A STUDY ON DIABETES MELLITUS AS A RISK FACTOR FOR PRIMARY OPEN ANGLE GLAUCOMA

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SUBMITTED FOR M.S.[OPHTHALMOLOGY]

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DEPARTMENT OF OPHTHALMOLOGY

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DECLARATION

I, **Dr. R. GAYATHIRI** solemnly declare that this dissertation titled **"A STUDY ON DIABETES MELLITUS AS A RISK FACTOR FOR PRIMARY OPEN ANGLE GLAUCOMA**" is a bonafide record of work done by me in the Department of Ophthalmology, Thanjavur Medical College, Thanjavur under the guidance and supervision of Professor **Dr. J. Gnanaselvan M.S.,D.O.,** Department of Ophthalmology, Thanjavur Medical college, Thanjavur between May 2017 – May 2020.

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CONTENTS

PART I

1. INTRODUCTION

Glaucoma is a chronic degenerative optic neuropathy which may or may not be associated with raised intraocular pressure (IOP). It is estimated to contribute to blindness in 11.2 million people with prevalence reaching approximately 80 million.

Diabetes has been proposed as one of the many risk factors in POAG. In the paper published by Armstrong et al, POAG was prevalent in 4.1% of diabetics and 1.7% of diabetics were found to have(1). Increased prevalence (6 -11%) of Diabetes has been reported in Glaucoma populations.

In comparison of diabetic and non-diabetic population with POAG, there was a higher proportion of patients with elevated mean IOP. It was also found that there is a higher prevalence of glaucoma among diabetics as compare to the general population.

It has been proposed that there is a common pathophysiological association between diabetes mellitus and primary open angle glaucoma. Becker in 1971, stated “Diabetes Mellitus occurs more often in patients with primary open angle glaucoma than in non-glaucomatous populations. likewise, Glaucoma is more prevalent in diabetic than in non-diabetic population”(2).

Hyperglycemia causes glycation of lipids and abnormalities of lipid metabolism which promotes oxidative stress and causes apoptosis, thereby bringing about retinal ganglion cell loss resulting in glaucoma. It has been shown in various studies that hyperglycemia can induce excess extracellular matrix (ECM) synthesis by trabecular meshwork cells. This may lead to ECM accumulation in the trabecular meshwork, contributing to blockage of aqueous outflow.

However, Population based prevalence data studies in South-Asian ethnicity which evaluate this association are minimal in number.

In this study, correlation between POAG and diabetes mellitus is evaluated with glaucomatous changes and Glycated Hemoglobin levels (HbA1c).

2. REVIEW OF LITERATURE

HISTORY OF GLAUCOMA

The first mention of glaucoma was by the Greeks who described diseased eyes as “glaukos” – These denoted glaucous hue (light blue, gray, or green). If either a healthy iris or a diseased pupil had appeared green, the term glaukos would likely have been used.

During the Hippocratic period, media opacity that was not dark was denoted by the term glaukos pupil. Glaucoma was used to describe blindness with glazy appearance of the pupil - “pupil if becomes sea colored, vision is destroyed, and blindness of the fellow eye follows”. Galen associated the glaucous hue with a large, anterior, or hard crystalline lens with visual loss. Originally, it was undifferentiated from cataract; both cataract and glaucoma were located in the lens, which was considered as the necessary organ of vision, and depended on a visual spirit disturbance.

During the early Common Era (CE), when couching was performed in Mediterranean Europe, descriptions of glaucous eye disease evolved. Celsus observed symptoms such as optic neuropathy, pain, a glaucous like hue, and pupil as precursors of poor outcome but did not connect the clinical picture to a syndrome.

Arabic authors in the Medieval era, described glaukos as zarqaa. The first association of this disease condition and rise in intraocular pressure was suggested by Abul Hasan Ahmad ibn Muhammad Tabari (c 916–986 AD). Tabari mentioned “migraine of the eye” (Shaqiqat Al-Ayn), which involved eye pain, a pressure sensation, opacification of the ocular fluids, and a dilated pupil. Abu Ali al-Husain Ibn Sina (c 980–1037 AD), known later as Avicenna wrote

that the zarqaa hue could occur due to anterior prominence of the lens and could occur in an acquired manner.

In 1348, Sams-ad-Din described glaucoma as “headache of the pupil” or “migraine of the eye” - associated with pain in the eye, unilateral headache, dilatation of the pupil along with cataractous lens changes. If this condition became chronic, raised tension of the eye and loss of vision followed.

Glaucoma with raised intraocular pressure was first described by Antoinne-Pierre Demours in 1818. The clinical picture was explained in detail and for the first time he described the appearance of the colors of a rainbow around the lights which was later on called as colored halos.

Glaucoma was classified as open and closed angle with the help of gonioscopy. Barkan in 1938, put forward that angle closure glaucoma resulted due to obstruction in the flow of aqueous through the pupil and so recommend a peripheral iridectomy so as to re-introduce the communication between the posterior and anterior chambers of eye as a way of surgical cure.

These revolutionary thoughts gave the ideas for the development of modern classification of glaucoma.

ANATOMY

Understanding the pathophysiology of glaucoma would not be possible without the knowledge of aqueous humor dynamics and the principle ocular structures associated with it.

Aqueous humor is secreted by the non-pigmented epithelium of the ciliary body. It is poured into the posterior chamber and subsequently into the anterior chamber from where it is drained by the trabecular meshwork present in the angle of the anterior chamber.

The anterior chamber is about 3 mm deep in the center in the adults. It is bounded posteriorly by the anterior surface of the iris, ciliary body and anteriorly by the posterior surface of the cornea. It communicated to the posterior chamber through the pupil. Its peripheral recess is called the angle of the anterior chamber and is mainly formed by the trabecular meshwork as described above.

ANGLE OF THE ANTERIOR CHAMBER

The angle of the anterior chamber plays an important role in the process of aqueous drainage. It comprises of:

1. Ciliary band
2. Scleral spur
3. Trabecular meshwork
4. Schwalbe's line

CILIARY BAND

The ciliary band is a gray or dark-brown band and is a portion of the ciliary body which is visible in the anterior chamber as a result of the insertion of the iris.

SCLERAL SPUR

This appears as a prominent white line between ciliary body band and functional trabecular meshwork. This is the posterior lip of the scleral sulcus.

TRABECULAR MESHWORK

It is seen as a band, just anterior to scleral spur. It has color varies from faint tan to dark-brown.

SCHWALBE'S LINE

It is a fine ridge seen just in front of the trabecular meshwork formed by the prominent end of Descemet's membrane of the cornea. It marks the anterior limit of the structures forming the angle of anterior chamber.

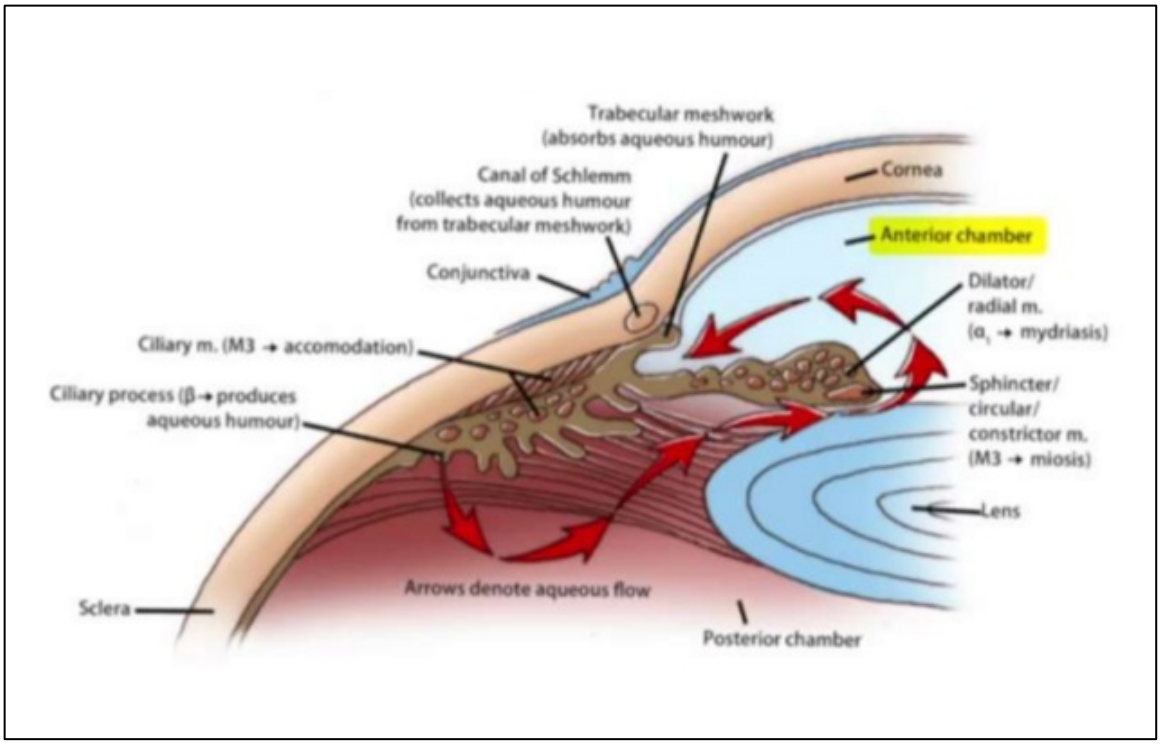

Fig 2.1. Anatomy of anterior chamber of the eye

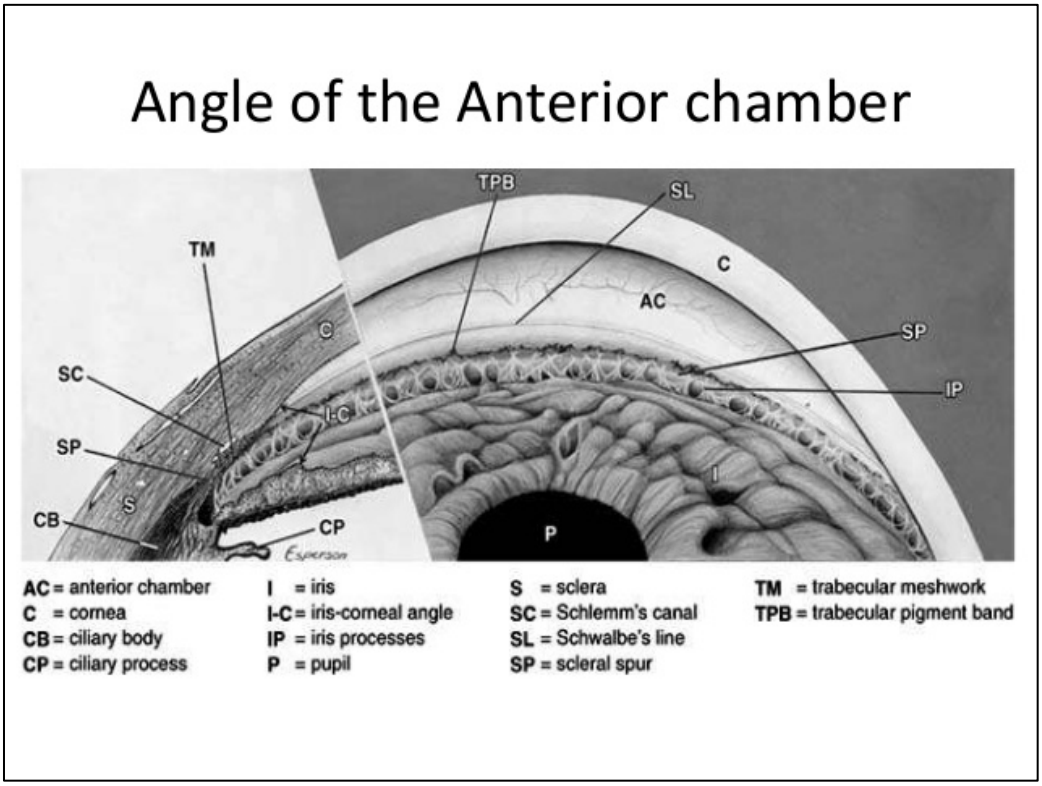

Fig 2.2. Angle of the anterior chamber

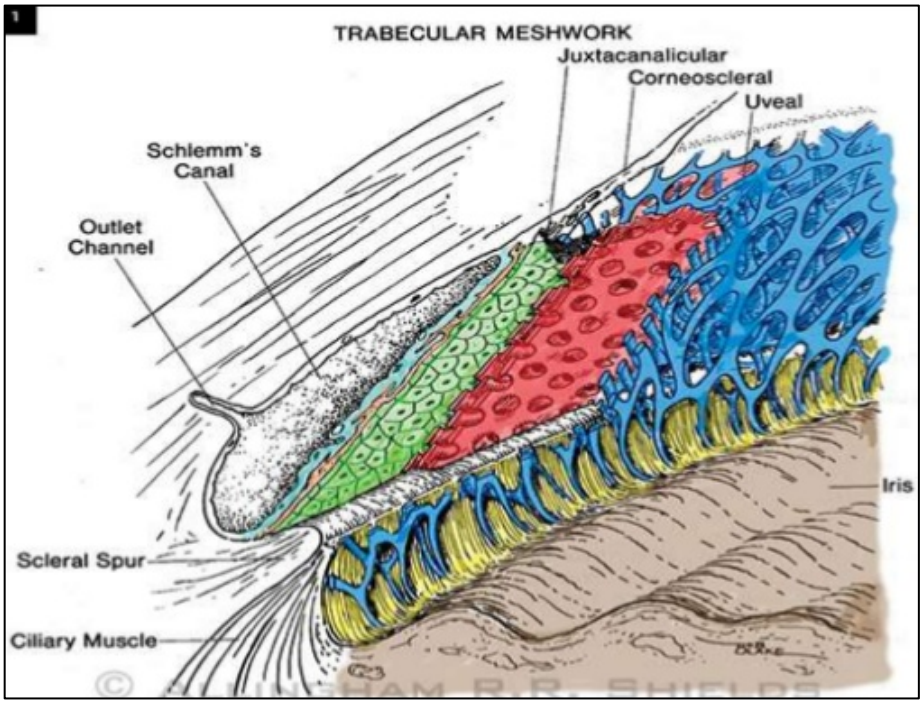

Fig 2.3. Trabecular meshwork

PHYSIOLOGY

Aqueous humor dynamics includes inflow (production) and outflow (drainage) of aqueous humor. These events are described below in detail.

INFLOW

FORMATION OF AQUEOUS HUMOR

Ciliary processes are the site of aqueous production. At present, it is agreed that diffusion, ultrafiltration, and secretion from the plasma within the capillary network play role in aqueous production at different levels. Active secretion accounts for 70% of aqueous production whereas ultrafiltration accounts for 20% and osmosis accounts only for 10%.

In the process of aqueous production, the lipid soluble substance are transported by diffusion through the lipid portions of the cell membrane of the ciliary processes, proportional to a concentration gradient across the membrane. The flow of water and water soluble substances through theoretical micropores in the protein part of the cell membrane in response to osmotic gradient or hydrostatic pressure is known as ultrafiltration. Secretion implies an active process that selectively transports some substances across the cell membrane against a concentration gradient. This is believed to be mediated by globular proteins in the membrane and requires energy.

