INTRODUCTION

Keratoconus is a degenerative, non-inflammatory corneal disorder, characterized by central and paracentral stromal thinning and conical ectasia. This condition is typically not associated with redness, inflammation or other "acute" symptoms. The typical patient with undiagnosed keratoconus complains of deteriorating vision, usually in one eye first, both at distance and near. Keratoconus patients often report multiple images or ghosting of images. Patients may also report irritating symptoms such as intolerance to glare, photophobia and a recurrent foreign body sensation**.** [(1)]

More definitive diagnosis can be obtained using corneal topography. The topographic diagnosis of keratoconus often is suggested by high central corneal power, large difference between the power of the corneal apex and of the periphery, and disparity between the two corneas of a given patient.[(2)]

Corneal ectasia after LASIK is a condition resembling keratoconus but comes from a different origin. It is a progressive corneal steepening, usually inferiorly, with an increase in myopia and astigmatism, loss of uncorrected visual acuity, and often loss of best corrected visual acuity that can present days to years after LASIK.[(3)]

Currently identified risk factors include low residual stromal bed thickness from excessive ablation or thick flap creation, keratoconus, high myopia and defined topographic abnormalities such as for me fruste keratoconus. Ectasia rarely occurs in patients without currently identifiable risk factors.[(3)]

Between 10-20% of patients with keratoconus progress to a point where rigid lenses no longer provide an adequate management solution and surgical intervention is required for adequate visual rehabilitation.[(4)]

Current surgical options include:

Intra-corneal ring segment inserts (Intacs and Ferrara Rings)

The development of intra-corneal ring segments has provided a surgical alternative to corneal transplantation in some eyes with keratoconus.[5] These ring segments have been used to reduce the irregularity of the cornea and flatten the apex of the cone in mild and moderate cases of keratoconus.[6]

Riboflavin / UVA corneal cross-linkage (CR3)

Corneal collagen cross-linkage (CR3) using riboflavin (vitamin B)/ ultraviolet A (370nm) light is a new therapeutic modality which may be the first available treatment to halt and stabilize the keratoconic process. It aims to increase the biomechanical stability of the corneal stroma; the riboflavin has the dual function of acting as a photosynthestiser for the production of oxygen free radicals as well as absorbing the UVA irradiation and preventing damage to deeper ocular structures such as the corneal endothelium, the lens and the retina. The production of oxygen free radicals by this photochemical process is thought to induce (CR3) by the natural lysyloxidase pathway.[7]

Penetrating Keratoplasty

Indicated in patients with advanced progressive disease, especially with significant corneal scarring.[8]

Deep anterior lamellar keratoplasty

Allowing replacement of only the diseased stroma, leaving healthy endothelium and not penetrating the ocular wall.[9] Lamellar keratoplasty negates the risk of endothelial rejection and improves postoperative biomechanical corneal stability.[10]

Phakic IOL

Addressing the correction of the irregular astigmatism induced in keratoconus refractive lens exchange and toric phakic intraocular lens insertion may be of some benefit in correcting myopia and astigmatism in selected eyes with early/ mild disease with good best spectacle corrected visual acuity (BSCVA). Published studies have reported significant improvements in unaided visual performance with good safety and efficacy indices for both refractive lens exchange and toric phakic intraocular lens insertion.[(11)]

AIM OF THE WORK

This work will cover the various procedures of refractive surgery in management of keratoconus and post Lasik corneal ectasia with the aim of stopping the progression of the disease and getting the best visual acuity.

Chapter (I): Anatomy of the Cornea

Gross Anatomy:

The cornea is a clear avascular dome-shaped window at the front of the eye (Fig. 1), comprising one-fifth of the fibrous coat of the eyeball.[12]

The anterior surface of the cornea appears elliptical being 11.7 mm wide horizontally and 10.6 mm vertically. Posteriorly, the cornea is concave and circular measuring about 11.7 mm in diameter.[13]

It is thinner centrally, averaging about 580 µm, whereas the periphery measures approximately 900-1000 µm. The radius of curvature of anterior surface is about 7.7 mm and of the posterior surface 6.9 mm.[13]

