RECENT ADVANCE IN MANAGEMENT OF KERATOCONUS

Essay

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List of Abbreviations

AGEs	Advanced glycation end products
ALTK	Automated lamellar therapeutic keratoplasty
BCVA	Best corrected visual acuity
CLEK	Collaborative longitudinal evaluation of keratoconus
CM	Confocal Microscopy
CR3	Corneal cross-linking
D	Diopter
DALK	Deep anterior lamellar keratoplasty
EDS	Ehlers Danlos syndrome
Epi-LASIK	Epikeratome laser-assisted keratomileusis
FDA	Food and Drug Administration
FHI	Fuchs' heterochromic iridocyclitis
FR	Ferrara ring
HGF	Human growth factor
HLA	Human leukocytic antigen
HLK	Hyperopic lamellar keratotomy
HO:YAG	Holmium:yttrium-aluminum-granet
ICRs	Intracorneal rings
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INTACS	Intrastromal corneal ring segments
KC	Keratoconus
Kd	Kilo Dalton

LASEK	Laser-assisted sub-epithelial keratectomy
LASIK	Laser in situ keratomileusis
LTK	Laser thermokeratoplasty
MHC	Major histocompatibility complex
MMPS	Matrix metalloproteinases
OCT	Optical coherence tomography
PAR	Posterior apical radius imaging device
PAR CTS	PAR Corneal topography system
PAS	Periodic acid Schiff
PK	Penetrating Keratoplasty
PMMA	Polymethylmethacrylate
PRK	Photorefractive keratectomy
PSX	Pseudoexfoliation syndrome
PTK	Phototherapeutic Keratectomy
RGP	Rigid gas permeable
ROS	Reactive oxygen species
SAI	Surface asymmetry index
Sim K	Simulated keratometry readings
SRI	Surface regularity index
TIMP	Tissue inhibitor of metalloproteinase
TNF	Tumor necrosis factor
UCVA	Uncorrected visual acuity
VHF	Very high frequency

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INTRODUCTION

Keratoconus is a degenerative, non-inflammatory corneal disorder, characterized by central and para-central stromal thinning and conical ectasia. Early cases can be corrected effectively with astigmatic spectacle correction and soft toric contact lenses. As the condition progresses rigid contact lenses become the mainstay of treatment and in the majority of eyes provide satisfactory visual rehabilitation. However, discomfort, poor fitting and patient preference may limit their usage. (Wilson and Kim.,1998)

For these various reasons, 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. (Rabinowtiz.,2005). Current surgical options are multiple and varied,(Javadi and Motlagh.,2005) and include:

-Intra-corneal ring segment insert

1) Intacs
2) Ferrara Rings

-UVA / riboflavin corneal cross linkage (CR3)

-Corneal transplantation

1) Penetrating keratoplasty
2) Deep anterior lamellar keratoplasty

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(Boxer and Christie.,2003). 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.(Miranda and Sartori.,2003)

Riboflavin / UVA corneal cross-linkage(CR3)

Corneal collagen cross-linkage (CR3) using riboflavin (vitamin B2) / ultraviolet A (370nm) light is a new therapeutic modality which may be the first available treatment to halt and stabilise the keratoconic process. Its aims are 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 collagen cross-linkage by the natural lysyloxidaze pathway.(Wollensak.,2006)

Penetrating Keratoplasty

Indicated in patients with advanced progressive disease,especially with significant corneal scarring.(Pramanik and Musch.,2006).

Deep anterior lamellar keratoplasty

Allowing replacement of only the diseased stroma, leaving healthy endothelium and not penetrating the ocular wall.(Al-Torbak and Al-Motowa.,2006). Lamellar keratoplasty negates the risk of endothelial rejection and improves postoperative biomechanical corneal stability. (Vabres et al., 2006).

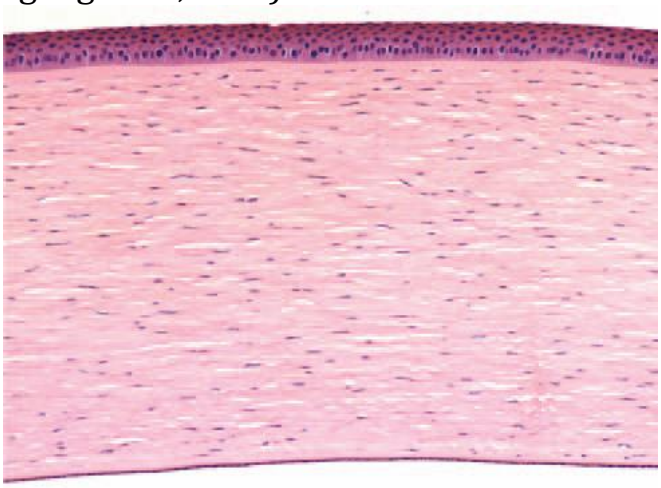
Aim of the work:

This work will cover the revolutionary advances in management of keratoconous with the aim of stopping the progression of the disease and getting the best visual acuity.