Thus, in the formation of aqueous humour, most substances pass easily from the capillaries of the ciliary body across the stroma through the process of ultrafiltration. Subsequently, there is active transportation of stromal filtrate across mainly the tight junctions between the non-pigmented epithelial cells (Blood-aqueous barrier). This is evident due to the abundance of Na/K ATPase in the non-pigmented epithelium, mitochondria, higher adenyl cyclase activity, higher specific gravity for glycolytic enzymes and preferential incorporation of labelled

sulphate into macromolecules. The pigmented epithelium also plays a role in active transportation as shown by recent studies. Passive transportation of water, chloride and other small plasma constituents then occurs to maintain the balance of osmotic and electric gradient.

The aqueous humour thus produced flows from posterior to anterior chamber due to a thermal gradient between the cooler anterior chamber (due to avascular cornea and evaporation of tears from the corneal surface) and the warmer vascular iris. Therefore, the aqueous humour in the posterior part of the anterior chamber moves along the warmer iris and in the anterior part, down the cooler cornea.

OUTFLOW

The Aqueous humor is drained mainly through the following routes:

- Trabecular (conventional) outflow
- Uveoscleral (unconventional) outflow

UVEOSCLERAL OUTFLOW

This is responsible for 10-25% of the total aqueous flow. The aqueous humor is drained by the venous circulation from the ciliary body through the suprachoroidal space into the choroid, sclera and orbital tissues. This output is approximately 0.3 ml/min and is independent of changes in intraocular pressures.

TRABECULAR OUTFLOW

This is the main outlet for aqueous from the anterior chamber accounting for 75-90%. Aqueous flow occurs from trabecular meshwork in the angle of the anterior chamber up to the

juxtacanalicular tissue which along with the inner wall of the Schlemm's canal provides resistance to the outflow. The aqueous humor is thus transported into collector channels and episcleral veins through various proposed passive filter (Leaky endothelial cells, Sonderman's channels, Contractile microfilaments, Pores in endothelial cells and Vacuolation theory) and active pump mechanisms.

CLASSIFICATION OF GLAUCOMAS

Glaucomas may be classified depending on:

1. The etiology: Alteration in aqueous humor dynamics due to an underlying disorder.

2. The mechanism: a rise in intraocular pressure due to specific alteration in the anterior chamber angle.

Primary glaucomas are disorders that have no association with systemic or other ocular disorders that might lead to the alteration. They have a genetic basis and are usually bilateral. Secondary glaucomas, on the other hand are associated with systemic or ocular abnormalities that are probably the cause for the alteration in aqueous humor dynamics. They can be inherited or acquired and may be unilateral or bilateral.

Given below is a classification based on the pathogenesis(3).

I. Angle Closure Glaucoma
    a. Primary Angle Closure Disease

        Irido-trabecular contact is the final common pathway of angle closure, obstructing outflow.

        i. Natural history

1. Primary angle closure suspect
2. Primary angle closure
3. Primary angle closure glaucoma

ii. Anterior segment mechanisms of closure

1. Iris-pupil obstruction (e.g. Pupillary block)
2. Ciliary body anomalies (e.g. Plateau iris syndrome)
3. Lens-pupil block (e.g. Phacomorphic bock)

b. Secondary Angle Closures

i. Anterior pulling mechanism

Iris is pulled forward by some process in the angle by contraction of a membrane or peripheral anterior synechiae.

1. Neovascular glaucoma
2. Iridocorneal endothelial syndromes (e.g. Chandler's syndrome)
3. Posterior polymorphous dystrophy
4. Epithelial downgrowth
5. Fibrous ingrowth
6. Flat anterior chamber
7. Inflammation
8. Penetrating keratoplasty
9. Aniridia

ii. Posterior pushing mechanism

There is some condition pushing the iris forward in the posterior segment. Often the ciliary body is rotated anteriorly, allowing the lens to come forward.

1. Ciliary block glaucoma (malignant glaucoma)
2. Cysts of iris and ciliary body
3. Intraocular tumours
4. Nanopthalmos
5. Suprachoroidal haemorrhage
6. Intravitreal air injection (e.g. Retinal pneumopexy)
7. Ciliochoroidal effusions (e.g. Panretinal photocoagulation)
8. Scleral buckling procedure
9. Retrolental fibroplasias

II. Open Angle Glaucoma

a. Primary Open Angle Glaucoma

i. IOPs higher than normal range

ii. IOPs within normal range (normal-tension glaucoma)

b. Secondary Open Angle Glaucoma

i. Pigmentary glaucoma

ii. Pseudoexfoliation glaucoma

iii. Steroid glaucoma

iv. Lens-induced glaucoma

1. Phacolytic glaucoma
2. Lens-particle glaucoma
3. Phacoanaphylaxis

v. Glaucoma after cataract surgery

1. α-Chymorypsin glaucoma
2. Glaucoma with viscoelastics

3. Glaucoma with pigment dispersion and intraocular lens
4. Uveitis-Glaucoma-Hyphema syndrome
5. Glaucoma after Nd:YAG laser posterior capsulotomy
6. Glaucoma with vitreous in anterior chamber

vi. Glaucoma after trauma

1. Chemical burns
2. Electric shock
3. Radiation
4. Penetrating injury
5. Contusion injury

vii. Glaucoma associated with intraocular haemorrhage

1. Ghost cell glaucoma
2. Haemolytic glaucoma
3. Hemosiderosis

viii. Glaucoma associated with retinal detachment

ix. Glaucoma after vitrectomy

1. Intraocular gas
2. Intraocular silicone oil

x. Glaucoma with uveitis

1. Fusch's heterochromic iridocyclitis
2. Glaucomatocyclitic crisis (Posner-Schlossman)
3. Precipitates on trabecular meshwork (trabeculitis)
4. Herpes simplex
5. Herpes zoster

6. Sarcoidosis
7. Juvenile Rheumatoid arthritis
8. Syphilis
9. HIV infection

xi. Glaucoma with intraocular tumours

1. Malignant melanoma
2. Metastatic lesions
3. Leukaemia and lymphoma
4. Benign lesions

xii. Amyloidosis

xiii. Increased episcleral venous pressure

1. Obstruction of venous drainage (e.g. SVC obstruction)
2. Arteriovenous fistula (e.g. Carotid cavernous)
3. Ocular episcleral venous anomalies (e.g. Sturge-Weber syndrome)

III. Developmental Glaucoma

Anomalies of anterior segment are present at birth. Glaucoma may be present at birth or may appear in the first decades of life.

a. Primary Congenital (Infantile)Glaucoma

i. Congenital glaucoma

ii. Autosomal dominant juvenile glaucoma

iii. Glaucoma associated with systemic abnormalities

iv. Glaucoma associated with ocular abnormalities

b. Secondary Glaucoma

i. Traumatic glaucoma

ii. Glaucoma with intraocular neoplasm
iii. Uveitis glaucoma
iv. Lens induced glaucoma
v. Glaucoma after congenital cataract surgery
vi. Steroid induced glaucoma
vii. Neovascular glaucoma
viii. Secondary angle closure glaucoma
ix. Glaucoma with elevated episcleral venous pressure
x. Glaucoma secondary to intraocular infection

PRIMARY OPEN ANGLE GLAUCOMA

Primary open angle glaucoma (POAG) is considered as a chronic progressive anterior optic neuropathy of adult onset. It is characterized by intraocular pressure > 21 mmHg, glaucomatous optic nerve damage, open anterior chamber angle, characteristic progressive visual field loss and absence of signs of secondary glaucoma or non-glaucomatous cause of optic neuropathy. It is the commonest of all glaucomas accounting for 60-70% of cases in the United States(3). It is postulated that a series of genetically determined events cause molecular and pathophysiological changes resulting in increased resistance to aqueous outflow and increased susceptibility of the optic nerve head to raised intraocular pressure level. It is associated with optic nerve damage with resultant visual loss which may or may not be associated with elevated intraocular pressure (IOP). The normal IOP is between 10 and 21 (in millimetres of Mercury or mm Hg). Though POAG occurs in a patient with IOP greater than 21, significant portion of POAG patients do not have elevated IOP; and this is called “normal tension” glaucoma.

EPIDEMIOLOGY

PREVALENCE

It is estimated that about 79.6 million people will be diagnosed with glaucoma of which 74% will have primary open angle glaucoma(4). About 47% of these patients will be Asians and 5.9 million people will be affected by bilateral blindness due to primary open angle glaucoma(4). In a meta-analysis of 56 population-based studies on prevalence of primary open angle glaucoma, it was estimated that the prevalence of POAG in white racial group accounted for 0.4 to 8.5% of the older population. In Asian populations, POAG was present in 0.03 to 3.9% of the older population. In the Hispanic population in POAG was present in 2.0 – 4.7% of the older population, whereas black racial groups and mixed racial groups accounted for 2.1 – 20.0% and 1.5 – 3.8% of the older population(5). From meta-analysis of various studies done by Kapetanakis et al, it is clear that the black population is at a higher risk of developing POAG than in other populations(6).

Race / Location	**Prevalence of Primary Open-Angle Glaucoma in older age population (generally over age 40)**
White populations	0.4 – 8.5 %
Asian populations	0.03 – 3.9 %
Hispanic population	2.0 - 4.7 %
Black populations	2.1 – 20.0 %
Mixed populations	1.5 – 3.8%

Table 2.1. Prevalence of primary open-angle glaucoma in different world populations(5).

With reference to the Indian population, George et al estimated that 11.2 million people more than 40 years of age will develop glaucoma with 6.48 million being primary open angle glaucoma(7). In a study done by Vijaya et al in Thiruvallur and Kancheepuram districts of Tamil Nadu, the prevalence of primary open angle glaucoma was found to be 1.62% with 98.5% being unaware of the disease(8). The prevalence was found to be 3.51% higher in an urban population in Chennai with more than 90% being unaware of the disease(9).

However, there are several risk factors that are associated with the development of POAG and the black race is one such risk factor. Other risk factors include older age, family history of glaucoma, male gender, and elevated intraocular pressure. If first-degree relative (parent or sibling) has glaucoma, chance of developing glaucoma increases by 2 to 4 fold. If intraocular pressure is over 30 (mm Hg), the chance of developing glaucoma is 40 times greater than if the IOP is under 15. Thin cornea, where the IOP value is under-estimated, myopia, low diastolic blood pressure, and diabetes mellitus are other risk factors for POAG. Several studies suggest the risk of becoming blind in a glaucoma patient can range from 0 up to 30% as studied by Cedrone et al(5).

RISK FACTORS

NON-OCULAR RISK FACTORS

- Age: Age more than 60 is considered a risk factor, but some studies show age more than 40 to be significant (10–12).
- Race: African Americans have a six-fold higher risk of developing glaucoma and the onset of glaucoma is ten years earlier. Hispanics and Asians are also at an increased risk (6).

- Gender: There is no clear gender predilection, though few studies like the Barbados eye study have reported male preponderance(13).
- Family History: Persons with first degree relative diagnosed with open angle glaucoma (primary or secondary) have an increased lifetime risk of 10%. A person with a sibling with glaucoma has an increase in risk of 4%.
- Systemic Conditions:
    - Diabetes: Multiple case-control studies and population-based cohort studies have implicated the link between diabetes and glaucoma(12,14,15).
    - Hypertension: The Blue Mountains Eye Study showed that increased systolic blood pressure is linked to increased IOP(15). Barbados Eye studied also showed low diastolic pressure may be associated with glaucoma(13).
    - Thyroid disorders: Glaucoma has been associated with Graves' disease
    - Migraine: The Blue mountain study also reported association between glaucoma and migraine. Gramer G et al showed that migraines were more common in patients with glaucoma(16).
    - Vasospasm: Peripheral vasospasm causes reduced or disordered blood flow resulting in normal tension glaucoma (NTG)(16).
    - Obstructive Sleep Apnoea: Obstructive sleep apnoea causes transient hypoxia hence leading to optic nerve damage in glaucoma (17).
- Heredity: It has been found to have autosomal dominant, autosomal recessive and sex-linked inheritance patterns. GLC1A gene located on chromosome 1q23-25 has been associated with Juvenile-onset open angle glaucoma and about 3-4% of adult glaucomas(18). Another gene GLC2B located on chromosome 1 has been associated with adult-onset glaucoma(19). Other studies have also unearthed various other

mutations such as mutations in chromosome 15(20), chromosome 3(21), polymorphisms in methylenetetrahydrofolate reductase gene(22), endothelial nitric oxide gene(23).

OCULAR RISK FACTORS

- Myopia: It has been found that there is a higher risk for open angle glaucoma due to increased axial length and myopia. This effect of myopia may be a direct influence or maybe secondary to increased IOP and larger cup-disc ratio.

- IOP: It is well established that elevated IOP is a risk factor for glaucoma. Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study showed the association between glaucoma and elevated IOP(24). Even in patients with normal IOP, it has been noted that there is often asymmetric cupping and field loss in the eye with the relatively higher pressure(25,26). The OHTS also showed that higher the IOP, worse was the outcome(24). However, as some patients with high IOP did not develop glaucoma, it is assumed that this cannot be the only risk factor.

- Corneal thickness: The differences in prevalence of glaucoma amongst various racial groups has been attributed to the difference in corneal thickness. The black racial group has been found to have thin corneas and accordingly higher prevalence of glaucoma. Thus, thinner corneas are at higher risk for glaucomatous damage(27). This is thought to be due to reduced amount of supporting tissue in the optic nerve and hence higher liability to damage secondary to increase in intraocular pressure or vascular injury. The researchers called CCT a “predictive factor” as it is still unknown if CCT is an

independent risk factor regardless of IOP or if the proposed risk is linked to its association with IOP.

PATHOGENESIS

The underlying pathophysiologic mechanism behind visual loss in glaucoma is due to loss of retinal ganglion cells. There are various factors that act on the cell bodies or their axons causing death of the retinal ganglion cell. Raised intraocular pressure (IOP) and vascular compromise brings about reduced axoplasmic flow within the RGC at the lamina cribriosa and alters the microcirculation at the optic nerve level. There are also changes that occur to the laminar glial and connective tissue.

These primary changes are worsened by damage caused by release of neurotransmitters like glutamate or glycine from injured neurons and production of Nitric oxide and other reactive oxygen species that cause oxidative damage. These primary and secondary changes result in dysfunction and eventual death of RGC resulting in visual loss as seen in advanced glaucoma patients(28).

