front Aberrations Analysis

Wave front Aberrations Analysis is a diagnostic technique that measure how light waves are distorted as they pass the eye especially the cornea. it generates a detailed map of optical imperfections known as aberrations including HOAs that cannot be fixed with glasses or lenses. The best diagnostic for identifying surface anomalies in KC is this coma along the y-axis (Z_{13}) which provides a sensitive and early diagnosis of the disease (128).

7.5 Confocal Microscopy

Confocal microscopy is a technique that takes multiple 2D images at different planes to create 3D images very clear of the different layers of the cornea. In KC there is several important changes (126):

- There are fewer keratocytes in both front and back parts.
- Polymegatism and pleomorphism.
- The nerves under the surface of the cornea become thicker.
- Presence of posterior stromal folds “Vogt’s stria”.

These changes in cell density are linked to how severe the disease is. This is why In vivo confocal microscopy is helpful it lets us detect these small changes in the cornea early, before they get worse.

8. Management Modalities:

Gomes et al have redefined the management of KC in 2015, it is focused on visual rehabilitation, which involves glasses, and CL or intraocular rings .The second choice is to stop the KC progression by Interventional procedures (129).

8.1 Non-interventional managements:

Non-interventional managements include spectacle correction and the very advanced technology of contact lenses.

8.1.1 Spectacle correction:

Reduced visual acuity due to KC is initially managed with spectacles, which can suffice to correct the regular astigmatism and the very low irregular astigmatism. But in Mild-to- moderate cases spectacles may still be the best choice when the case is stable and the quality and quantity of vision are reasonable (130).

8.1.2 Contact lenses:

As the condition progresses, spectacles may no longer provide the patient with a satisfying visual acuity. The main goal of fitting is to improve it visual with comfort without compromising the health of the cornea. Diameter, base curve and power of the CL are important criteria in selecting the first lens (131).

- **Soft contact lenses:** Is reserved for mild, mostly regular astigmatism.
- **Rigid gas-permeable lenses (RGP):** With their small diameter can help to correct refractive errors while flattening the cornea when worn. They are not suitable for advanced stages due to the irregular shape of the cornea; the lens often becomes unstable, ulcerate the apex, and fall off frequently.
- **Hybrid lenses:** These lenses have a central rigid zone and a soft edge. This type is generally better tolerated than RGP alone.
- **Scleral lenses:** Are larger in diameter and vault over the cornea, creating a reservoir of tears in the center. They are particularly well tolerated in patients with high Kmax values and are prescribed in case of repeated ulcerations.
- **Piggyback lens system:** This consists of placing soft under a rigid lens to improve comfort and tolerance.

Fitting CL in KC can improve the vision and delay or obviate the need for keratoplasty.

8.2 Interventional procedures:

- **ICRS:** were developed for low-myopia correction but have now been approved for both of myopia and irregular astigmatism associated with KC (132).
  The patient must have a clear cornea, a corneal thickness > 450 µm, and Kmax below 55 diopters. Where the ring are implanted through 2 mm incisions either made manually or using a femtosecond laser. These rings help to flatten the cornea and reduce Kmax (about 2 diopters).In most cases, CL still necessary after ring implantation (133).

- **Corneal Transplantation:** Keratoconus is the second most common indication for corneal transplantation, a high success rates, with good visual outcomes and a low rate of rejection is noted. After the graft stabilization, an optical correction may be recommended for the patient. There are different methods of corneal transplantation (133),including:
  -DALK: This involves transplantation of the stroma, while preserving the patient's endothelium (133).
  -PK: A full-thickness transplant including both the stroma and the endothelium (133).

- **Cross-Linking:** Is proposed in cases of progressive KC. The technique aims to accelerate the cornea's natural collagen cross-linking reaction. Two elements are used: UVA light acts as a catalyst, and riboflavin as a photosensitizer. The effect of UVA on riboflavin stimulates a photochemical reaction that creates links between collagen fibers. After CXL, KC stabilizes in 90% of cases.

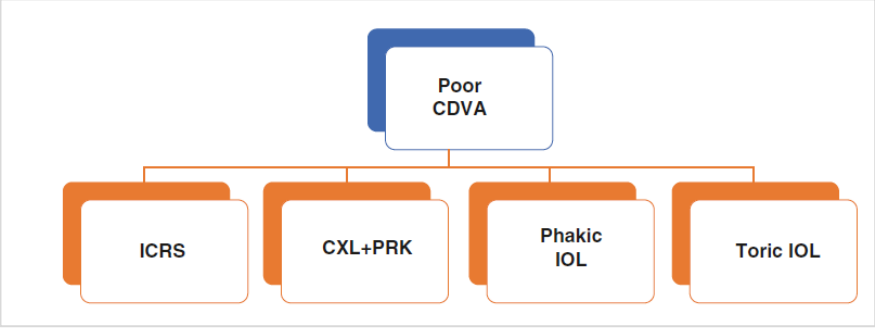


Figure 18**:** Refractive surgical treatment options to improve visual acuity in patients with KC (134).

Conclusion

keratoconus is a non-inflammatory, progressive corneal ecstatic condition that can cause severe visual impairment. The cornea's structural integrity gets damaged during its development due to a confluence of biomechanical, environmental, and genetic factors. Effective treatments and the reduction of long-term visual impairment depend on an early and precise diagnosis. In order to enhance clinical practice and encourage developments in early detection measures, especially in at-risk populations thorough understanding the basic characteristics, risk factors, and diagnostic instruments related with keratoconus is needed.

Chapter 03: Early diagnosis of KC: When should one suspect it?

Introduction

Keratoconus is often diagnosed at advanced stages when clinical signs are already seen and visual impairment become noticeable. The lack of diagnostic tools made early detection challenging leading to limited diagnosis and treatment options. However, with the evolution of imaging technologies and topographic analysis, the ability to identify keratoconus at earliest stages has significantly improved. This progress has given rise to new terms, such as forme fruste keratoconus and subclinical keratoconus, many indicators have been suggested to diagnose them.

Early detection is now a cornerstone especially in candidate for refractive surgery where undiagnosed early KC can have serious consequences.

1. Early Diagnostic Entities:

Much early diagnosis is now possible thanks to developments in diagnostic imaging. Where early keratoconus cases can be classified topographically and clinically to: a) subclinical keratoconus (a normal eye compared with an eye with manifest keratoconus), b) forme fruste (atypical topographic findings without clinical signs), and c) suspicion of keratoconus (typical imaging findings but without clinical signs) are the topographic and clinical classifications for early keratoconus cases.

1.1 Subclinical keratoconus (SCK):

According to Oxford Languages ‘subclinical’ is relating to or denoting a disease which is not severe enough to present definite or readily observable symptoms.

In the systematic review titled "A Systematic Review of Subclinical Keratoconus and Forme Fruste Keratoconus", the authors aimed to identify the definitions used for the terms SCK and FFKC in published articles (33).Where SCK is frequently defined by the following criteria: normal cornea on slit-lamp, biomicroscopy, keratometry, retinoscopy and ophthalmoscopy. Despite this, I-S asymmetry, bow-tie pattern with skewed radial axis and diagnosis of KC in the opposite eye (if it’s bilateral KC).

Table 12 : Frequency of Parameters Used in the Definition of Subclinical Keratoconus in the Analyzed Studies (33)

Parameter	Frequency
Diagnosis of keratoconus in the fellow eye	72.72% (24/33)
Normal-appearing cornea on slit-lamp, keratometry, retinoscopy, ophthalmoscopy	45.45% (15/33)
I-S asymmetry and/or bow-tie pattern with skewed radial axes	36.36% (12/33)
No KC-related signs on slit-lamp examination	33.33% (11/33)
No history of contact lens wear, ocular surgery, or trauma	21.21% (7/33)
Topography: abnormal localized steepening, asymmetric bow tie, or claw-shaped	21.21% (7/33)
One of: keratometry >47 D, oblique cylinder >1.5 D, CCT <500 µm	12.12% (4/33)
I-S <1.4 D and/or Kmax ≤47 D	12.12% (4/33)
KISA index between 60–100%	9.09% (3/33)
KISA index <60%	9.09% (3/33)
Normal topography (no asymmetric bow tie, no focal/inferior steepening)	9.09% (3/33)
No significant topographic findings to diagnose clinical KC	6.06% (2/33)
Keratoconus severity score (value not specified)	6.06% (2/33)
Biomicroscopic signs: Vogt's striae, Fleischer ring >2 mm, SRAX >20–21°, KPI >30%, KSI >30%, abnormal KCI	6.06% (2/33)
CDVA 20/20 or better (Snellen)	6.06% (2/33)
KSS score 0, 1, or 2	6.06% (2/33)
Paracentral I–S asymmetry gradient of 1.4–1.9 D	6.06% (2/33)
BAD-D <1.60 (Belin/Ambrósio index, Pentacam)	3.03% (1/33)
CBI >0.5 in both eyes (Corvis Biomechanical Index)	3.03% (1/33)
Simulated central corneal power between 47.2–48.7 D	3.03% (1/33)
Kmax ≥47 or 47.2 D	3.03% (1/33)
Posterior elevation (no specific value)	3.03% (1/33)

1.2 Form fruste keratoconus (FFKC):

The term "forme fruste keratoconus" (FFKC) was first introduced by Marc Amsler in 1937 (135). Which is a very early and subtle form of subclinical KC often undetectable through standard anterior corneal topography. The term was refined by researchers such as Klyce et al ,to characterize “The fellow eye (of a clinical manifest keratoconus eye) that has no clinical findings of any sort except for certain topographical changes (vide infra)”(136).

The review previously referenced defines FFKC as normal topography with normal slit-lamp examination, and KC in the opposite eye (33).Some researchers consider that FFKC and SCK to be very similar or even the same in certain cases.

Table 13 : Frequency of Parameters Used in the Definition of Forme Fruste Keratoconus in the Analyzed Studies (33)

Parameter	Frequency
Keratoconus (KC) in the fellow eye	77.27% (17/22)
Normal topography	59.09% (13/22)
Normal slit-lamp examination	40.90% (9/22)
Lack of any KC-related findings/signs in the slit-lamp biomicroscopy	13.63% (3/22)
Superior-inferior (I-S) power difference in 4-mm central zone >1.5 D	9.09% (2/22)
KISA values between 60% and 100%	9.09% (2/22)
Nidek Corneal Navigator (NCN) score: non null score similarity to KC in fellow eye	9.09% (2/22)
Mean keratometry <47 D	4.54% (1/22)
Paracentral I–S dioptric asymmetry ≤1.4 D	4.54% (1/22)
Cone apex not centered at 6 o’clock semi-meridian	4.54% (1/22)
Apex corneal thickness ≈30 µm thinner than corresponding distance above pupil center	4.54% (1/22)
Inferior or superior steepening (unspecified value) or minor topographic asymmetry	4.54% (1/22)
Corneal steepness >47.00 D	4.54% (1/22)
KISA <60%	4.54% (1/22)
Keratoconus severity score (KSS) of 1 or 2, regardless of fellow eye status	9.09% (2/22)

Oblique cylinder >1.5 D	4.54% (1/22)
NCN score: null score similarity to suspect KC and KC	4.54% (1/22)
KSS of 0, 1, or 2 if fellow eye has KSS ≥3	4.54% (1/22)
Asymptomatic Pentacam tomography and elevation	4.54% (1/22)

1.3 Suspected form of keratoconus:

The suspected form of keratoconus represents an intermediate stage characterized by: Progressive increase in myopia and irregular, oblique, or inverse astigmatism (137) , Specific parameters on corneal topography such as central corneal refractive power, difference in central corneal refractive power between eyes, difference in inferior-superior diopter, difference in anterior and posterior corneal surface...(138).

A combination of increased vertical coma and higher inferior-superior (I-S) topographic value can better distinguish normal eyes, eyes with suspected keratoconus, and eyes with early keratoconus, compared to using aberrometry or topography alone (138) .

About 20% of eyes with suspected keratoconus may progress to true keratoconus within 6 years and these eyes tend to have greater asymmetry and regular astigmatism on initial examination (139) .

2. Differential diagnosis of keratoconus :

Similar tomographic results from corneal disorders are included in the differential diagnosis of keratoconus. To be able to choose the best course of action, they need to be distinguished from KC.

2.1 Pellucid marginal degeneration (PMD):

Pellucid marginal degeneration is usually a bilateral asymptomatic corneal ectatic disease that affects the inferior periphery of the cornea, most commonly detected in the third to fifth decades of life. The thinning area in PMD comprises a band in the peripheral that may reach from the 4 to 8 o'clock position, where the cornea remains transparent without showing the typical KC clinical signs in spite of advanced thinning located in the periphery of the cornea in a distance of 1–2 mm from the limbus, the cornea above the band is characterized by a flattening of the vertical meridian and an "against-the-rule"

astigmatism. It should be mentioned that some cases diagnosed as PMD based on the 'crab claw' pattern may actually be inferior keratoconus that were misclassified (140).

2.2 Keratoglobus :

keratoglobus is a bilateral congenital disorder that is non progressive or only minimally progressive during lifetime. It is defined by a worldwide protrusion of the cornea with thinning from limbus to limbus and the greatest thinning at the periphery. It can be linked to connective tissue diseases like Marfan or Ehlers-Danlos syndrome. There are none of the usual KC symptoms, such as Vogt striae and Fleischer rings or scarring with cornea of normal size but globally thinned and protruding, without signs of glaucoma (115) .

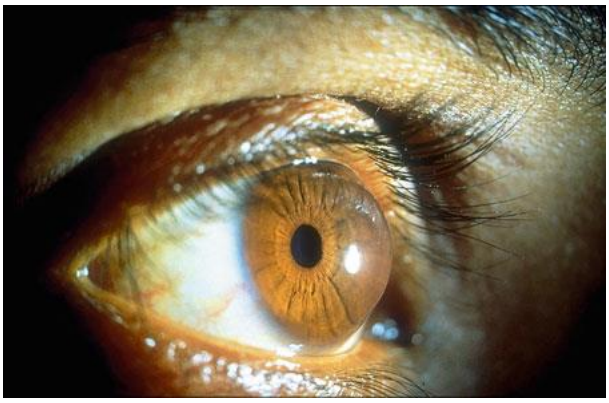


Figure 19: Keratoglobus (115) .

2.3 Pellucid-like keratoconus (PLK) :

A non-inflammatory degenerative corneal condition marked by localized central or paracentral stromal thinning and protrusion which resembles the inferior "crab claw" or "butterfly" pattern typically observed in PMD on corneal topography. PLK causes irregular astigmatism and increasing visual distortion. Despite these similarities, PLK is distinct from PMD in that peak ectasia is located closer to the visual axis rather than in the inferior periphery there is no real peripheral thinning and there is no "bell sign" on pachymetry , Table 15 summarizes the difference between PLK and PMD (115) .

