INTRODUCTION

Rheumatoid arthritis is a chronic progressive autoimmune disease that affects primarily the joints, it is one of the most common connective tissue disease affecting many tissues of the body including the cornea.[1]

Rheumatoid arthritis has a broad effect on the eye , with Keratoconjunctivitis sicca being the commonest one , others like episcleritis , scleritis and peripheral ulcerative keratitis may also occur but to a lesser degree.[1]

Corneal biomechanical properties are probably affected by this disease[2] and can be estimated by Ocular Response Analyzer (ORA)[3] , these changes in biomechanical properties can affect the IOP measurements.[2]

Ocular Response Analyzer is a non-contact non-invasive device that analyze corneal biomechanics in simple and rapid way, giving the results in the form of factors [Corneal Hysteresis (CH), Corneal Resistance Factor (CRF), Corneal Compensated Intraocular Pressure (IOPcc) and Goldmann-correlated IOP (IOPg)].[4]

Corneal hysteresis seems not affected by refractive error or axial length of the eyeball.[5] [6]

In this study we will estimate the different aspects of this effect and correlate them to the normal population with respect to IOP difference, Central Corneal Thickness and Corneal Hysteresis.

AIM OF THE WORK

Measuring the Corneal Biomechanical properties and IOP in Rheumatoid arthritis patients and compare them to age match normal subjects.

Chapter 1

ANATOMY

Anatomy of the corneal layers

The cornea with the lens form the refractive surface of the eye and with the sclera forms the outermost coating of the eyeball. The corneal epithelium is derived from the surface ectoderm while the mesoderm gives rise to Bowman's layer, the stroma, Descemet's membrane and the endothelium. The average diameter of the cornea varies from 11 to 12 mm horizontally and 9 to 11 mm vertically (figure 1). The cornea is responsible for about 42 diopters of the total power of the eye. The posterior surface of the cornea is more spherical than the anterior surface and the central cornea is thinner (520 μm) compared to the peripheral cornea (650 μm or more). The tear film covers the anterior corneal surface while the posterior corneal surface is in contact with the aqueous humor.[7]

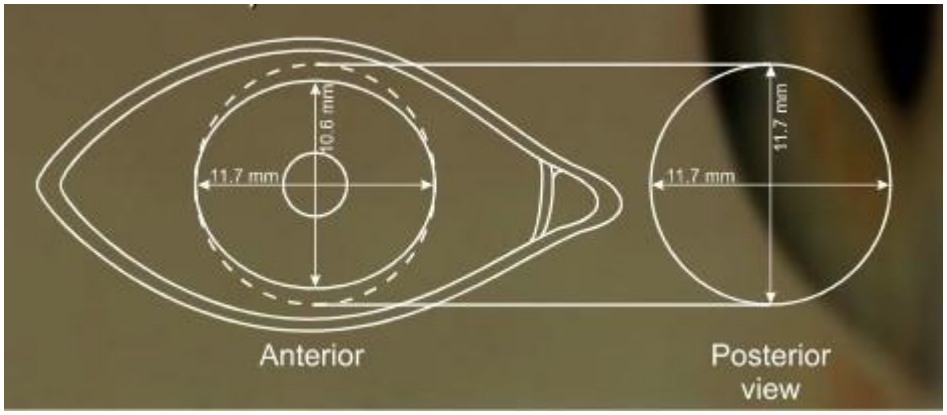

Figure (1): Corneal Dimensions [8]

Precorneal Tear Film:

The tear film is 7 μm thick and has a volume of 6.5 ± 0.3 μL. The tear film is made up of an outer lipid layer (0.1 μm), middle aqueous layer (7 μm), and innermost mucin layer (0.02 to 0.05 μm).[7] (figure 2)

The tear film keeps the corneal surface moist and prevents the adherence of microbes.[7]

