INTRODUCTION

Keratoconus is a corneal ectatic disease in which the cornea develops a conical shape, due to thinning of the corneal stroma, with subsequent irregular astigmatism and myopia leading to marked impairment of vision. [1]

Keratoconus typically manifests at puberty and progresses until the third decade of age, the disease is common with estimate of prevalence for Keratoconus approximately 1 in 2000 individuals of all ethnicities and with equal distribution between men and women. [2]

Cross linking was originally used in industry to stiffen polymers, also in prosthetic valves, Cross linking involving corneal collagen was investigated initially in diabetics who had been noted to have a reduced incidence of keratoconus and it was therefore postulated that the collagen of diabetics was more cross linked.[3]

The application of cross linking to corneal tissue via riboflavin was first reported by Theo Seiler, Michael Huhle, and Eberhard Spoerl in 1998.[4, 5]

Cross linking can occur in a variety of settings and from different pathways, so if it could be purposefully driven and in a controlled setting, then it could be used as a treatment modality for progression of keratoconus.[6]

Riboflavin-induced UVA cross linking for Keratoconus has established itself as a safe and what so far appears to be an efficacious and lasting treatment when detected in the early stages of the disease. [7]

The widespread availability of corneal topography and the now common detection during laser vision correction screening evaluations makes detection of Keratoconus in its early stages much easier. Although improvement in vision has been noted in a large percentage of patients after cross linking, it is not a definite expectation. Patients should realize that the goal is to halt the progression of the disease before vision decreases. (7)

Intrastromal corneal ring segments (ICRSs) are made of PMMA (polymethylmethacrylate). They are implanted in the deep corneal stroma to modify the corneal curvature. This procedure does not involve corneal tissue nor does it invade the central optical zone. The intrastromal ring concept was proposed by Reynolds in 1978. (8)

It was originally discussed as a treatment for myopia by Keravision. INTACS® technology for myopia received European CE Certification in 1996 and Food and Drug Administration (FDA) approval in 1999. (9)

Colin et al were the first to report find that INTACS reduced the corneal steepening and astigmatism associated with Keratoconus, they were the first to report that effect. (10)

Femtosecond lasers have been used successfully in ophthalmic surgery since 2001.(11)

Intrastromal corneal ring implantation with the use of a Femtosecond laser was a safe procedure, with low risk of complications and significant improvement on visual acuity and topographic data in this setting of patients with secondary corneal ectasia.[12]

The combination of intracorneal ring segments implantation followed by sequential same-day PRK/CXL may be a reasonable option for improving visual acuity in select patients with keratoconus.[13]

AIM OF THE WORK

Review the literature regarding combined Riboflavin-induced ultraviolet light (UV) cross linking and Intrastromal corneal rings uses in treatment of Keratoconus and preview of its most recent advances studying the following items:

- Understanding Keratoconus.
- Recent advances in Keratoconus diagnostic investigations
- Corneal cross linking.
- Intrastromal corneal rings.
- Combined Corneal cross linking and Intrastromal corneal rings.

KERATOCONUS (KC)

Keratoconus (KC), a term which comes from the Greek words keras (cornea) and konos (cone), was first described in the literature in 1854 (Nottingham). It is a corneal collagen disorder in which the central portion of the cornea becomes thinner and bulges forward in a cone-shaped fashion resulting in myopia, irregular astigmatism, and eventually visual impairment. Until some years ago, the definition of KC included the notion of a non-inflammatory process[1, 2].

Etiology

Despite the major advances in diagnosing and managing keratoconus, the cause of KC is unknown. Many suggest that it's multifactorial, various genes, proteinases, and environmental factors have been implicated in its etiology. Although classically defined as a predominantly degenerative disease, with mechanically induced trauma accelerating its course, however accumulating evidence suggests a pivotal role for inflammation in the pathophysiology of KC. Several reports have linked various inflammatory mediators (cytokines) with KC[3].

Eye rubbing is strongly linked with keratoconus[4-10]. Many studies reported increased level of MMP-1, MMP-13, IL-6& TNF-α in keratoconus patients rubbing their eyes[11-17].

Increased duration of sun exposure increases risk of KC in sunny countries[18-23] compared to other countries[24-26].

Studies that was conducted in different ethnicities living in the same geographic area[22, 27, 28].

Keratoconus is associated with the presence of Down syndrome, Sleep apnea syndrome, Ehlers Danlos connective tissue disorder, Leber's congenital marousis, retinitis pigmentosa, osteogenesis imperfecta and pseudoxanthoma elasticum[1, 2].

Prevalence

Keratoconus typically manifests at puberty and progresses until the third decade of age[29-33], the disease is common with estimate of prevalence for Keratoconus approximately 1 in 2000 individuals of all ethnicities and with equal distribution between men and women[34]. Papers published after 1970 noted that KC is more common in females[4, 27, 28, 31, 35-37].