2.4 Terrien marginal degeneration:

It has an impact on a similar age range as PMD. Terrien marginal degeneration may occur on both sides. The superior cornea is primarily impacted and the area of thinning is frequently linked to

vascularization and lipid deposition , even if this condition can be linked to significant astigmatism WTR or oblique it can be distinguished from PMD (115).

2.5 Furrow degeneration:

A non-inflammatory peripheral corneal thinning condition that usually affects older patients. It is distinguished by an epithelialized, avascular and transparent thinning close to the limbus, frequently next to the arcus senilis, with no normal cornea in between. In contrast to PMD it may affect the superior cornea and be linked to systemic autoimmune conditions (115).

2.6 Corneal warpage (pseudokeratoconus):

The look of PMD and PLK on corneal topography can be mimicked by contact lens-induced corneal warping. A history of prolonged contact lens uses and corneal topography capture following a suitable cessation of use retain corneal regularity, which sets the case apart from PMD and PLK.

Table 14 : Comparison between PLK and PMD (115).

Parameter	PLK	PMD
Nature	Central or paracentral ectasia	Peripheral ectasia
Age of presentation	Early teens	20–40
Slitlamp and Scheimpflug	Central or paracentral thinning	Inferior peripheral thinning
Curvature map	Butterfly	Butterfly
Elevation maps – Cone	Central or paracentral cone	Central, paracentral, or inferior peripheral cone
Elevation maps – Kissing birds	Present occasionally	Present in early and moderate cases
Thickness map – “Bell” sign	Absent	Present in moderate and advanced cases
Thinnest location	May be displaced	Usually largely displaced
Keratoconus curve diagram	Deviated	Deviated and usually inverted in advanced cases

3. Diagnosis of keratoconus

3.1 Anamnesis and initial approach:

KC is frequently asymptomatic in its early or subclinical phases and goes misdiagnosed unless certain topographic or tomographic tests are carried out. When keratoconus patients are symptomatic, they usually exhibit gradually increasing blurriness or distortion of vision, usually in one eye initially but later affecting both. Depending on the severity of the condition KC symptoms vary (141).

Given the patient's refraction and distance visual acuity, near visual acuity is frequently initially intact and better than expected. If patients read the vision chart slowly, they can frequently achieve a reasonably excellent Snellen acuity. However, if they are required to read the letters rapidly their vision deteriorates significantly and try to find a comfortable position for the head and eyes when viewing the optotypes. In addition, the difference in refractions in a light or dark room may indicate early stages "fluctuating ", patients may also have monocular diplopia, glare, halos, diminished contrast sensitivity, or "shadowed vision" as the disease progress (141).

3.2 Clinical findings:

3.2.1 External signs:

- **Munson's sign:** A V-shaped profile of the lower lid appears when the patient is instructed to stare downward, it is typically seen in moderate-to-severe KC, while mild cases do not show it (115).



Figure 20:Munson’s sign (115).

- **Rizzuti's sign:** When light is delivered into the cornea from a temporal direction, one can notice it by seeing a light on the nasal anterior sclera. Similar to Munson's sign, it is less sensitive for mild KC and more accurate for moderate to severe (115).

3.2.2 Skiascopy signs:

KC (as well as all other types of irregular astigmatism) can be diagnosed with excellent accuracy with the scissoring effect of the retinal reflex observed during retinoscopy. It is most noticeable when there is dilation of the pupils. The scissoring effect is thought to be sensitive to even early forms (142).

3.2.3 Slit lamp biomicroscopy signs:

- **Focal thinning:** The cone apex, which is often situated inferior to the center of the cornea, is where focal thinning takes place. In PMD, this focal thinning is found in the lower third of the cornea.

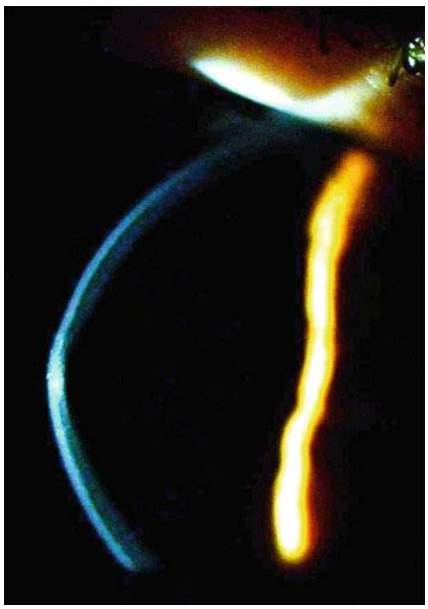


Figure 21:Slit lamp view of the focal thinning (115).

- **Fleischer's iron ring:** It results from ferritin particles building up in the basal epithelial cells of the cornea. It encloses the cone's base entirely or in part (143).

- **Fading star symptom (fireworks):** rarefaction of corneal stroma in the developing ectasia zone, resulting from the anterior corneal stroma's collagen plate architecture being impaired (143).

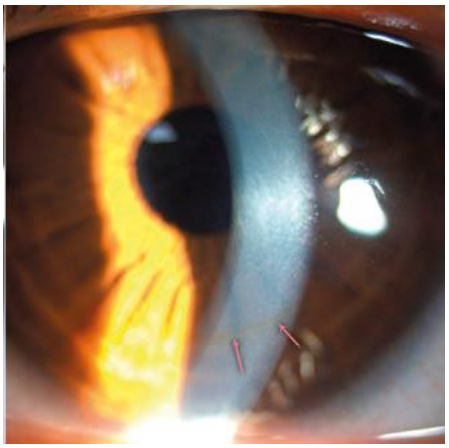


Figure 22: Fleischer's ring in slit-lamp imaging (143).

- **Vogt's striae:** or stromal striae are the apical vertical stripes in the corneal stroma that form when the stroma overstretches (143).

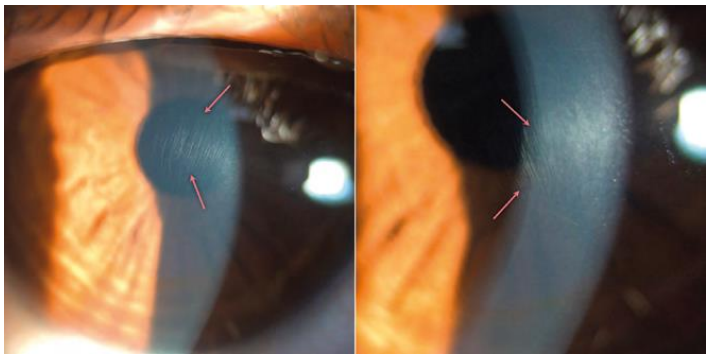


Figure 23: Vogt's striae (143).

3.2.4 Keratoscopy and photokeratoscopy signs:

By looking at the reflected Placido ring pattern through a central pee-phole, keratoscopy enables the physician to visually evaluate corneal shape. The similar idea underlies photokeratoscopy, which produces a more objective image of corneal abnormalities by capturing the reflection with a camera and strobe light. Under a keratoscope or photokeratoscope, the reflected rings appear to be widely distributed when the cornea is flatter and closely spaced where the curvature is steep (115).

- On a normal cornea, the rings are circular.

- In astigmatism, they become oval.
- In KC, the rings are distorted and compressed in the cone.

Modern corneal topographers replaced these traditional methods by employing computer analysis of ring reflections to produce intricate color maps and numerical indexes.

4. Corneal Topography/Tomography for Keratoconus Diagnosis:

4.1 Refractive maps display:

Axial curvature, anterior elevation (BFS), posterior elevation, and pachymetry are all combined in the Pentacam's "four refractive maps" display. To effectively screen for keratoconus (KC) (144).

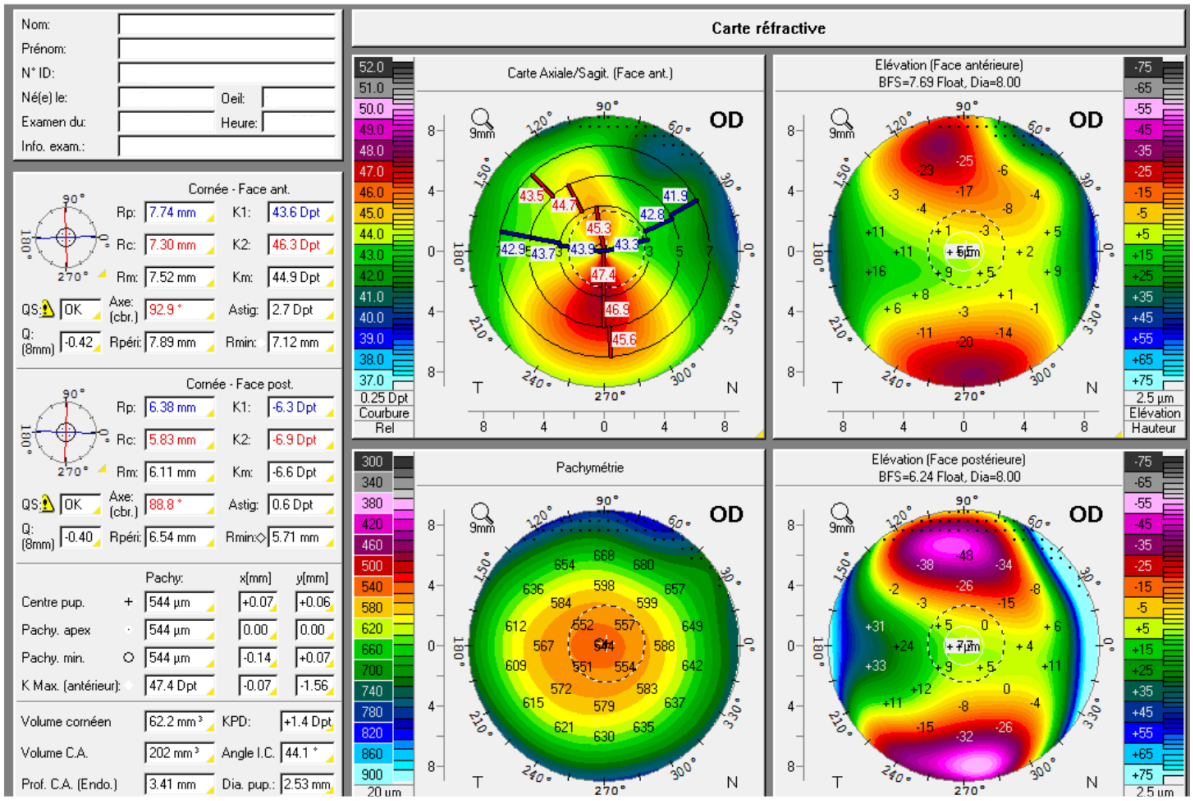


Figure 24 : Four refractive maps showing the anterior axial curvature map, the pachymetry map, and the elevations with best-fit sphere (BFS) maps.

4.2 Anterior axial curvature map:

Using the right color scales and procedures is crucial for identifying irregularities when evaluating refractive maps for keratoconus (KC) screening. A 0.5-D color step scale improves sensitivity for early

detection; however, 1-D or 1.5-D steps are more effective in detecting cone apex in moderate to advanced KC. Overly complex color maps, such as 61-color maps, may become less clear. In order to identify early or subclinical KC, clinicians should search for patterns including inferior asymmetry, focal steepening, skewed meridians, high keratometry values (>47 D), and increased corneal asphericity (Q > –0.5) (144).

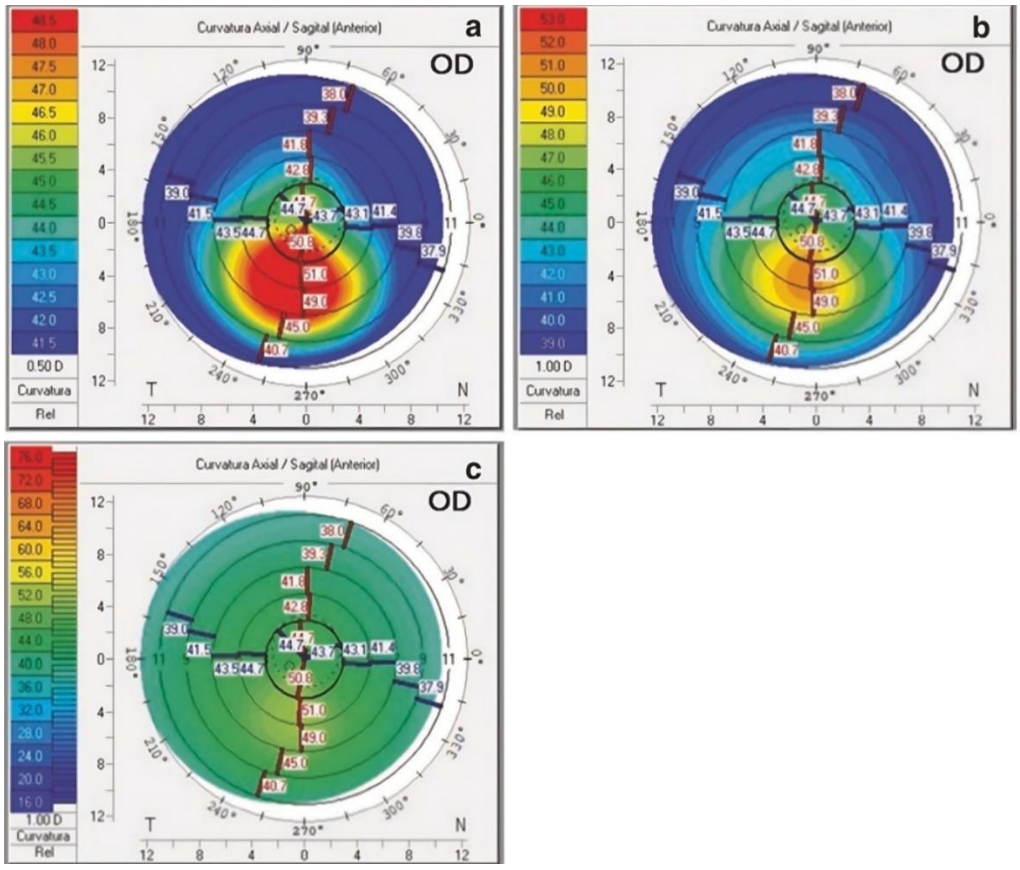


Figure 25 : Several anterior axial curvature maps of the right eye from the same patient. (**a**) Map with a 0.5-D-step relative scale and 15 colors. In this case, it is possible to observe that the red color makes it more difficult to locate the cone apex. (**b**) Map with a 1-D-step relative scale and 15 colors. This combination allows identification of the cone apex. (**c**) Map with a 1-D step but a 61-color combination showing how the several shades of green diminish sensitivity and make it difficult to see the cone (144).

