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Abbreviations

- VA = Visual Acuity
- RI = Refractive Index
- IOL = Intraocular lens
- UV = Ultraviolet
- Kps = Keratitic Precipitates.
- BSS = Balanced Saline Solution
- SD = Std = Standard Deviation
- *P*= probability index.
- LASIK= Laser In Situ Keratomelieusis
- AC= Anterior Chamber
- ACD= Anterior Chamber Depth
- OVD = Ophthalmic Visco-elastic Device.
- DUVA= distant uncorrected visual acuity
- NUVA=near uncorrected visual acuity
- DCVA= distant corrected visual acuity
- NVA with Add= near visual acuity with Add
- NVA with distant correction = near visual acuity with distant correction

- **Anatomy of the Lens, Iris & Ciliary Body**

(A) Anatomy of the Crystalline lens:

Gross Anatomy:

The adult lens is an asymmetric oblate spheroid which does not possess nerves, vessels or connective tissue. The biconvex shape results from the anterior surface being less convex than posterior surface. The poles represent the central points of these 2 surfaces; the optic axis runs from the anterior to the posterior pole (Polar Axis). The equator represents the lateral region of the lens, where the anterior and the posterior surfaces meet. The equatorial axis is at right angles to the optic axis. **(Kuszak et al, 1996).**

The lens is located behind the iris and the pupil in the anterior compartment of the eye. The anterior surface is in contact with the aqueous on the corneal side; the posterior surface is in contact with the vitreous and faces the retina. The anterior pole of the lens and the front of the cornea are separated by anterior chamber which is approximately 3.5mm **(Saude, 1993)**

The lens is held in place by the zonular fibers, which originate from the region of the ciliary epithelium, are a series of fibers that converge in a circular zone on the lens. Both an anterior and a posterior sheet meet the capsule 1-2 mm from the equator and are embedded into the outer part of the capsule (1-2 mm). It is also thought that a series of fibers meet the capsule at the equator **(Leaming,1998).**

The Lens Capsule:

The lens is sheathed by an elastic basement membrane which serves to contain epithelial cells and fibers as a structural unit, and allows the passage of small molecules both into and out the Crystalline lens. In contrast to other basement membranes, the capsule is produced continuously throughout the life; as a result, the thickest region of the capsule represents the thickest basement membrane in the body. The capsule is generated anteriorly by the basal membranes of elongating fiber cells. The thickness of the capsule depends upon both age and the region of the capsule being measured. **(Snell and Lemp, 1989).**

The thickest region (up to 23 microns) is located close to the equator on both the anterior and the posterior surfaces; the thinnest region is that of the posterior pole (4 microns), while the equator (17 microns) and the anterior pole (9-14 microns) are of intermediate thickness. The lens capsule is composed of a number of lamellae (fibers) stacked on top of each other. The lamellae are narrowest near the exterior of the capsule and widest near the cell mass. **(Seland, 1992).**

The anterior capsule also contains linear densities. The major structural proteins (Type IV collagen, laminin, heparin Sulphate Proteoglycan and entactin) and a small amount of fibronectin are found within the lamellae**.**

Although the precise interactive role of these different components is not known, experiments using lens epithelial cells in culture have shown that collagen IV promotes cellular adhesion and fibronectin promotes migration **(Olivero and Furcht, 1996).**

Epithelial Cells:

The lens epithelium arises as a single layer of cells beneath the anterior capsule and extends to the equatorial lens bow. These cells have a cuboids shape, being approximately 10 microns high and 15 microns wide. Their basal surface adheres to the capsule, whereas their anterior surface is in contact with the newly formed elongating fibers. Adjacent cells are attached to each other by intercellular junctions, such as desmosomes. **(Kuszak et al, 1996).**

Evidence exists to suggest that the main type is occluding junctions In most epithelial sheets those junctions serve to block the movement of macromolecules through the extra-cellular space, however, this barrier does not appear to restrict the movement of those diffusing molecules (ions and water). Gap junctions, composed of connexion 43, allows the passage of small molecules between neighboring cells without the use of energy **(Low and Harding, 1983)**.