Starting 2009, with the use of videokeratographers more accurate prevalence studies started to show up in the Middle east and Asia. One of the most accurate studies is the Mildot et al study in which keratoconus was diagnosed as a combination of topographic pattern, dioptric power of the apex of the cornea and inferior-superior asymmetry[36].

Diagnosis

The onset of the disease usually occurs in the second decade of life presenting later on , although some cases may present in early adulthood [2]. It is a progressive condition which usually stabilizes by the fourth decade of life[1, 38].

KC starts asymptomatic, with progressive symptoms as visual acuity deterioration, visual distortion and significant visual loss; these develop as the result of development of myopia, irregular astigmatism, corneal thinning more inferior than superior which corresponds with corneal steepening and scarring or Bowman breaks , the condition should be suspected with scissoring movement while using the retinoscope, distorted keratometric images with inferior steepening and skewed axis, progressive thinning of the cornea or the other classic signs of KC, Acute hydrops maybe the first presentation of KC[39, 40]. Corneal sensitivity to touch which may be due to tear deficiency, and thinning of the cornea in KC[41-43]. The disease is bilateral, although asymmetrical[2]. Initially it is often unilateral, the prevalence of which ranges from 14.3% to 41% when detected by keratometry alone[1, 44, 45]. With computerized topography the prevalence of unilaterality is greatly diminished from 0.5% to 4%[46-49]. It worth mentioning that most of the unilateral cases will develop KC in the other eye as well[50].

Early bio-microscopic signs include Fleischer's ring, which is a partial or complete circle of iron deposition in the epithelium surrounding the base of the cornea and Vogt's striae, which are fine vertical -rarely horizontal- lines produced by compression of Descemet's membrane. As the disease progresses, a Munson's sign, a V-shaped deformation of the lower lid, becomes noticeable as the eye looks in the downward position, as well as a bright reflection of the nasal area of the limbus called Rizzuti's sign[51]. Less common are breaks in Descemet's membrane known as hydrops, which cause stromal edema, vision loss, and associated pain[52, 53]. For patients who wear contact lenses, corneal scarring is a very common feature as well as decreased corneal sensitivity[54].

Diagnostic procedures:

Early detection of keratoconus is vital for proper management of keratoconus yet. This requires higher levels of clinical suspicion. Diagnosis depends on full ophthalmic history, family eye history, history of allergies, rubbing eyes. Slit-lamp examination. Hard or gas permeable contact lenses trial. good vision means corneal irregularities. Keratometry. Ultrasound pachymetry. Corneal topography Placido disc. Pentacam (Schimpflug camera). Anterior segment OCT pachymetry[55].

Advances in diagnostic investigations:

Diagnosis used to be based on the clinical signs of KC, the first ever keratoscope was invented by Antonio Placcido in the year 1880. The first computerized keratographer was introduced in the 1980s when photographs were hand digitized then processed by a computer, later on the photographs were shot by a digital camera and directly processed by a computer[56]. All instruments prior to 1990s were good for detection of already established KC cases; however, they missed the ability to detect early cases or those with suspicion of presence of KC. Hence the need for more sophisticated indices and instruments emerged.

A study carried out by Rabinowitz and Rasheed compared a new index, keratoconus percentage index (KISA%), derived from the aforementioned topographic parameters (K value, I-S value, SRAX, and AST) with modified Rabinowitz/McDonnell (K value and I-S value) and Maeda/Klyce (keratoconus prediction index [KCI] and KCI%) indices, and demonstrated that with a cut-off value of 100%, KISA% yielded an improvement in the rate of correct diagnosis (99.6%). In order to further elucidate the diagnostic accuracy of the KISA% index, the study compared the K value, I-S value, SRAX, and AST corneal topographic indices in 25 individuals suffering from bilateral keratoconus[57].

a) ORBSCAN:

In 1995, a new device, the Orbscan (Orbtek, Inc.), became commercially available. The device was based on the innovative principle of measuring the dimensions of a slit-scanning beam projected on the cornea. Using slit or parallelopiped methodology, the curvature of the anterior surface of the cornea can be assessed along with the posterior surface and the anterior surface of the lens and iris. The Orbscan was designed to acquire elevation information directly, but important curvature information can be derived from this.

Later in the development of computerized topography (1999), the Orbscan II (Orbtek, Inc.) evolved. This incorporated a Placido-disk attachment to obtain curvature measurements directly and so attain the benefits of both approaches to corneal topography.