4.3 Pachymetric map:

Finding the cornea's thinnest point and its location in relation to the corneal apex is crucial for identifying aberrant corneas during Pachymetric map analysis. Early keratoconus may be indicated by corneas that are thinner than usual (less than 480 µm) and by the thinnest point located far from the apex. The narrowest point is typically located inferotemporal to the apex. Suspicious distances are those that are more than 0.5 mm from the apex, either horizontally or vertically (144).

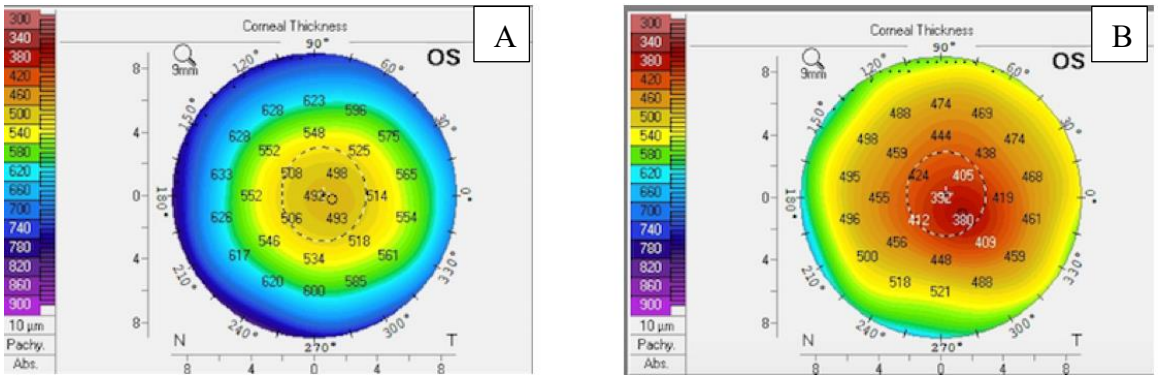


Figure 26 : pachymetric maps. A) pachymetric map for normal eye with regular astigmatism. B) pachymetric map for KC eye.

4.4 Elevation Maps (Best-Fit Sphere):

Elevation maps compare the corneal surfaces to reference shapes like spheres (BFS).

In normal corneas with regular astigmatism, they show a "saddle" pattern with elevated flat meridians and depressed steep meridians. In early keratoconus, the map may show a shifted saddle or an “island” of elevation, indicating a protrusion. On anterior maps, elevations above 5–7 µm may be abnormal, and on posterior maps, values above 12 µm are suspicious (144).

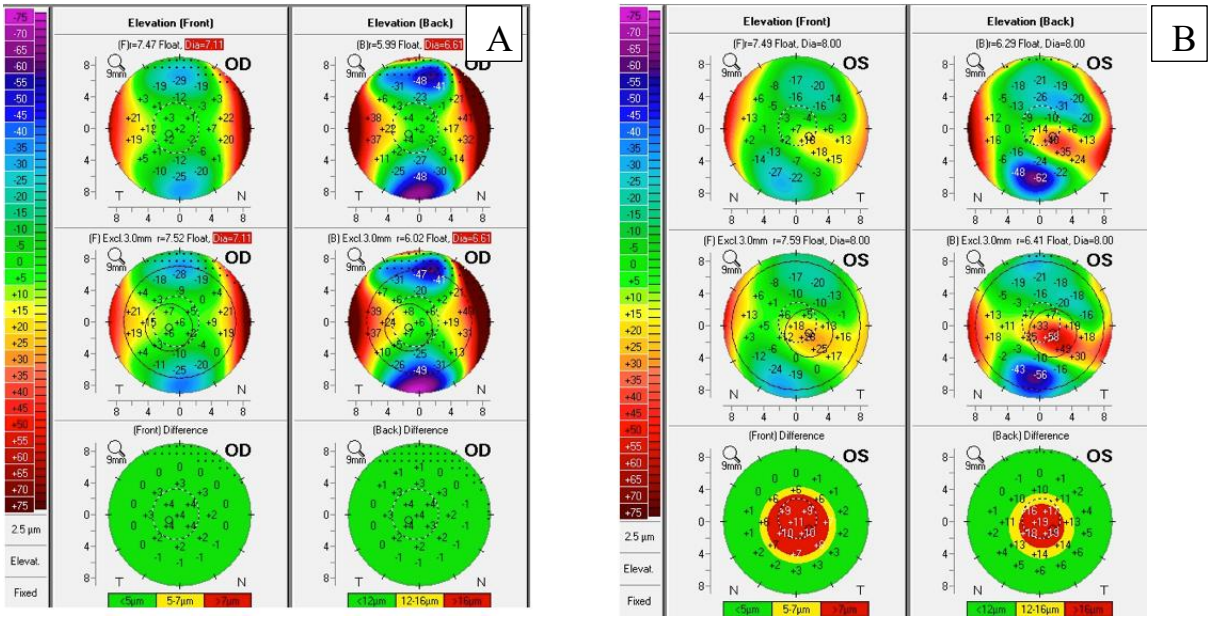


Figure 27 : Representation of elevation maps. A) elevation maps of normal eye showing a “saddle” pattern. B) elevation maps for keratoconus eye showing an “island” pattern.

4.5 Indices for evaluating corneal surface irregularities (KC signs):

Keratoconus severity can be measured using indicators, which is useful for monitoring development over time and assessing aggregated data in studies. Certain corneal indices and detection systems have been created by a number of authors to support the topographic diagnosis of keratoconus(145).

- **Inferior–Superior Value (I-S):** In the corneal region situated 3 mm from the corneal apex at spatial intervals of 30°, the inferior–superior value (I-S value) index is calculated by subtracting the mean of the keratometric values acquired at five points in the inferior hemisphere from the mean of five points in the superior hemisphere. An inferior curvature is higher when the I-S value is positive, while a superior curvature is higher when the value is negative. The cutoff thresholds for clinical keratoconus are values more than 1.8 D, while I-S levels between 1.4 and 1.8 D are seen to be suggestive of probable keratoconus (145).

- **Index of Surface Variance (ISV):** The anterior corneal surface's curvature is measured irregularly by the Index of Surface Variance (ISV), which represents the deviation from the mean curvature. Inconsistent astigmatism is indicated by high ISV counts. An ISV above 37 is deemed abnormal and values above 41 are pathological (145).

- **Index of Vertical Asymmetry (IVA):** The degree of asymmetry between the superior and inferior corneal curvatures is measured by the Index of Vertical Asymmetry (IVA). The manufacturer's handbook states that an IVA of 0.28 or higher is abnormal and that values of 0.32 or above are pathological (145).

- **Index of Height Asymmetry (IHA):** The symmetry of height data with respect to the horizontal meridian is reflected in the Index of Height Asymmetry (IHA), which calculates the elevation difference between the superior and inferior corneas. IHA is more sensitive than IVA because it is based on corneal elevation. The manufacturer's handbook states that an IHA score of more than 19 is deemed abnormal, while values more than 21 are deemed pathological (145).

- **Index of Height Decentration (IHD):** Utilising Fourier analysis on a 3 mm ring, the Index of Height Decentration (IHD) calculates the vertical decentration of corneal elevation data. The manufacturer states that results over 0.014 are considered abnormal and those over 0.016 are considered pathological (145).

- **Center Keratoconus Index (CKI):** Central corneal steepening is reflected by the Centre Keratoconus Index (CKI), which is the ratio of the mean peripheral to central sagittal radii. The severity of central keratoconus causes it to rise. The manufacturer states that a CKI result more than 1.03 is deemed pathological or aberrant (145).

- **Keratoconus Index (KI):** The Keratoconus Index (KI), which measures the ratio of the mean sagittal radii of the superior and inferior corneas, is a unitless number calculated from a number of Placido-derived indices. The manufacturer defines a KI above 1.07 as abnormal or pathological (145).

- **Skew of the Steepest Radial Axis (SRAX):** The SRAX index, which operates on ring powers ranging from 5 to 16 mm, calculates the angle between the steepest superior and inferior semi meridians. It is computed by taking 180° and subtracting the smallest angle between them. When the SRAX is 0°, alignment is present. Only when corneal astigmatism surpasses 1.5 D may values above 20° be considered a credible indicator of keratoconus (145).

- **KISA% Index:** The four components of KISA% steepest radial axis (SRAX), keratometric astigmatism (AST), inferior–superior value (I-S), and maximal keratometry minus 47 D were developed by Rabinowitz and Rasheed:
    1. <60% = normal
    2. 60–100% = suspected keratoconus
    3. >100% = clinical keratoconus

Although it is sensitive and specific, it is not a reliable screening tool for refractive surgery since it may overlook early or subclinical cases (145).

It is important to note that many external and physiological factors, like poor fixation, tear film instability and improper alignment, also recent contact lens wear can affect the corneal measurements and lead to inaccurate or misleading index values.

2.6 Summary of topographic criteria of keratoconus:

The presence of more than one of the following criteria supports the diagnosis of keratoconus, early-stage KC or at the very least. A suspected case depends on the severity and number of signs:

- On the sagittal map:

  - K-readings > 48 dpt - SRAX > 22º - Superior–inferior difference (S-I) on the 5 mm circle > 2.5 dpt- Inferior–Superior difference (I-S) > 1.5 dpt- Corneal astigmatism on either surface should not be higher than 6 D - Against the rule, astigmatism is considered suspicious.

- On the thickness map:

  - Cone-like shape, Superior–inferior at 5 mm circle > 30 µm -Thinnest location < 470 µm - Difference in thickness between both eyes at thinnest locations > 30 µm - Thickness at pachy apex – thickness at thinnest location > 10 µm.

- On the elevation maps:

  - Isolated island or tongue-like extension (BFS mode) on either surface - Values > 12 µm within the central 5 mm on the anterior elevation map (BFTE mode) - Values > 15 µm within the central 5 mm on the posterior elevation map (BFTE mode).

5. Pseudo-progression Versus real progression:

The widely used definition for progression state is an increase in maximum keratometry of 1.0 D or more in 2 consecutive measurements with same imaging tool over 12 months period. The Validity of keratometry measurements decreases as KC becomes more advanced (146):

- If Kmax < 50.0 D the measurement error is approximately 0.4 D.
- If Kmax > 55.0 D the error increases to about 1.7 D.

This means that in severe cases a change of more than 1.0 D may result from measurement variability not an actual disease progression, some authors make a clear distinction (146):

- **True progression**: actual worsening of keratoconus.
- **Pseudo-progression**: increase in keratometry readings without real disease progression which can be caused by: Measurement errors, superficial punctate keratopathy, corneal stromal scarring, contact lens wear, vernal or atopic keratoconjunctivitis…etc. If there is clear thickening of the epithelium but no change in stroma or posterior elevation then the change in keratometry is due to epithelial remodeling not real progression of KC (147).

The advanced diagnostic tools help clinicians avoid unnecessary treatment by identifying whether an increase in keratometry is due to epithelial changes or true stromal changes which is key in deciding whether or not to perform corneal CXL or repeat it (147).

Conclusion

Diagnosing keratoconus requires a comprehensive strategy that combines multiple corneal imaging modalities and indicators, particularly in its early or subclinical stages. Asymmetric patterns, particularly inferior steepening, SRAX or thinnest point displacement, may raise clinicians' suspicion when they appear on curvature or elevation maps. Pachymetry maps that show focal thinning, especially away from the apex, and elevation maps that show localized ridges are also strong indicators. Additional indicators that can strengthen the diagnosis include I-S, ISV, IVA, IHD, and KISA%. Diagnosing keratoconus requires seeing similar patterns across multiple diagnostic tools, as no single feature is completely reliable on its own.

Problem statement

Keratoconus is a progressive corneal ectasia that often begins with subtle and non-specific signs with astigmatism being the earliest and most common. Despite advances in diagnostic imaging and topographic analysis. KC often remains undetected until it reaches significant stages, leaving many cases unidentified.

- **Objective of the Study:**

  - KC is more violent throughout during puberty than in adulthood. When a patient presents with newly formed or fast advancing astigmatism, early screening and diagnosis are crucial. Our study's objective is to evaluate the findings of an optometric and ophthalmological examination related to corneal topography for early detection of KC. Through completely asymptomatic patients who consulted for various reasons such as updating their prescriptions, refractive surgery, allergy symptoms…etc.

  - Our study is a retrospective analysis that aims to evaluate refractive parameters and identify predictive thresholds and indices related to astigmatism progression that may indicate early forms of keratoconus. Our goal is to close the gap between clinical practice and theoretical understanding by accomplishing this.

1. Patients, Materials and Methods:

1.1 Study Design:

Our study is a retrospective approach with data collected from 32 patients. It was carried out in two ophthalmology clinics located in two different areas ,"SERENA Ophthalmology Clinic" in Setif and "Hamou Boutlelis Ophthalmology Clinic (CONIOT) " .

1.2 Sample Description:

Out of 45 initially identified patients, 32 were selected based on specific inclusion and exclusion criteria. The selection aimed to focus on early cases of keratoconus in a young population.

Inclusion Criteria:

- Age under 25 years.
- Diagnosed with stage 1 or stage 2 keratoconus.
- Asymptomatic individuals who consulted for reasons unrelated to keratoconus. diagnosis, such as: - Updating eyeglass prescriptions
  - Refractive surgery
  - Ocular allergy

Exclusion Criteria:

- Corneal conditions other than keratoconus, including: - Central corneal opacities
  - Corneal dystrophies
- Ocular trauma.
- Ocular surgery.
- Eye diseases such as glaucoma, cataract, or retinal pathologies.
- Advanced stages of keratoconus.
- History of corneal transplantation.

1.3 Data collection period:

Data were collected over a three-month period from February 2, 2025 to May 2, 2025.

1.4 Materials:

- A distance optotype: Monoyer chart in French and Arabic and Snellen's E chart.
- A near vision optotype: Parinaud scale.
- A Retinoscope (for uncooperative patients).
- A slit lamp.
- An autorefractor.
- A phoropter.

- A Scheimpflug-based anterior segment imaging device: Pentacam (Oculus), providing corneal topography, tomography, and pachymetry.

1.5 Patient data acquisition:

Patient files were obtained from the clinics record system which included informations such as:

- Refraction, visual acuity, age, sex, ocular and systemic medical history.
- Topographic and tomographic maps (Pentacam system).

The administrations of the clinics gave their approval and agreement for all data collection, «Ethical standards were strictly maintained».

1.6 Clinical Methods:

- **Anamnesis:** This step helps guide the rest of the clinical examination.
  The following information was gathered: full name, age, gender, patient's academic or professional informations, reason for the initial consultation (optical or surgical management), ophthalmologic and general medical history, allergic symptoms, eye rubbing …etc.
- **Visual Acuity:** Measurement of distance visual acuity to examine the patient's vision.
- **Objective Refraction:** The patient's refractive error was objectively assessed using an autorefractor.
- **Subjective Refraction:** Identifying the best optical correction depending on the patient's answers.
- **Slit-lamp examination:** The corneal surface is examined with a slit lamp to evaluate its transparency and identify any signs of advanced stages of KC.
- **Corneal Topography and Tomography/pachymetry:** Were provided by the Pentacam (Oculus). The resulting maps and indices were interpreted.