The proliferative capacity of epithelial cells varies according to their location. Most epithelial cells are found in the central zone, a region in which cells normally do not proliferate, although they may do under pathologic circumstances. Cells in this zone are the largest epithelial cells found in the lens. As the epithelial cells approach the equator their proliferative capacity increases. Cells in the pre-germinative zone constitute the stem cells population of the lens and, therefore; are responsible for the formation all new fibers and subsequent increase in size and weight of the lens throughout age. **(Kuszak et al, 1996).**

Since cells in the germinative zone are dividing constantly, newly formed cells are forced into the transitional zone where they elongate and differentiate to form the fiber mass of the lens. **(Kuszak et al, 1996).**

Lens Substance:

The adult lens consists of the nucleus and the cortex. Although the size of these 2 regions is age dependent, studies of the lenses with an average age of 61 years indicate that the nucleus accounts for about 84% of the diameter and thickness of the lens and the cortex for the remaining 16%**.** Then the nucleus is further subdivided into embryonic, fetal infantile and adult nuclei. The embryonic nucleus contains the original primary cells that are formed in the lens vesicle. The rest of nuclei are composed of secondary fibers, which are added concentrically at the different stages of growth by encircling the previously formed nucleus. (**Kuszak et al, 1996**).

The fetal nucleus contains the embryonic nucleus and all fibers added to the lens before birth. The embryonic and fetal nuclei, together with all the fibers added until four years of age, compose the infantile nucleus. The adult nucleus is composed of the 3 previously formed nuclei and all fibers added before sexual maturation. The cortex which is peripherally located is composed of secondary fibers formed after sexual maturation and can be divided into deep, intermediate and superficial cortex. The region between the hardened embryonic and fetal nuclear core and the soft cortex (fibers added to form the infantile and adult nuclei), is sometimes referred to as the epinucleus. The region between the deep cortex and adult nucleus is sometimes referred to as the perinuclear region. (**Kuszak et al, 1996**).

Fibers are constantly formed throughout life by the elongation of the germinative zone lens epithelium. Initially, transitional columnar cells are formed beneath the anterior epithelial cell layer and the posterior end is pushed backward along the posterior capsule. The ends of this U-shaped fiber run towards the poles of both capsular surfaces Once, fully matured, the fiber detaches from the anterior epithelium and the posterior capsule. Each new layer of secondary fibers formed at the periphery of the lens constitutes a new growth shell. In some regions, neighboring fibers fuse together to maintain these columns and ensure that spaces do not develop between the fibers as the lens grows (**Kuszak et al, 1996**).

The formation of a new fiber is associated with the production of components of the fiber cell membrane: major intrinsic protein 26 (MIP 26 or MP 26), lipids , phospholipids and peripheral proteins. The major sterol is cholesterol (50-60% of total lipid) and the major phospholipids is shingomyelin (47% - 56% of the total phospholipids). The predominant saturated fatty acid is Palmitate. The high levels of these 3constitutes result in a highly ordered membrane with very little fluidity (**Olivero and Furcht, 1996**).

The newly formed lens fibers have a consistent shape. They have six faces , two of which are broad and four of which are narrow (hexagonal in cross section), being approximately 2 microns thickness, 10 microns wide and up to 10 microns long. The more centrally located fibers lose their uniform shape and adopt an irregular polygonal profile in cross section.

Lens fibers are held together by the interlocking of the lateral plasma membranes of adjacent fibers to form ball and socket (and tongue and groove) joints. These joints which are formed at regular intervals along the length of their membranes are characterized by square array membranes. Once matured, fibers have polygonal domains of furrowed membranes along both their broad and narrow faces. Both Desmosomes and tight junctions are absent from mature lens fibers, although Desmosoms are found between elongating fibers. (**Kuszak et al, 1996**).

<u>Sutures:</u>

Sutures are found at both anterior and posterior poles. They are formed by the overlap of ends of secondary fibers in each growth shell. No sutures are found between the primary fibers in the embryonic nucleus. Each growth shell of secondary fibers formed before birth has an anterior suture shaped as an (*erect Y)* and a posterior suture shaped as an *(inverted Y*). Each of these symmetric sutures is composed of 3 branches, each 120 apart. The anterior and the posterior sutures are offset by 60 degrees. After birth, suture pattern complexity increases with age, because of the addition of progressively more fibers and changes in both fibers length and shape.