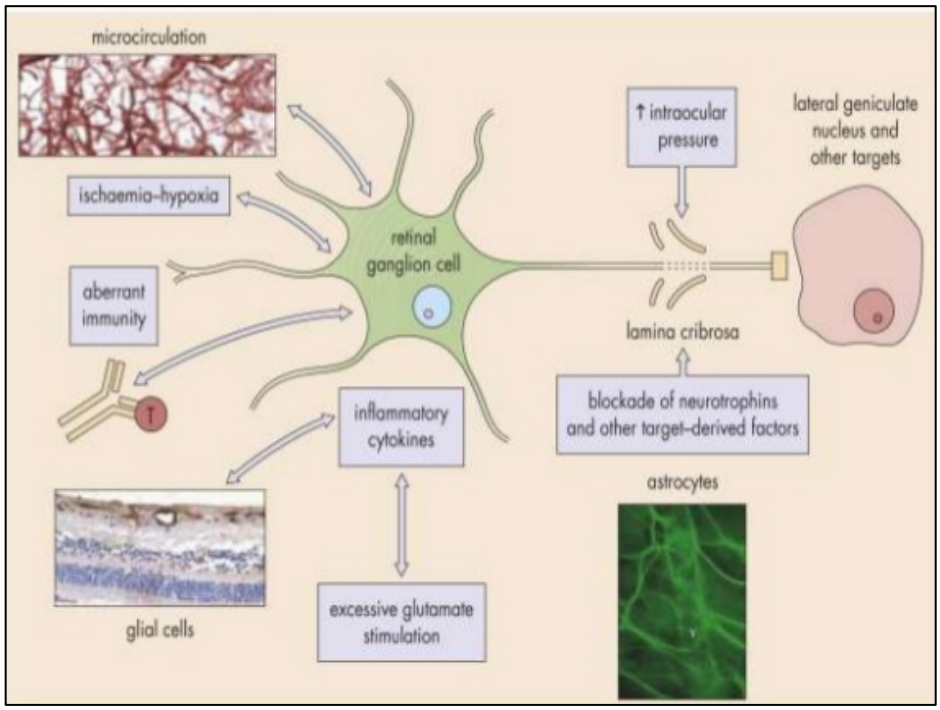

Fig 2.4. Pathophysiology of glaucoma

NEURONAL LOSS IN GLAUCOMA BY APOPTOSIS

The changes described above cause death of axons and hence loss of ganglion cell bodies in the retina and ganglion cell axon terminals in the dorsal lateral geniculate body.

This cell death of RGCs in glaucoma takes place by apoptosis(29), which is also the method of normal developmental organization of the visual pathway by elimination of RGCs. This programmed cell death occurs without any accompanying inflammation and is associated with DNA fragmentation, chromosome clumping, cell shrinkage and bleb formation on the membrane (30).

This is followed by breaking down of the cell into multiple membrane-bound vesicles which are engulfed by neighbouring cells. On the other hand, necrosis may also contribute to the pathogenesis of glaucoma at a later stage as observed in rats subjected to optic nerve transection(31).

The caspases which are enzymes belonging to cysteine aspartyl-specific proteases are key molecules in apoptosis. Their activation which occurs through an extrinsic and an intrinsic pathway is essential for apoptosis to occur thereby causing proteolytic destruction of both cytoplasmic and nuclear components and thus, cell death. The extrinsic pathway involves interaction of specific ligands such as tumour necrosis factor-alpha (TNF-A) with the pro-apoptotic cell surface receptors while the intrinsic pathway is regulated by pro-apoptotic molecules released from the mitochondrion.

Spalding et al have also suggested the presence of a caspase-independent pathway in RGC death under certain conditions(32).

As described above, the presence of glaucoma in patients with normal intraocular pressures and absence of glaucoma in patients with elevated IOP has led to the question if elevated IOP is the sole risk factor for glaucoma. Changes in aqueous humour dynamics due to changes in trabecular meshwork causing impaired drainage of aqueous eventually causes an elevation of IOP. It has been shown that there occur changes in the cytoskeletal structure of cells in the trabecular meshwork(33) associated with decreased cellularity(34) and extracellular matrix changes.

There are studies that correlate elevated IOP with RGC death in glaucomatous rats(35–37). There exists a time-dependent RGC cell death with increasing axonal loss with a higher duration of elevated IOP. Elevated IOP causes RGC death in two phases.

The first phase is a rapid phase which lasts for about three weeks and occurs due to apoptosis(38). This phase results in loss of approximately 12% RGCs per week. This is followed by a second phase of neuronal loss which occurs slowly. The second phase is

attributed to the toxic effects of the primary degenerating neurons along with exposure to raised IOP(39).

MOLECULAR CHANGES IN RESPONSE TO ELEVATED IOP

In response to elevated IOP, there is change in the extracellular matrix (ECM)(40). Remodelling of ECM with collagen I and IV, Matrix metalloproteinase-1 (MMP-1) and transforming growth factor-β (TGF-β)(41) has been observed in patients with glaucoma. This change in the ECM components causes interruption of cell-cell and cell-ECM interactions causing apoptosis.

Increased amount of MMPs such as MMP-9 causes disintegration of Laminin, a component of ECM which is essential for cell adherence and survival by interacting with cellular integrins. This leads to hampered cell-ECM interaction eventually causing apoptosis. Li Guo et al showed that increased MMP-9 activity causes this degradation of Laminin in ECM in optic nerve heads in rats(42). It has also been postulated that the mechanical damage to RGC axons due to elevated IOP may cause retrograde injury to the RGC body leading to visual loss. Another hypothesis is that, the elevated MMP may be secondary to increased glutamate levels due to elevated IOP. The raise in IOP has also been found to activate retinal astrocytes which in turn release MMPs and bring about changes in the ECM(43).

Growth factors such as neurotrophin factor, TGF-β2 play an essential role in normal development and function of the trabecular meshwork. They are expressed in the optic nerve astrocytes and lamina cribrosa cells as well. Elevated IOP causes a decrease in brain derived neurotrophin factor (BDNF) which along with increased TGF-β2 released from activated

astrocytes pushes the cell towards apoptosis. It has also been found that in the setting of elevated IOP, there is an increase in TNF-α leading to microglial activation, loss of RGCs.

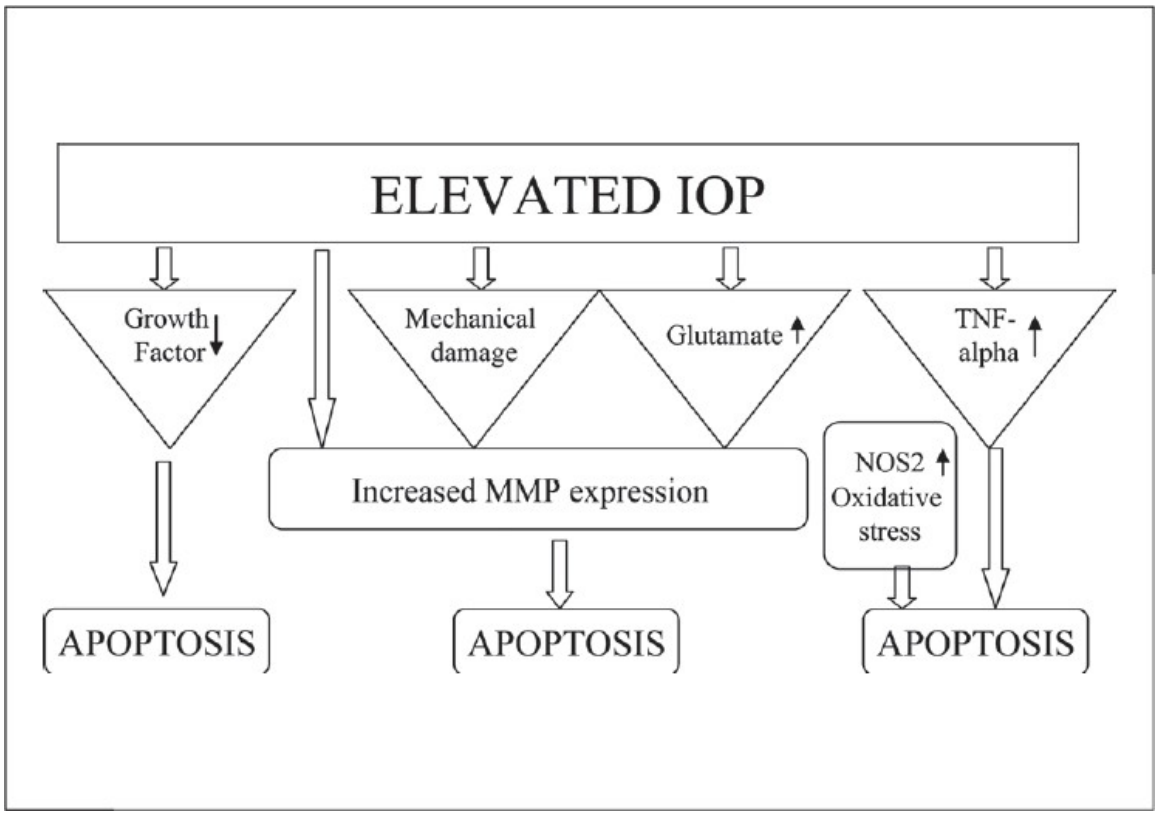

Fig 2.5. Molecular changes in response to elevated IOP

VASCULAR INSUFFICIENCY IN GLAUCOMA

Association of glaucoma with migraine and other peripheral vascular disorders has brought to notice the potential role of vascular insufficiency in glaucoma. It has been shown that there is increased sensitivity to Endothelin-1 mediated vasoconstriction. Glaucoma has also been associated with pan cerebral ischemia and cerebral infarcts(44).

Autoregulation ensures constant blood flow to the retinal and the optic nerve head. These autoregulatory mechanisms are not robust in an older population and hence result in ischemia and glaucomatous neuronal damage. This is evidenced by patients with reduced diastolic perfusion pressure having a high risk of glaucoma.

Elevated levels of Glutamate and nitric oxide have been implicated to be responsible for neuronal toxicity in glaucoma patients(45). Excessive formation of free radicals and oxidative stress has now been recognized to play a role in the pathogenesis of glaucoma(46,47). This causes damage to the DNA of trabecular meshwork cells. Hence there is altered adhesions of the trabecular cells, rearrangement of cytoskeleton in the ECM and increased resistance to the outflow causing elevated IOP.

CLINICAL FEATURES

SYMPTOMS

Primary open angle glaucoma is usually described as an insidious, slowly progressive, bilateral condition. Most patients are asymptomatic and present at advanced stages of glaucomatous damage.

If patients are not diagnosed early, they may become symptomatic due to loss of peripheral vision, which interferes with activities of daily living. Glaucomatous damage to the optic nerve occurs gradually over a period of months to years. Quality of life is generally not affected until late, but as the glaucoma progresses and the treatment is more aggressive quality of life may be impaired

SIGNS

ELEVATED INTRAOCULAR PRESSURE

Most patients with POAG have elevated intraocular pressures in the range of 22 to 40 mmHg. Some patients have much higher values, which occasionally reach levels of 60 or even 80 mm Hg.

Intraocular pressure fluctuates throughout the day. Intraocular pressure shows variation throughout the day with highest pressures being more common recorded in the morning. Occasionally peak IOP may be measured in the evening or may not have a regular pattern. Diurnal intraocular pressure measurements maybe useful in diagnosis, efficacy of treatment, detecting progressive damage despite treatment and differentiating normal tension glaucoma from primary open angle glaucoma.

ANGLE

Angle of the anterior chamber was assessed using indirect gonioscopy using goldmann three mirror and the grading used is Shaffer's grading.

Angles in POAG are open but can be narrow but there cannot be any peripheral anterior synechiae, opposition between iris and trabecular meshwork and developmental abnormalities of trabecular meshwork.

Shaffer's Grade	Angle width	Configuration	Chance of closure	Structures involved
IV	35-45^{o}	Wide open	Nil	SL, TM, SS, CBB
III	20-35^{o}	Open	Nil	SL, TM, SS,
II	20^{o}	Moderately narrow	Possible	SL, TM,
I	10^{o}	Very narrow	High	SL only
0	0^{o}	Closed	Closed	None visible

Table 2.2. Shaffer's Grading system of Gonioscopy in Glaucoma

CBB – Ciliary body band, SS – Scleral spur, TM – Trabecular meshwork, SL – Schwalbe's line

OPTIC DISC CHANGES

The key parameters for early detection of glaucomatous optic nerve damage are:

a. Change in neuroretinal rim thickness

b. Change in Cup-Disc ratio

c. Retinal nerve fibre layer defects and hemorrhages

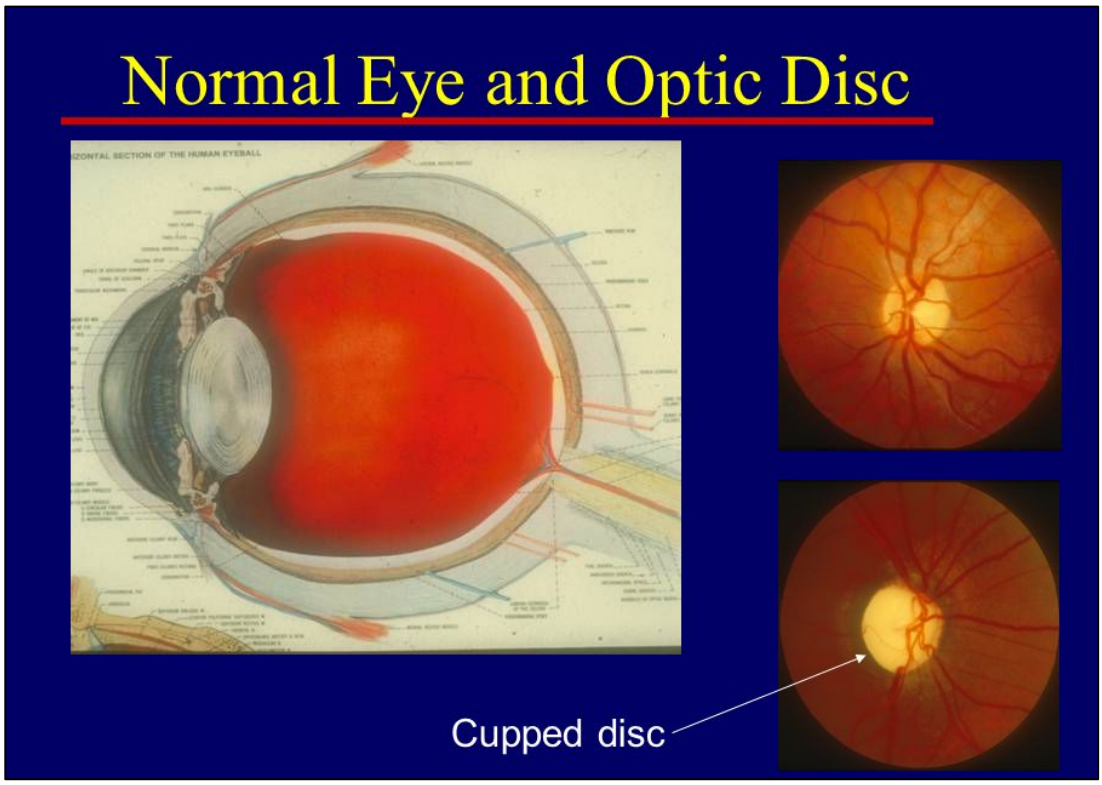

Fig 2.6. Normal optic Disc

With progressive destruction of axonal bundles, thinning of the neuroretinal rim occurs as described below:

1. Papillary changes
    a. Concentric enlargement of cup
    b. Focal narrowing of neuroretinal rim
    c. Assymetric cupping

d. Saucerisation

e. Bayonetting of vessels

f. Laminar dot sign – Multiple fenestrations of Lamina cribrosa seen through deepened optic disc cup

g. Pallor /Cup discrepancy

h. Advanced glaucomatous cupping – All neuroretinal rim tissue is lost resulting in Bean-pot cupping.

