INTRODUCTION

Glaucoma is the most common optic neuropathy that is characterized by progressive loss of retinal ganglion cells and progressive excavation of the optic nerve head, associated with defects in the visual field. It is not a disease, but the final result of united and yet completely unidentified cellular and subcellular processes and effects of many factors responsible for changes in retinal ganglion cells leading to their accelerated apoptosis ***(Dervisevic et al., 2016)*.**

Changes in the optic disc and retinal nerve fiber layer (RNFL) often precede the appearance of visual field defect with standard automated perimetry. Unfortunately, RNFL defect is difficult to be identified during clinical examination and early detection of glaucoma is still controversial ***(Zaky et al., 2016)*.**

The early detection of glaucoma remains a challenging problem. However, the pattern Electroretinogram (PERG) directly reflects retinal ganglion cell function ***(Bode et al., 2011)*.**

The PERG is an electrophysiological technique that can serve as a sensitive biomarker for retinal ganglion cell function. With appropriate paradigms, PERG assist in identifying those patients with elevated intraocular pressure

in whom glaucoma damage is incipient before the occurrence of visual field changes ***(Michael and Michael, 2008)*.**

The PERG responses obtained from the central macula can detect early-stage of reversible glaucomatous dysfunction ***(Wilsey and Fortune, 2016),*** hence, it can be used to identify glaucoma patients up to 4 years before visual field changes occur ***(Bode et al., 2011)*.**

The conversion rate from untreated ocular hypertension (OHT) to glaucoma is only approximately 1% per year. Discrimination of non-converters and potential converters would help reserve preventative treatment for those who need it and thus avoid unnecessary side effects and expenditure for those who do not. In ocular hypertension cases the pattern Electroretinogram can help to predict stability or progression to glaucoma ***(Bach et al., 2006)*.**

AIM OF THE WORK

The aim of this study is to evaluate the role of PERG in early detection of glaucoma suspect patients in comparison with visual field and optical coherence tomography retinal nerve fiber layer.

Chapter (I)

ANATOMY

- **Optic nerve anatomy**

The optic nerve (ON) originates in the retinal ganglion cells (RGCs) of the retina. In a healthy, middle-aged adult, the ON is composed of approximately 0.8–1.2 million axons. The number of RGCs diminishes gradually throughout life as a result of an estimated loss of 5000 nerve fibers per year in healthy eyes. The ON is divided into four segments: the intraocular part (1 mm) (Fig.1), which consists of the retinal nerve fiber layer (RNFL), the prelaminar, laminar, and retrolaminar ON portions; the intraorbital part (20–25 mm); the intracanalicular part (4–10 mm); and the intracranial part (10 mm). The RGC axons make synapses to the lateral geniculate body, from which the optic radiation to the primary visual cortex originates ***(Hogan et al., 1971)*.**

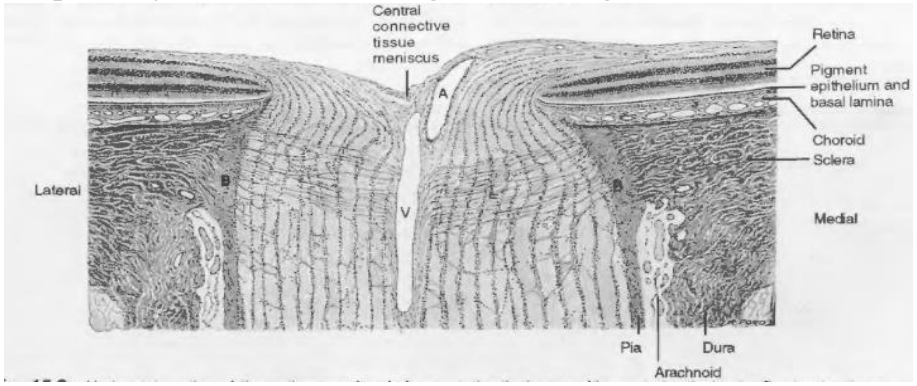

Figure (1): Horizontal section of the optic nerve head. A = central retinal artery; V = central retinal vein; B = border tissue; l = lamina cribrosa ***(Bron et al., 1997)***

The prelaminar, laminar, and retrolaminar portions of the ON are referred to as the optic nerve head (ONH) or optic disc or papilla. It is usually slightly more elongated vertically (1.9 mm) than horizontally (1.7 mm). There is significant variation in the size, shape, and topography of normal discs. The area occupied by the neuroretinal rim is normally pink-orange and ranges from 1.4 to 2.0 mm2 in normal subjects. Histologically, the RNFL is composed mainly of non-myelinated axons with some astroglial tissue. In the ONH, the axons are arranged in approximately 1000 bundles or fascicles. The axons originating from more peripheral RGCs turn into the ON closer to the scleral rim, therefore occupying the periphery of the ON. The more central (axial) fibers exit the eye closer to the ON center. The central retinal artery and vein emerge from the ONH near the center of the cup in most eyes ***(Hoffmann et al., 2007)*.**