More than 98% of the volume of tears is water. The tear film has many essential substances, such as electrolytes, glucose, immunoglobulins, lactoferrin, lysozyme, albumin and oxygen. It also has many biologically active substances such as histamines, interleukins, prostaglandins and growth factors. These factors control corneal epithelial migration, proliferation, and differentiation . [9]

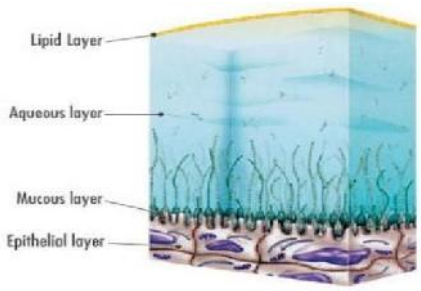

Figure (2): Layers of tear film [10]

Anatomy Of The Cornea

The cornea consists of 6 layers: epithelium, Bowman's layer, stroma, Dua's layer, Descemet's membrane, and the endothelium (figure 3).

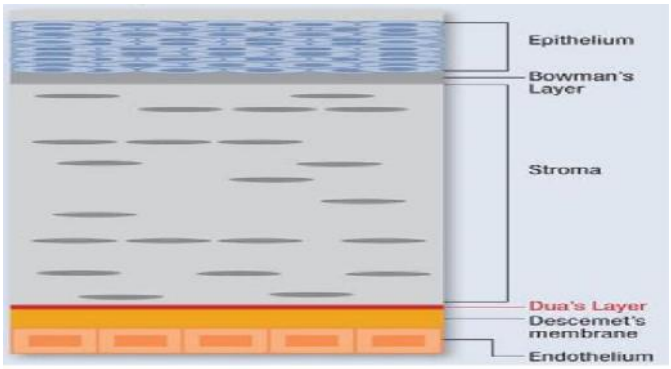

Figure (3): Layers of The Cornea [11]

Epithelium:

The corneal epithelium has a thickness of 50 to 60 µm and comprises 5 to 7 layers of stratified, squamous, and non keratinized cells (figures 4, 5). The epithelium forms approximately 10% of the total corneal thickness.[12]

The cells of the corneal epithelium are divided into 3 types: squamous cells, which are present superficially, middle wing cells, and deeper basal cells.(12)

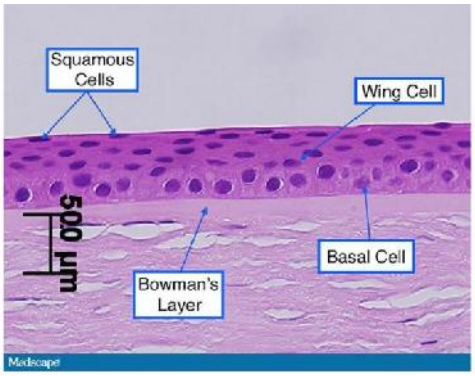

Figure (4): Histology of Corneal Epithelium (13)

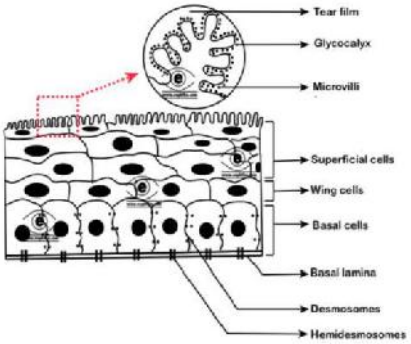

Figure (5): Diagram of Corneal Epithelium cells(14)

Superficial Layer of Squamous Cells, forms the outermost 1 to 2 layers of the corneal epithelium. The oldest epithelial cells disintegrate and shed into the tear film by the process of desquamation.(15)

These superficial cells are composed of microscopic projections in the form of microvilli, reticulations, or microplicae. The fibrillar glycocalyx is present on these ramifications, which interacts with the mucinous tear film. The epithelial cells are replaced approximately every 7 to 14 days.(15)

