Recent trends in management of keratoconus

Essay submitted for partial fulfillment of master degree in ophthalmology

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Pathogenesis of keratoconus

- ***Normal corneal anatomy***

The cornea is the transparent outer layer of the eye (called the tunic fibrosa), it is the primary most powerful structure focusing light entering the eye, it is composed for the most part of connective tissue with a thin layer of epithelium on the surface. It is composed of 5 layers, from the front to the back ***(Fig. 1)***

1-Epithelium
2-Bowman's layer
3-Stroma
4-Descemet's membrane.
5-Endothelium. [1]

1-Epithelium

The epithelium is the most anterior cell layer of the cornea, It's non keratinized stratified squamous type of epithelium, It's thickness is about 60um, Itself is 4-5 layers thick: superficial layer of flattened cells, intermediate 2-3 layers of polyhedral cells (wing cells), basal germinal layer (one cell thick), superficially they become more keratinized and then are shed after seven days, basement membrane of the germinal layer: Periodic acid shiff positive, type IV collagen, firmly attached to Bowman's layer. [2]

2-Bowman's layer

It is the acellular condensation of the corneal stroma, its thickness is about 12 um, it is composed of collagen type I, III, VI, V.

3-Stroma

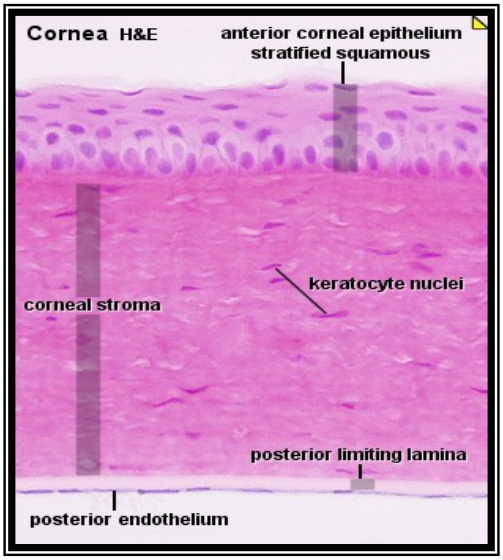
It forms about 90% of thickness of the cornea, it's mostly type I collagen (55%)and type VI (35%).It is composed of 300 lamella of collagen fibrils of uniform diameter and regular spacing, fibrils in any one lamellae are parallel but perpendicular to fibres in adjacent lamellae, ground substance is made up of proteoglycan. [3]

4-Descemet's membrane

Periodic acid shiff positive glassy basement membrane of the endothelial cells, it regenerates if injured.

5-Endothelium

It is a single layer of flattened cells facing the anterior chamber; it is highly active in maintaining corneal transparency by regulating water content of the stroma. [4]



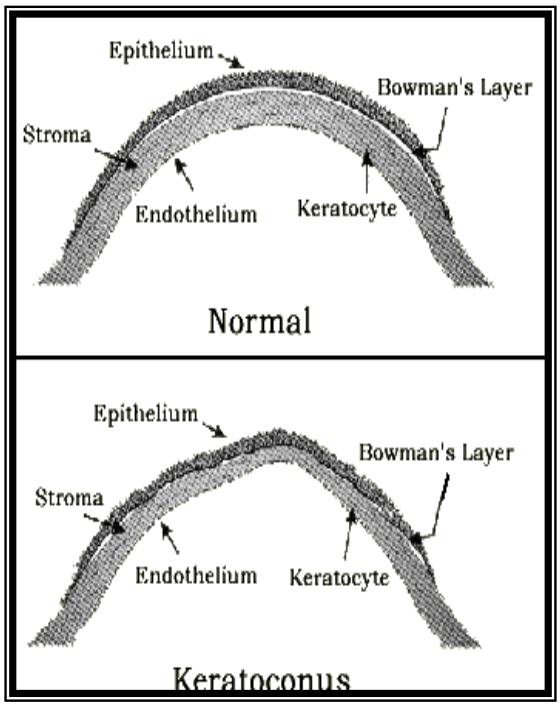
(Fig.1): Normal microscopic anatomy of the cornea [1]

- ***Keratoconus***

Keratoconus is a structural non- inflammatory disorder of the cornea in which the cornea assumes an irregular conical shape. It was found that over time, a cascade of events occurred, leading to alterations in the layers of the cornea and resulting in the thinning of the stromal layer. This weakened the structural integrity of the cornea and in turn resulted in a bulging, cone-like distortion of the normally spherical cornea. [5] ***(Fig.2)***

Etiology

Although the major etiological factors are genetic, the pathogenetic mechanism of keratoconus is unknown. Most of cases are sporadic, with unknown mode of inheritance Dominant, recessive, and irregular transmissions all appear to have been implicated**.** [6]