The optic nerve head may be divided into four portions from anterior to posterior (Fig.2) ***(Allingham et al., 2011)*.**

1. Surface Nerve Fiber Layer

The innermost portion of the optic nerve head is composed predominantly of nerve fibers. The axonal bundles acquire progressively more interaxonal glial tissue in the intraocular portion of the nerve head as this structure is followed posteriorly.

2. Prelaminar Region

The prelaminar region is also called the anterior portion of the lamina cribrosa. The predominant structures at this level are nerve axons and astrocytes, with a significant increase in the quantity of astroglial tissue.

3. Lamina Cribrosa Region

This portion contains fenestrated sheets of scleral connective tissue and occasional elastic fibers. Astrocytes separate the sheets and line the fenestrae, and the fascicles of neurons leave the eye through these openings.

4. Retrolaminar Region

This area is characterized by a decrease in astrocytes and the acquisition of myelin that is supplied by oligodendrocytes. The axonal bundles are surrounded by connective tissue septa.

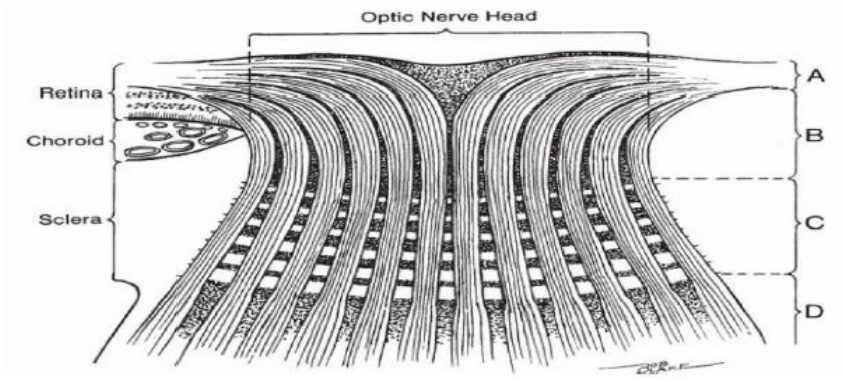

Figure (2): Divisions of the optic nerve head. A: Surface nerve fiber layer. B: Prelaminar region. C: Lamina cribrosa region. D: Retrolaminar region ***(Allingham et al., 2011)*.**

The lamina cribrosa (to which the different portions of the intraocular ONH area are spatially related) is a distinct histological structure, located in Elschnig's rim; thus it is not a part of the surrounding sclera. It is composed of 8 to 12 roughly parallel layers of connective and elastic tissue with 500 to 600 pores of variable diameter, which convey the nerve fascicles. The superior and inferior pores of the lamina cribrosa are larger than the nasal and temporal pores. The larger pores accommodate thicker nerve fascicles. The lamina cribrosa, nerve bundles, capillaries, and astroglia constitute the laminar portion of the ONH. The turnover of the extracellular material is regulated by astroglial. The retrolaminar portion of the ONH is short and corresponds to the area in which myelin produced by oligodendrocyte begins to "wrap" the nerve, nearly doubling its diameter to 3–4 mm ***(Yablonsky and Asamoto, 1993)*.**

- **Retinal nerve fibers:**

The retinal nerve fibers are arranged in a precise pattern which forms the basis for the characteristic optic disc(Fig 3) and visual field changes.

1. Macular fibers—these have straight course to the optic disc forming spindle shaped papillomacular bundle.The papillomacular fibers spread over approximately one third of the distal optic nerve,primarily infro-temporally, where the axonal density is higher. They get affected last with

retention of central vision until the advanced stage of glaucoma.