During the acquisition, the Placcido disk is illuminated and the mire's reflection from the anterior corneal surface is stored. Subsequently, 40 slits, 20 from the right and 20 from the left, each 12.50 mm high and 0.30 mm wide, are projected on the cornea at an angle of 45 degrees to the instrument axis. As the light from these slits passes through the cornea, it is scattered in all directions, but, crucially, it is backscattered toward the digital video camera of the device, which records the appearance in 2-dimensional images.

Applications included estimation[58] of Anterior and posterior corneal elevations Corneal pachymetry, ACD, AC angle, KC detection, Ectasia after refractive surgery detection, Calculation of IOL for patients undergoing post refractive cataract surgery.

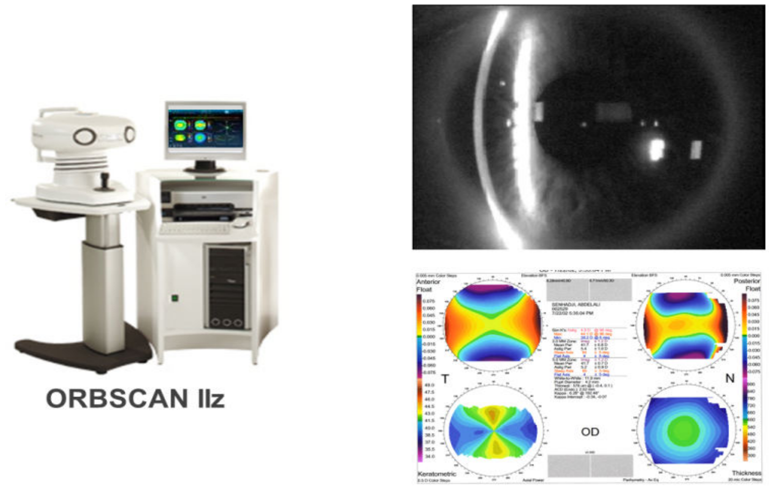

Figure (1): Showing recent model of ORBSCAN[59].

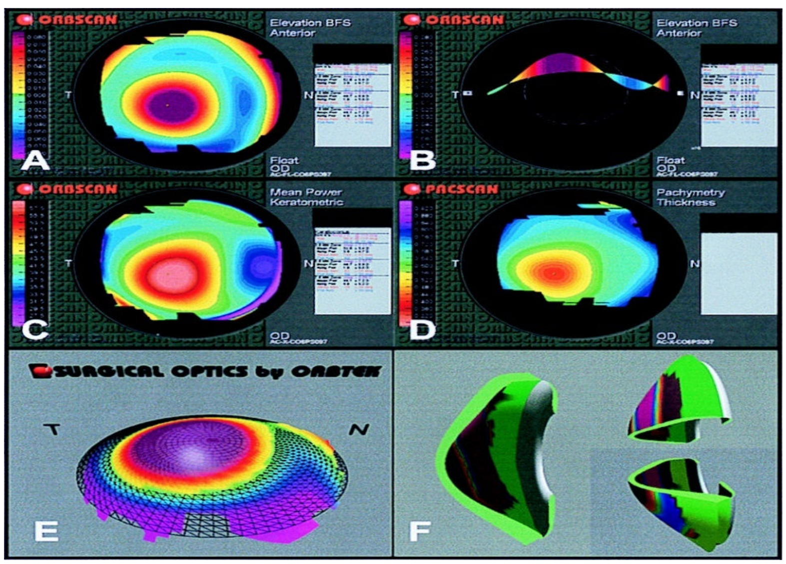

Figure (2): Showing Examples of keratoconic corneal topography maps created with the ORBSCAN system. *A*: Elevation map (in relation to a best fit sphere). *B*: Elevation map, side view (in relation to a best fit sphere), showing the extent of the keratoconus. *C*: Mean power keratometric map. *D*: Pachymetry map of the cornea. *E*: 3D illustration of elevation map. F: 3D illustration of keratoconus shape[60].

b) OCULUS Pentacam:

Oculus Pentacam combines a rotating Scheimpflug camera with a static camera to acquire multiple photographs of the anterior eye segment. The Scheimpflug camera rotates along with a monochromatic slit-light source around the optical axis to obtain the slit images. This rotating system performs a corneal scan from zero to 180° and each one of the photographs is an image of the cornea at a specific angle. The static camera is placed in the center to detect the pupil's contours and control fixation (this captures and corrects eye movements). The photographs are used in the reconstruction of the anterior and posterior corneal topographies from height data. Analyses of corneal pachymetry, corneal wavefront aberrations, densitometry and the complete anterior chamber are also provided by the Pentacam. Three Pentacam models are available: Basic, Classic and High Resolution (HR). The versions all differ mostly in the software features, and HR also provides upgraded hardware[58].