2. Results:

2.1 Analysis of the Study Population:

2.1.1 Distribution of the sample according to risk factors:

AGE:

The age distribution within our sample showed that 19% of the participants were between 10 and 15 years old, 40% were aged 16 to 20, and 41% fell within the 21 to 25 age range.

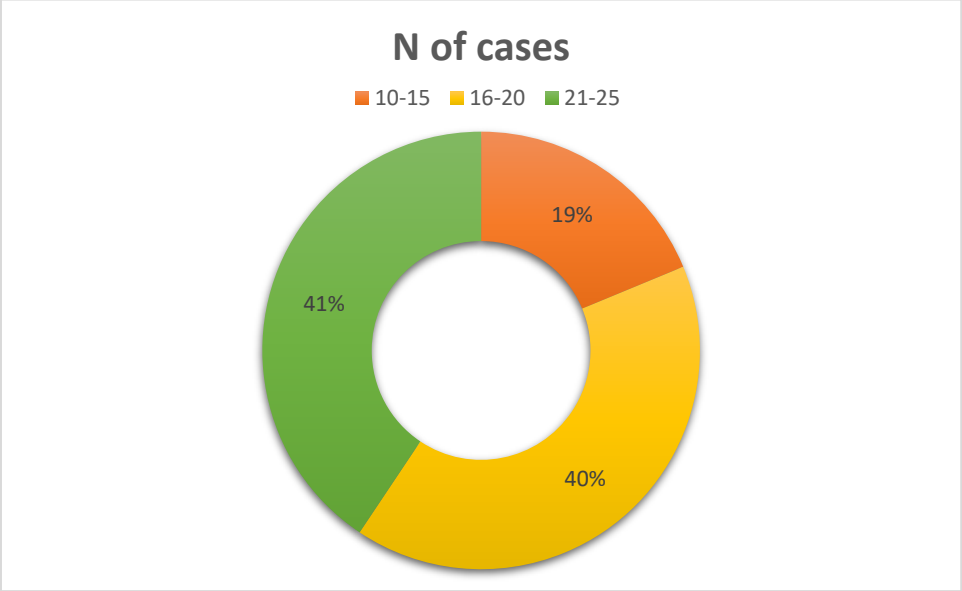


Figure 28: Age distribution of the sample.

GENDER:

Females made up the majority of our sample 75% with males representing 25%.

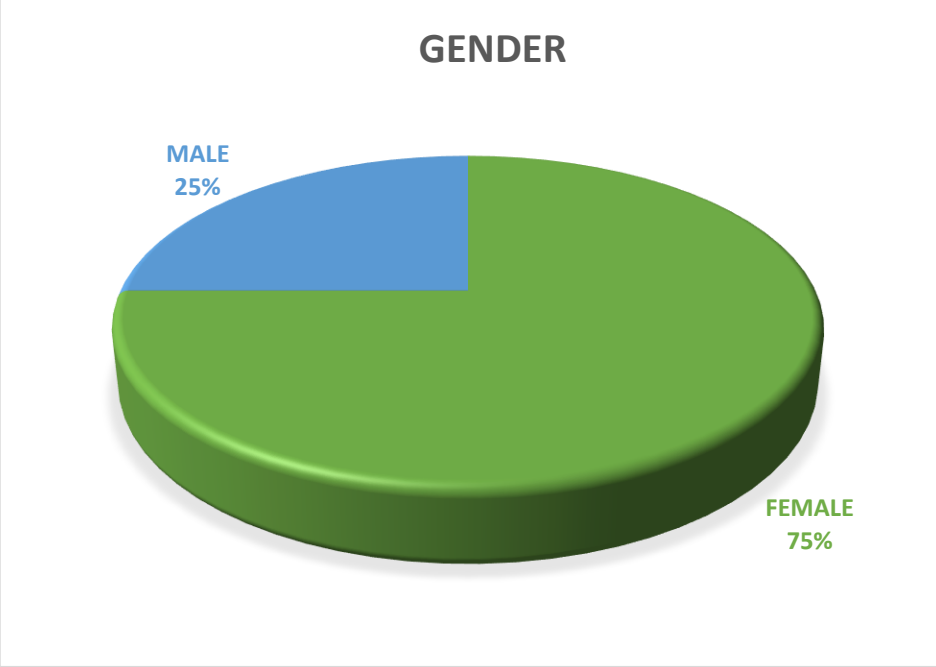


Figure 29:Gender Distribution of the Study Population.

MEDICAL HSITORY:

The Allergies were reported in 8 cases making it the most common antecedents. A family history of KC noted in 2 cases, other specific conditions included: blepharospasm, superficial punctate keratitis (SPK) and giant papillary conjunctivitis (GPC) each present in 1 case. Papillary vernal conjunctivitis (PVC) was identified in 4 cases with 15 cases in other medical histories not specified.

These results highlight the diversity of medical antecedents present in the studied sample.

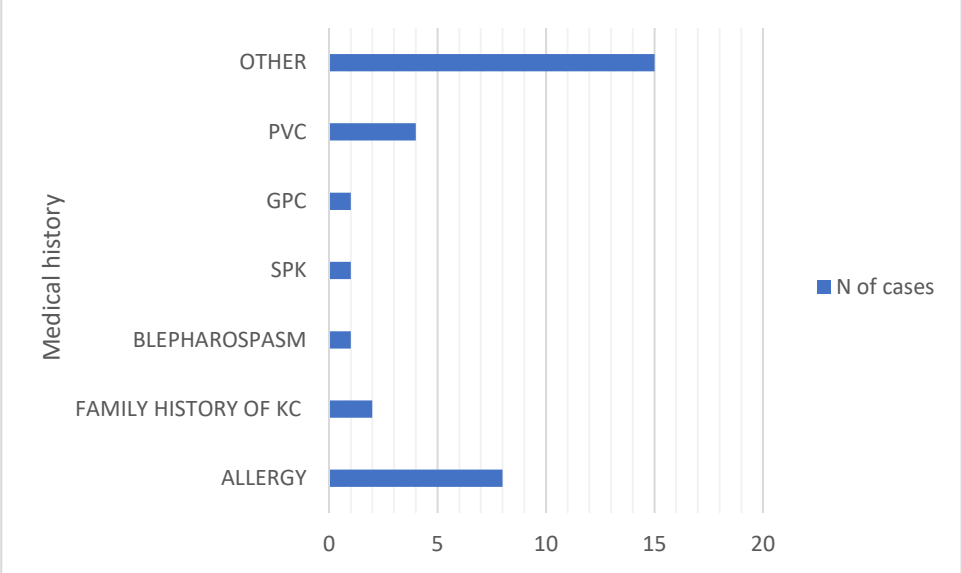


Figure 30:Distribution of Participants' Medical History.

2.2 Refraction analysis

AMETROPIA:

Among the eyes that were later diagnosed with KC the most common type of ametropia observed in their earlier refractive exams was myopic astigmatism (92%). Mixed astigmatism was found in 5% of cases, and only 3% had simple myopia. This distribution may support the role of myopic astigmatism as an early refractive marker of the disease.

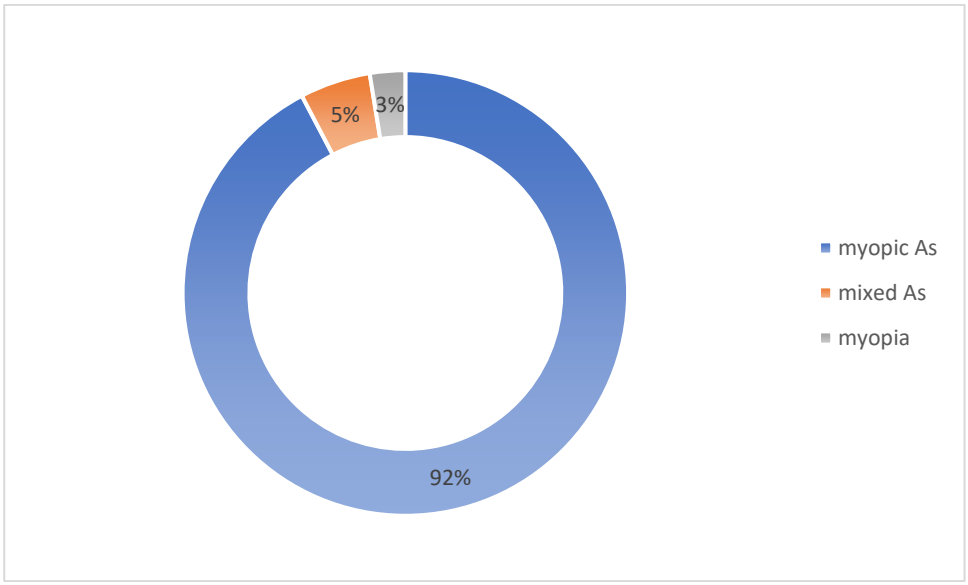


Figure 31 : Distribution of Ametropia Types.

ASTIGMATISM AXIS ORIENTATION EVOLUTION:

The distribution of astigmatism axis orientation types: WTR, ATR and oblique was analyzed at two time points (T1and T2) in both non-KC eyes and KC eyes (table15).

- **Non-KC eyes**: WTR decreased from **61% to 48%**, ATR increased from **17% to 24%** and oblique increased from **22% to 28%**.**28%** of these eyes showing axis type change over time. While these eyes were not clinically diagnosed with KC.

- **KC eyes**: WTR astigmatism decreased from **46% at T1** to **38% at T2**, while ATR increased from **22% to 26%** and oblique astigmatism increased from **32% to 36%**. Over a duration of two years, **33%** of these eyes changed their axis orientation type.

Table 15 : Distribution and Evolution of Astigmatism Axis Orientation in Confirmed and Non confirmed KC Eyes Over "2" Year Period.

Group	Time Point	WTR (%)	ATR (%)	Oblique (%)	AxisOrientation Change (%)
Non-KC	T1	61%	17%	22%	---
Non-KC	T2	48%	24%	28%	28%
KC	T1	46%	22%	32%	---
KC	T2	38%	26%	36%	33%

T1: Astigmatism axis orientation 2 years before detection. T2: Axis orientation at the time of KC detection.

CYLINDER PROGRESSION:

Over two years, the average increase in cylinder was **1.5 D** for the keratoconus (KC) eyes and **0,5 D** In Non-KC group.

CORRELATION BETWEEN ASTIGMATISM SEVERITY AND CORNEAL PARAMETERS: Kmax /Pachy min

Table 16 : Mean K max and Pachy min according to astigmatism severity**.**

Cylinder Groupe	CYL Range	Mean Kmax (D)	Mean Pachy min (µm)
Low AS (16 eye)	CYL ≤ 1.5 D	46,0 D	487,7 µm
Moderate AS (27 eye)	1,5-3 D	48,0 D	492,4 µm
High AS (21 eye)	CYL > 3 D	49,97 D	442,8 µm

- In low astigmatism, the pachymetry is a little bit below the normal value (487,7 µm) and Kmax is borderline.

- In moderate astigmatism, the cornea becomes steeper (Kmax=48 D) and thin (492,4 µm)

- For the severe astigmatism higher than 3 D, the cornea shows an ectatic patterns with a Kmax of 49,97 and a pachymetry of 442,8 µm.

2.3 Evaluation of topographic/tomographic indices:

To identify the most effective indices for the early detection of KC a comparative analysis was performed between KC and non-KC eyes using Receiver Operating Characteristic (ROC) curve analysis to calculate the Area Under the Curve (AUC), p-values, and mean ± standard deviation were calculated for each index. In addition, the optimal cut-off value was determined based on the maximum Youden index, which identifies the threshold that best balances sensitivity and specificity.

Table 17 : Pentacam indices for keratoconus detection: Mean ± SD, AUC, and p-values.

Indices	AUC	KC (Mean ± SD)	Non-KC (Mean ± SD)	P-value
ISV	0.837	50.64 ± 17.95	33.52 ± 13.26	< 0.001
IVA	0.865	0.49 ± 0.25	0.27 ± 0.2	< 0.001
KI	0.854	1.14 ± 0.12	1.06 ± 0.04	0.001
CKI	0.657	1.028 ± 0.025	1.016 ± 0.138	0.024
IHA	0.835	27.8 ± 13.3	13.67 ± 8.3	< 0.001
IHD	0.803	0.09 ± 0.17	0.033 ± 0.049	0.11
IS	0.859	3.63 ± 2.053	1.48 ± 1.28	< 0.001

- Pentacam indices such as **IVA**, **ISV**, **KI**, **IS** and **IHA** showed good discriminative power as confirmed by AUC values **(AUC > 0.83)**, with statistically significant differences between KC and non-KC eyes (**$p \leq 0.001$**).

- The **CKI** showed limited discriminative ability **(AUC = 0.657)**, while IHD did not reach statistical significance **($p = 0.11$)**, thereby limiting the clinical utility of both parameters in distinguishing KC from non-KC eyes.

- The mean values for these indices were higher in the KC group than the other reflecting increased corneal irregularity and asymmetry.

OPTIMAL PENTACAM INDICES CUT-OFFS:

To evaluate the diagnostic performance of different Pentacam indices in detecting keratoconus, we analyzed their sensitivity and specificity at the established cut-off values and calculated the corresponding Youden Index to assess overall diagnostic effectiveness.

Youden index =J= {sensitivity +specificity −1}

Table 18 : Performance of Pentacam Indices at Cut-off Values.