2. Nasal fibers—these have relatively straight course to the optic disc.

3. Temporal fibers—they follow an arcuate path around the papillomacular bundle. There is an imaginary horizontal raphe dividing the superior and inferior part. These fibers are most sensitive to glaucomatous changes ***(Jogi, 2009)*.**

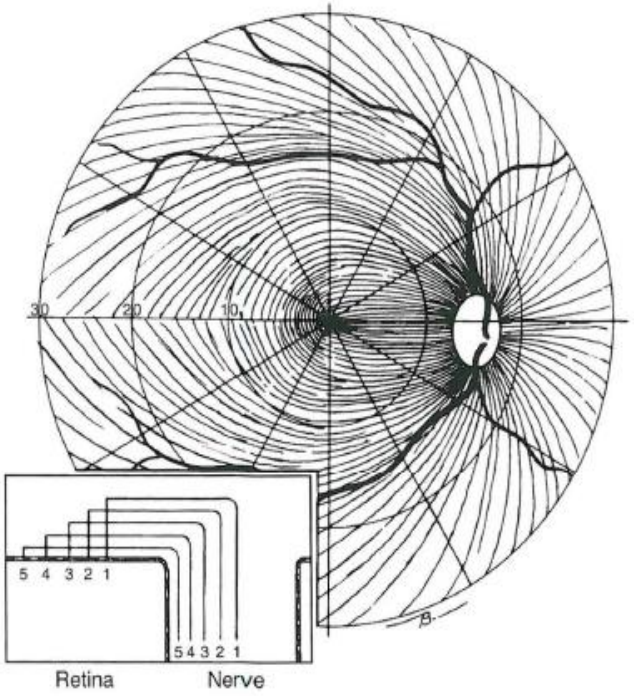

Figure (3): Distribution of retinal nerve fibers, arching above and below the fovea of fibers temporal to the optic nerve head. Inset depicts cross-sectional arrangement of axons, with fibers originating from peripheral retina running closer to choroid and periphery of optic nerve, while fibers originating nearer to the nerve head are situated closer to the vitreous and occupy a more central portion of the nerve ***(Allingham et al., 2011)*.**

Chapter (II)

GLAUCOMA

• Introduction

Glaucoma is a group of eye diseases which result in damage to the optic nerve and vision loss. The most common type is open-angle glaucoma with less common types including closed-angle glaucoma and normal-tension glaucoma. Vision loss from glaucoma, once it occurred it will be permanent. It occurs more commonly among older people. Closed-angle glaucoma is more common in women ***(Mantravadi and Vadhar, 2015)***.

According to the World Health Organization (WHO) and the World Association of Glaucomatologist (WGO), in the year 2010, 66.8 million people worldwide suffer from glaucoma, and 6.7 million are blind from this disease ***(Dervisevic et al., 2016).***

Glaucoma is often divided into 2 major subtypes; open angle and angle closure (Fig 4), both of which result in characteristic optic nerve degeneration. Both can be further subdivided into primary or secondary due to some other inciting factors. Secondary glaucoma can result from many other pathologic processes, including but not limited to vasculopathic, malignant, and traumatic ***(Mantravadi and Vadhar, 2015).***

