Anatomy

Trabecular Meshwork:

The trabecular meshwork is an area of tissue in the eye located around the base of the cornea near the ciliary body and is responsible for draining the aqueous humor from the eye via the anterior chamber. The tissue is spongy and lined by trabeculocytes, it allows fluid to drain into a set of tubes called Schlemm canal flowing into the blood stream. In cross section the trabecular meshwork is a triangular porous structure that spans the opening of the internal scleral sulcus and over lies Schlemm canal The trabecular meshwork has 3 components :The Uveoscleral,Corneoscleral ,and Juxta canalicular meshwork ***.(Morrison and Pollack,2003).***

Uveoscleral meshwork:

It lies most internal forming the border of the anterior chamber. It consists of thick bands of connective tissue that are covered with endothelium with large intervening spaces that measure between 25-75 microns.These cord like bands originate from the root of iris forming a network anterior to the scleral spur that inserts at Schwalbe' line ***(Gong et al ,1989)***

Corneo scleral meshwork:

It makes up the middle and most extensive portion of the trabecular meshwork This consists of connective tissue plates with a complex extracellular matrix The outer layers of these connective tissue bands are sheet like, the closer they are to Schlemm canal. These sheets contain round or oval pores that gradually decrease as they approach Schlemm canal. Endothelial cells lining these structures upon a basement membrane and are interconnected by desmosomes and gap junction***. (Raviola and Raviola ,1981)***

Tight junctions do not exist between these cells,however aqueous humor can apparently pass freely between them. These endothelial cells also have been shown to contain intermediate actin like filaments that may be important for cell motility and phagocytosis ***(Gipson and Anderson ,1979)***

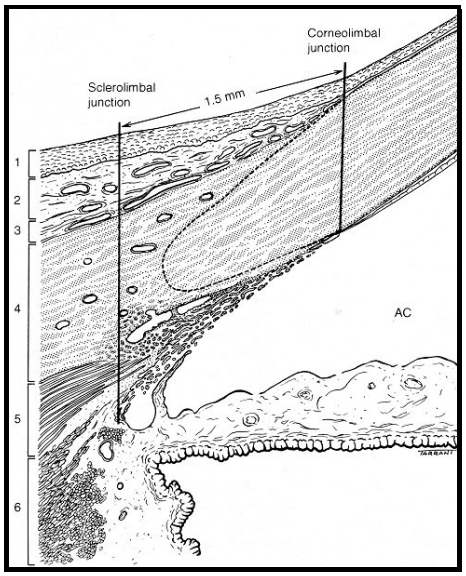


Fig.(1) the structures of limbus (superficial, middle and deep limbus) ***(Snell and Lemp, 2006)***. Superficial limbus:

1- Conjunctival epithelium.
2- Conjunctival stroma
3- Tenon's capsule and episclera.
4- Limbal or corneoscleral stroma.
5- Fiber of ciliary muscle adjacent to the canal of schlemm and trabecular meshwork.

Juxtacanalicular Meshwork:

It is the outermost region of the trabecular meshwork . It is thought to provide much of the resistance to Aqueous humor outflow. It consists of a single amorphous layer of tissue that borders Schlemm canal. Its inner endothelial layers continuous with that of corneoscleral meshwork has similar features. The connective tissue core also comprises a complex extracellular matrix within it. The extracellular matrix includes amorphous basement membrane materials as well as sheaths that surround what are felt to be elastic tendons***.(Holmberg,1965).***

The outer most portion of the Juxtacanclicular Meshwork consists of a layer of endothelial cells that form the inner wall of Schlemm canal. These cells which also contain actin filaments possess variable numbers of large vacuoles that project into Schlemm canal and small pores. ***(Holmberg, 1965)***

These features plus the endothelial cells give the inner wall surface of Schlemm canal an irregular appearance that is distinctly different from that of the outer wall. Intercellular junctions have been demonstrated between these endothelial cells and the restrict aqueous flow from the trabecular meshwork into Schlemm canal ***(Bhatt et al ,1995)***

Viewed from within the outer wall of Schlemm canal it is generally smooth .It contains scattered large openings of aqueous collector channels. Through these channels aqueous traverses the limbal sclera to empty into the episcleral veins and then to the ophthalmic veins and the general circulation ***(Morison and Pollack,2003)***