Indices	CUT-OFF	SENSITIVITY	1-SPECIFICITY	Youden index
ISV	39.5	71.8 %	12 %	0.598
IVA	0.315	71.8 %	12 %	0.598
KI	1.085	79.5 %	12 %	0.675
CKI	1.03	41 %	0.08 %	0.330
IHA	20.75	76.9 %	16 %	0.609
IHD	0.024	79.5 %	28 %	0.515
I-S	1.96	76.9 %	16 %	0.609

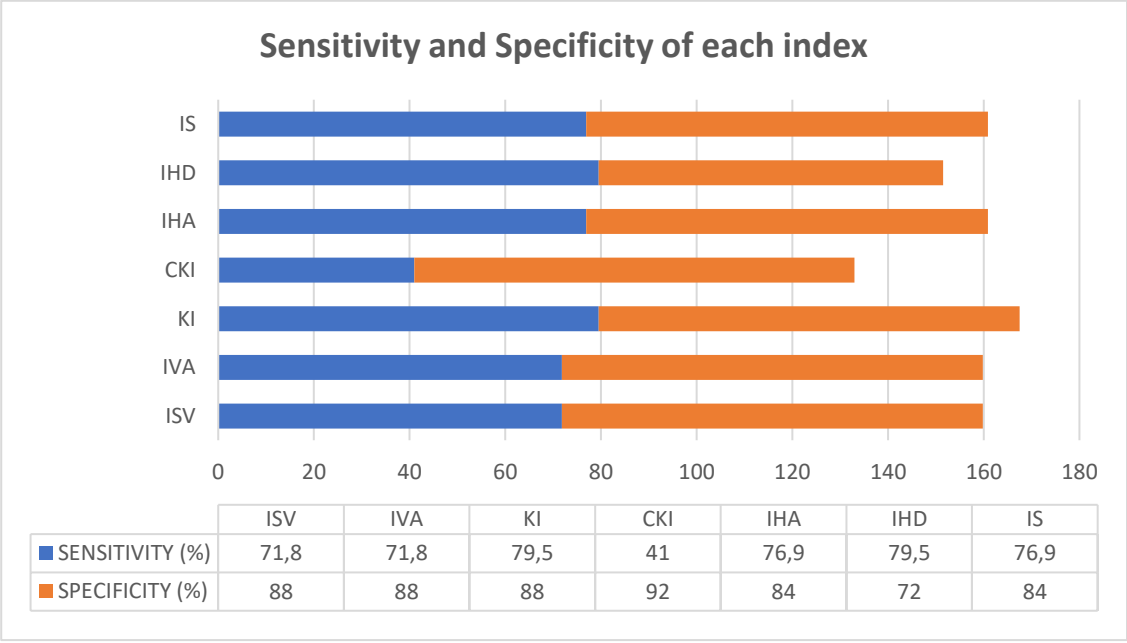


Figure 32: Sensitivity and Specificity of Pentacam Indices.

- At a cut-off of **1.085**, the KI index showed the best overall diagnostic performance among the evaluated indices with ***J* = 0.675**.

- At their respective cut-off values **IHA = 20.75**; **I-S = 1.96**, both indices showed a sensitivity of **76.9%** and a specificity of **84%** with ***J* = 0.609**, indicating balanced and good diagnostic performance.

- With optimal cut-offs **ISV = 39.5; IVA = 0.315**, both indices showed good sensitivity and high specificity **(71.8% / 88%)** with a Youden Index of **0.598**.

- At a cut-off of **0.024** the IHD index showed high sensitivity and moderate specificity with a Youden Index of **0.515**.

- The **CKI=1.03** demonstrated high specificity **(92%)** but low sensitivity **(41%)** with the lowest Youden Index **(*J*=0.330)** among the evaluated indices.

3. Discussion:

Our study on 32(64 eyes) asymptomatic patients under the age of 25 y.o highlights several important elements supporting early detection of KC. The sample was mostly aged 16–25 with a female predominance (75%) showed frequent allergic histories and some familial cases signaling the multifactorial nature of keratoconus and the importance of early screening in at-risk individuals. The most notable findings include a high prevalence of myopic astigmatism (92%) a notable evolution in astigmatic axis orientation over two years (with up to 33% of KC eyes showing change) and a correlation between the severity of astigmatism corneal thinning (Pachy Min) and increased curvature (Kmax). Additionally, a number of topographic indices obtained from Pentacam (ISV, IVA, KI, IHA and IS) showed excellent diagnostic performance (AUC > 0.83, $p < 0.001$).

The analysis of medical history reveals a predominance of allergies, supporting the role of atopic conditions and chronic eye rubbing in the development of keratoconus, further reinforced by the presence of inflammatory ocular diseases such as PVC, SPK, and GPC. The presence of 19% of subjects aged 10 to 15 underscores the importance of early screening specially in familial or high-risk cases and makes clear the need to consider medical history in the examination process.

Refraction analysis was the first of several crucial analytical steps that we took in order to monitor astigmatism for the early diagnosis of KC. The majority of eyes that later developed keratoconus were found to have myopic astigmatism as their initial refractive error. Specifically, 92% of keratoconic eyes presented with myopic astigmatism, indicating that this ametropia may be an early refractive sign of the disease. Mixed astigmatism and simple myopia were less frequently observed at 5% and 3%. These findings suggest that myopic astigmatism could serve as a clinical alert, especially when observed in young patients or in the presence of other risk factors such as eye rubbing or family history.

Our analysis of the astigmatism axis orientation's change over time provided some information with major implications for clinical monitoring and KC early detection techniques. KC and non-KC eyes showed important changes when the astigmatism types (WTR), (ATR), and oblique were analyzed at two different time points. The decrease in WTR percentage, the increase in ATR and oblique astigmatism, and the 28% astigmatism type change seen in non-KC eyes could all be signs of underlying corneal biomechanical abnormalities. However, these changes were more noticeable in the KC group, where 33% of the eyes displayed an axis orientation shift. This suggests that axis orientation instability is more

prevalent in keratoconus and could be a reflection of the cornea's continuous structural deformation. This observation is further supported by previous findings (148) .

Increase in cylinder over two years was 1.5 diopters in the KC group and 0.5 D in non-kc group. This disparity lends support to the theory that progressive alterations in refractive astigmatism are more evident in eyes with keratoconus. According to Belin and al (149) , a value of 1.5 D indicating considerable progression.

The analysis of corneal parameters across different levels of astigmatism reveals meaningful patterns that reinforce the link between astigmatism severity and structural corneal changes associated with keratoconus. High astigmatism (> 3 D) was associated with clear ectatic signs, including a significantly steeper Kmax (49.97 D) and a marked reduction in minimum pachymetry (442.8 µm). While moderate astigmatism (1.5–3 D) showed a steeper Kmax (48.0 D) the mean pachymetry (492.4 µm) was slightly higher than in the low astigmatism group (487.7 µm), This contradiction may reflect individual variation, measurement distribution within small sample sizes, or early biomechanical weakening that precedes steepening in some eyes. Despite this exception the overall trend remains as astigmatism increases, corneal steepening and thinning become more pronounced indicating progressive ectatic risk. These findings underscore the importance of monitoring both the power and axis of astigmatism, and of integrating topographic indices such as Kmax and minimum pachymetry into early keratoconus detection protocols. To support our results, we refer to the findings of Toprak et al (150), who emphasized that kmax and pachy min are key hallmarks of keratoconus progression.

The ROC curve analysis identified five Pentacam indices ISV, IVA, KI, IHA, and I-S as having excellent diagnostic performance, with area under the curve (AUC) values > 0.83 and statistically significant differences ($p \leq 0.001$) between KC and non-KC eyes. These indices are highly performant because they specifically quantify the morphological abnormalities that are characteristic of KC such as surface variance, vertical asymmetry, curvature imbalance and elevation asymmetry. In contrast, the CKI showed limited general discriminative ability (AUC = 0.657) because it focuses on central steepening which is often minimal or absent in early KC leading to reduced sensitivity for detecting the disease at its initial stages. Similarly, the IHD did not reach statistical significance ($p = 0.11$); this can be explained by the fact that IHD measures posterior elevation decentration which tends to be minimal in early keratoconus and may overlap with normal anatomical variations, thus limiting the clinical utility of both parameters in distinguishing KC from non-KC eyes.

To complement the ROC findings, we further evaluated the diagnostic thresholds (cut-offs) of these indices using sensitivity, specificity, and the Youden Index. This additional analysis reinforces their clinical utility and highlights the most balanced diagnostic markers.

In our study, the KI at a cut-off =1.085 showed the best overall diagnostic performance among the evaluated indices with a sensitivity of 79.5%, specificity of 88% and a Youden Index of 0.675 indicating a strong sensitivity-specificity balance. This can be explained by what the KI measures. Such as greater steepness of the inferior cornea, making the KI effective for detecting the disease before advanced signs appear. The cut-off aligns with the 1.07–1.15 range defined for early KC in the Kanellopoulos Pentacam-based classification, supporting its relevance for early detection. Our results are consistent with the literature showing that KI has strong diagnostic accuracy for KC although it is less reliable in subclinical cases where combining it with other indices is recommended (151).

At their respective cut-off values (IHA = 20.75; I-S = 1.96) both indices showed good and balanced diagnostic performance (sensitivity = 76.9%, specificity = 84%, Youden index = 0.609). This can be attributed to the fact that IHA quantifies the asymmetry of corneal elevation relative to the horizontal meridian while I-S assesses the difference in power between inferior and superior cornea. The IHA cut-off aligns with the range 19–21 defined by Alvarez et al supporting its relevance for early KC detection (152). In contrast, the I-S cut-off in our study does not match the value reported by Doroodgar et al, who suggested that normal inferior–superior differences within the 5-mm central zone should be under 2.5 D (151) , The discrepancy may reflect our small sample, higher proportion of early KC cases where inferior steepening is less marked and protocol differences, possible differences in measurement zones, underscoring the need to interpret I-S cut-offs within each study's context of each population and protocol.

ISV and IVA demonstrated similarly strong diagnostic ability, with cut-offs of 39.5 and 0.315, respectively. Both had sensitivity = 71.8%, specificity = 88%, and a Youden Index = 0.598, reflecting reliable performance in capturing irregular surface topography. This can be explained by the fact that keratoconus typically manifests as a loss of corneal curvature regularity (detected by ISV) and vertical asymmetry (detected by IVA). These abnormalities can be identified even before more advanced signs, These cut-off values are close to those reported by Shetty et al. in 2017 (153), supporting their relevance for keratoconus detection. Hashemi et al also highlighted their usefulness in preclinical cases (154), while other authors have shown their value in postoperative follow-up and monitoring of KC progression over time.

At a cut-off of 0.024, the IHD index showed high sensitivity and moderate specificity, with a Youden Index of 0.515, indicating fair diagnostic performance compared to other indices. This can be explained by the fact that IHD quantifies the decentration of corneal elevation relative to the center. In KC especially cases where the cone is decentered IHD tends to be elevated which contributes to its high sensitivity. However, since decentration can also be influenced by other factors such as eyelid pressure or fixation errors during imaging, the specificity is more moderate. This reflects that while IHD is useful for detecting KC it is less effective on its own in distinguishing KC from other conditions that also cause decentration. Our cut-off value does not match that reported by Shetty et al (153), likely due to the already mentioned differences in population, methodology, or measurement protocols .

The CKI = 1.03 demonstrated high specificity (92%) but low sensitivity (41%), with the lowest Youden Index (J = 0.330) among the evaluated indices, indicating limited utility for screening. When CKI is normal, it is very likely that the cornea is healthy. However, CKI fails to detect many KC cases (low sensitivity) particularly in early or mild forms of the disease because this index mainly reflects central corneal steepening. In the initial stages of keratoconus changes are often peripheral or asymmetric so CKI values may still fall within the normal value. This explains why CKI useful in confirming normal corneas and less effective as a tool for screening KC. Our cut-off value is the same as that found by Shetty et al (153), which shows that it is useful for detecting confirmed cases of KC.

According to Alvarez et al (152), there is a correlation between refractive cylinder values and a number of topographic indices specifically **KI, ISV, IHA**. Their findings highlighted the diagnostic significance of combining refractive data with topographic indices for KC screening. Hashem et al (155) , confirmed that **KI, IVA** and **ISV** are among the most effective indices for detecting keratoconus in adolescent and pediatric populations.

Certain limitations must be acknowledged. Such as the modest sample size (32 patients) and the lack of longitudinal follow-up limit the External validity of the results.

Through this study, we faced several challenges. One difficulty was collecting retrospective data as some clinics do not store patient information systematically. Additionally, some topographic data contained errors due to examiner mistakes. Moreover, obtaining accurate measurements was complicated by the difficulty of controlling certain patients such as the lack of cooperation during the examination.

Prospective studies with longitudinal follow-up over several years with big sample would be necessary to confirm the predictive value of observed abnormalities. The integration of corneal biomechanical measurements such as those obtained with: ORA or Corvis ST could further improve early detection. It would also be related to develop multivariate predictive models that integrate clinical, topographic, and historical data (family history, allergies, eye rubbing...etc.). This shows how important it is to use different types of data to better detect keratoconus early and avoid missing cases.

CONCLUSION

Keratoconus represents a real diagnostic challenge especially in its early stages when clinical signs are absent. This work aimed to evaluate the diagnostic value of astigmatism characteristics and corneal topographic indices in the early detection of keratoconus.

This research made clear how important the role of astigmatism monitoring in the early detection of keratoconus. Through the exploration of the optical and clinical foundations of astigmatism and keratoconus, demonstrating that the type of astigmatism and its progressive changes especially axis instability and increased cylinder power were frequently associated with corneal topographies suggestive of keratoconus. These findings support the systematic integration of astigmatism analysis into optometric screening protocols, particularly for young patients, contact lens wearers, and individuals with family history or risk factors (rubbing, allergies, atopy).

They also prepare the way for the development of simple, accessible screening tools based on longitudinal refractive monitoring, complemented by corneal topography exams including a specific key topographic indices in both diagnostic and confirmation of keratoconus presence.

Finally, this study highlights the essential role of the optometrist in preventing severe forms of keratoconus, acting as a key player in primary screening. It encourages improved understanding and ongoing training in the interpretation of early signs to reduce diagnostic delays and improve visual outcomes for patients.

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Appendices

Appendix 01: List of Keratoconus Genes and Identified Variants

Method (reference)	Gene name	Position	Variant(s)	Location	Gene function/phenotype
GWAS, TG	PNPLA2	11p15.5	rs6874614	Intron	Catalyzes the initial step in triglyceride hydrolysis
GWAS, TG	MAML2	11q21	rs10813500	Intron	Transcriptional factor

S	TGFBI	5q31.1	Multiple rare variants	Exon	Transforming growth factor beta induced, involved in corneal dystrophies
GWLS/LD/FM/S/NA/TG	LOX	5q23.2	rs10519694, rs2956540, rs1800449, rs2288393, rs41407546	Intron/ Missense	Lysyl oxidase, participates in collagen cross-linking
GWLS/FM/GWAS/MA/WES	COL5A1	9q34.2.3	rs1536482, rs7044529, IVS50-4C > G	5′ near gene / Intron / Splice site	Collagen type V, alpha 1 chain; variants are associated with population in CCT
GWAS, TG	RAB3GAP1	2q21.3	rs4954218	5′ near gene	Regulates exocytosis; mutations are associated with ocular diseases
GWAS, TG	HGF	7q21.1	rs3735520	Promoter	Involved in corneal wound healing, decreased serum levels in KC patients carrying minor allele
GWAS, MA	FNDC3B	3q26.31	rs4894535	Intron	Fibronectin extracellular matrix protein; variants are associated with population variation in CCT, CH, CRF
GWAS, MA, TG	FOXO1	13q14.1	rs2721051	3′ near gene	Transcription factor; variants are associated with population variation in CCT, CH, CRF
GWLS/GWAS/S	DOCK9	13q32.2	c.2262A > C, p.Gln754His	Missense	Guanine nucleotide exchange factor
GWAS/TG	MPDZ/NF1B	9p23	rs1324183	Intergenic	Intergenic region involved in genetic regulation of CCT, CH, CRF

S	TSC1	9q34	rs751398082, rs550526986	Missense	Hamartin, regulates cell growth and proliferation
GWAS/TG/S/TA	ZNF469	16q24.2	rs9938149, Multiple rare variants	3′ near gene / Exons	Transcription factor, regulates corneal collagen structure and synthesis, involved in genetic regulation of CCT, CH, CRF
GWLS, LD, FM, S	PPIP5K2	5q21.2	c.1255 T > GS419A, c.2528 A > GN843S	Missense	Kinase/phosphate-se involved in normal corneal function; defects lead to pathological corneal thinning in mouse model of KC

Abbreviations: GWLS: genome-wide linkage study, S: sequencing, GWAS: genome-wide association study, TG: targeted genotyping, LD: linkage disequilibrium, MA: meta-analysis, FM: fine mapping.