i. Advanced cupping in end stage glaucoma

2. Peripapillary changes

a. Optic disc haemorrhages

b. Changes in nerve fibre layer

c. Variation in diameter of retinal arterioles

d. Peripapillary choroidal atrophy

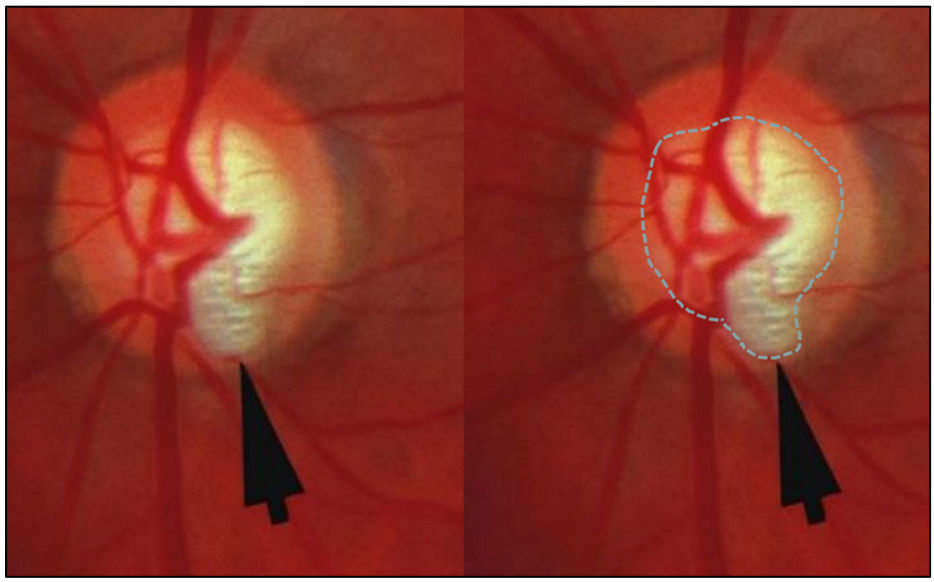

Fig 2.7. Focal narrowing of neuroretinal rim

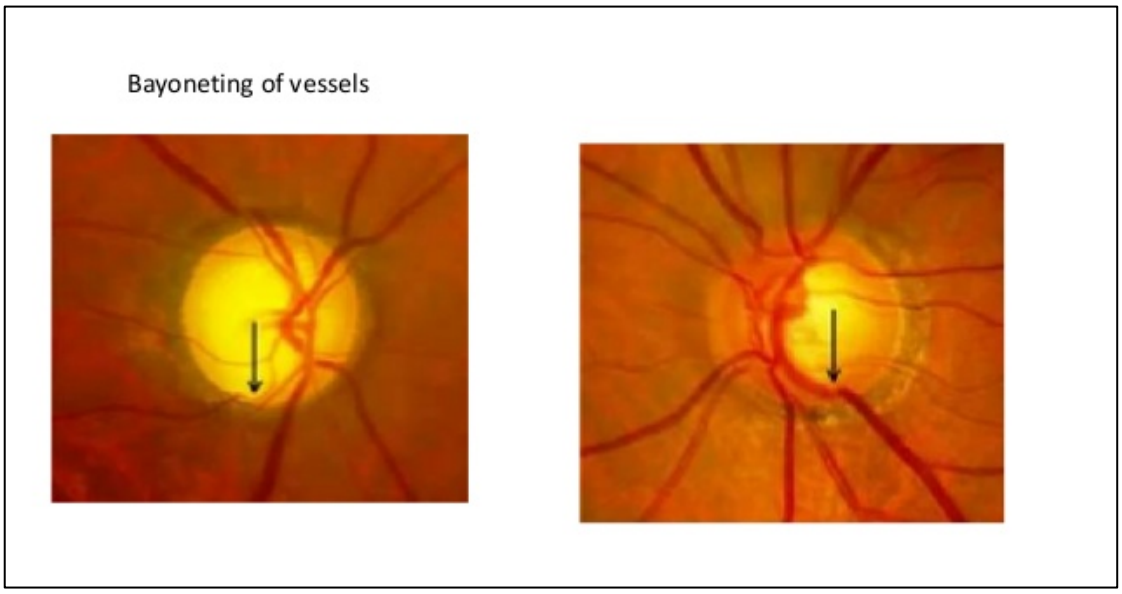

Fig. 2.8. Bayoneting of vessels

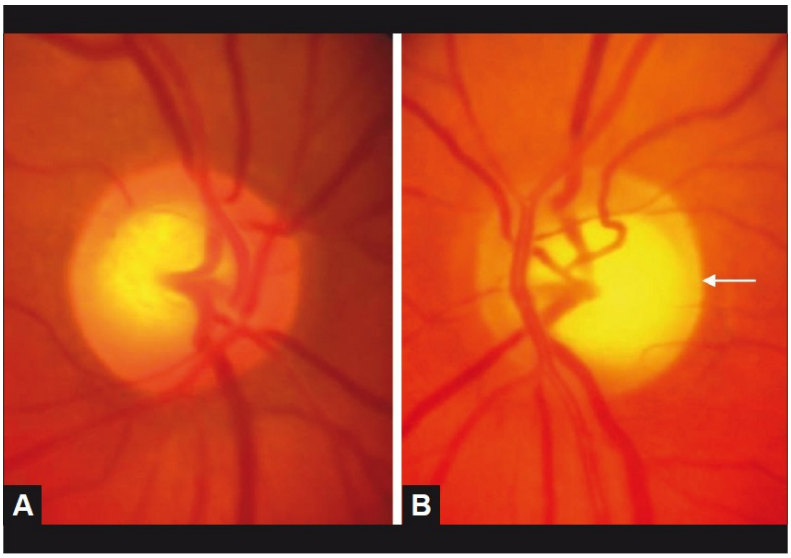

Fig 2.9. A. Pallor B. Enlargement of cup with neuroretinal rim thinning

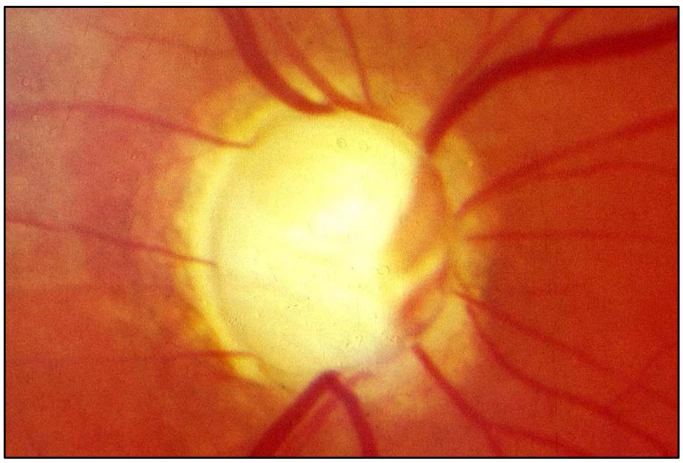

Fig 2.10. Advanced cupping in end stage glaucoma

In the early stage of glaucomatous optic atrophy, enlargement of the cup may progress ahead of that of the area of pallor. This can be contrasted with larger area of pallor than the cup in other causes of optic atrophy.

VASCULAR SIGNS

1. Optic disc haemorrhages: Splinter haemorrhages near the margin of the optic nerve head are most commonly present in normal tension glaucoma.

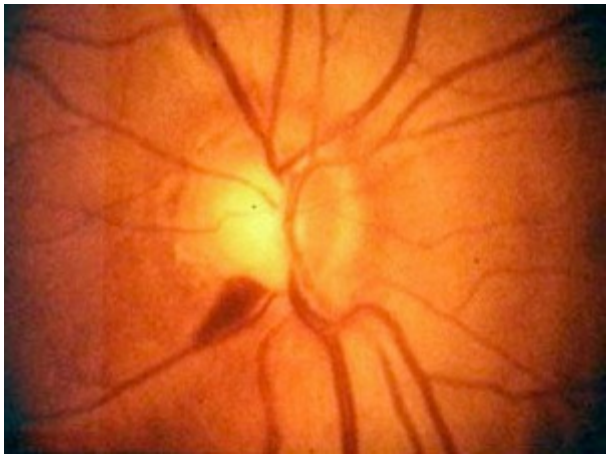

Fig 2.11. Splinter (Drance) Hemorrhage

2. Tortuosity of retinal vessels: This represents collateral vessels due to chronic central retinal vessel occlusion.
3. Baring of retinal vessels: In glaucomatous optic cup enlargement, the circumlinear vessels are “bared” from the margin of the cup.
4. Nasalisation of the retinal vessels

GONIOSCOPY

Gonioscopy in POAG reveals the angle of the anterior chamber to be open.

VISUAL FIELD ABNORMALITIES

1. Generalized depression of visual field: Diffuse reduction in visual threshold is a non-specific change in glaucoma. Concentric contraction of the nasal visual field, also called isoptre contraction is one of the earliest detectable glaucomatous change..
2. Blindspot Enlargement
3. Angioscotoma: Long, branching scotomas above and below the blind spot are caused due to shadows created by large retinal vessels.
4. Nerve fibre bundle defects: These defects are more specific for glaucoma and are definitive early evidence of visual field loss.
5. Field defects:
    a. Paracentral scotoma: It is the earliest clinically significant field defect.
    b. Siedel’s scotoma: Paracentral scotoma, on joining the blind spot forms a sickle shaped scotoma known as Siedel’s scotoma.

c. Arcuate or Bjerrum scotoma: This field defect starts from blind spot and arches above or below fixation to the horizontal median raphe corresponding to arcuate retinal fibres.

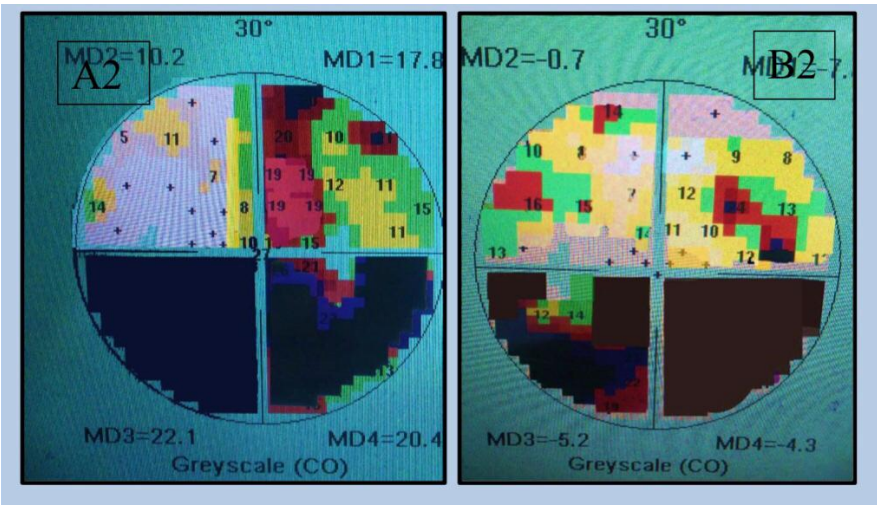

Fig 2.12. Arcuate scotoma

d. Ring scotoma or double arcuate scotoma: This defect results from meeting of two arcuate scotomas.

e. Ronne's central nasal step – This defect is created when two arcuate scotomas run in different arcs and meet to form a sharp right-angled defect at the horizontal meridian.

f. Advanced glaucomatous field change - Visual field is reduced to central and temporal island of vision as the temporal island of vision is more resistant to damage.

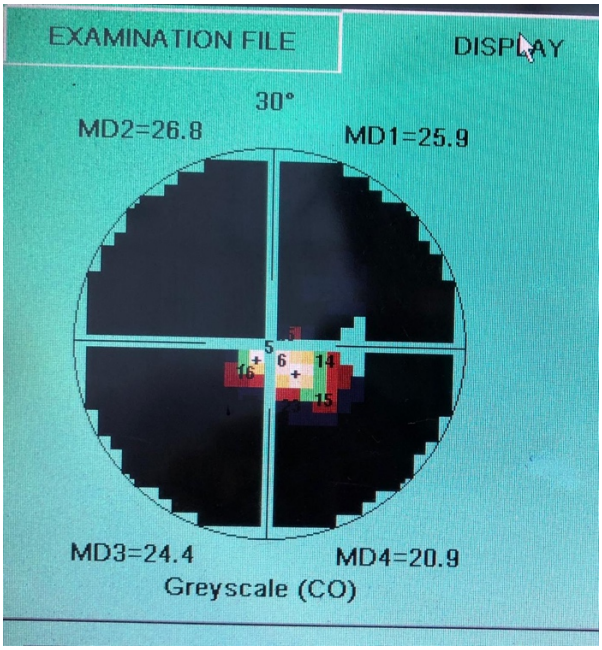

Fig 2.13. Advanced glaucomatous field changes with central and temporal field of vision spared

Correlation between optic nerve head and visual field defects is that clinically recognizable disc changes precede detectable field loss. The extent of axonal loss is much greater than the corresponding visual field change. The nature of optic nerve head cupping can also be used to predict the type of field loss.

6. Miscellaneous defects:
    a. Abnormal dark adaptation
    b. A relative afferent pupillary defect.
7. Other psychological tests:
    a. Colour vision deficit
    b. Reduced Contrast sensitivity
    c. Electrophysiological studies:
        i. Reduced amplitude in Electroretinography
        ii. Reduced response in Visually Evoked Potential

iii. Increased baseline Electrooculography values

Optic nerve head and retinal nerve fibre layer changes represent the early stages of glaucoma, while progressive visual field loss is a feature of advanced disease.