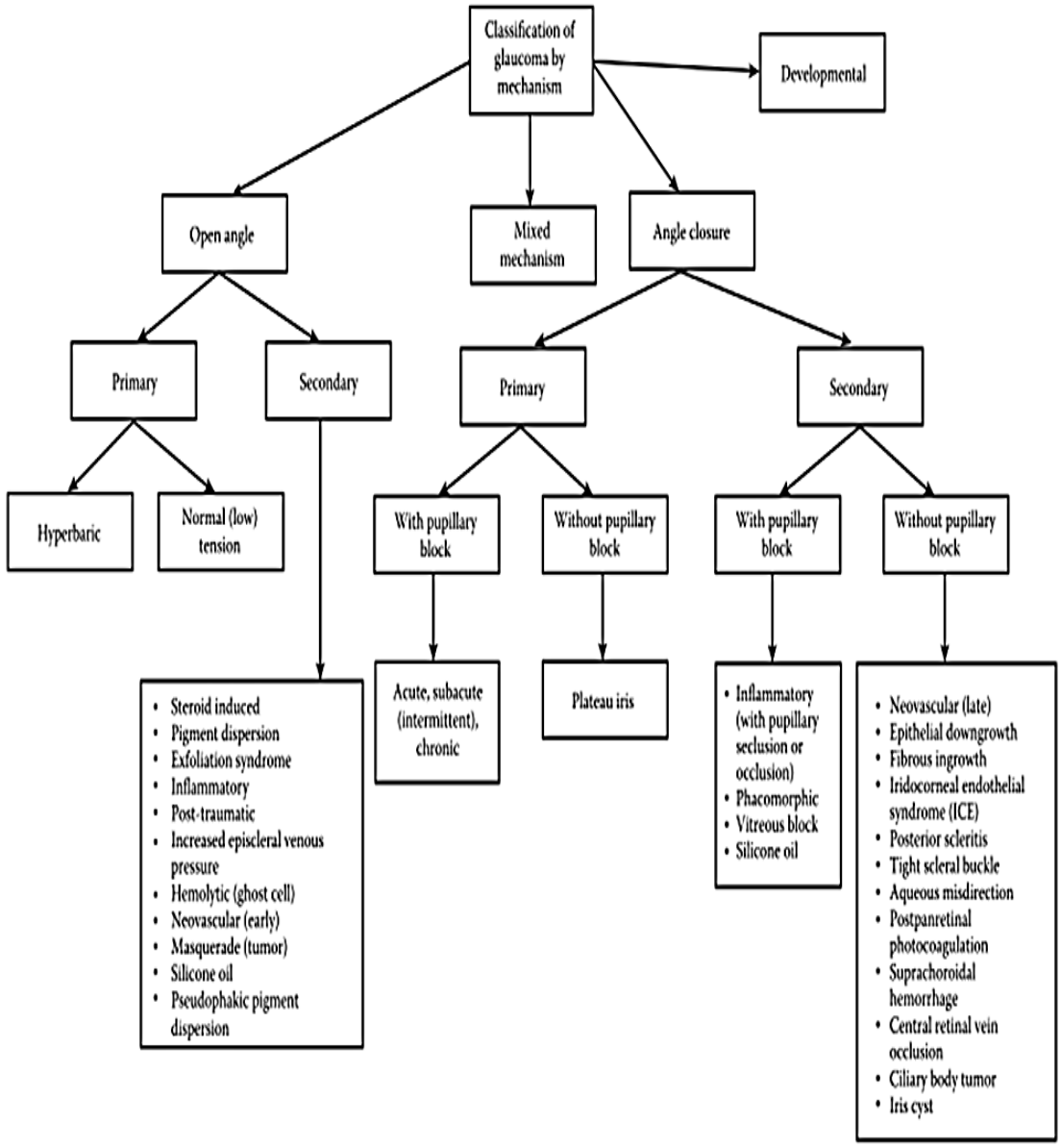

Figure (4): Classification of glaucoma by mechanism. Note the main subdivisions are open angle and angle closure ***(Choplin and Traverso, 2014)***.

Angle-closure glaucoma can be an acute process with more immediate signs and symptoms but may also present insidiously and tends to be a more visually destructive subtype. It accounts for approximately half the cases of glaucoma worldwide and, when acute, is considered an ocular emergency because loss of vision can occur within hours to days ***(Hyams, 1990)*.**

While open-angle glaucoma is a chronic insidious process, Patients are often unaware of their disease until vision loss has progressed significantly, known as the "sneak thief of sight". Early diagnosis remains a challenge given the insidious nature of the onset of this process and, therefore, formal ophthalmologic evaluation of any patient with risk factors is critical for prompt detection ***(Mantravadi and Vadhar, 2015)*.**

- **Pathophysiology**

Although the pathogenesis of glaucoma is not fully understood, the level of intraocular pressure is thought to be related to retinal ganglion cell death. IOP can be maintained by the balance between secretion of aqueous humor by the ciliary body and its drainage through the trabecular meshwork and uveoscleral outflow pathway ***(Tamm et al., 2007)*.**

On the other hand, some patients with normal pressure develop similar glaucomatous disc and visual field changes, which indicates there must be other risk factors involved in the pathogenesis of the disease, several studies support the idea that circulatory abnormalities are included among these additional risk factors for glaucoma ***(Stewart et al., 2000)*.**

The mechanical theory:

Normally, the IOP is a balance of aqueous humor production by the ciliary body and aqueous humor drainage through the internal outflow system (fig 5). A major component of the outflow system is the trabecular meshwork located in an area denoted as the angle. In open-angle glaucoma, the major site of resistance to outflow of aqueous humor is thought to be at the level of the trabecular meshwork. The consequence of outflow dysfunction is, therefore, elevated IOPs. ***(Choplin and Traverso, 2014)*.**