Appendix 02: Patients Data.

CLINICAL RECORD

optometrist

N°

PATIENT INFORMATIONS

NAME: DATE:

GENDER:

AGE :

MEDICAL HISTORY

OPHTALMIC HISTORY:

FAMILY HISTORY:

REFRACTION

AMETROPIA:

OBJECTIF REFRACTION :

- OD:
- OG:

SUBJECTIF REFRACTION :

- OD:
- OG:

EVOLUTION:

- OD:
- OG:

CLINICAL EXAMINIATION

SLIT-LAMP:

TOPOGRAPHY :

- OD:

K1: K2: KMAX:

- OG :

K1: K2: KMAX:

PACHYMETRY :

- OD:
- OG :

TOPOGRAPHIC INDICES :

DIAGNOSIS:

SOUMIABENNOUR29@GMAIL.COM
DOUNIALAGHBALI@GMAIL.COM

patients	Rx 01	Rx 05	VA	Other criteria	Age at time of detection	gender
patient 01	OD:(-2.00 x 170°)	OD:-2.00(-2.00 x 177°)	OD: 10/10	Blepharospasm,itching,Allergic conjunctivitis,Irritation	22	Female
	OS:(-2.00 x 175°)	OS: -3.00 (-2.50 x 6°)				
patient 02	OD:(-4.00 x 20°)	OD:-0.25(-5.00 x 15°)	OD: 4/10	CXL OD	19	Male
	OS: -0.25(-1.75 x 155°)	OS:-0.50(-3.00 x 165°)	OS: 4/10			
patient 03	OD:-4.00	OD:-4.00(-0.75 x 155°)	OD: 4/10	Allergic conjunctivitis , CXL OD	20	Female
	OS: -0.50(-2.00 x 155°)	OS: -6.00(-2.50 x 30°)	OS: 9/10			
patient 04	OD:-2.75(-4.50 x 25°)	OD:-2.00(-4.00 x 25°)		CXL OD	17	Female
	OS: -0.50(-2.00 x 125°)	OS: -0.25(-2.00 x 130°)				
patient 05	OD:-4.50(-2.50 x 180°)	OD:-6.25(-2.50x 175°)	OD: 6/10	SPK OS, hyperthermia	20	Female
	OS: -4.75(-2.50 x 5°)	OS: -8.25(-3.00 x 5°)	OS: 2/10			
patient 06	OD:-1.00(-1.00 x 60°)	OD:-1.25(-2.50 x 15°)		GPC, ODS FFKC	15	Male
	OS: -0.75(-0.75 x 100°)	OS: -0.75(-1.255 x 115°)				
patient 07	OD:-1.00(-1.00 x 09°)	detection		.Follow-up in one year	13	Female
	OS: -0.50(-1.75 x 170°)	detection				
patient 08	OD:-6.00(-2.50 x 180°)	OD:-7.25(-4.00 x 7°)		Follicles, moderate myopia . Follow-up in one year	24	Female
	OS: -3.50(-3.00 x 160°)	OS: -5.25(-4.00 x 160°)				
patient 09	OD:+0.25(-0.75 x 55°)	detection		AL	21	Female

	OS: +2.25(-4.00 x 110°)	detection				
patient 10	OD:-5.00(-1.00 x 15°)	OD:-6.75(-1.25 x 70°)		AL	23	Female
	OS: -8.00(-1.50x 155°)	OS:-10.00(-2.00x 110°)				
patient 11	OD:(-2.00 x 20°)	OD:+1.00 (-3.75 x 23°)		. Follow-up in one year.	21	Female
	OS:+0.50(-1.50x 155°)	OS:+1.00 (-2.50x 155°)				
patient 12	OD:-1.25(-2.50 x 60°)	OD:-0.50(-3.50 x 65°)		. Follow-up in one year.	20	Female
	OS:-1.00	OS: -0.50(-0.50x 50°)				
patient 13	OD:-3.50(-1.00 x 110°)	OD:-12.50(-4.50 x 85°)	OD: 8/10		23	Female
	OS: -0.25	OS: -3.25(-0.50x 68°)				
patient 14	OD:-1.00(-1.50 x 20°)	OD:+0.25(-1.25 x 35°)	OD: 6/10	/	16	Female
	OS: -1.50(-1.50x 150°)	OS: -0.75(-2.00x 90°)	OD: 3/10			
patient 15	OD:-2.00(-1.50 x 140°)	detection		External topography.	15	Male
	OS: -1.25(-0.75 x 45°)	detection				
patient 16	OD:-1.25(-2.25 x 50°)	detection		AL	21	Female
	OS:-1.50(-3.00 x 120°)	detection				
patient 17	OD:-0.50(-3.00 x 20°)	OD:-0.50(-3.75 x 20°)		AL	19	Female
	OS: -0.50	OS:-0.75(-1.00 x 140°)				
patient 18	OD:-2.00(-2.00 x 25°)	detection		KC Suspected . Follow-up in 6 M	22	Female
	OS: -2.5(-1.75 x 155°)	detection				

patient 19	OD:-2.00(-1.25 x 25°)	OD:-1.50(-1.50 x 25°)		Family history	24	Female
	OS: -0.75(-1.25 x 160°)	OS: -1.00(-2.00 x 170°)				
patient 20	OD:-3.00(-2.25 x 50°)	OD:-3.00(-4.00 x 40°)		Keratoconjunctivitis.	16	Female
	OS: -0.50(-0.50 x 165°)	OS: -1.50(-1.50 x 100°)				
patient 21	OD:-1.50(-0.50 x 15°)	OD:(-2.50 x 100°)	OD:7/10	PVC	25	Male
	OS: -0.75(-0.50 x 180°)	OS: -0.75(-0.25 x 135°)	OS: 10/10			
patient 22	OD:-16,25(-2.50 x 32°)	OD: -22(-6,25x 45 °)	OD:4/10	AST/ allergie	21	Female
	OS: -14 (-1,75)141 °	OS: -18(-4 x140°)	OS: 4/10			
patient 23	OD:pl(-0.75 x 50°)	OD: pl (-1,5x 35°)	OD:9/10	RAS	17	Female
	OS: pl (-1,25 x125°)	OS: pl (-1,75 x130°)	OS: 9/10			
patient 24	OD:-3,5 (-3.50 x 92°)	OD: -2 (-4,5 x 94°)	OD:3/10	FAMILY history of KC	15	Male
	OS: -9 (-4,5 x85°)	OS: -8,5 (-6,5 x80°)	OS: 2/10			
patient 25	OD:-3 (-1 x 33°)	OD: -3,75 (-2x 39°)	OD:5/10	RAS	14	Female
	OS: -4 (-0,5 x50°)	OS: -4,5 (-0,75 x96°)	OS: 10/10			
patient 26	OD:-12,75 (-4.25 x 51°)	OD: -16 (-9,5 x 70°)		PVC/allergie	17	Female
	OS: -10,75 (-4,5 x109°)	OS: -15 (-7,75 x127°)				
patient 27	OD:-7(-3.75 x 20°)	OD: -6,5(-3,25 x 39°)		PVC	20	Male
	OS: -5(-4,25 x173°)	OS: -5,5 (-3,25 x170°)				
patient 28	OD:-pl(-2,5 x 5°)	OD: pl(-3 x 5°)	OD:10/10	PVC/ TWIN	16	Male

	OS: -pl(-2,25 x10°)	OS: -0,5 (-5 x162°)	OS: 10/10			
patient 29	OD:-7(-2,5x 75°)	OD: -7,5(-1 x 99°)	OD:4/10	FF	22	Female
	OS: -5,5(-4,5 x80°)	OS: -6 (-2,5 x99°)	OS: 2/10			
patient 30	OD:-1,75(-1,75 x 63°)	OD:-2,5(-1,75 x 53°)	OD:6/10	RAS	23	Female
	OS: -4(-2 x134°)	OS: -9 (-3,25 x145°)	OS: 3/10			
patient 31	OD:pl(-0,25 x 28°)	OD: -0,75(-2,5 x 28°)		AST	13	Female
	OS: pl(-0,25 x153°)	OS: -0,75 (-2,25 x153°)				
patient 32	OD:pl(-2x 78°)	OD: -2,75(-2 x 59°)		HTA under TRT	19	Female
	OS: pl(-2 x106°)	OS: -2,75 (-2 x138°)				

DSZ	ISV	IVA	KI	CKI	IHD	IS	IHA
0	35	0,32	1,09	1,01	0,035	2,11	30,8
0	36	0,28	1,09	1,01	0,027	1,68	23,2
0	62	0,6	1,17	1,05	0,107	4,35	17,7
1	28	0,27	1,08	1,02	0,038	1,9	29,6
0	72	0,81	1,22	1,05	0,056	5,94	29,6
0	46	0,52	1,14	1,02	0,035	3,86	3
0	77	0,77	1,22	1,07	1,115	5,18	19
1	28	0,22	1,07	1,02	0,24	1,34	1,99
1	37	0,28	1,06	1,02	0,014	1,4	16
1	36	0,3	1,07	1,03	0,016	1,9	20
0	89	0,96	1,26	1,08	0,148	6,99	40,6
0	31	0,3	1,1	1,02	0,042	2,41	30,5
1	29	0,2	1,01	1	0,018	0,36	16,8
1	35	0,11	1,03	1	0,004	0,17	4,5
1	24	0,14	1	1	0,008	0,5	6,1
1	26	0,08	1,01	1,01	0,005	0,05	0,4
1	16	0,13	1,04	1	0,01	0,76	6,4
0	70	0,9	1,17	0,99	0,092	6,18	26
0	108	1,43	1,3	1,02	0,192	10,64	50,1
0	44	0,54	1,09	0,98	0,064	3,66	26,2
1	36	0,19	1,06	1,01	0,009	0,48	7,3
1	31	0,23	1,06	1,01	0,021	1,51	13,5
0	59	0,72	1,16	1,02	0,08	5,28	40,3
1	21	0,14	1,03	1	0,02	0,92	16,7
1	45	0,47	1,13	1,03	0,056	3,2	20,5
1	11	0,07	1,03	1,01	0,007	0,42	5,7
1	46	0,59	1,1	1,04	0,061	3,4	31,7
1	83	1,06	1,21	1,06	0,12	5,9	30,8
0	47	0,41	1,12	1,04	0,056	2,25	38,5
0	37	0,33	1,06	1,03	0,085	1,41	32,6
0	67	0,7	1,18	1,05	0,098	5,16	66,8
0	84	0,93	1,24	1,06	0,121	6,96	10,5
0	59	0,6	1,18	1,03	0,095	4,59	44,2
0	33	0,37	1,08	1,01	0,05	1,7	31,6
1	27	0,2	1,03	1,01	0,018	0,41	12,9
1	25	0,14	1,04	1,01	0,013	0,06	0,2
0	51	0,4	1,04	1,05	0,108	4,1	17
0	60	0,35	1,2	1,05	0,1	4,3	21
0	45	0,3	1,8	1,08	0,14	6,9	25
0	40	0,28	1	1,03	0,04	2,4	18
0	50	0,41	1,09	1,06	0,066	4,5	23
1	37	0,31	1,07	1,02	0,014	1,9	19
0	38	0,38	1,08	1,05	0,062	1,5	21
0	42	0,29	1,08	1,02	0,018	3,86	16

0	35	0,28	1,04	1,01	0,015	2,7	12,6
1	38	0,3	1,03	1,01	0,017	2	17
1	39	0,27	1,08	1,02	0,018	1,71	16
0	36	0,28	1,09	1,01	0,027	1,68	23,2
0	41	0,3	1,1	1	0,044	2	21
1	28	0,27	1,08	1,02	0,038	1,9	17,7
0	35	0,32	1,09	1,01	0,021	2,15	30,8
0	31	0,35	1,1	1,02	0,042	2,41	30,5
0	40	0,38	1,17	1,05	0,099	4,34	62,4
0	42	0,33	1,2	1,04	0,016	2,11	41
1	39	0,27	1,08	1,02	0,03	1,93	17,7
0	46	0,28	1,1	1,01	0,02	1,56	30,5
1	36	0,23	1,06	1,01	0,021	1,51	13,5
0	40	0,45	1,1	1,06	0,015	1,9	30,5
1	37	0,3	1,07	1,02	0,018	1,5	21
0	50	0,8	1,2	1	0,03	4	27
0	43	0,3	1,09	1,01	0,019	1,65	22
0	60	0,5	1,22	1,04	0,02	3,5	2,8
0	55	0,41	1,09	0,98	0,095	2	26,2
0	39	0,28	1,07	1,01	0,03	1,7	23,2