DIAGNOSIS

A diagnosis of POAG can be made based on:

1. Intraocular pressure recording
2. Optic nerve head assay
3. Gonioscopy
4. Visual field analysis

INTRAOCULAR PRESSURE RECORDING:

a) Tonometer is used to measure the intraocular pressure by measuring the relative deformation of the globe to the force causing it. There are two basic types of tonometers according to the shape of the deformation of cornea: indentation and applanation (flattening).
b) Provocative Tests: The water-drinking test stresses the outflow channels of the eye hence aiding the differentiation of those with risk of POAG.

i) Schiotz Indentation Tonometer

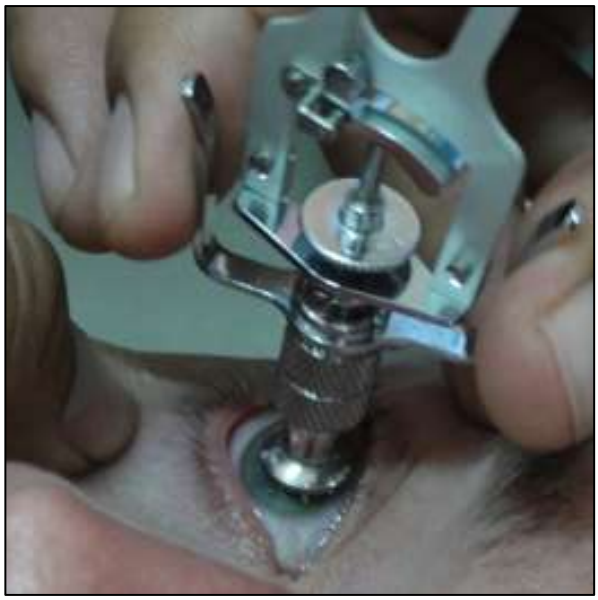

Fig 2.14. Schiotz indentation tonometer

ii) Applanation Tonometers

Fig 2.15. Applanation tonometer

GONIOSCOPY

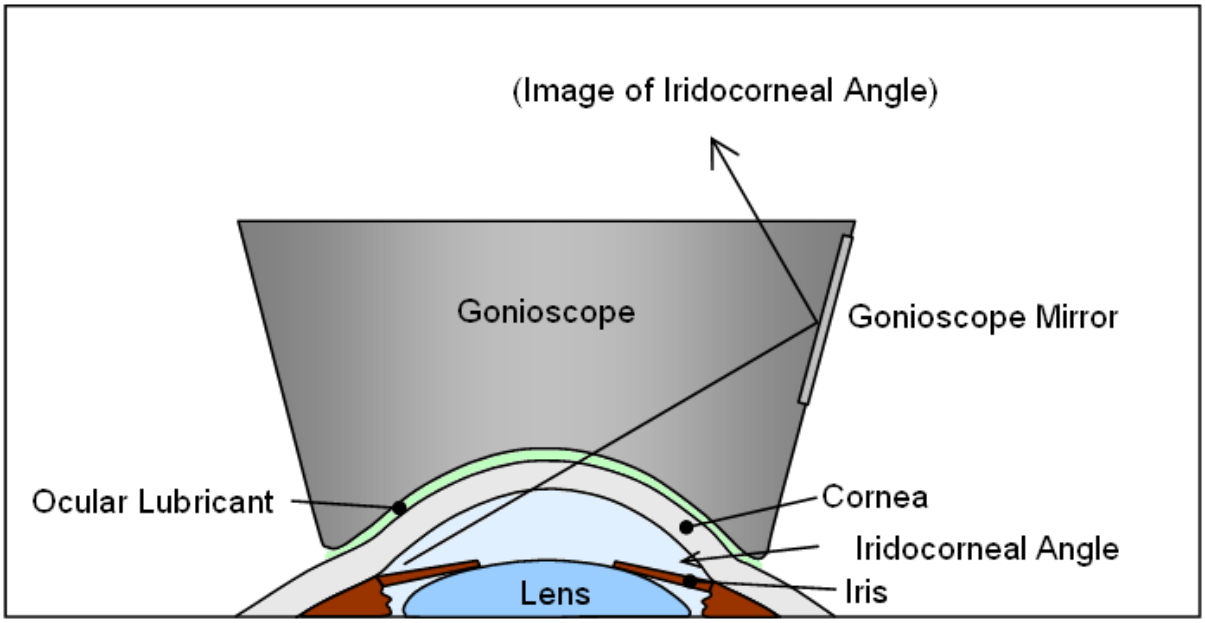

Fig 2.16. Schematic diagram of gonioscopy

It is one of the main diagnostic procedures to differentiate POAG, angle closure and other secondary glaucomas. This uses Goldmann indirect gonio lens.

PERIMETRY

Perimetry is done by adapting the eye (with best corrected visual acuity) to a photoptic background luminescence over which a brighter test stimulus is displayed in a kinetic or static manner. This may be achieved by manually operated or automatic devices.

KINETIC TECHNIQUES

The test object is moved from a non-seeing to a seeing area and the point first seen in relation to fixation is recorded. E.g. Listers' perimeter and Goldmann's perimeter.

STATIC TECHNIQUES

Stationary test objects are used utilizing either suprathreshold or threshold presentations. Goldmann perimetry is the present standard perimetry. 12e is the standard test stimulus used for the central 5-15 degrees isopters and the nasal and temporal meridians. The depth is determined by increasing stimulus size or intensity. 14e stimulus is used for peripheral charting.

AUTOMATED PERIMETERS

Automated computerized perimetry is a more accurate and informative technique. The Delta program with the Octopus perimeter and the STATPAC with the Humphrey Field Analyzer are the most commonly used. The STATPAC uses a large normal database whereas STATPAC II uses a database of stable glaucoma patients.

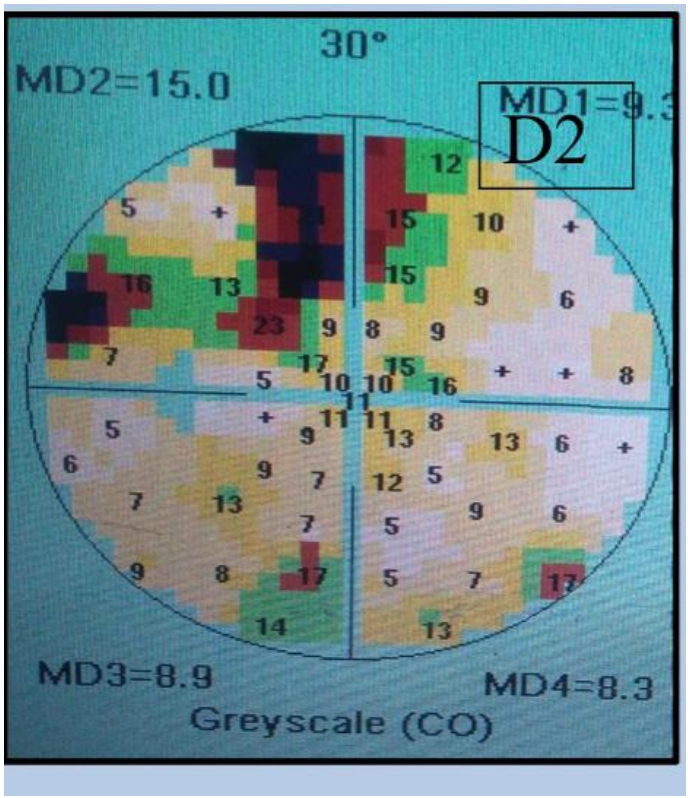

Fig 2.17. Paracentral scotoma

DIABETES MELLITUS: AN OVERVIEW

Diabetes mellitus is a chronic metabolic disease with varied etiology that is marked by chronic hyperglycemia and disturbances in carbohydrate, fat and protein metabolism due to a defect in insulin secretion, action or both. There are four types of diabetes mellitus: type 1 diabetes, type 2 diabetes, gestational diabetes, and latent autoimmune diabetes in adults (LADA). However, researchers are now even considering a fifth type, as Alzheimer's is often referred to as type 3 diabetes due to a strong link between blood sugar and brain health. These diseases may be related to lifestyle or to genetic causes, and they may affect people at different life stages. Since the patients enrolled in the study are above 40 years of age, Type 2 DM is discussed in detail.

Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance) accounts for ~90–95% of those with diabetes. It was previously referred to as non-insulin-dependent diabetes, type II diabetes, or adult-onset diabetes and encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency

In patients with Type 2 diabetes or non-insulin dependent diabetes mellitus, there is no destruction of the insulin secreting beta cells by autoimmune mechanism. Instead it is believed to occur secondary to the resistance to the action of insulin secondary to central obesity. There is a gradually worsening hyperglycaemia and unlike Type 1 diabetics, ketoacidosis rarely occurs, especially in the presence of sepsis. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycaemia but is seldom restored to normal.

Increasing age, genetic predisposition, obesity, lack of physical activity, women with prior GDM, hypertension or dyslipidaemia and ethnicity are risk factors for type 2 diabetes.

SYMPTOMS AND SIGNS OF DIABETES MELLITUS

Symptoms vary depending on how much the blood glucose is elevated. Patients are often asymptomatic in the initial phase, whereas in type 1 diabetes, symptoms tend occur earlier and are more severe.

Symptoms and signs of diabetes include:

- Increased thirst
- Frequent urination
- Extreme hunger
- Unexplained weight loss
- Presence of ketones in the urine (ketones are a by-product of the breakdown of muscle and fat that happens when there's not enough available insulin)
- Fatigue
- Irritability
- Blurred vision
- Slow-healing sores
- Predisposition to infections

Type 2 diabetes is more common in people older than 40 whereas type 1 diabetes can develop at any age, though it often appears during childhood or adolescence.

COMPLICATIONS

Long-term complications of diabetes develop gradually.

Possible complications include:

- Cardiovascular disease**:** Diabetes dramatically increases the risk of various cardiovascular problems, including coronary artery disease with chest pain (angina), heart attack, stroke and narrowing of arteries (atherosclerosis).
- Neuropathy**:** Excess glucose can cause damage to capillaries that nourish nerves especially in the lower limbs. Patients experience tingling, numbness, burning or pain that usually begins at the tips of the toes or fingers and gradually spreads upward.
- Nephropathy: Diabetes can cause damage to the glomerular membrane leading to renal failure or irreversible end-stage kidney disease, which may require dialysis or a kidney transplant.
- Retinopathy: Diabetes can damage the blood vessels of the retina (diabetic retinopathy), potentially leading to blindness. Diabetes also increases the risk of other ocular conditions, such as cataracts and glaucoma more commonly POAG.
- Diabetic foot**:** Nerve damage in the feet or poor blood flow to the feet increases the risk of various foot complications. Trivial trauma can develop into life or limb threatening necrotising soft tissue infections. These may require amputation, thus altering the quality of life of these patients.

IMPAIRED GLUCOSE TOLERANCE (IGT) AND IMPAIRED FASTING GLUCOSE (IFG)

The WHO Expert Committee defines a group of patients whose glucose levels are not diagnostic of diabetes, but are also not normal.(51). This group is defined as having fasting plasma glucose (FPG) levels ≥100 mg/dl (5.6 mmol/l) but <126 mg/dl (7.0 mmol/l) or 2-hr

values in the oral glucose tolerance test (OGTT) of ≥140 mg/dl (7.8 mmol/l) but <200 mg/dl (11.1 mmol/l).

Thus, the categories of FPG values are as follows:

- FPG <100 mg/dl (5.6 mmol/l) = normal fasting glucose;
- FPG 100–125 mg/dl (5.6–6.9 mmol/l) = IFG (impaired fasting glucose);
- FPG ≥126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described below).

The corresponding categories when the OGTT is used are the following:

- 2-h post load glucose <140 mg/dl (7.8 mmol/l) = normal glucose tolerance;
- 2-h post load glucose 140–199 mg/dl (7.8–11.1 mmol/l) = IGT (impaired glucose tolerance);
- 2-h post load glucose ≥200 mg/dl (11.1 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described below).

Patients with IFG and/or IGT are now referred to as having “pre-diabetes” indicating the relatively high risk for development of diabetes in these patients. In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes as well as cardiovascular disease. IFG and IGT are associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidaemia of the high-triglyceride and/or low-HDL type, and hypertension. It is worth mentioning that medical nutrition therapy aimed at producing 5–10% loss of body weight, exercise, and certain pharmacological agents have been variably demonstrated to prevent or delay the development

of diabetes in people with IGT; the potential impact of such interventions to reduce cardiovascular risk has not been examined to date.

Individuals with IFG or IGT may have normal or near normal glycated haemoglobin levels. Individuals with IGT often manifest hyperglycaemia only when challenged with the oral glucose load used in the standardized OGTT.

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

- Symptoms of diabetes such as polyuria, polydipsia, and unexplained weight loss with random (regardless of meal) plasma glucose concentration ≥200 mg/dl (11.1 mmol/l).
- Post OGTT glucose ≥200 mg/dl
- Fasting (No calorie intake of at least 8 hours) plasma glucose ≥126 mg/dl (7.0 mmol/l).
- Glycated haemoglobin (HbA1c) > 6.5 g%.

Glycated haemoglobin (HbA1c) was initially identified as haemoglobin variant in patients with diabetes. The A1c-derived average glucose study (ADAG) study of 643 patients established a validated relationship between A1C levels and average glucose across a range of diabetes types and patient(52).

HbA1c denotes the average plasma glucose over the previous 8 to 12 weeks . It does not require any special preparation such as fasting and can be performed at any time irrespective of meals. These properties have made it the preferred test for assessing glycaemic control in people with diabetes. It has been recommended for use as a diagnostic and screening tool for diabetes mellitus.

GLYCATED HEMOGLOBIN

Hyperglycemia causes attachment of glycosylated end product on various cell surfaces. On one hand, it coats the adhesion molecules present in inflammatory cells, thus promoting immunocompromised state. It also binds with hemoglobin (Hb) of RBCs. In normal healthy adult, RBCs contain approximately HbA - 97%, HbA2- 2.5% and HbF- 0.5 percent. Among total HbA, approximately 6% are HbA1. Based upon electrophoretic properties, HbA1 are separated into HbA1a1, HbA1a2, HbA1b and HbA1c fractions, among which HbA1c is the

predominant fractions and comprises 5% of total HbA. Glucose binds to β-Val-1, β-Lys-66, and α-Lys-61 sites on the haemoglobin. Glycation of Hb is a physiological process. During the process of glycation of Hb, aldimine is formed and it is a reversible process. Later, aldimine is slowly converted into irreversible ketoamine form. As the blood glucose level increases, level of HbA1c will also increase. In the patients with Diabetes Mellitus, there were increased levels of HbA1c which was reported by Rahbar et al. in 1969(51). Bunn et al identified the pathway leading to the formation of HbA1c in 1976(53). Later in 1976 Koenig et al proposed the use of HbA1c as a biomarker to monitor blood glucose levels among diabetic patients(54).

The life span of RBC is approximately 120 days. Since formation of glycosylated HbA1c is an irreversible process and RBCs live longer, detection of its level may not only be of diagnostic importance, but also for the assessment of diabetes mellitus during the management. HbA1C can be used as one of the strong predictive tools with regards to diabetic complications. Though, HbA1c has been used to monitor the glucose level, compliance of diets and medications as per physicians' recommendations, it was not included as a diagnostic tool till 2011. World Health Organization, in 2011 along with International expert committee in 2009 and American diabetic association in 2010, included it one of the bio-marker in diagnosing diabetes mellitus.

METHODS OF ESTIMATION

In clinical laboratory, HbA1c level is measured by various methods. The basic principal of its estimation is either, method on which Hb fractions are separated or chemical reactions. Separation method includes ion exchange chromatography, affinity chromatography and capillary electrophoresis.

Chemical method includes immunoassay and enzymatic assays. In the later method, HbA1c concentration is measured based on a specific chemical reaction to the glycated N-terminal valine of the β-chain. HbA1c concentration is calculated using HbA1c and total Hb values. In clinical laboratory, boronate affinity chromatography, ion-exchange high-performance liquid chromatography, immunoturbidimetry and enzymatic assay are the commonly used methods.

PART II

3. AIMS AND OBJECTIVES

To study the role of diabetes mellitus (DM) and glycemic exposure in predicting outcomes in primary open angle glaucoma (POAG)

4. INCLUSION CRITERIA

- Patients diagnosed with primary open angle glaucoma
- Patients diagnosed with diabetes mellitus (DM)
- Age more than 40 years

5. EXCLUSION CRITERIA

- Patients with ocular complications of diabetes mellitus like diabetic retinopathy, cataract
- Patients with systemic complications like diabetic ketoacidosis
- Unstable patients
- Age less than 40 years

6. METHODOLOGY

The study was designed as a prospective observational study. It was conducted in the Department of Ophthalmology, Government Raja Mirasdar Hospital, Thanjavur Medical College, Thanjavur from December 2017 to May 2019.

Patients who satisfied the inclusion criteria were recruited into the study after obtaining informed consent. There were 120 patients with primary open angle glaucoma out of which 76 patients were diabetic and 44 were non-diabetic. A structured questionnaire detailing the patient demographics, ophthalmological and systemic parameters was presented to the patient by the principal investigator.