The superficial cells adhere to each other by the presence of desmosomes and junctional complexes. These complexes consist of tight junctions that circumvent the entire cell and resist the flow of fluid through the epithelial surface.(15)

The Middle Layer of the corneal epithelium consists of wing cells, which have lateral, thin, wing-like projections protruding from a more rounded cell body. The wing cells are connected to each other by desmosomal junctions and gap junctions. (15)

The deep layer of the corneal epithelium consists of basal cells, which are cuboidal to columnar in shape and have a diameter of 8 to 10 μm. Posteriorly, the cells are flat and have a basal lamina to which they anchor with the help of hemidesmosomes. (16)

The basal cells are metabolically active and are responsible for division, and they form the wing and the superficial cells. (16)

The corneal epithelium acts as a tough protective shield against microorganisms and foreign bodies; however, it is partially permeable to small molecules such as glucose, sodium, oxygen, and carbon dioxide.(16)

The basal cells of the corneal epithelium are anchored with the help of hemidesmosomes to the basement membrane, which is located between the corneal epithelium and Bowman's membrane. The basement membrane is primarily made up of type IV , VII collagen and glycoproteins, It has 2 parts, the superficial lamina lucida layer and the deeper lamina densa layer. (16)

BOWMAN'S LAYER:

The Bowman's layer is an acellular membrane-like zone with a thickness of approximately 8 to 14 μm. It has numerous pores for the passage of corneal nerves into the corneal epithelium. On examination with electron microscopy, it is made up of a fine meshwork of uniform type I and III collagen fibrils. [17]

CORNEAL STROMA:

The corneal stroma, with a thickness of approximately 500 μm, is responsible for 90% of the thickness of the cornea. It is located between Bowman's layer and Descemet's membrane. It is composed of lamellae, which are formed of flattened bundles of collagen fibers, stromal keratocytes, and ground substances like keratan sulphate (figures 6 ,7).[17]

The major structural component of the corneal stroma is collagen (type I is the major constituent, types III and VI are also present). There are 200 to 250 bundles of collagen fibrils, each bundle has fibrils of 2 μm thickness and 9 to 260 μm length. The collagen fibers are arranged in a regular manner, parallel to the corneal surface. Such a uniform arrangement and equal spacing of collagen fibers creates a lattice or 3-dimensional diffraction grating, which is responsible for the ability of the cornea to scatter 98% of incoming light rays.[17]

The lamellae in the posterior part of the stroma have an orthogonal layering (i.e, the bundles are at right angles to each other). In the anterior one-third of the stroma, the lamellae have a more oblique layering. The arrangement of the anterior and posterior lamellar stromal fibers is different. The fibers are more compact anteriorly so that their compactness and their oblique arrangement make lamellar dissection more difficult anteriorly. On the other hand, the arrangement of the fibers is less oblique and loose posteriorly so that manual dissection is simpler in the posterior part. (17)

The primary glycosaminoglycans of the stroma are keratin sulfate and chondroitin sulfate, which occur at a ratio of 3:1. The lamellar stroma is secreted and maintained by stromal fibroblasts called keratocytes, which occupy 3% to 5% of the stromal volume. They are responsible for the maintenance of stromal components, and they synthesize collagen degradative enzymes such as matrix metalloproteinases (MMPs).(17)

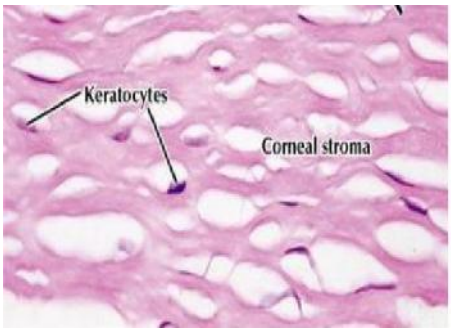

Figure (6): Histology of Corneal Stroma(18)