DSZ: disease; **0:** for KC; **1:** for NON-KC

Appendix 04: ROC curves used in practical study

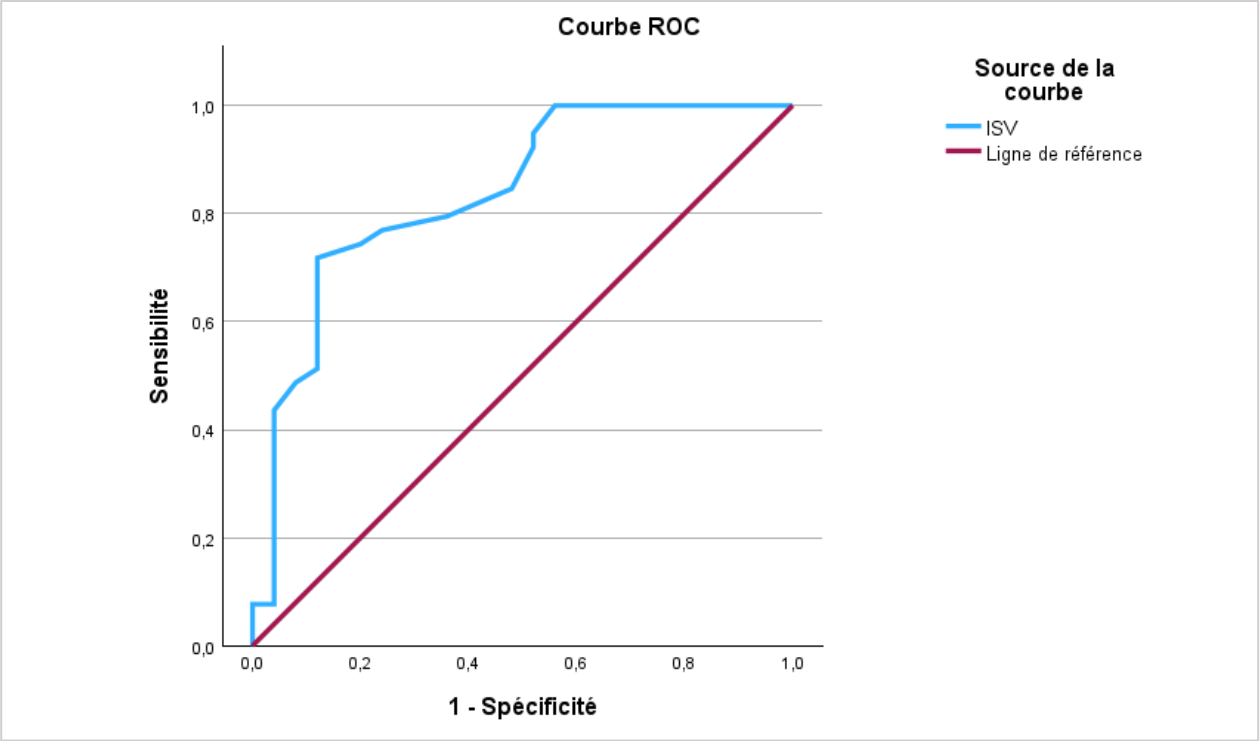


Figure 01: ISV ROC Curve generated with SPSS

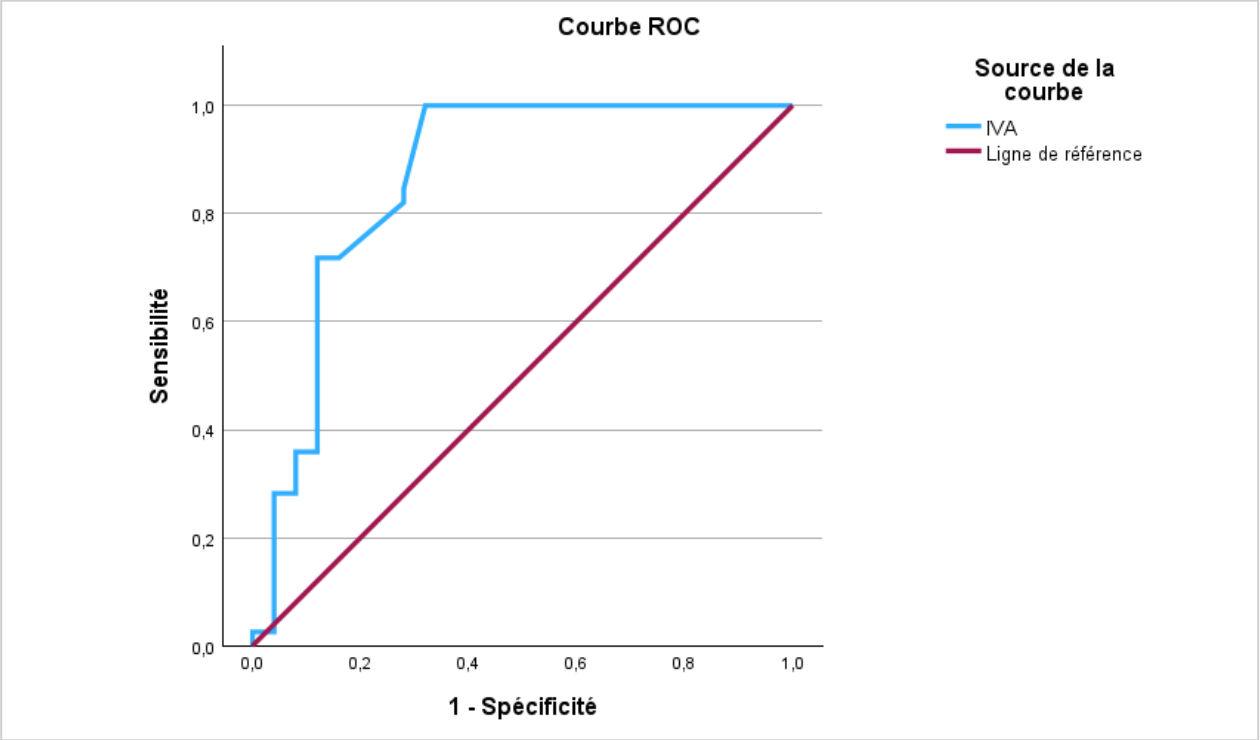


Figure 02: IVA ROC Curve generated with SPSS.

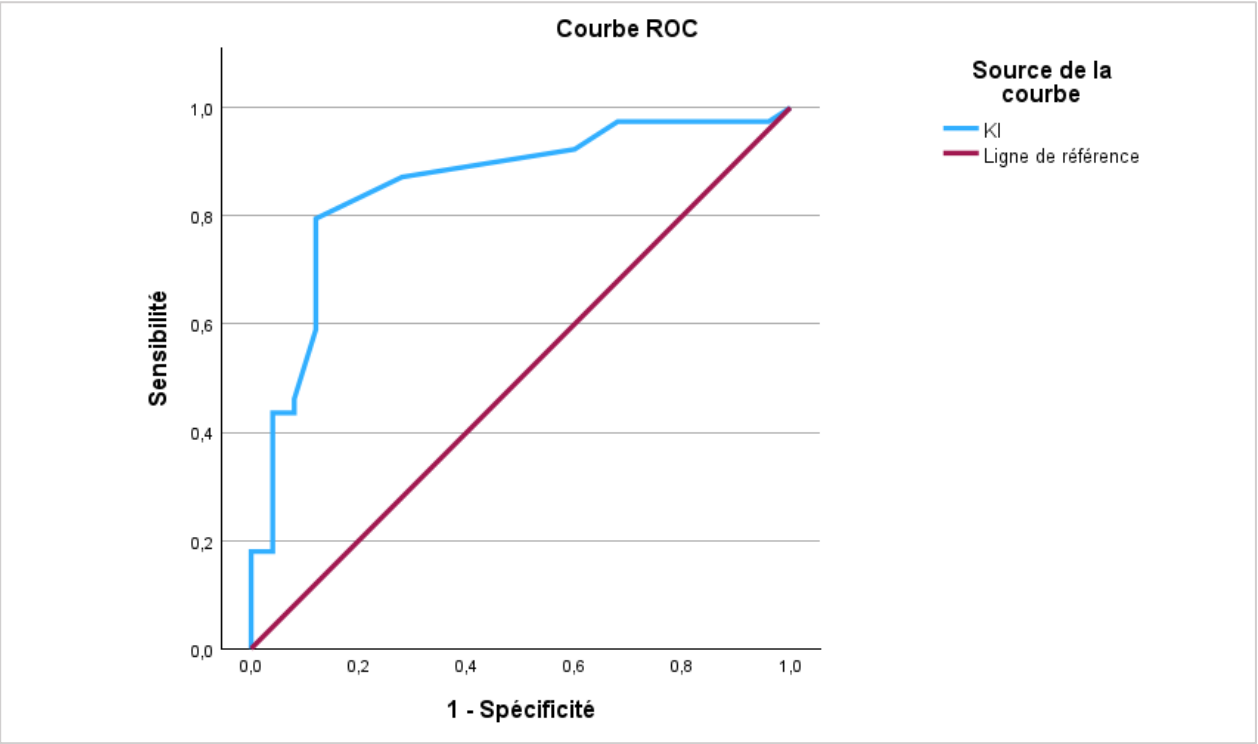


Figure 03: KI ROC Curve generated with SPSS.

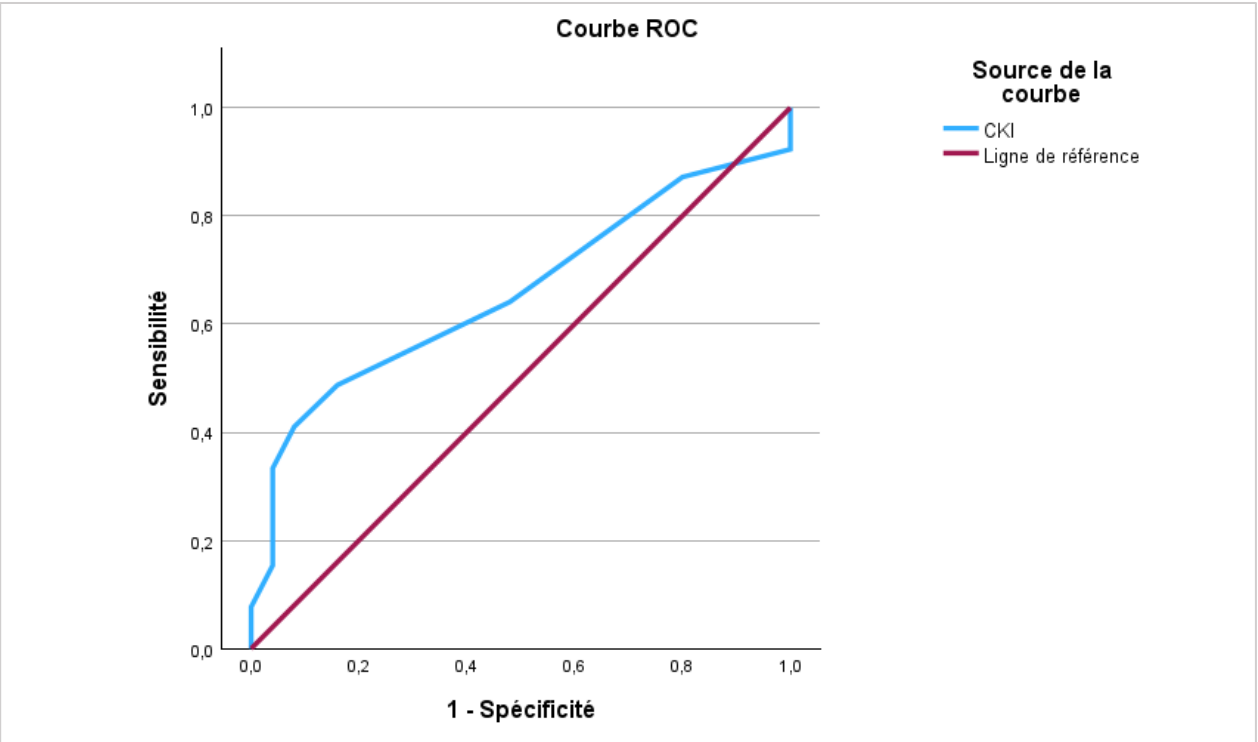


Figure 04: CKI ROC Curve generated with SPSS.

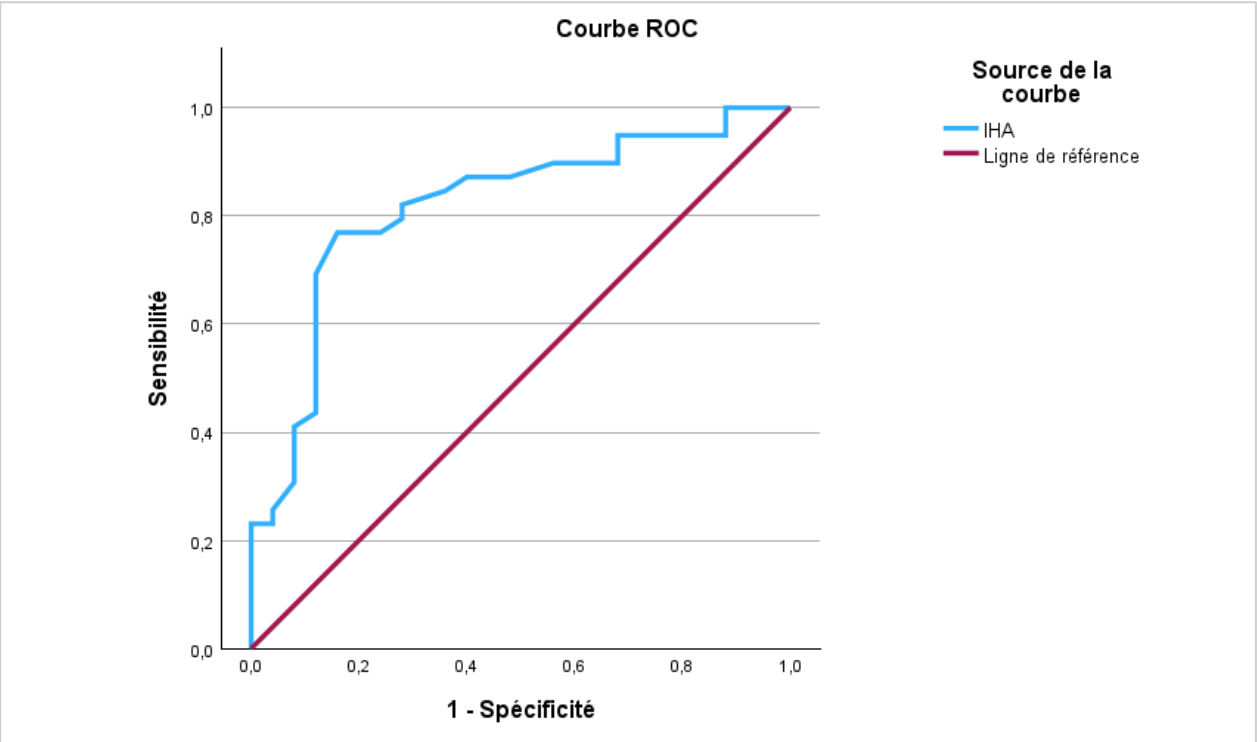


Figure 05: IHA ROC Curve generated with SPSS.