Ophthalmological parameters assessed included:

- Routine clinical ophthalmological examination
- Slit lamp examination for examination of anterior segment for pupillary and lens changes
- binocular indirect ophthalmoscope with +20D lens was used to examine the fundus in a fully dilated pupil in the supine position in a dark room. Scleral indentation was done to view the retinal periphery and ora serrata.
- Direct ophthalmoscopy

- Optic disc examination with slit lamp exam using +90D lens to assess Cup-disc ratio, Neuro-retinal rim thinning, Glaucomatous optic atrophy.
- Gonioscopy - Indirect gonioscopy with gonioprism (goldmann three mirror) was done to examine the angle of the anterior chamber. Patients' cornea was anaesthetised with the patient positioned at the slit lamp, and the gonioprism was placed against the cornea with fluid bridge. The lens was rotated to allow the visualisation of 360 degrees of the angle. Grading of angle was done using Shaffer's grading system.
- Intra-ocular pressure measurement by applanation tonometry using Haag Streit slit lamp- Cornea was anaesthetised and fluorescein dye strip was used to stain the cornea and the cornea was viewed through cobalt blue light.
- Visual field assessment by OCTOPUS Haag Streit automated perimetry.
- Corneal thickness assessment by Pachymetry.
- Visual acuity by Snellen's chart.

Systemic parameters measured included:

- Fasting and Post prandial blood glucose – Serum samples were obtained from patients in fluoride coated vacutainers and Fasting and post prandial blood glucose was measured using Hexokinase enzymatic method.
- Glycated hemoglobin – Serum samples were obtained from patients in EDTA coated vacutainers and glycated hemoglobin was estimated using ion exchange high pressure liquid chromatography (HBLC) and Capillary electrophoresis method.

- Urine glucose – Urine sample was obtained from patients and semi-quantitative estimation was done by dipstick Benedict's method.

Data collected was entered using EpiData Manager version 4.6.0.0 r1511 and EpiData Entry Client version 4.6.0.0 r701 and exported to Microsoft Excel (2016) for analysis.

For the ease of analysis, the following subgroups were created for analytical purposes: Glycated hemoglobin was divided into three subgroups (HbA1c < 6.5 g% was considered as normal):

- Mild (6.5 – 7 g%)
- Moderate (7.1 – 9 g%) and
- Severe (>9 g%)

Visual acuity was grouped into the following groups:

- Poor vision
    a. No perception of light
    b. Perception of light
    c. Counting fingers
    d. Hand movements
- Reduced vision
    a. Visual acuity < 6/6

Disc changes were grouped into the following categories:

- Cup disc ratio (CDR) - 0.5-0.7 (Normal value 0.3-0.5)

- CDR >/= 0.8

Field changes were grouped in Early and advanced as described below:

- Early
    a. Enlargement of blindspot
    b. Paracentral scotoma
- Advanced
    a. Other glaucoma field defects
    b. Arcuate defects (nerve fiber bundle defects)
    c. Nasal step
    d. Central and temporal islands

7. STATISTICAL ANALYSIS

Data was exported in Microsoft Excel (2016) spread sheet and variables were coded accordingly. The statistical analyses were performed using Graph Pad Prism version 5 software. Data was presented as mean with Standard deviation for normal distribution/scale data (age and various time durations). Data was presented as frequency with proportion n (%) for categorical data. Fisher's exact test was used to compare the frequencies between the groups. One-way ANOVA with Tukey's post hoc test was used to compare the variances between the three groups (mild, moderate and severe elevation in HbA1C groups). $p<0.05$ were considered statistically significant.

8. RESULTS

PATIENT DEMOGRAPHICS

Age of the patients in our study population of 76, ranged from 41 to 82 years. The mean age was 61. 3 years with a standard deviation of 9.14 years. The age distribution in our study population is detailed in the table below.

Table 8.1: Frequency distribution of type of age category in years observed in the study.

S. No	Age category	n	%
1	41- 50 years	10	13.2
2	51 – 60 years	31	40.8
3	61 – 70 years	26	34.2
4	>70 years	9	11.8

Data are expressed as n with %. The total N=76

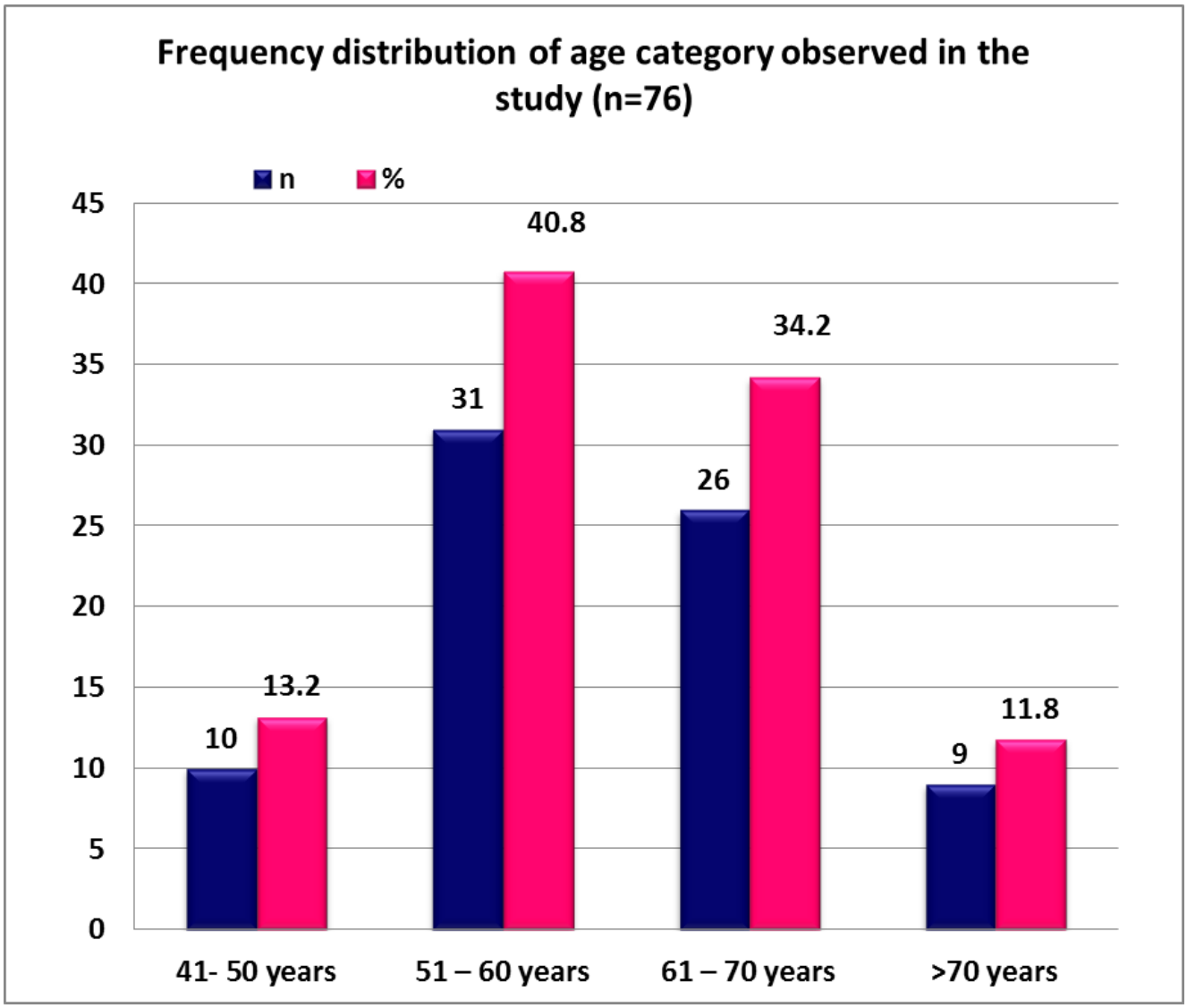

Fig 8.1 Frequency distribution of age category

There were 51 male patients and 25 female patients in the study population accounting for 2:1 M: F ratio.

Table 8.2. Frequency distribution of type of gender observed in the study.

S. No	Gender	n	%
1	Female	25	32.9
2	Male	51	67.1

Data are expressed as n with %. The total N=76

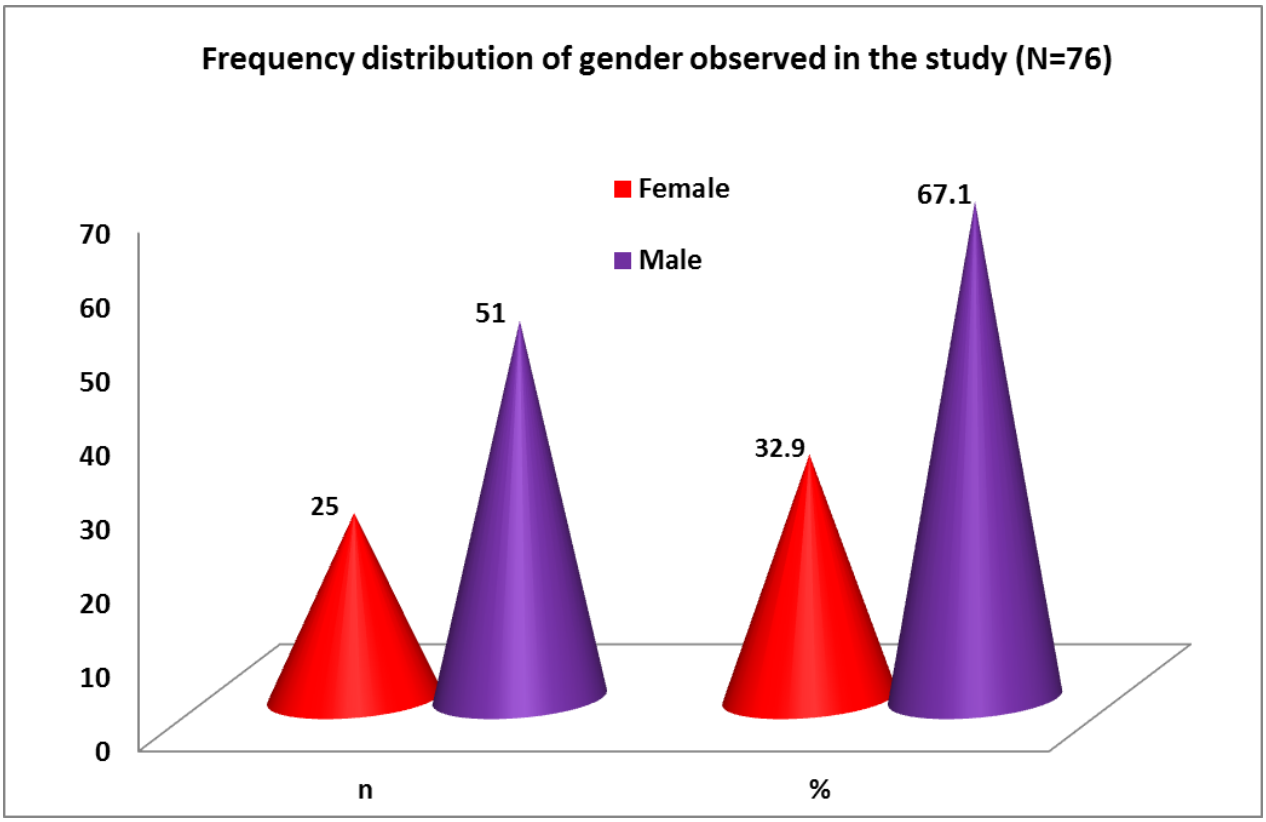

Fig 8.2 Frequency distribution of gender

OPHTHALMOLOGICAL PARAMETERS

SLIT LAMP EXAMINATION

Slit lamp examination of the anterior chamber of the eye, the lens and the pupil was done. This showed normal anterior segment in 92.1% of the right eye and 94.7% of the left eye. The pupil was normal in 69.7% of right eye and 77.6% of left eye. Lens changes were observed in 69.7% of right eye and 67.1% of left eye. These results are summarized in the table below.

Table 8.3. Frequency distribution of type of anterior segment

S. No	Anterior segment	Right eye		Left eye	
		n	%	n	%
1	Abnormal	6	7.9	4	5.3
2	Normal	70	92.1	72	94.7

Data are expressed as n with %. The total N=76

Table 8.4. Frequency distribution of type of pupil observed in the study.

S. No	Pupil	Right eye		Left eye	
		n	%	n	%
1	Abnormal	23	30.3	17	22.4
2	Normal	53	69.7	59	77.6

Data are expressed as n with %. The total N=76

Table 8.5. Frequency distribution of lens changes observed in the study.

S. No	Lens changes	Right eye		Left eye	
		n	%	n	%
1	Present	53	69.7	51	67.1
2	Absent	23	30.3	25	32.9

Data are expressed as n with %. The total N=76

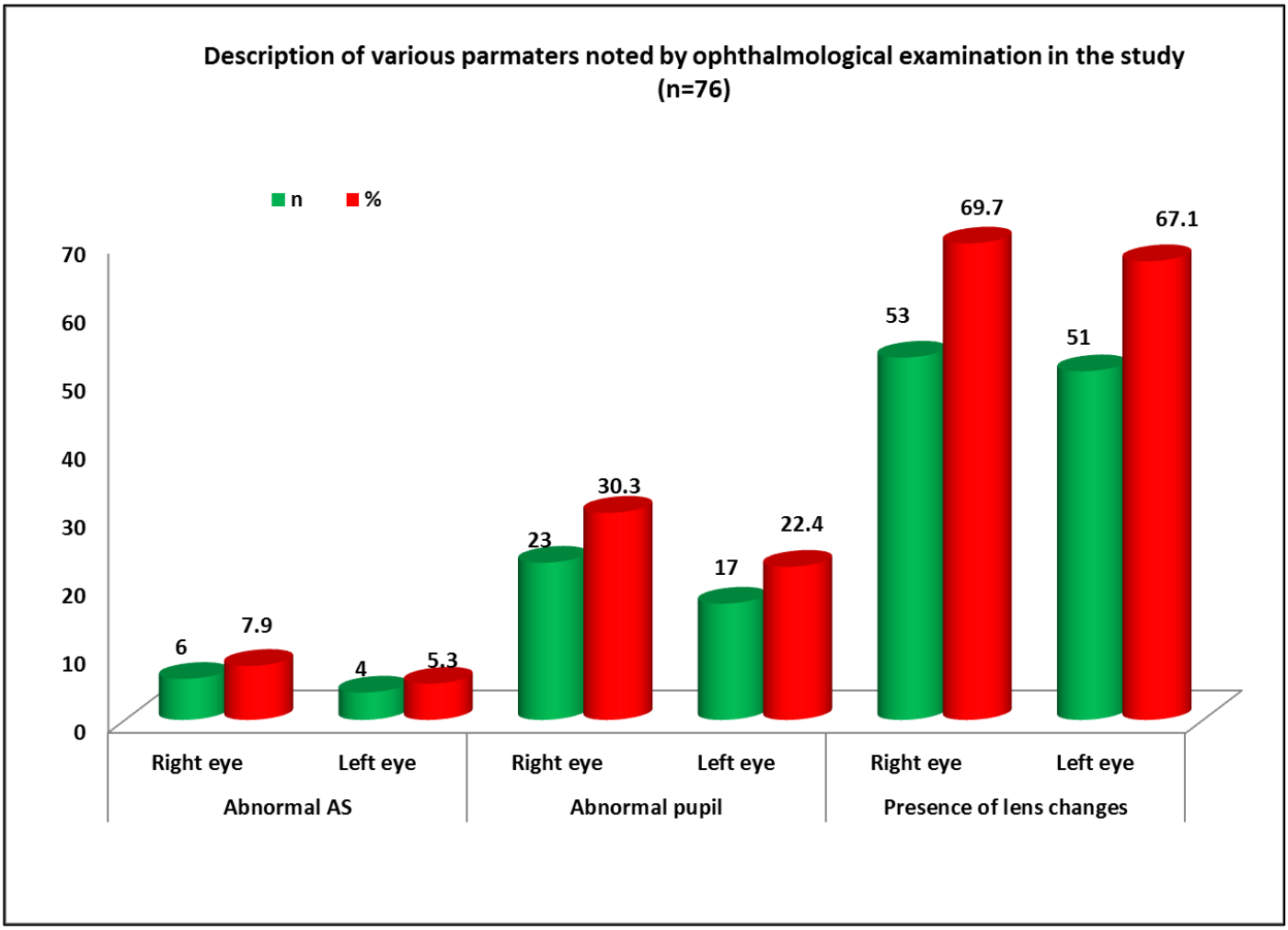

Fig 8.3. Description of various ophthalmological parameters

INTRAOCULAR PRESSURE

Intraocular pressure measured by applanation tonometry was categorized into three groups.