The cornea can be divided into four zones; **central (optical) zone** 2-4 mm in diameter, **paracentral zone** 6-8 mm in diameter, **peripheral zone** 7-11 mm in diameter and the **limbal zone** 11.5-12 mm in diameter.[14]

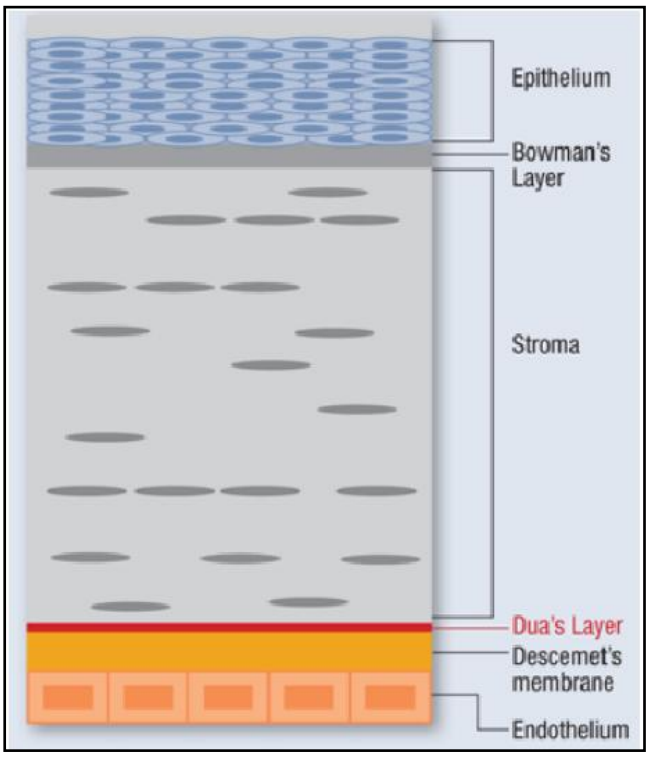

Figure (1): Anatomy of the cornea.[15]

Microscopic anatomy:

It is made up of six layers (Fig. 1). Starting from the outer layer, they are:

1-Epithelium:

The corneal epithelium is stratified squamous epithelium of uniform thickness (50 to 90 µm). It is consists of basal zone formed of a single layer of columnar cells where mitosis occurs. The daughter cells move upward differentiating into wing cells of middle zone, which is formed of two to three layers. Finally the superficial zone formed of two to three layers.[16]

The cells adhere to one another via desmosomes[13] and the bottom layer attaches themselves to Bowman's layer by hemidesmosomes.[17]

2-Bowman's Layer:

It is a narrow, acellular, homogenous zone 8-14 µm thick, immediately adjacent to the epithelial basement membrane. The anterior surface is smooth and parallel to that of the cornea. Although sharply defined from the overlying epithelium anteriorly, it is infiltrated by the lamina densa and merges into the stroma behind. It is currently described as modified region of the anterior stroma.[13]

3- Stroma:

The stroma, which constitutes over 90% of the thickness of the cornea, is a highly specialized connective tissue. The stromal matrix is made up of tightly packed orthogonal layers of collagen fibrils and abundant keratan and dermatan sulfate proteoglycans.[18]

Keratocytes are dispersed in the stromal lamellae. In transverse section of cornea they appear as long, thin, flattened cells (maximally

2 µm thick) running parallel to the corneal surface and viewed from either corneal surface as satellite cells with many processes in tangential sections.[13]

Collagen is essential for the strength of the cornea, and the interactions between collagen and proteoglycans contribute to the proper collagen spacing and in turn, to corneal transparency.[18]

In the posterior two thirds of the human cornea, lamellae lie in the plane of the cornea and run without interruption from limbus to limbus with a limited anteroposterior interweave. At the limbus, the collagen fibrils pursue a circular or pseudocircular course. Although the preferred direction of the posterior lamellae is in the inferior-superior and nasal-temporal directions, the lamellae of the anterior stroma have little preferred meridional arrangement. In the anterior stroma, there is an extensive anteroposterior interweave, and a proportion of the lamellae that arise in the limbus insert into the region of Bowman's layer. This arrangement is thought to be essential for the maintenance of corneal shape.[19]

4-Dua's layer:

It is a well-defined, acellular, and strong layer of five to eight lamellae of type-1 collagen bundles. It is about six to 15 µm thickness. The bundles are coarse and arranged in transverse, longitudinal, and oblique directions. Bundle spacing is similar to that in stromal tissue, but Dua's layer is entirely free of keratocytes. It is also distinguished from the adjacent Descemet's membrane, which consists of finer, closer spaced, parallel collagen bundles in banded and non-banded layers with endothelial cells.[15]

5- Descemet's Membrane:

It is a strong resistant sheet formed of type I collagen. It is closely applied to the back of the corneal stroma.[13]

It has a laminated structure, demonstrated by polarization or electron microscopy.[20]

It appears at the second month of gestation. Its synthesis continues throughout adult life, so that while it is only 3-4 µm thick at birth it is 5 µm in childhood and reaches 10-12 µm in adult. The anterior third of the adult Descemet's membrane corresponds to that part produced in fetal life and is therefore oldest. The posterior two-thirds of the membrane are formed after birth, and consist of a homogeneous fibrillgranular material. The zone adjoining the endothelium is the most recently formed.[13]

6-Endothelium:

It is a single layer of hexagonal, cuboidal cells applied to the posterior surface of Descemet's membrane. Endothelial cells have a limited regenerative ability. Cell loss results in enlargement and spread of neighboring cells to cover the defective area. The cells decrease in number and become thinner and more attenuated with age. Endothelial cell density is 6000/mm^2 at birth and falls 26% in the first year, and a further 26% over the next 11 years. They decrease constantly henceforth. They actively pump water out of the cornea keeping it transparent.[21]

Their lateral borders are markedly convoluted to produce a complex interdigitation with neighboring cells. The anterior (basal) and the posterior (apical) cell membranes are relatively flat, however the surface of the posterior cell membrane shows 20-30 microvilli per cell which increases the absorptive surface area. The anterior cell membrane is attached to Descemet's membrane by modified hemidesmosomes.[22]

Nerves of the Cornea:

The cornea is supplied by the ophthalmic division of the trigeminal nerve via the anterior ciliary nerves and those of the surrounding conjunctiva. There is also a supply from the cervical sympathetic providing adrenergic fibers to the limbus.[13]

The nerves pass into the cornea as 60-80 flattened mainly myelinated branches about 8 µm wide and surrounded by perineurium. After about 1-2 mm, they usually lose their myelin sheaths and divide into two groups anterior and posterior. The anterior nerves (40-50) pass through the substance of the corneal stroma and form a plexus subjacent to the anterior limiting membrane. The posterior group of nerves (40-50) passes to the posterior part of the cornea to innervate the posterior stroma excluding Descemet's membrane.[13]

Chapter (II): Epidemiology and Etiology of Keratoconus

Keratoconus is a disease characterized by ectasia of the cornea in the absence of inflammation, a cone-like anterior protrusion of the cornea occurs, generally involving the central and inferior paracentral areas. The involved stroma is thin, has decreased tensile strength, and may scar. A high degree of irregular myopic astigmatism occur causing variable amount of visual impairment.[23]

It is a bilateral disease, with no gender predominance. Epidemiologic data on keratoconus is derived mostly from hospital-based studies. The reported incidence ranges from 1.3 to 25 per 100 000 per year across different populations, and a prevalence of 8.8–229 per 100 000.[24,25,26,29,30]

Two of these studies reported a significantly higher incidence and prevalence in Asians compared with whites, suggesting the ethnic influence.[28,29]

The onset of keratoconus is generally during puberty, with a variable amount of progression, which may last until the third or fourth decade of life, when the corneal shape generally becomes stable. The Collaborative Longitudinal Evaluation of Keratoconus study prospectively studied 1 209 patients with keratoconus, with annual examinations for eight years. The authors found a decrease in high-contrast and low-contrast visual acuity and progressive steepening of the cornea in the study subjects. The incidence of corneal scarring was 20%.[31]

Disease associations include atopy, vernal keratoconjunctivitis, retinitis pigmentosa, Leber congenital amaurosis, eye rubbing, hard contact lens wear, mitral valve prolapse, Down syndrome, and non-

inflammatory connective tissue disorders, such as Ehlers–Danlos syndrome, and osteogenesis imperfecta.[24,26,32,33]

A cause and effect relationship is often difficult to establish. Some associations may point towards a common genetically determined cause, others may potentially cause corneal ectasia by recurrent mechanical trauma. However, it makes sense to look for evidence of systemic atopic disease or signs of ocular allergy in patients with keratoconus. Conversely, patients with a diagnosis of Down syndrome or non-inflammatory connective tissue disease coming for an eye examination should be carefully examined for signs of keratoconus.