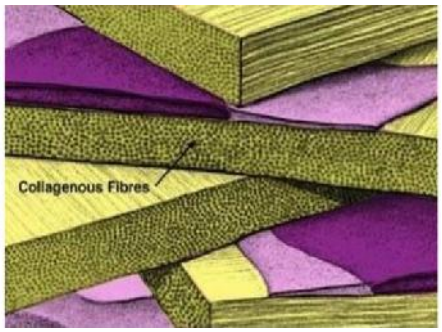

Figure (7): Diagram of Stromal Collagen Bundles(19)

DESCEMET'S MEMBRANE:

Descemet's membrane is the basement membrane of the corneal endothelium and is synthesized by the endothelium. At birth, the human Descemet's membrane is 3 μm wide, but in adulthood, the width increases to 12 μm. There are 2 distinct regions in Descemet's membrane: the anterior one-third, which is banded; and the posterior two-third, which is non banded.[17]

DUA'S LAYER:

Recently, another layer of the cornea, called Dua's layer, has been described. This is a novel, well-defined, acellular, strong layer in the pre-Descemet's cornea. It separates along the last row of keratocytes in most cases with the big bubble technique (figure 8). Its recognition will have a considerable impact on posterior corneal surgery and the understanding of corneal biomechanics and posterior corneal pathology, such as acute hydrops, descemetocele, and pre-Descemet's dystrophies.[20]

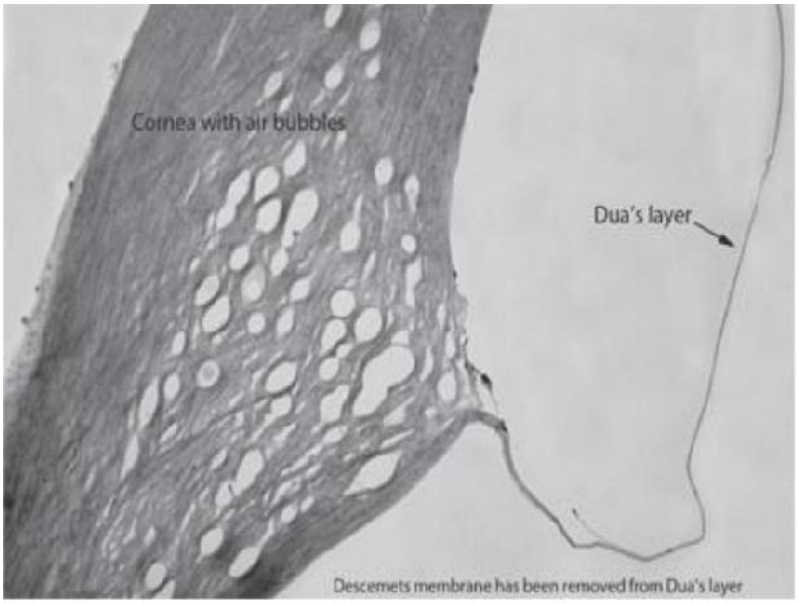

Figure (8): Separation of Dua's layer by big bubble technique[21]

ENDOTHELIUM:

The corneal endothelium is a single-layered, low cuboidal endothelium. It has approximately 400,000 cells and a thickness of 4 to 6 μm. The endothelial cells have a hexagonal shape and are 20 μm wide.[22]

They have tight lateral interdigitations, which prevent seepage of the aqueous humor into the stroma. Specific functional complexes are also present near the apical membranes. [22]

The number of endothelial cells decreases with age at the rate of 0.3% to 0.6% per year. At birth, cell densities range from 3500 to 4000 cells/mm2, whereas an adult's cell densities range from 1400 to 2500 cells/mm2. As cells decrease in

number, they become thinner and attenuated. The cornea loses it clarity when the endothelial cell densities reach 400 to 700 cells/mm2, below which corneal edema occurs.[22] (figure 9)