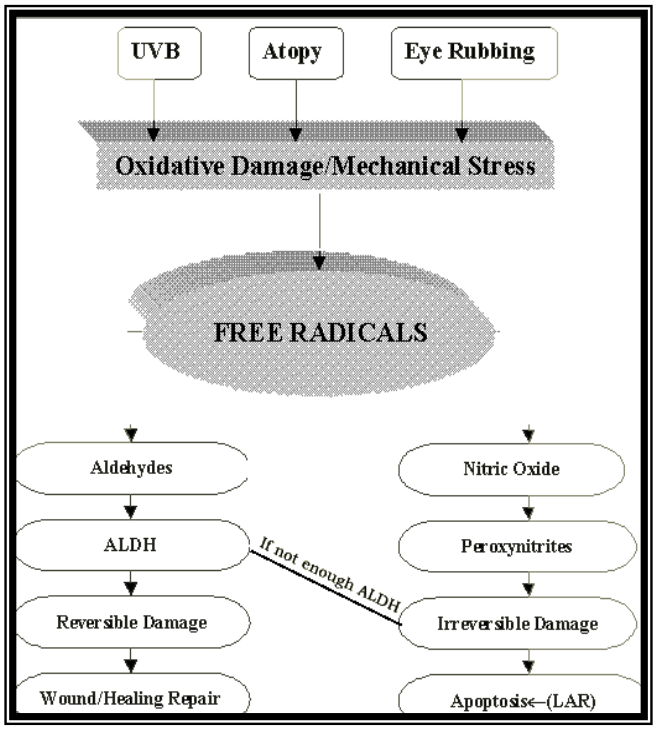


(Fig. :2): (a): Normal cornea (b): Keratoconus cornea **(5)**

Recent studies revealed biochemical changes

The enzyme activities of the keratoconus corneas were increased compared to normal ones with significant reduction of inhibitors for these enzymes as Cathepsin B and G (lysosomal enzymes) [(7)], also increased membrane-type 1 matrix metalloproteinase (MT1-MMP)and MMP-2 expression was noticed**.** [(8)]

The cornea is responsible for approximately 80 percent of the absorbtion of ultraviolet-B light that if enters the eye generates free oxygen radicals, which if unchecked can damage tissue, so they are removed from the cornea via anti oxidants (such as superoxide dismutase catalase and glutathione reductase) which are resident in normal corneal tissue. If those are not removed, they undergo reactions that form aldhydes, which can be destructive to the tissue ***(Fig. 3)***.



(Fig.:3): Biochemical changes in keratoconus [(9)]

Normally the cornea protects itself from these aldhydes with An enzyme called Aldhyde Dehydrogenase (ALDH) which detoxifies these aldhydes, in keratoconus there is decreased activity of the ALDH enzyme. [9]Recent data demonstrates nerve growth factor (NGF) alteration in the NGF pathway in keratoconus affected cornras and total absence of the NGF-receptor. [10]

When cells of keratoconus are damaged in this way they undergo apoptosis, it occurs in the anterior stroma and epithelium, especially at areas of breaks in Bowman's layer ***(Fig. 2)***. [11]

Histopathological examination of keratoconus corneas removed after operations of penetrating keratoplasty (PKP) confirms that the tissue is thinnest at the apex of the cones, thinning occurs with breaks in Bowman's layer.

Epithelial changes

Scientists found that the initial changes of keratoconus were related to degradation of the cornea's basement membrane. Epithelium shows massive changes of cyto-skeleton, reduced extra cellular disorders of tear quality, lowered tear film break up time**.** [12]

Basal layers of the epithelium are involved at an early stage of the disease squamous metaplasia of the epithelium, and goblet cell loss occurs. Some of the basal cells are pale edematous and contains pyknotic nuclei, deposition of circumscribed sector of iron deposition in basal and lower wing cell layers at base of the cone, which is called Flischer ring. [13]

As the disease advances, the cell membrane breaks, the basal cells disappear leaving one or two layers of flattened superficial epithelial cells lying on an altered basement membrane on Bowman's layer. [14]

Bowman's membrane changes

It appears multiple, wavy, fine fibrils rather than presenting its normal, homogenous and structureless appearance. As the disease advances, Bowman's layer shows multiple narrow gaps. These gaps, at the base of the cone as well as it's apex are filled either with newly formed connective tissue or epithelium and may correspond to the linear superficial scars seen by clinical examination **.**[15]

Stromal changes

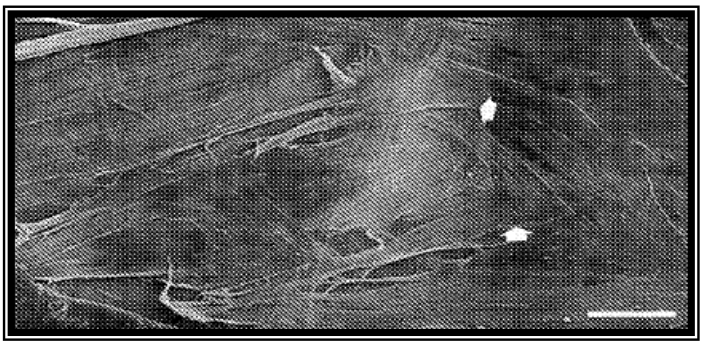
Abnormal thinning and anterior protrusion of the central portion of the cornea at the apex, the stroma is one third or less of its normal thickness. Altered organization of collagen in the apex of keratoconus corneas was revealed by scanning electron microscopy examination of a specimen of the apex of the cornea, in the para apical regions the arrangements of collagen lamellae doesn't differ from that in normal corneas but in the apical regions it was altered, there are no delimited lamellae can be differentiated within its layers, collagen fibrils have lost their parallel orientation and change directions along their length, Interlacing between adjacent layers is decreased or absent.***(Fig 4,a,b,c).*** [16]