Unconventional Pathway:

This route of aqueous outflow encompasses all pathways that do not initially involve anteriorly through the cornea and posteriorly into the vitreous then out of the eye the trabecular meshwork .Small quantities of aqueous humor diffuse through the retina or optic nerve head . The bulk of this extracanalicular outflow occurs through the anterior uvea .That is why it is named "Uveoscleral outflow" This pathway most likely begins at the base of the ciliary muscle.This region is identifiable gonioscopically as the ciliary body band. ***(Inomata et al, 1972)***

Aqueous flows within the loose connective tissue that exists between the fibers of the longitudinal portion of the ciliary muscle . These can also penetrate into the vessels of the iris and ciliary body leading to the vortex veins .This pathway is called "Uveovortex pathway" ***(Sherman et al,1978).***

Corneoscleral Limbus:

The corneoscleral limbus is a translucent transitional zone about 1.5 mm in diameter between clear cornea and opaque sclera but wider in the vertical plane . Centrally the corneolimbal junction is demarcated by a line joining the termination of Bowman's layer to the termination of Descemet's membrane .Peripherally the sclerolimbal junction is demarcated by a parallel line passing through the scleral spur**.** ***(Garron et al,1959)***

The limbus can be divided into three zones:

1)The deep limbus that contains the trabecular meshwork and Schlemm canal.

2)The mid limbus containing the transitional corneoscleral stroma that projects with a conoid profile into the scleral limbus ,it also contains the intrascleral venous plexus.

3)The superficial limbus that consists of the episclera Tenon's capsule ,the conjunctival stroma and the limbal conjunctival epithelium with its specialized anatomical features ***(Garron et al,1959)***

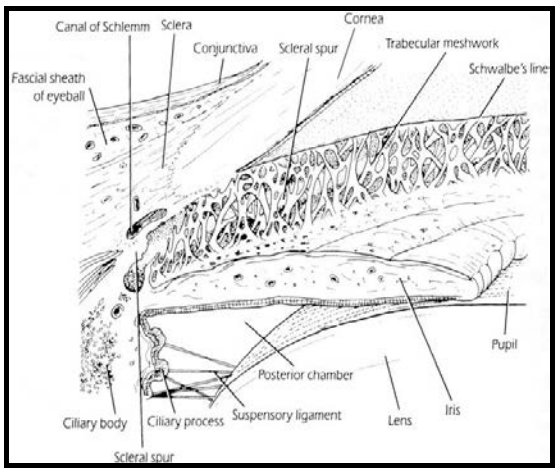
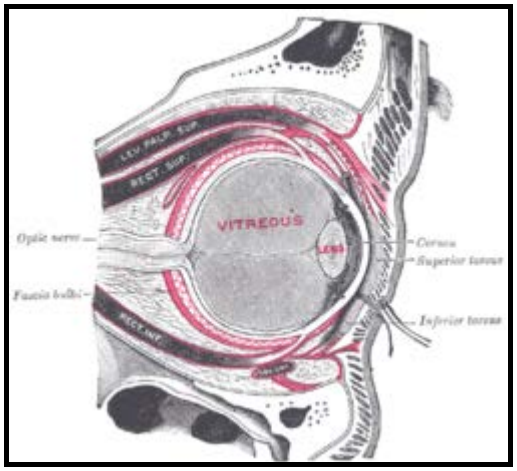


Fig. (2): The structures of the anterior chamber angle.(Snell and Lemp,2006)

The Fascia Bulbi (Tenon's capsule):

The fascia bulbi is a thin fibrous sheath that envelops the globe from the margin of the cornea to the optic nerve ,its inner surface is well defined and in contact with the sclera connected to it by fine trabeculae**.** The fascia is attached to the globe in front posteriorly the external surface of the fascia is in contact with orbital fat .anteriorly it is thinner merging gradually into the subconjuctival connective tissue. Inferiorly it is thickened to form a sling that supports the globe as the"Suspensory ligament of Lockwood" ***(Nutt,1955)***