The Oculus Pentacam is a non-invasive system for measuring and characterizing the anterior segment using Scheimpflug photography. After processing all corneal information, the internal software provides a large number of different calculations. It performs automatically the conversion of the corneal elevation profile into corneal wavefront data[58]. Other applications of the OCULUS Pentacam are the same of those of the ORBSCAN.

Figure (3): Showing recent image of Oculus Pentacam

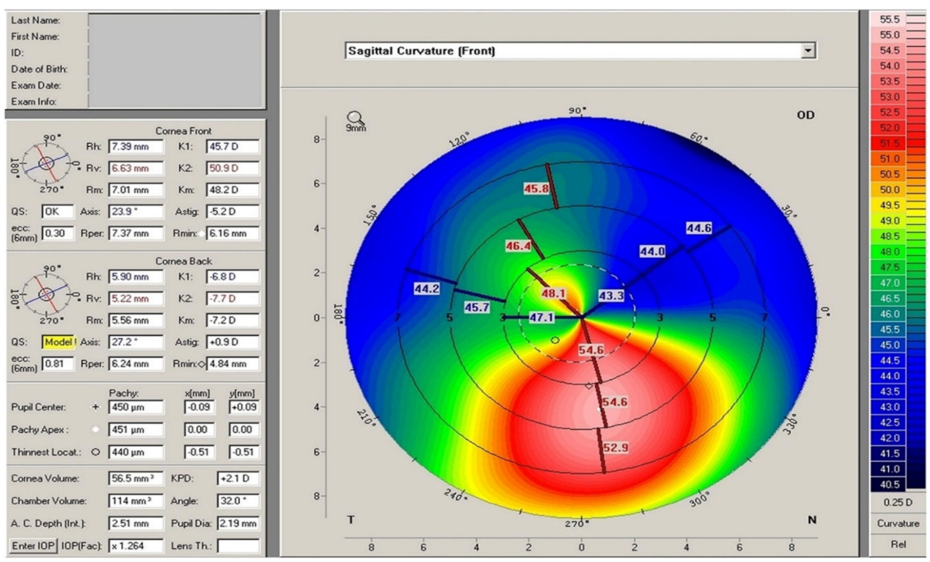

Figure (4): Axial curvature map of a keratoconic cornea obtained by Oculus Pentacam.

c) CSO Sirius Pentacam:

The Sirius combines a rotating Scheimpflug camera and a small-angle Placcido-disk topographer with 22 rings. The scanning process acquires a series of 25 Scheimpflug images (meridians) and 1 Placcido top-view image. The ring edges are detected on the Placcido image so that height, slope, and curvature data are calculated using the arc-step method with conic curves. The profiles of anterior cornea, posterior cornea, anterior lens, and iris are derived from the Scheimpflug images. Data for the anterior surface from the Placcido image and the Scheimpflug images are merged using a proprietary method. All the other measurements for internal structures (posterior cornea, anterior lens, and iris) are derived solely from Scheimpflug data. Analysis of present data was performed using software version 1.0 and included mean simulated-K (calculated by averaging the axial curvature from the fourth to the eighth Placcido ring), posterior corneal power, thinnest corneal thickness, and distance between the corneal endothelium and the lens[61].

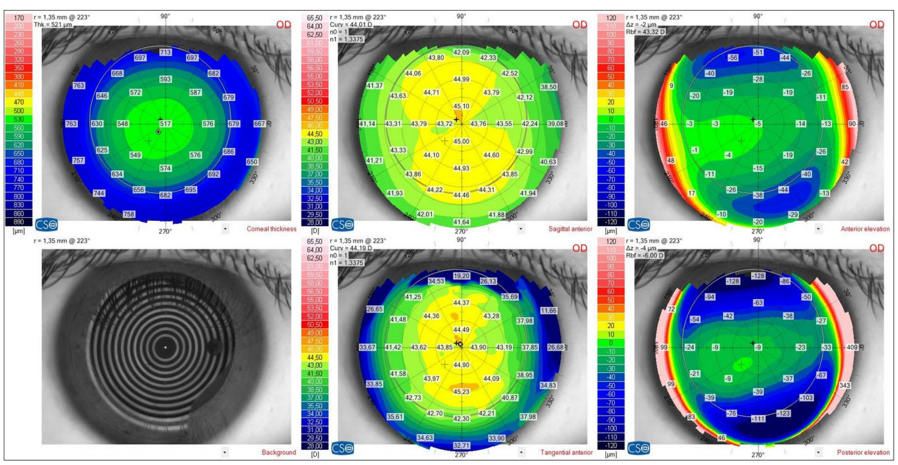

Figure (5): Showing 6 map customizable display obtained by a CSO Pentacam[62].

Figure (6): Showing recent model of CSO Pentacam[62].