A genetic basis for keratoconus has been suspected due to clustering of cases within families as well as high concordance in monozygotic twins. A number of linkage studies and a few association studies have been performed to investigate several candidate genes, including those coding for different types of collagen and proteinase inhibitors as well as antioxidant genes and genes belonging to the homeobox family.[34] Multiple studies have rarely identified the same loci as being related to keratoconus. Again, no mutations in any genes have been identified in the multiple loci mapped in familial keratoconus.[35] The multitude of loci implicated in keratoconus suggests that more than simple Mendelian genetics may be involved.

Keratoconus has conventionally been held to be a non-inflammatory condition. Studies on tear film and serum cytokines, enzyme levels, and tear proteomics have challenged this view in recent years. Jun et al studied levels of multiple cytokines in the tear film and sera of subjects with keratoconus as well as controls. They found no difference in serum levels of cytokines between keratoconus and control subjects, confirming the belief that keratoconus is not associated with major systemic inflammation. Levels of interleukin (IL)-6 and IL-17 were increased, while those of IL-12, tumor necrosis factor alpha, chemokine

(C-C motif) ligand 5(CCL5), and IL-13 were decreased in keratoconus compared with control tear fluids. It is concluded that, rather than a global increase in proinflammatory cytokines in eyes with keratoconus, it is a complex imbalance between proinflammatory and anti-inflammatory molecules that disrupts the corneal homeostasis.[36]

Balasubramanian et al, in a recent review, concluded that levels of matrix metalloproteinases are altered in keratoconic corneas. The same group also studied tear film proteomics, and found decreased levels of total protein, lactoferrin, and secretory Immunoglobulin A (IgA) in keratoconus compared with control tears.[38]

Chapter (III): Histopathology

Keratoconus involves every layer of the cornea. Early corneal thinning suggests that there is a functional loss of structural elements. A reduction in corneal tensile strength is expressed by signs of rupture and scarring in Bowman's layer, scarring in the stroma and breaks in Descemet's membrane.[23] (fig.2).

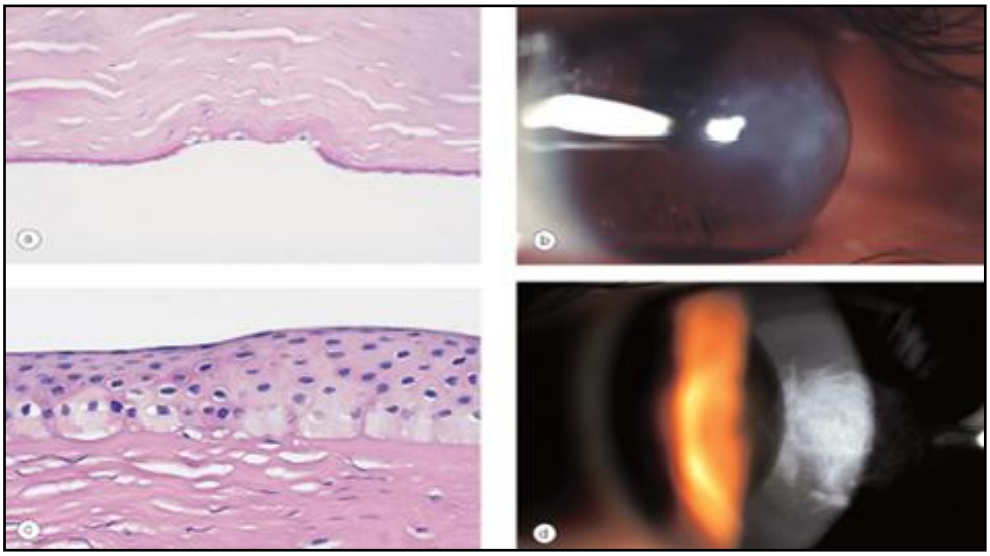

Figure (2): Advanced keratoconus. (a) Histology shows a defect in Descemet's membrane; (b) acute hydrops; (c) histology shows edema of basal epithelial cells and partial loss of Bowman layer; (d) apical scarring.[27]