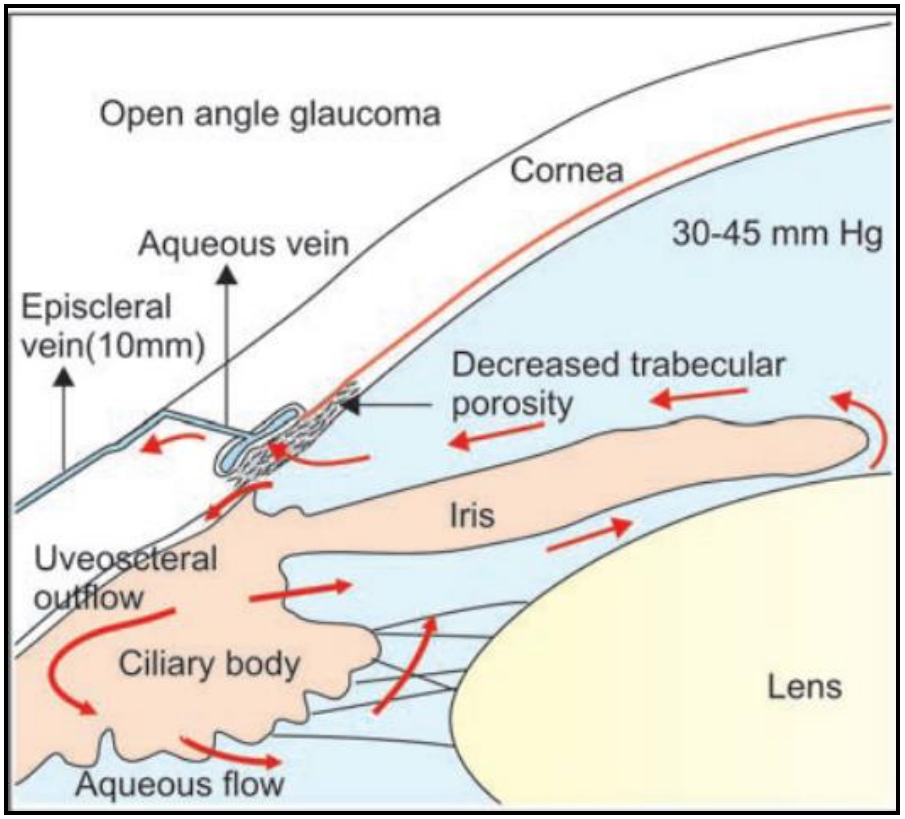

Figure (5): Mechanism of rise in intraocular pressure in open angle glaucoma ***(Jogi, 2009)*.**

The mechanical theory supposes that the increased pressure leads to elongation, stretching and collapse of the laminar beams and their backward displacement so that the axons of the retinal ganglion cells become damaged directly, by increased pressure and pressure gradient, or indirectly by tissue deformation. The axoplasmatic transport is thought to be impeded which may ultimately induce cell death, for example due to a lack of trophic factors ***(Flammer et al., 2002)*.**

In the last decade, glaucomatous optic neuropathy has been considered as a result of a complex dysregulation process. In addition to dysregulation in the trabecular meshwork (which leads to elevation of IOP), the retinal ganglion cells and their axons also suffer from a group of insults, which are mainly initiated at the level of the lamina cribrosa. In primary open angle glaucoma, production and turnover of the extracellular material in the lamina cribrosa is dysregulated ***(Morgan, 2009)*.**

As a consequence, some functions of the lamina cribrosa (mechanical resistance and elasticity) become insufficient. This leads to glaucomatous damage via increased mechanical deformation of the lamina cribrosa and shared stress of the axons passing through it, particularly at the superior and inferior poles of the ONH where the laminar pores are larger and therefore potentially more sensitive to mechanical damage ***(Downs et al., 2009)*.**

Elevation of IOP blocks the axonal transport processes in level of the lamina cribrosa. This is due to the increase of translaminar pressure gradient. As a consequence, the intracellular organelles produced in the cell body of the RGCs (e.g., mitochondria) cannot move further along the long axon (blockage of the orthograde transport). This leads to decreased energy supply. At the same time, neurotrophic factors produced by the brain cannot reach the ganglion cell body (blockage of the retrograde transport), which stimulate

apoptosis-mediated lethal damage of the RGCs ***(Morgan, 2009)*.**

The vascular theory:

The suggestion of the vascular theory comes from two facts, Firstly is that the therapeutic control of IOP in many patients is not sufficient to improve the visual functions and arrest the progression of the disease process , Secondly is that the glaucomatous changes have been observed in individuals with normal IOP. So These facts produce the suggestion of a critical role of other factors in the initiation and progression of glaucomatous changes ***(Chauhan, 1995)*.**

Many reasons point towards a relation between vascular insufficiency and glaucoma, as observation of a positive association of glaucoma with migraine ***(Wang et al., 1997),*** and peripheral vascular abnormalities that involve dysregulation of cerebral and peripheral vasculature respectively ***(O'Brien and Butt, 1999)*.**

One of the strongest points for the vascular theory is the relation between glaucomatous disc changes and endothelin-1-mediated vasoconstriction ***(Gass et al., 1997)*** , as it was found that some of glaucoma patients show increasing in plasma levels of endothelin-1 ***(Cellini et al., 1997)***, and it is also detected in the aqueous humor of some glaucoma patients ***(Noske et al., 1997)*.**