ANATOMY

The cornea is a transparent avascular tissue with a smooth,convex outer surface and concave inner surface, which resembles a small watch-glass. The main function of the cornea is optical ; it forms the principal refractive surface accounting for (40-45 diopters).(Bron et al .,1997).

In front the cornea appears elliptical,being (11.7 mm) wide in the horizontal meridian and (10.6 mm) in the vertical meridian in adults(Maurice.,1970). The posterior surface of the cornea appears circular about (11.7 mm) in diameter. The axial thickness of the cornea is (520 um) with a peripheral thickness of (670 um) (Lisesegang et al.,2003). The cornea consists of 5 layers:



Figure(1) Layers of the cornea(Weng et al.,2005)

1)Epithelium:

The corneal epithelium is stratified, squamous and non-keratinized. It is continuous with that of the conjunctiva at the corneal limbus, but differs in possessing no goblet cells. The epithelium is (50-90 um)thick and consists of five to six layers of nucleated cells. The basal cells stand in a palisade like manner in perfect alignment on a basal lamina. These basal cells are columnar(10 um) wide and (15 um) tall, with rounded heads and flat bases. Each nucleus is oval and oriented parallel to the cell long axis.(Mathers et al.,1992).

The 2nd epithelial layer (the wing or umbrella cells) consists of polyhedral cells,convex anteriorly which cap the basal cells and send processes between them. The long axes of their oval nuclei are parallel to corneal surface. (Tsubota et al.,1995)

The next two or three layers are also polyhedral and become wider and increasingly flattend towards the surface.

The surface cells have the largest surface area and this greater in the periphery(850 um) compared to centrally (560 um). The most superficial cells may be as wide as (50 um) and (4 um) in depth; they retain their nuclei and do not show keratinization. Their flattened nuclei project backwards,leaving the surface perfectly smooth.They are hexagonal and firmly attached to each other at relatively straight cell boundaries by desmosomes,it exhibit surface microvilli or microplicae. (Tomii et al.,1994).

The basal lamina is secreted by the basal cells which also synthesize the hemidesmosomal structures concerned in attachment of epithelium to the lamina. The basal lamina is an irregular zone (0.5-1um) wide of granulomorphous and filamentry materials. A deep osmiophilic densa (30-60 nm) and a superficial lamina lucida (24 nm) are distinguished ultrastructurally.(Snip et al.,1980).

2) <u>Bowman's layer (anterior limiting lamina):</u>

Before electron microscope was developed, Bowman's layer was thought to be a specialized corneal membrane, but it is now described as a modified region of the anterior stroma.(Bron et al .,1997).

Bowman's layer is a narrow acellular homogeneous zone, (8-14 um) thick immediately subjacent to the basal lamina of the corneal epithelium.The anterior surface is smooth and parallel to that of the cornea , though sharply defined from the overlying epithelium anteriorly it is infiltrated by the lamina densa and merges into the stroma behind.The periphery of Bowman's layer has a rounded border, delineates the anterior junction between cornea and limbus and is marked clinically by summits of the marginal arcades of the limbal capillaries.(Bron et al .,1997).

Ultrastructurally Bowman's layer consists of a felted meshwork of fine collagen fibrils of uniform size, lying in a ground substance. Fibril diameter (24-27 nm) is less than that of substantia propria . In the posterior region of this layer the fibrils become progressively more orderly in their orientation, blending and interweaving with the fibrils of the anterior stroma. Here and there anteriorly , bundles of the sromal lamella insert into the Bowman's layer. The compacted arrangement of the collagen confers great strength to this zone. Bowman's layer is relatively resistant to trauma; both mechanical and infective, once destroyed it is not renewed but is replaced by coarse scar tissue. It is perforated in many places by unmyelinated nerves transit to the corneal epithelium.(Tripathi.,1984).

3) <u>Stroma (substantia propria)</u>:

The stroma ,about (500 um) thick consists of regularly arranged lamellae of collagen bundles. They lie in a proteoglycan ground substance together with a relatively small population of cells ,the keratocytes. (Bron et al .,1997)

Transparency of the corneal stroma depends particularly on the degree of spatial order of its collagen fibrils which are narrow in diameter and closely packed in a regular array. The collagen fibrils themselves are weak scatterers.Since their fibril diameter is less than the wavelength of light, and fibril refractive index is close to that of the ground substance. There is little variation in fibril diameter and separation between the anterior and posterior cornea.(Muller et al.,2001)

The stromal fibrils are further organized into bundles or lamellae of which there are approximately (300 um) in central cornea and (500 um) close to the limbus . The posterior lamellae course directally across the full width of the cornea without a break, having their origins in fibers which wind around the limbus at the corneoscleral junction or , have a pseudocircular organization at the limbus, forming the ligamentum circulare cornae . On the basis of X- ray diffraction studies, about 49% of like stromal lamellae are preferentially aligned orthogonally,