Epithelial cells have early degeneration of their basal layer and disruption of the basement membrane. Some of the basal cells become pale, edematous and contain pyknotic nuclei. In advanced stages, the cell membrane may break up; the basal cells eventually disappear, leaving only one or two layers of flattened superficial epithelial cells on an altered basement membrane, on Bowman's layer, or directly on the anterior stroma.[60]

Bowman's layer initially has fibrillation and irregularity. Breaks in Bowman's layer are common. These breaks may fill with stromal collagen, keratocytes and epithelial cells. Z-shaped interruptions of Bowman's layer formed by epithelium growing posteriorly and stromal collagen growing anteriorly are classically described findings in keratoconus.[39]

Deposits of fine granular Periodic Acid-Schiff positive material are also found within these interruptions. These deposits may be produced by abnormal keratocytes in the areas of thinning as well as the stroma.[40]

Stroma has thinning which is a primary finding in keratoconus. However, its mechanism is poorly understood. Stromal collagen fibrils are normal in thickness but they are less in number in the areas of thinning.[39]

In keratoconus the gross organization of the stromal lamellae was dramatically changed, and the collagen fibrillar mass was unevenly distributed, particularly around the presumed apex of the cone. The development of keratoconus involves a high degree of inter- and probably intralamellar displacement and slippage that leads to thinning of the central cornea and associated changes in corneal curvature. This slippage may be promoted by a loss of cohesive forces and mechanical failure in regions where lamellae bifurcate.[41]

There is also pronounced reflectivity and irregular arrangement of stromal keratocytes, structurally abnormal anterior stromal keratocyte nuclei, folds in the anterior, mid, and posterior stroma.[42]

Hyperreflective keratocyte nuclei observed with confocal microscopy are thought to indicate the presence of fibroblastic cells seen with light microscope. Increasing levels of haze detected with confocal microscopy were found with light microscope to be due to fibroblast accumulation and irregular collagen fiber.[43]

Descemet's membrane may rupture in its central portion in advanced stages, resulting in acute hydrops. This break is initially replaced by flattening of adjacent endothelial cells that have enlarged to fill in the defect that later disrupted and characterized by formation of scar tissue.[44]

Endothelial cells polymorphism and polymegathism are common findings but may be related to contact lens wear in the keratoconic patient population. Later in the course of the disease, endothelial cells show degeneration, and deposition of fibrin and inflammatory cells on the endothelial surface.[45]

CHAPTER (IV): CLINICAL PICTURE

Presentation is typically during puberty with unilateral impairment of vision due to progressive myopia and astigmatism, which subsequently becomes irregular. The patient may report frequent changes in spectacle prescription or decreased tolerance to contact lens (CL) wear. Because of the asymmetrical nature of the condition, the fellow eye usually has normal vision with negligible astigmatism at presentation. Approximately 50% of normal fellow eyes will progress to keratoconus within 16 years; the greatest risk is within the first six years of onset.[27]

Symptoms and signs of keratoconus are highly variable and are in part dependent on the stage of the disease. Early in the disease, there may be no symptoms or the patient reports monocular diplopia and complains of distortion rather than blurring at both distance and near vision. Some report halos around lights and photophobia. In advanced disease, there is significant distortion of vision. Often keratoconus patients have had several spectacle prescriptions in a short period, and none was satisfactory.[39]

Early in the disease, the cornea may appear normal on slit-lamp biomicroscopy. However, there may be slight distortion or steepening of the keratometry mires centrally or inferiorly. In such instances, it is useful to dilate the pupil. In addition, retinoscopy shows a scissoring reflex and direct ophthalmoscopy may show a shadow. If the pupil is dilated and a +6 D lens is in the ophthalmoscopic system, the cone may appear as an oil or honey droplet when the red reflex is observed.(fig.3).[46]