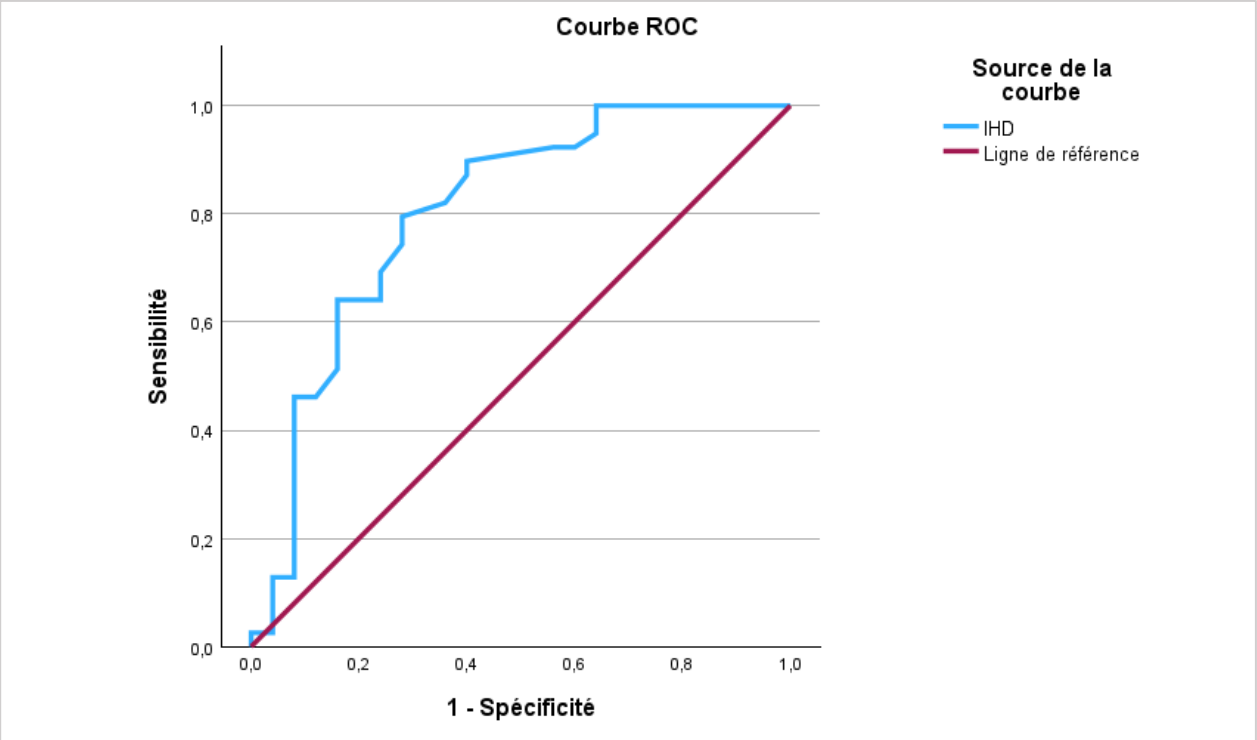


Figure 06: IHD ROC Curve generated with SPSS.

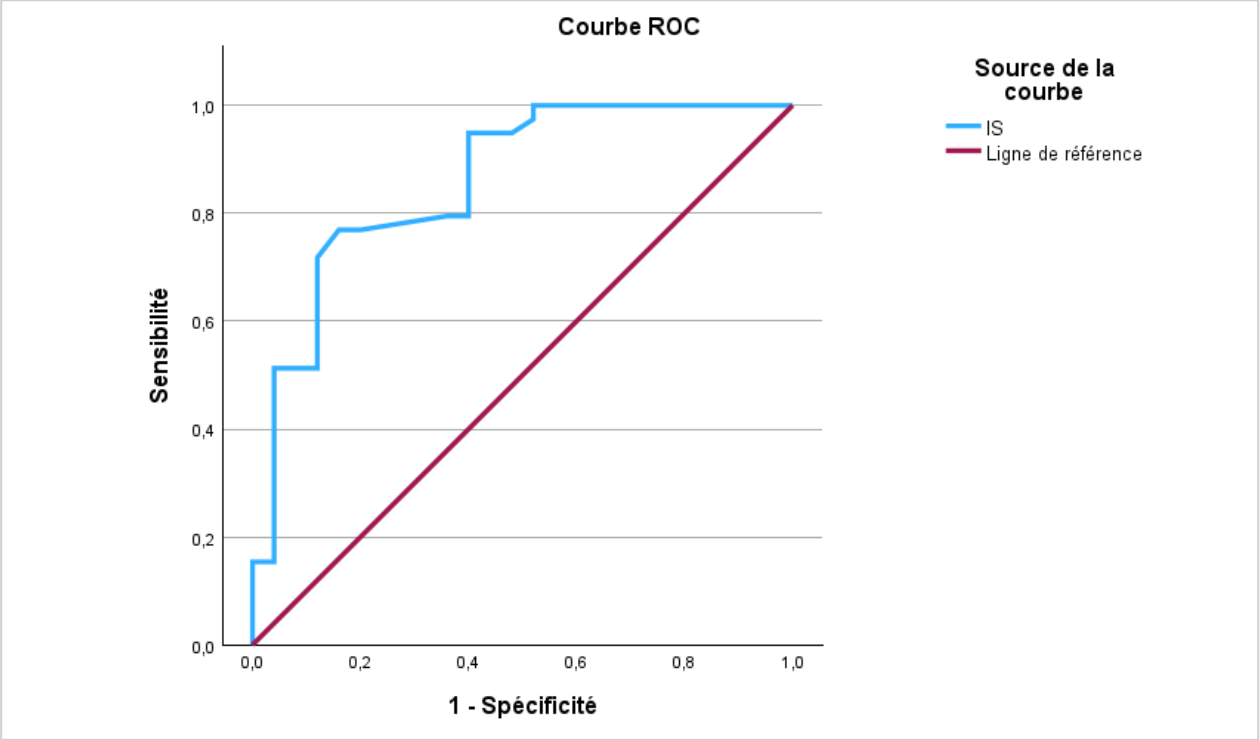


Figure 07: IS ROC Curve generated with SPSS.

Appendix 05: ROC curves coordinates

Variable(s) de résultats tests: ISV

Positif si supérieur ou égal à[a]	Sensibilité	1 - Spécificité	Indice de Youden
10,00	1,000	1,000	,000
13,50	1,000	,960	,040
18,50	1,000	,920	,080
22,50	1,000	,880	,120
24,50	1,000	,840	,160
25,50	1,000	,800	,200
26,50	1,000	,760	,240
27,50	1,000	,720	,280
28,50	1,000	,600	,400
30,00	1,000	,560	,440
32,00	,949	,520	,429
34,00	,923	,520	,403
35,50	,846	,480	,366
36,50	,795	,360	,435
37,50	,769	,240	,529
38,50	,744	,200	,544
39,50	,718	,120	,598
40,50	,641	,120	,521
41,50	,615	,120	,495
42,50	,564	,120	,444
43,50	,538	,120	,418
44,50	,513	,120	,393
45,50	,487	,080	,407
46,50	,436	,040	,396
48,50	,410	,040	,370
50,50	,359	,040	,319
53,00	,333	,040	,293
57,00	,308	,040	,268
59,50	,256	,040	,216
61,00	,205	,040	,165
64,50	,179	,040	,139
68,50	,154	,040	,114
71,00	,128	,040	,088

74,50	,103	,040	,063
80,00	,077	,040	,037
83,50	,077	,000	,077
86,50	,051	,000	,051
98,50	,026	,000	,026
109,00	,000	,000	,000

Variable(s) de résultats tests: IVA

Positif si supérieur ou égal à[a]	Sensibilité	1 - Spécificité	Indice de Youden
,9300	1,000	1,000	,000
,0750	1,000	,960	,040
,0950	1,000	,920	,080
,1200	1,000	,880	,120
,1350	1,000	,840	,160
,1650	1,000	,720	,280
,1950	1,000	,680	,320
,2100	1,000	,600	,400
,2250	1,000	,560	,440
,2500	1,000	,480	,520
,2750	1,000	,320	,680
,2850	,846	,280	,566
,2950	,821	,280	,541
,3050	,718	,160	,558
,3150	,718	,120	,598
,3250	,667	,120	,547
,3400	,615	,120	,495
,3600	,564	,120	,444
,3750	,538	,120	,418
,3900	,487	,120	,367
,4050	,462	,120	,342
,4300	,385	,120	,265
,4600	,359	,120	,239
,4850	,359	,080	,279
,5100	,333	,080	,253
,5300	,308	,080	,228
,5650	,282	,080	,202
,5950	,282	,040	,242

,6500	,231	,040	,191
,7100	,205	,040	,165
,7450	,179	,040	,139
,7850	,154	,040	,114
,8050	,128	,040	,088
,8550	,103	,040	,063
,9150	,077	,040	,037
,9450	,051	,040	,011
1,0100	,026	,040	-,014
1,2450	,026	,000	,026
2,4300	,000	,000	,000

Variable(s) de résultats tests: KI

Positif si supérieur ou égal à[a]	Sensibilité	1 - Spécificité	Indice de Youden
,0000	1,000	1,000	,000
1,0050	,974	,960	,014
1,0200	,974	,880	,094
1,0350	,974	,680	,294
1,0500	,923	,600	,323
1,0650	,897	,440	,457
1,0750	,872	,280	,592
1,0850	,795	,120	,675
1,0950	,590	,120	,470
1,1100	,462	,080	,382
1,1250	,436	,080	,356
1,1350	,436	,040	,396
1,1500	,410	,040	,370
1,1650	,385	,040	,345
1,1750	,308	,040	,268
1,1900	,256	,040	,216
1,2050	,179	,040	,139
1,2150	,179	,000	,179
1,2300	,103	,000	,103
1,2500	,077	,000	,077
1,2800	,051	,000	,051
1,5500	,026	,000	,026
2,8000	,000	,000	,000

Variable(s) de résultats tests: CKI

Positif si supérieur ou égal à[a]	Sensibilité	1 - Spécificité	Indice de Youden
-,0200	1,000	1,000	,000
,9850	,949	1,000	-,051
,9950	,923	1,000	-,077
1,0050	,872	,800	,072
1,0150	,641	,480	,161
1,0250	,487	,160	,327
1,0350	,410	,080	,330
1,0450	,333	,040	,293
1,0550	,154	,040	,114
1,0650	,077	,000	,077
1,0750	,051	,000	,051
2,0800	,000	,000	,000

Variable(s) de résultats tests: IHA

Positif si supérieur ou égal à[a]	Sensibilité	1 - Spécificité	Indice de Youden
-,8000	1,000	1,000	,000
,3000	1,000	,960	,040
1,1950	1,000	,920	,080
2,3950	1,000	,880	,120
2,9000	,974	,880	,094
3,7500	,949	,880	,069
5,1000	,949	,840	,109
5,9000	,949	,800	,149
6,2500	,949	,760	,189
6,8500	,949	,720	,229
8,9000	,949	,680	,269
11,5500	,923	,680	,243
12,7500	,897	,680	,217
13,2000	,897	,640	,257
14,7500	,897	,560	,337
16,3500	,872	,480	,392
16,7500	,872	,440	,432
16,9000	,872	,400	,472
17,3500	,846	,360	,486

17,8500	,821	,280	,541
18,5000	,795	,280	,515
19,5000	,769	,240	,529
20,2500	,769	,200	,569
20,7500	,769	,160	,609
21,5000	,692	,120	,572
22,5000	,667	,120	,547
23,1000	,641	,120	,521
24,1000	,564	,120	,444
25,5000	,538	,120	,418
26,1000	,513	,120	,393
26,6000	,462	,120	,342
28,3000	,436	,120	,316
30,0500	,410	,080	,330
30,6500	,308	,080	,228
31,2000	,256	,040	,216
31,6500	,231	,040	,191
32,1500	,231	,000	,231
35,5500	,205	,000	,205
39,4000	,179	,000	,179
40,4500	,154	,000	,154
40,8000	,128	,000	,128
42,6000	,103	,000	,103
47,1500	,077	,000	,077
56,2500	,051	,000	,051
64,6000	,026	,000	,026
67,8000	,000	,000	,000

Variable(s) de résultats tests: IHD

Positif si supérieur ou égal à[a]	Sensibilité	1 - Spécificité	Indice de Youden
-,99600	1,000	1,000	,000
,00450	1,000	,960	,040
,00600	1,000	,920	,080
,00750	1,000	,880	,120
,00850	1,000	,840	,160
,00950	1,000	,800	,200
,01150	1,000	,760	,240
,01350	1,000	,720	,280

,01450	1,000	,640	,360
,01550	,949	,640	,309
,01650	,923	,600	,323
,01750	,923	,560	,363
,01850	,897	,400	,497
,01950	,872	,400	,472
,02050	,821	,360	,461
,02400	,795	,280	,515
,02850	,744	,280	,464
,03250	,692	,240	,452
,03650	,641	,240	,401
,03900	,641	,160	,481
,04100	,615	,160	,455
,04300	,564	,160	,404
,04700	,538	,160	,378
,05300	,513	,160	,353
,05850	,462	,120	,342
,06150	,462	,080	,382
,06300	,436	,080	,356
,06500	,410	,080	,330
,07300	,385	,080	,305
,08250	,359	,080	,279
,08850	,333	,080	,253
,09350	,308	,080	,228
,09650	,256	,080	,176
,09850	,231	,080	,151
,09950	,205	,080	,125
,10350	,179	,080	,099
,10750	,154	,080	,074
,11400	,128	,080	,048
,12050	,128	,040	,088
,13050	,103	,040	,063
,14400	,077	,040	,037
,17000	,051	,040	,011
,21600	,026	,040	-,014
,67750	,026	,000	,026
2,11500	,000	,000	,000

Variable(s) de résultats tests: IS

Positif si supérieur ou égal à[a]	Sensibilité	1 - Spécificité	Indice de Youden
-,9500	1,000	1,000	,000
,0550	1,000	,960	,040
,1150	1,000	,920	,080
,2650	1,000	,880	,120
,3850	1,000	,840	,160
,4150	1,000	,800	,200
,4500	1,000	,760	,240
,4900	1,000	,720	,280
,6300	1,000	,680	,320
,8400	1,000	,640	,360
1,1300	1,000	,600	,400
1,3700	1,000	,560	,440
1,4050	1,000	,520	,480
1,4550	,974	,520	,454
1,5050	,949	,480	,469
1,5350	,949	,400	,549
1,6050	,923	,400	,523
1,6650	,897	,400	,497
1,6900	,846	,400	,446
1,7050	,795	,400	,395
1,8050	,795	,360	,435
1,9150	,769	,200	,569
1,9650	,769	,160	,609
2,0550	,718	,120	,598
2,1300	,667	,120	,547
2,2000	,641	,120	,521
2,3250	,615	,120	,495
2,4050	,590	,120	,470
2,5550	,538	,120	,418
2,9500	,513	,120	,393
3,3000	,513	,080	,433
3,4500	,513	,040	,473
3,5800	,487	,040	,447
3,7600	,462	,040	,422
3,9300	,410	,040	,370
4,0500	,385	,040	,345
4,2000	,359	,040	,319
4,3200	,333	,040	,293

4,3450	,308	,040	,268
4,4250	,282	,040	,242
4,5450	,256	,040	,216
4,8750	,231	,040	,191
5,1700	,205	,040	,165
5,2300	,179	,040	,139
5,5900	,154	,040	,114
5,9200	,154	,000	,154
6,0600	,128	,000	,128
6,5400	,103	,000	,103
6,9300	,077	,000	,077
6,9750	,051	,000	,051
8,8150	,026	,000	,026
11,6400	,000	,000	,000