- 10 – 20 mmHg
- 21 – 30 mmHg
- > 30 mmHg

Half of the study population had intraocular pressure > 30 mmHg. Only 15.8% of patients had IOP between 10 and 20 mmHg.

Table 8.6. Frequency distribution of intra-ocular pressure category observed in the study.

S. No	IOP category	n	%
1	10 – 20 mm of Hg	12	15.8
2	21 – 30 mm of Hg	26	34.2
3	>30 mm of Hg	38	50

Data are expressed as n with %. The total N=76

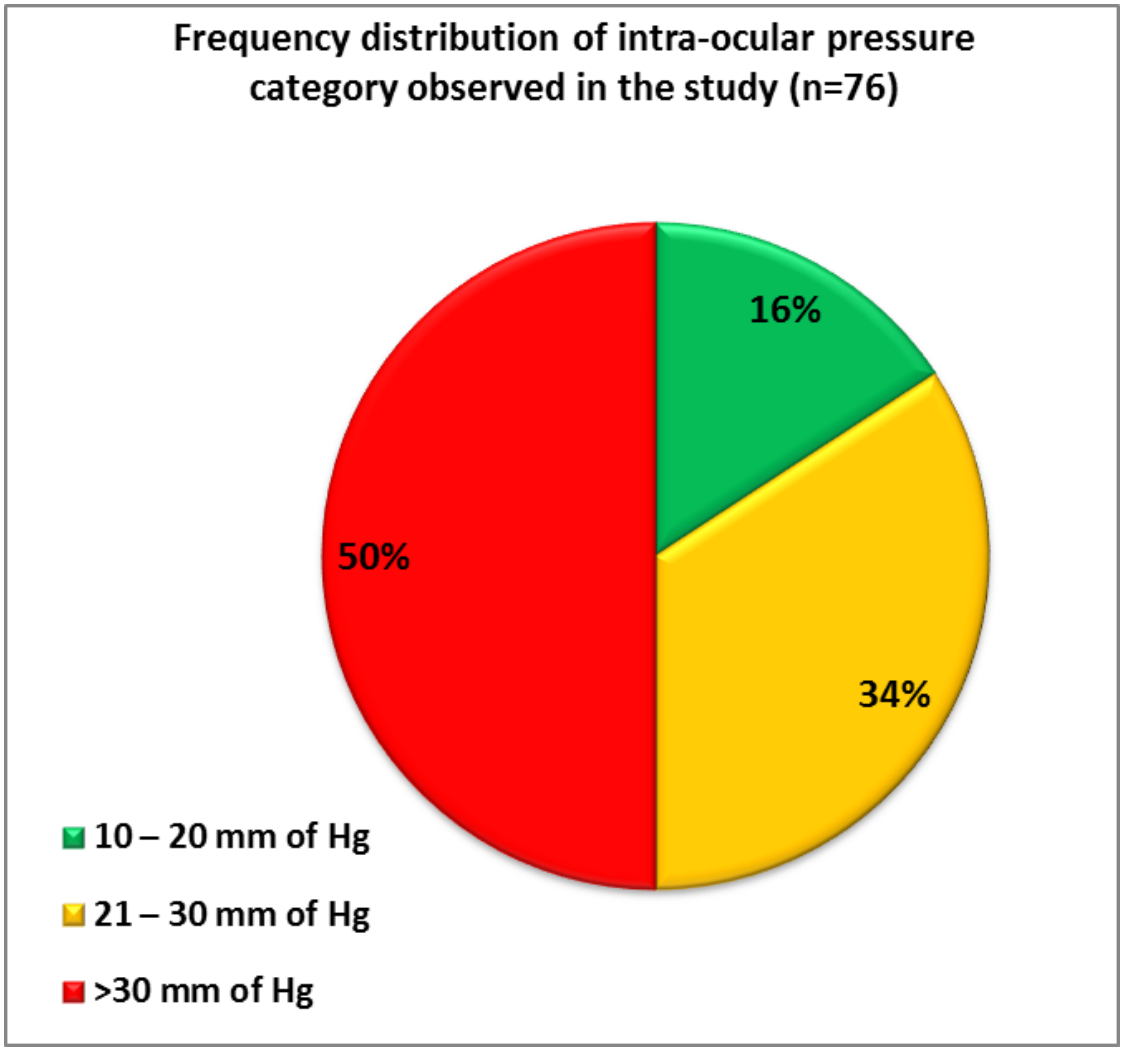

Fig 8.4. Frequency distribution of IOP

OTHER OPHTHALMOLOGICAL PARAMETERS

Other ophthalmological parameters such as presence of neuroretinal rim thinning, central corneal thinning, gonioscopy findings, nasalisation of vessels and field changes were studied in our study population and the results are summarized in the table below. All patients had normal gonioscopy and nasalisation of vessels. Neuroretinal rim thinning was present in 59.2% and central corneal thinning was present in 51.3% of patients. 59.2% of patients in our study population had late field changes suggestive of advanced glaucomatous disease.

Table 8.7. Frequency distribution of various ophthalmological parameters observed in the study.

S. No	Parameters	n	%
1	Presence of Central corneal thinning	39	51.3
2	Presence of Neuro-retinal rim thinning	45	59.2
3	Nasalisation of vessels	76	100
4	Normal gonioscopy	76	100
5	Early field changes	31	40.8
6	Advanced changes	45	59.2

Data are expressed as n with %. The total N=76

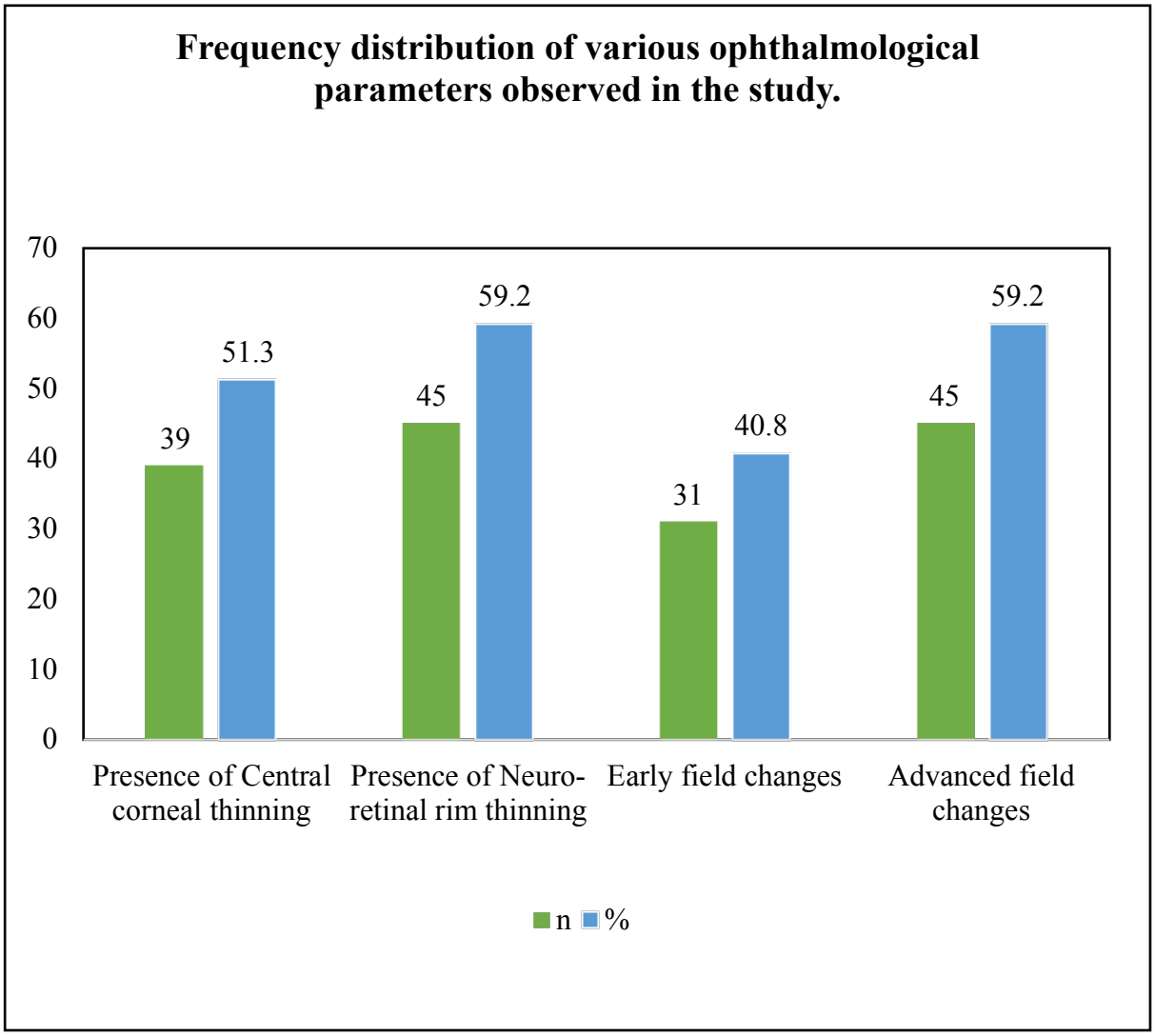

Fig 8.5. Frequency distribution of various ophthalmological parameters

VISUAL ACUITY

Visual acuity as obtained by using Snellen's chart was analyzed. This was subdivided into reduced vision and poor vision as described previously. 60.5% of the population had reduced vision whereas poor vision accounted for the remaining 30.5% of patients.

Table 8.8. Frequency distribution of visual acuity observed in the study.

S. No	Visual acuity	n	%
1	Poor vision	30	39.5
2	Reduced vision	46	60.5

Data are expressed as n with %. The total N=76

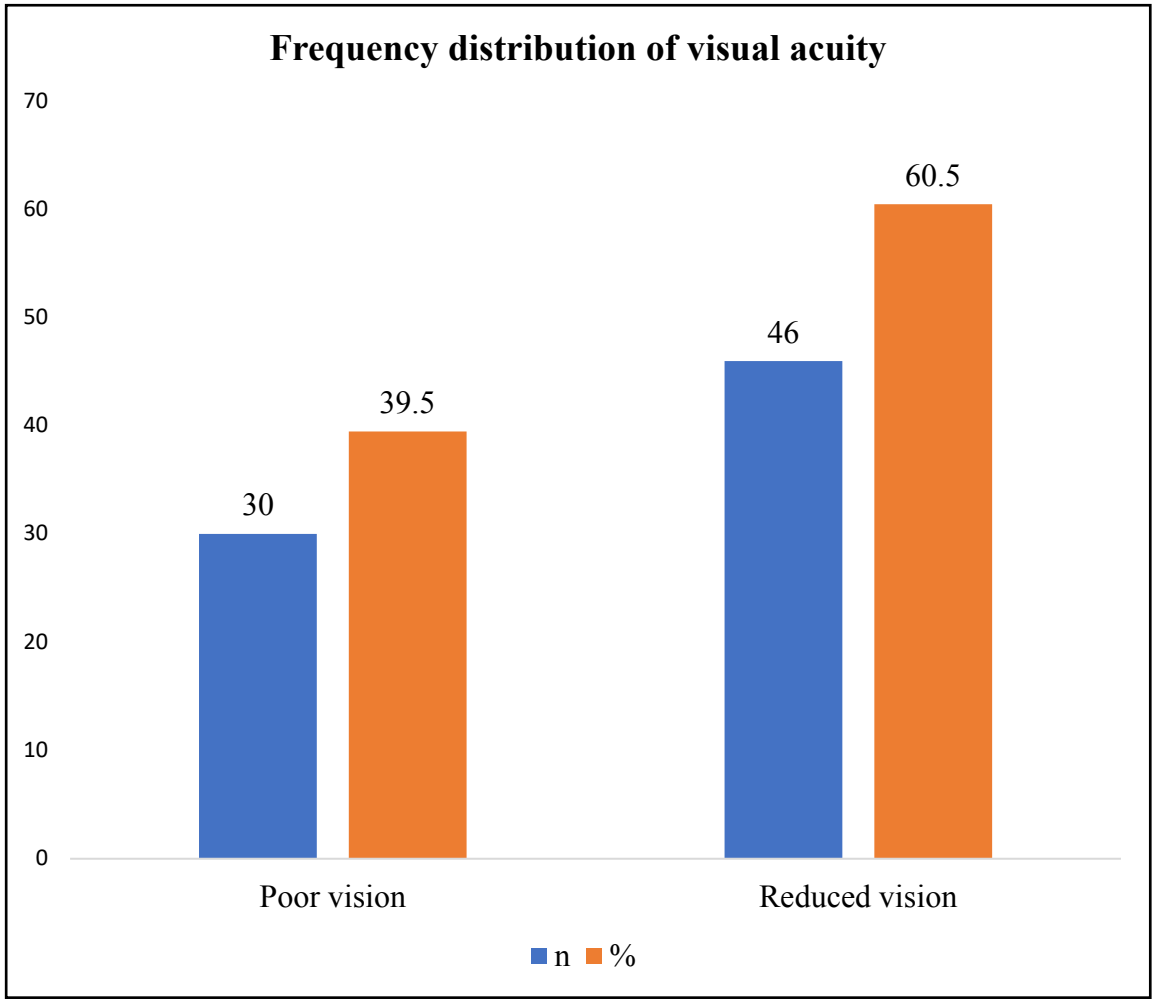

Fig 8.6. Frequency distribution of visual acuity

SYSTEMIC PARAMETERS

Glycated Hemoglobin (HbA1c) was measured in all patients to estimate the level of glycemic control. They were grouped into mild, moderate and severe. 48.7% of our study population belonged to the severe category with 14.5% belonging to moderate and 36.8% belonging to mild categories.