Descemet's membrane changes

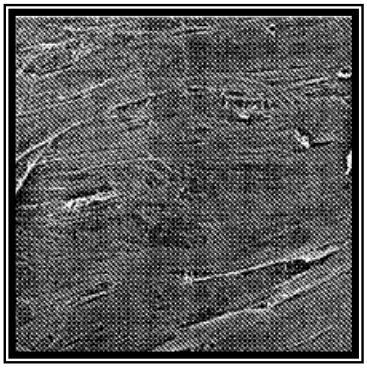
In early stages of Keratoconus, there may be folds in Descemet's membrane, and then it may rupture later in regions of greatest ectasia producing what is called hydrops. [17]

Endothelial changes

In early stages, it appears to be normal, as the condition progresses., the cells flatten and their nuclei lie further apart, this reflects stretching of the cells to maintain their continuity over the ectatic posterior surface, then changes occurs include pleomorphism, polymegathism, endothelial cell degeneration, and fibrin deposition. **(17)**



(Fig.4,a): *S*canning electron microscope of the central region of normal cornea, lamellae split into branches, cross at varying angles & are interlaced (white arrows) with one another. **(16)**



(Fig.4,b): *S*canning electron microscope of the apex of keratoconus, collagen fibrilis form a wide layer. Within this layer no delimited lamellae can be differentiated and many fibrils change directions along their length. No interlacing can be seen. **(16)**

(Fig.4,c): *S*canning electron microscope of the para apical region of the same keratoconus cornea, lamellae split into branches & can be well delimited, lamellae cross at varying angles & interlace. Within the lamellae, the fibrils are parallel. **(16)**

Clinical picture of Keratoconus

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 reports 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 has provided satisfactory vision correction. [18]

Clinical signs also differ depending on the severity of the disease. The only sign may be inability to refract to a clear 20/20 at the time of the presentation**.** [19]

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. Also retinoscopy shows a scissoring reflex, direct ophthalmoscopy may show a shadow. If the pupil is dilated and a +6.00 D lens is in the ophthalmoscopic system, the cone may appear as an oil or honey droplet when the red reflex is observed. ***(Fig.5)*** [20]

Fig.5: Oil droplet sign seen when the red reflex was observed using direct ophthalmoscope [20]

The slit lamp biomicroscope is the only tool, which allows a clinician to observe many classical signs of keratoconus such as:

- ***Fleischer's ring***

it is a yellow-brown to olive-green ring of pigment which surrounds the base of the cone ***(Fig. 6)***. It is formed when hemosiderin pigment is deposited deep in the epithelium. It becomes thinner and more discrete with progression. In approximately 50% of all cases., It is located by using a cobalt filter in the superior half of the cornea's epithelium.[21]

- ***Lines of Vogt***

They are small and brush-like lines, generally vertical but they can be oblique. These lines can be found in the deep layers of the keratoconic stroma ***(Fig.7)*** and form along the meridian of greatest curvature; the lines disappear when gentle pressure is exerted on the globe through the lid. [22]

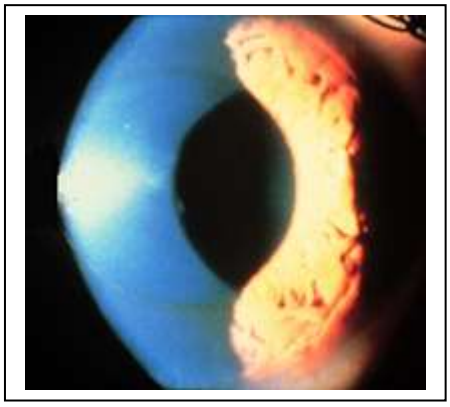


Fig.6: Fleischer's ring [21]

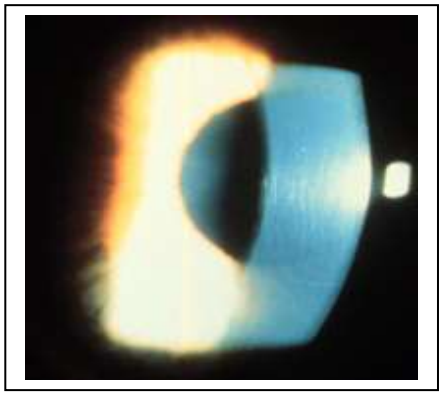


Fig.7: Lines of Vogt [22]