The sutures remain symmetric until sexual maturation. During childhood a simple star suture with 6 branches is formed. These changes start to be simple star suture, with nine branches during adolescence and finally to be a complex star suture, with 12 or more branches during adulthood.

Observations of the adult lens indicated these 4 different types of sutures: Y, simple star and complex star – all are found in fetal, infantile and adult nuclei and in the lens cortex respectively. The formation of sutures enables the shape of the lens to change from spheric to flattened biconvex sphere (**Kuszak et al, 1996**).

<u>Growth:</u>

The growth of the lens is throughout life, which is greatest in young diminishes with increasing age. During an average life span, the surface area of the lens capsule increases from 80 mm^2 at birth to 180 mm^2

The rates of increase in cell numbers parallels the increase in both mass and dimensions of the lens and therefore decrease dramatically after the second decade. The number of both epithelial cells and fibers increases by approximately 45-50% in the first 2 decades. After this , the increase in the cell numbers is reduced with the propotional increase in fibers being very small . (**Snell and Lemp, 1989**).

Mass:

The weight of the lens increases from 65mg at birth to 125 by the end of the first year. Then increases at about 2-8 mg/year until the end of the first decade, by which time the lens has reached 150 mg, thereafter the mass of the lens increases at a slower rate (1.4mg/year) to reach about 260 mg by the age of 90 years. (**Phelps and Brown, 1996**). The lenses of men are heavier than those of women of the same age with a mean difference being 7.9 ± 2.47 mg. (**Harding et al, 1977**).

Dimensions:

The equatorial diameter of the human lens increases throughout life although the rate of increase in reduced significantly after the second decade. The diameter increases from approximately 5 mm at birth to 9-10 mm in a 20 year old. The thickness of the lens increases at a much slower rate than does the equatorial diameter. The distance from the anterior to the posterior poles which is 3.5 -4 mm at birth increases throughout life, reaching up to 4.75 – 5 mm (unaccommodated)

(**Forrester et al , 1996**). The thickness of the nucleus decreases with age, as the result of compaction, whereas cortical thickness increases as more fibers are added at the periphery.

Since the increase cortical thickness is greater than the decrease in size of the nucleus, the polar axis of the lens increases with age. (**Cook et al, 1994**). The radius of curvature of the anterior surface decrease from 16 mm at the age of 10 years to 8 mm by the age of 80 years, as this surface becomes more curved. There is very little change in the radius of curvature of the posterior surface, which remains at approximately 8mm (**Brown, 1974**)

<u>Fine Lens Structure:</u>

Microtubules are abundant beneath the plasma membranes of lens fiber cells, where they probably play an important role in stabilizing the fiber cell membrane (**Kuwabara, 1968**). Microtubules may also be important for transporting vesicles to the apical and basal ends of the elongating fiber cells, although neither of these functions has been demonstrated in vivo.

In addition to microtubules, there is an abundant network of actin- containing microfilaments beneath the plasma membrane of lens fiber cells. These associate with the cytoplasmic surfaces of the adhesive junction between lens fibers and interact with the spectrin – containing sub-membrane meshwork (**Lee et al, 2000**); this sub-membrane scaffold also contains tropmyosin and troplodulin, and proteins that may alter the structure of the microfilaments (**Fisher et al, 2000**) . Lens fiber cells also contain vimentin (**Fitz, 1990**).

This is unusual because this protein is usually restricted to cells of mesodermal not epithelial origin. The role of vimentin – containing intermediate filaments in the lens is not evident. (**Colucci et al, 1994**). Over expression of vimentin in the lens leads to cataract formation and abnormal fiber cell maturation (**Capentanki et al, 1989**).

In addition, the lens contains intermediate filaments consisting of the proteins filensin and phakinin (**Georgatos et al, 1997**). These filaments have an unusual knobby structure leading to the name beaded filaments. (**Ireland and Maisel, 1984**) which have been found only in lens fiber cells. The normal function of beaded in the lens is unknown.