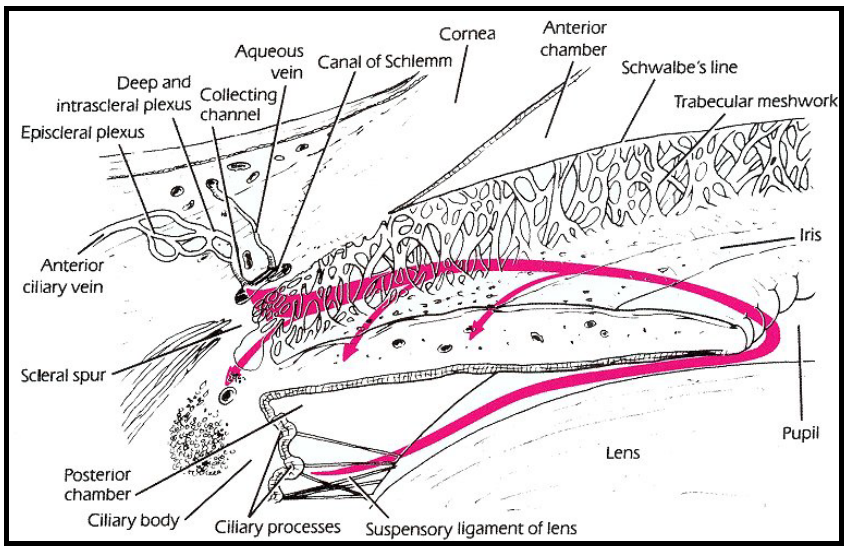


(Fig 3:Tenon capsule anatomy Snell and Lemp,2006)

PHISIOLOGY OF AQUEOUS HUMOR

Aqueous humor function:

It serves several purposes. It helps to maintain eye pressure at a level that will preserve normal ocular structure and function. It supports the metabolic functions of the avascular structures of the eye. It supplies glucose ,oxygen and amino acids and removes waste products such as lactic acid and carbon dioxide ***(Green and Pederson ,1973)***



(Fig 4:Aqueous humor pathway Snell and Lemp,2006)

Aqueous Humor formation :

Passage of aqueous into posterior chamber occurs through a combination of three processes: Ultrafiltration, Active Secreion, and Diffusion

Ultrafiltration:

It describes the movement of water and water soluble substances across a cell membrane. This is governed by the relative osmotic and hydrostatic pressure gradients that exist between the capillaries and stroma within the ciliary processes. Secretion is a metabolically active process that moves solutes across the cell membrane This process creates an osmotic gradient that drives the movement of water and other solutes into posterior chamber***..(Bill,1977)***

Active secretion accounts for up to 90% of total aqueous humor formation from the processes of ciliary epithelium. Diffusion is the passive movement of substances across a cell membrane down a concentration gradient. ***(Bill,1977)***

Ultrafiltration represents an important first step in aqueous production .This is the most likely mechanism by which plasma constituents gain entry into the ciliary process stroma creating a pool upon which the active secretory processes within the epithelium can act to move solutes into the posterior chamber ***(Bill,1968)***

The next step in aqueous formation is active secretion of ions by the non pigmented layer of ciliary epithelium . The tight junctions between the non pigmented ciliary epithelium cells ensure that the accumulation of ions in the intercellular cleft creates a strong osmotic gradient along which water will flow into the posterior chamber ***(Farahbakhsh,1987)***

The electrochemical imbalance created by the transport of sodium is corrected by negatively charged ions that follow sodium. One of these ions is bicarbonate produced by carbonic anhydrase enzyme that catalyzes the conversion of H2O and CO2 toHCO3 and H. This enzyme has been localized in the non pigmented epithelium. Carbonic anhydrase inhibitors can substantially reduce aqueous production ***(Kumpulainen,1983)***

Substances such as oxygen and glucose do not enter aqueous as parts of active secretion .They pass the blood aqueous barrier by simple diffusion. Their consumption from the aqueous establishes a concentration gradient that is the driving force for the continued diffusion of these substances into the posterior chamber***.(Morrison and Pollack,2003)***