Unlike the corneal epithelium, endothelial cells cannot undergo mitosis after birth. They decrease in density with increasing age, raised intraocular pressure, inflammation and after intraocular surgery.[23]

The corneal endothelium plays a major role in maintaining stromal hydration (normally 78%) through the sodium potassium–activated adenosine triphosphatase (ATPase) present in the basolateral borders of the cells. The endothelial cells are linked to each other by junctional complexes and gap junctions, but no desmosomes are present.[23]

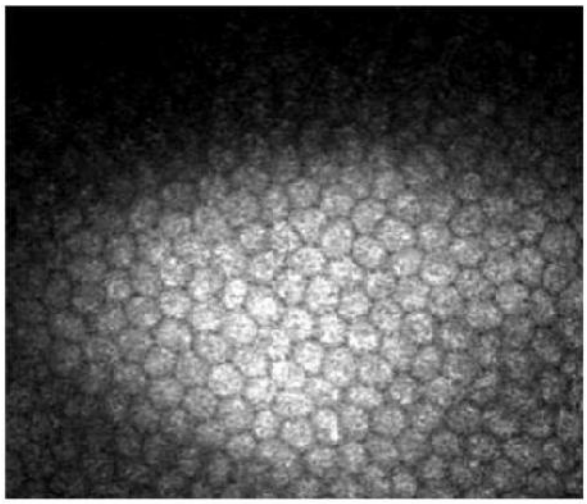

Figure (9): Normal Corneal Endothelial cells by specular microscopy[24]

NERVE SUPPLY OF THE CORNEA

The cornea is supplied by sensory nerves derived from the ciliary nerves of the ophthalmic branch of the trigeminal nerve. The long ciliary nerves supply the perilimbal nerve ring. Nerve fibers penetrate the cornea in the deep peripheral stroma radially and then course anteriorly, forming a terminal subepithelial plexus. [25]

The nerve fibers lose their myelination soon after penetrating the clear cornea, enter Bowman's layer, and terminate at the level of the wing cells. An autonomic sympathetic supply is also present in the cornea. [25]

BLOOD SUPPLY OF THE CORNEA

The cornea is one of the few avascular tissues in the body. The normal healthy cornea does not have any blood vessels. The anterior ciliary artery derived from the ophthalmic artery forms an arcade at the limbus.[23]

Cornea is supplied primarily from the diffusion of oxygen from the atmosphere into the tear film. To a lesser extent, oxygen is also obtained from the aqueous.[23]

Chapter 2

BIOMECHANICAL PROPERTIES OF THE CORNEA

Biomechanics is the study of the structure and function of the mechanical aspect of biological systems.[26]

Corneal Biomechanics is the physical composition of the cornea which gives its viscoelastic properties, meaning it exhibits elements of both elasticity and viscosity which awards it the quality of hysteresis.[27]

The elasticity refers to the ability of a substance to deform reversibly under stress , viscous materials on the other hand is the change happened to a substance and not regains its original shape after the applied force is removed.[28]

The viscoelastic materials exhibit both properties resulting in energy dissipation when stress is applied , The energy lost in this dissipation process called " Hysteresis ".[29]

Collagen and elastin are responsible for the strength and elasticity of the tissue, while the viscoelasticity is the result of collagen bundles themselves and/or the interaction between the collagen and the viscous matrix.[30]

The cornea should be soft enough to bulge out in an aspheric half-sphere but stiff enough to maintain its shape and resist the intraocular pressure. [31]

The Factors known to affect corneal biomechanical properties are:

1- Extracellular matrix (ECM) components.

2- Collagen Lamellae organization.

3- Hydration / Osmotic pressure.

4- Corneal layers.

5- Hormonal fluctuations

6- Environmental factors

Ocular Response Analyzer (ORA) (figure 10)

It is a tonometer tool which also measures the corneal hysteresis, which is an indication for the corneal biomechanical properties.[3]