In fiber cells at early stages of elongation, the lateral plasma membranes are smoother. However, as fiber cells reach the sutures, the membranes become progressively more inter-digitated, forming inter-locking ball and socket junctions (**Willekenes and Vrensen, 1982**) that may stabilize the lateral membranes of the fiber cells and ensure that the cells remain tightly connected during accommodation.

The membranes of mature fiber cells have an unusual lipid composition. Human lens fiber cells have the highest proportion of cholesterol of any plasma membrane in the body, and the amount increases as the fiber cells mature.

The cholesterol / phospholipids ratio is nearly 3 folds greater in nuclear than in cortical fiber cells. There is also a high percentage of shingomyelin in lens membrane phospholipids (**Borchman et al, 1989**). The presence of high concentration of cholesterol and sphingomyelin is likely to cause lens fiber cell membranes to be rigid. (**Gorin et al, 1984**)

The gap junctions of the lens are assembled from a unique set of subunits or connexins. The cell to cell transport of small molecules mediated by these gap junctions is important for the function of the lens because most of the fiber cells are far from nutrients supplied by the aqueous and vitreous humours (**Musil et al, 1990**). Lens fiber cells have the highest concentration of gap junction plaques of any cells in the body. (**Goodenough et al, 1980**)

Three connexins are found in lens cells : α_1, α_3 and α_8 . Connexin α_1 (also known as cx43) is present only in the epithelial cells (**Kistler et al, 1995**). Connexin α_3 (cx 46) and

α_8 (cx 50) are abundant in fiber cells. Gap junction plaques containing both connexins α_3 and α_8 are present along the lateral membranes of lens fiiber cells.

Although the presence of large number of gaps junctions seems to be essential for the normal functions of the lens, recent studies have shown that the lens of mice lacking either connexin α_3 or α_8 gene are only mildly affected.

Lens fiber cells are linked to their neighbors all along their lateral membranes by N-agherin, a calcium dependent, homophilic cell adhesion molecule (**Lagunowich and Grunwald, 1989**).

N-Cadherin is typically linked to the actin cytoskeleton by a complex of proteins that include α- and β- catenin. Therefore, as the lens changes shape during accommodation , the lateral membranes of the fiber cells are held together tightly by interlocking ball and socket junction and N-cadherin containing cell to cell adhesion complexes, thereby minimizing the extracellular space and reduceing light scattering.(**Bassenett et al, 1999**)

In addition to the lateral cell adhesion complexes, lens fiber cells are joined tightly to each other at their apical and basal ends. These complexes contain abundant N-cadherin and Vinculin, a protein that plays an important role in regulating the interaction between adhesion molecules and the actin cytoskeleton. Membrane complexes at the basal ends of the lens fiber cells, along the posterior capsule, probably attach the fiber cells to the capsule because they contain rich actin cytoskeleton, the contractile protein myosin, and integrin extra-cellular matrix receptors. It is possible that the basal membrane complex also plays a role in the migration of the basal ends of the lens fiber cells towards the sutures (**Bassenett et al, 1999**).

B) Anatomy of the Iris:

The iris is the most anterior extension of the uveal tract. It is made up of blood vessels and connective tissue, in addition to the melanocytes and pigment cells that are responsible for its distinctive color.

The iris diaphragm subdivides the anterior segment into the anterior and posterior chambers. The iris must be mobile to change the papillary size. Normally, the pupil is placed not quite at the center of the iris but rather slightly nasally and inferiorly. The size of the pupil varies with age (**Moses, 1981**).

Stroma:

The anterior border of the iris contains multiple crypts that vary in size, shape and depth. Its surface is not covered by a continuous layer of cells. Instead, it consists of an interrupted layer if connective tissue cells that merges with the ciliary body.

The iris stroma is composed of pigmented (melanocytes) and non – pigmented cells, collagen fibrils and a matrix of hyaluronidase – sensitive mucopolysaccharide. Differences in color are related to the amount of pigmentation in the anterior border layer and the deep stroma (**Moses, 1981**).

Vessels and nerves:

Blood vessels form the bulk of the iris stroma. The majority of vessels follow a course radial to the center of the pupil. Additional vessels pursue a concentric course in a corkscrew fashion around the pupil.

In the region of the collaret (the thickest portion of the iris) anastomosis occur between the arterial and venous arcade, however, the major arterial circle is located in the ciliary body (not the iris).