Pathopisiology of glaucoma

Glaucoma, the second leading cause of blindness, is characterized by changes in the optic disc and visual field defects. The elevated intraocular pressure was considered the prime factor responsible for the glaucomatous optic neuropathy involving death of retinal ganglion cells and their axons. Extensive investigations into the pathophysiology of glaucoma now reveal the role of multiple factors in the development of retinal ganglion cell death. A better understanding of the pathophysiological mechanisms involved in the onset and progression of glaucomatous optic neuropathy is crucial in the development of better therapeutic options***. (Agrawal et al,2009)***

Glaucoma, a leading cause of irreversible visual loss, is characterized by loss of retinal ganglion cells (RGC) and their axons over a period of many years. Glaucomatous optic neuropathy is characterized by changes in the optic disc and visual field defects. The morphologic changes in the optic disc are in the form of thinning of neuroretinal rim, pallor and progressive cupping of the optic disc. The hemorrhage-associated retinal nerve fiber layer defects precede measurable changes of the optic disc configuration. The visual field defects in glaucoma are often detected only after 40% of the axons are lost***.(Gupta and Weinreb ,1997)***

Multifactorial pathogenesis of glaucoma:

Glaucoma is a heterogeneous group of diseases and the pathophysiology of glaucoma is believed to be multifactorial. Multiple factors acting either on cell bodies or their axons are believed to lead to RGC death. According to various theories put forth, factors like elevated intraocular pressure (IOP) and vascular dysregulation primarily contribute to the initial insult during glaucomatous atrophy in the form of obstruction to axoplasmic flow within the RGC axons at the lamina cribrosa, altered optic nerve microcirculation at the level of lamina and changes in the laminar glial and connective tissue. The factors leading to secondary insult include excitotoxic damage caused by glutamate or glycine released from injured neurons and oxidative damage caused by over-production of nitric oxide (NO) and other reactive oxygen species. Whatever may be the primary and secondary factors, the end result in glaucomatous eyes is the dysfunction and death of RGCs leading to irreversible visual loss, as a result of a complex interplay of multiple factors rather than any one of them functioning individually. ***(Kaushik et al ,2003)***

Vascular insufficiency

A number of circumstantial evidences point towards an association between vascular insufficiency and glaucoma. A positive association of glaucoma has been observed with migraine and peripheral vascular abnormalities that involve dysregulation of cerebral and peripheral vasculature respectively. Increased sensitivity to endothelin-1-mediated vasoconstriction is implicated in these vascular abnormalities. The possible role of this vasoconstrictor is also suspected in the pathogenesis of glaucoma as increased levels of endothelin-1 have been detected in the aqueous humor and plasma of glaucoma patients***.(Tezel et al1997)***

Further evidences indicating a positive association between glaucoma and vascular insufficiency were provided by magnetic resonance imaging in glaucoma patients revealing pan-cerebral ischemia and increased incidence of cerebral infarcts. Aging is also considered an important risk factor for glaucoma and a progressive decline in cerebral and ocular perfusion has been observed with increasing age. Based on these observations it can be hypothesized that neuronal damage in glaucoma represents a chronic anterior ischemic optic neuropathy***.(Stroman et al,1995)***

In a healthy eye, a constant flow of blood is required in the retina and optic nerve head so as to meet the high metabolic needs in these vital parts of the eye. To maintain a constant rate of blood flow an efficient auto regulatory mechanism operates in arteries, arterioles and capillaries over a wide range of day-to-day fluctuations in ocular perfusion pressure that is dependent on both the systemic blood pressure and IOP. These auto regulatory mechanisms are not as robust in aging individuals as in youth***.(Chung et al ,1999)***

Evidence of this can be observed in a study done by Matsuura and Kawai, showing robust choroidal hyperperfusion in response to experimentally induced ocular hypertension in young rats while in older rats a similar increase in choroidal perfusion was not observed. Thus, deficient auto regulatory mechanisms leading to ischemia contribute to the development of glaucomatous neuronal damage with increasing age. Primary open angle glaucoma (POAG) and normal tension glaucoma (NTG) patients have also shown a chronically reduced optic nerve head and retinal blood flow especially in people with low systemic blood pressure leading to reduced ocular perfusion pressure. Reduced diastolic perfusion pressure is now recognized as an important risk factor for POAG. ***(Chung et al,1999)***