In humans, the anterior border layer is normally avascular. Medullated and non medullated nerve fibers sensory, vasomotor and muscular functions throughout the stroma (**Green, 1996**)

Posterior Pigmented layer:

The posterior surface of the iris is densely pigmented and appears as velvety smooth and uniform. It is continuous with non pigmented epithelium of the ciliary body and the neuro-sensory portion of the retina. The basal surface of the pigmented layer borders the posterior chamber. The apical surface faces the stroma and is adherent t the anterior pigmented layer, the dilator muscle.

The posterior pigmented layer of the iris curves around the papillary margin and extends for a short distance onto the anterior border layer of the iris stroma (Physiologic ectropion) (**Green, 1996**)

Dilator Muscle:

It lies parallel and anterior to the posterior pigmented epithelium of the iris. The smooth muscle cells contain fine myofilaments and melanosomes. The myofibrils are confined mainly to the basal portion of the cells and extend anteriorly into the iris stroma. The melanosomes and the nucleus are located in the apical region of each myopepithelial cell.

Morphologically, there is evidence of a dual sympathetic and parasympathetic innervations. In vitro organ bath, experiments on the dilator muscle indicate that it contracts in response to Alpha2 adrenergic sympathetic stimulation, but there may be an inhibitory role for cholinergic sympathetic stimulation (**Green, 1996**).

Sphincter Muscle:

It is composed of a circular band of smooth muscle fibers. It is located near the papillary margin in the deep stroma anterior to the pigment epithelium of the iris. Like the dilator muscle, it is derived from neuro-ectoderm. Although a dual innervations has been demonstrated morphologically, the sphincter muscle receives its primary innervation from parasympathetic nerve fibers that originate in the cranial nerve III nucleus. The sympathetic reciprocal innervation to the sphincter appears to serve an inhibitory role, helping to relax the sphincter in darkness (**Green, 1996**).

C) Anatomy of the ciliary Body:

It is divided into 2 parts: the Pars Plicata anteriorly and the Pars Plana posteriorly. The Pars Plicata is 2 mm in length and is composed of about 70 ciliary processes arranged radially. Attached to the ciliary processes and along the Pars Plana are the zonular fibers to the lens.

The ciliary processes consist of vascularized stromal cores surrounded by 2 layers of epithelium, the inner pigmented layer and the outer non pigmented layer. The cells of these 2 layers are arranged apex to apex with tight junctions between them (**Green, 1996**).

The Zonula Occludens near the apices of the non pigmented epithelial cells form the blood aqueous barrier. The non pigmented epithelium also is the site of aqueous secretion.

Arterioles regulate blood flow through the ciliary body influencing the rate of aqueous formation.

The Pars Plana is a flat structure, 4 mm in length , located between the Pars Plicata and the Ora Serrata. (**Atellah et al, 1992**). The inner layer of the Pars Plana comprises pigmented epithelial cells that are uniformly cuboid in shape, while the outer layer comprises non pigmented epithelial cells that are columnar near the Pars Plicata and more cuboidal as they near the Ora Serrata. The non pigmented epithelium secretes acid mucopolysacchride, one of the main components of the vitreous.

Adjacent to the Pars Plicata, the ciliary body is composed of 3 layers of smooth, non striated, muscular tissue. The bulk of the tissue comprises the outer longitudinal layer, which is attached to the scleral spur. The circular and radial muscles originate from the middle and inner ciliary body respectively. The 3 layers act as a unit and are innervated primarily by the parasympathetic nervous system. **(Park, 1999**)

Accommodation and Presbyopia

- *Presbyopia* (derived from the Greek word 'old eye') is a gradual age -related loss in accommodative ability of the eye.
- *Accommodation* is a dioptric change in power of the eye to allow near objects to be focused on the retina.

Rate of loss of Accommodation:

Accommodative loss begins early in life. Objective measurements show 2 to 3 diopters loss per decade, resulting in a complete loss of accommodation by 50.8 years. **(Koretz et al, 1989)** . Most of the accommodative amplitude is lost between the ages of 15 and 45. **(Kaufman and Alm, 2003)**

Figure (1): Scatter gram showing the relation between the age and loss of accommodation