Role of elevated IOP

Until recently it was believed that elevated IOP plays a major role in RGC apoptosis and it is also true that reduction of elevated IOP often helps in slowing down the progression of degenerative changes in glaucoma. However, among glaucoma patients only one-third to half of all glaucoma patients have elevated IOP at the initial stages. On an average, 30-40% of patients with glaucomatous visual field defects are being diagnosed as having normal tension glaucoma (NTG) . Therefore, elevated IOP is an important but not the only factor responsible for optic nerve damage***(Klein et al,1992).***

Growth factors and their receptors are known to regulate cellular functions, cytoskeletal organizations and components of ECM in ocular tissue. Trabecular meshwork, optic nerve astrocytes as well as lamina cribrosa cells express a wide variety of growth factors such as neurotrophin factor and TGF-β2. These growth factors may play an important role by affecting the normal development and cellular functions in the trabecular meshwork as well as retina***.(Nickells,1996)***

In the retina retrograde axoplasmic transport block, as a result of elevated IOP can deprive the RGCs of the supply of brain-derived neurotrophin factor (BDNF), important for regulating cell metabolism and cell survival. Deficiency of BDNF can further lead to progression of RGC apoptosis. These effects seem to be further modulated by increased release of TGF- β2 by activated astrocytes in response to elevated IOP***.(Nickells,1996)***

An up regulation of TNF-A in the astrocytes was also detected in human glaucomatous optic nerve head and this expression was found to parallel the progression of neurodegeneration. TNF-A stimulation seems to contribute to neuronal damage by both a direct effect on the axons of the RGCs and by inducing nitric oxide synthase (NOS)-2 in astrocytes***.(Nickells,1996)***

Neuronal loss in glaucoma by apoptosis

The characteristic change in the optic nerve head in glaucoma is a "cupping" of the optic disc where ganglion cell axons have been lost. The death of the axons is associated with a loss of ganglion cell bodies in the retina and ganglion cell axon terminals in the dorsal lateral geniculate body. Death of RGCs in glaucomatous human eyes and experimental animal models of glaucoma takes place by apoptosis ***(Pease et al,2000).***

Which is also the means of eliminating 50% of the RGCs during normal developmental organization of the visual pathway. Apoptosis is a process of programmed cell death in the absence of inflammation, characterized by DNA fragmentation, chromosome clumping, cell shrinkage and membrane

blebbing. Nuclear damage is followed by breaking down of the cell into multiple membrane-bound vesicles which are engulfed by neighboring cells. Some researchers have suggested preferential loss of larger ganglion cells in the retina belonging to parasol and midget cell classes. ***(Glovinsky et al,1993)***

The caspases, a family of cysteine aspartyl-specific proteases have emerged as the central regulators of apoptosis. These enzymes are present as inactive zymogens and once activated initiate an ordered cascade leading to proteolysis of key cytosolic and nuclear components and eventual destruction of the The activation of caspases involves an extrinsic and an intrinsic pathway. The extrinsic pathway involves interaction of specific ligands such as tumor necrosis factor-alpha (TNF-A) with the proapoptotic cell surface receptors while the intrinsic pathway is regulated by proapoptotic molecules***.(Dreixler et al 2011)***

Cellular responses, leading to apoptosis of RGCs are not well understood. A possible mechanism of RGC apoptosis seems to be related to changes in extracelluar matrix components in the retina of glaucomatous eyes in response to elevated IOP. Extensive remodeling of the ECM, including collagen I and IV, transforming growth factor-β2 (TGF-β2), and matrix metalloproteinase (MMP)-1 have been detected in glaucomatous eyes. ECM is responsible .for providing adherence signals thereby controlling the cell functions and cell survival (Werb,1997), MMPs are the major matrix-degrading enzymes. In a recent study enhanced MMP-9 activity was detected in apoptotic RGCs along with decreased deposition of laminin in the RGC layer suggesting increased degradation of the ECM at the retinal site in response to exposure to elevated IOP. Laminin is an important ECM component, which facilitates cell adherence and survival by interacting with cellular integrins. Disintegration and loss of laminin as a result of increased amount of proteases such as MMP-9 leads to deficient cell-ECM communication thereby favoring cell loss by apoptosis***. (Grossmann,2002)***