Table 8.9. Frequency distribution of HbA1c status observed in the study

HbA1c status	n	%
Mild (6.5-7%)	28	36.8
Moderate (7.1-9%)	11	14.5
Severe (>9%)	37	48.7

Data are expressed as n with %. The total N=76

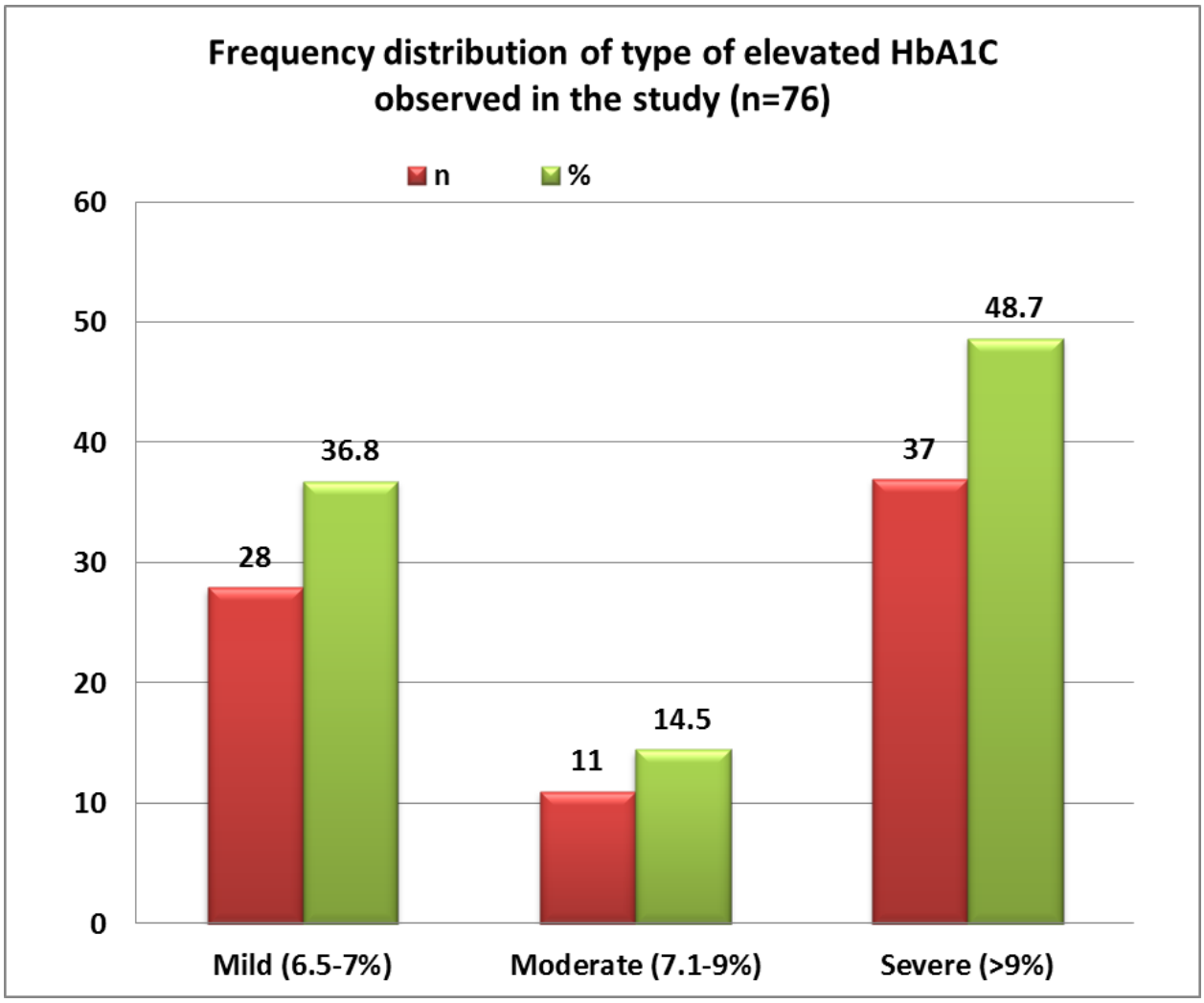

Fig 8.7. Frequency distribution of elevated HbA1c levels

Fasting, postprandial glucose and urine glucose were also estimated in the study population. The mean fasting blood sugar was 135.5 mg/dl with a standard deviation of 56.6 mg/dl. The mean postprandial glucose was 207.5 mg/dl with a standard deviation of 75.1 mg/dl. Urine glucose was found to be positive in 89.5% of the study population.

Table 8.10. Frequency distribution of Urine glucose status observed in the study

Parameters	n	%
Urine glucose		
Present	68	89.5
Absent	8	10.5

Data are expressed as n with %. The total N=76

COMPARITIVE ANALYSIS

INTRAOCULAR PRESSURE AND HbA1C

On comparing intraocular pressure with HbA1c, it was found that majority of patients with IOP >30 mmHg also belonged to the severe level of HbA1c (>9 g%) (78.4%) whereas majority of the other categories of IOP predominantly had HbA1c levels in the mild (6.5 – 7 g%). This correlation between intraocular pressure and HbA1c was found to be statistically significant (p value <0.0001)

Table 8.11. Comparison of intra-ocular pressure category with respect to HbA1C

S. No	IOP category	Mild HbA1c elevation (n=28)		Moderate HbA1C elevation (n=11)		Severe HbA1C elevation (n=37)		P value
		n	%	n	%	n	%	
1	10 – 20 mm of Hg	12	42.9	0	0	0	0	<0.0001*
2	21 – 30 mm of Hg	14	50	4	36.4	8	21.6	
3	>30 mm of Hg	2	7.1	7	63.6	29	78.4	
Statistic: Chi-square value: 40.99; df=4								

Data are expressed as n (%). Fisher's exact test was used to compare the proportions frequency between the groups. *indicates p<0.05 and considered statistically significant.

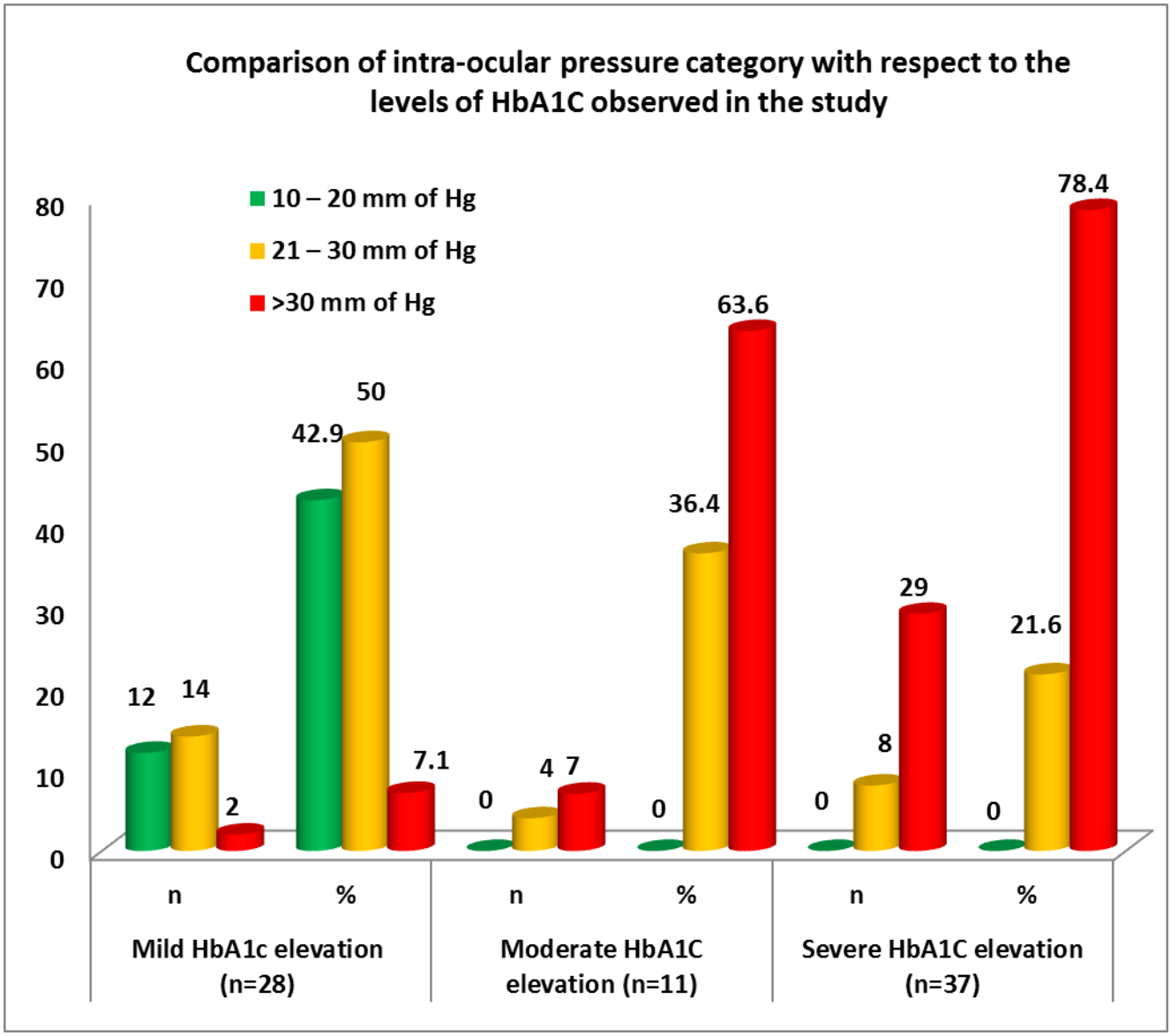

Fig 8.8. Comparison of IOP vs HbA1c levels

NEURORETINAL RIM THINNING AND HBA1C LEVELS

The presence of neuroretinal rim thinning and HbA1c levels were compared. 83.6% of patients with severe HbA1c (>9 g%) were found to have neuroretinal rim thinning whereas it was found to be present in 28.6% of patients with mild HbA1c (6.5 – 7 g%). This correlation between presence of neuroretinal rim thinning and HbA1c levels was statistically significant (p value <0.0001).

Table 8.12. Comparison of Neuro-retinal rim thinning noted with respect HbA1C

S. No	**Neuro-retinal rim thinning**	**Mild HbA1c elevation (n=28)**		**Moderate HbA1C elevation (n=11)**		**Severe HbA1C elevation (n=37)**		**P value**
		n	**%**	**n**	**%**	**n**	**%**	
1	Present	8	28.6	6	54.5	31	83.6	<0.0001*
2	Absent	20	71.4	5	45.5	6	16.2	
Statistic: Chi-square value: 20.23; df=2								

Data are expressed as n (%). Fisher's exact test was used to compare the proportions frequency between the groups. *indicates p<0.05 and considered statistically significant.

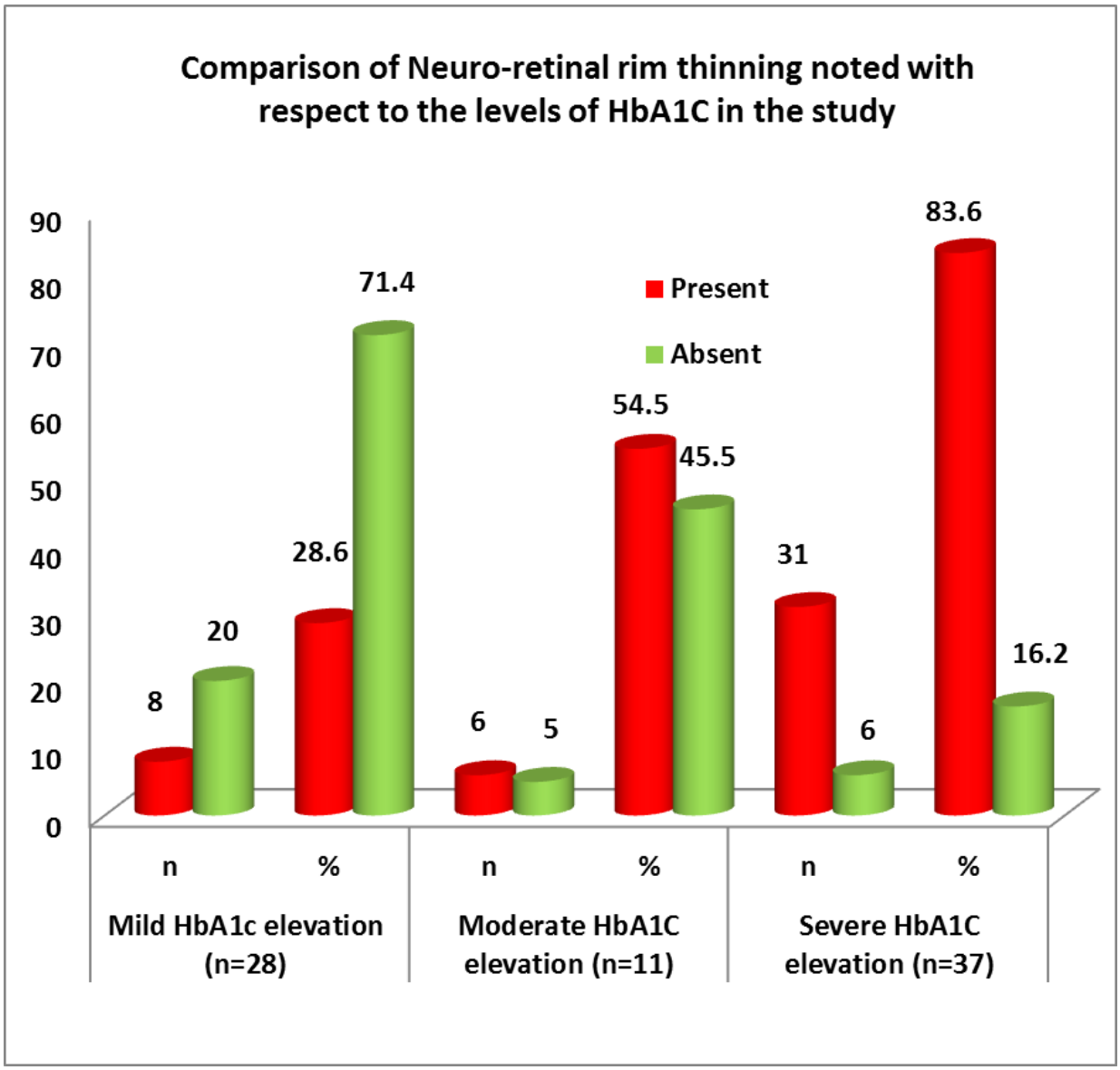

Fig 8.9. Comparison of neuroretinal rim thinning vs HbA1C levels

FIELD CHANGES AND HbA1C

Comparison of presence of early or advanced field changes was done with HbA1c levels. 89.2% of patients with severe HbA1c levels (> 9 g%) were found to have advanced field changes. As opposed to this, 75% patients in the mild HbA1c group had early field changes. This correlation was found to be statistically significant (p value <0.0001).

Table 8.13. Comparison of field changes noted with respect to the levels of HbA1C in the study.

S. No	Field changes	Mild HbA1c elevation (n=28)		Moderate HbA1C elevation (n=11)		Severe HbA1C elevation (n=37)		P value
		n	%	n	%	n	%	
1	Early Field changes	21	75	6	54.5	4	10.8	<0.0001*
2	Late field changes	7	25	5	45.5	33	89.2	
Statistic: Chi-square value: 28.19; df=2								

Data are expressed as n (%). Fisher's exact test was used to compare the proportions frequency between the groups. *indicates p<0.05 and considered statistically significant.

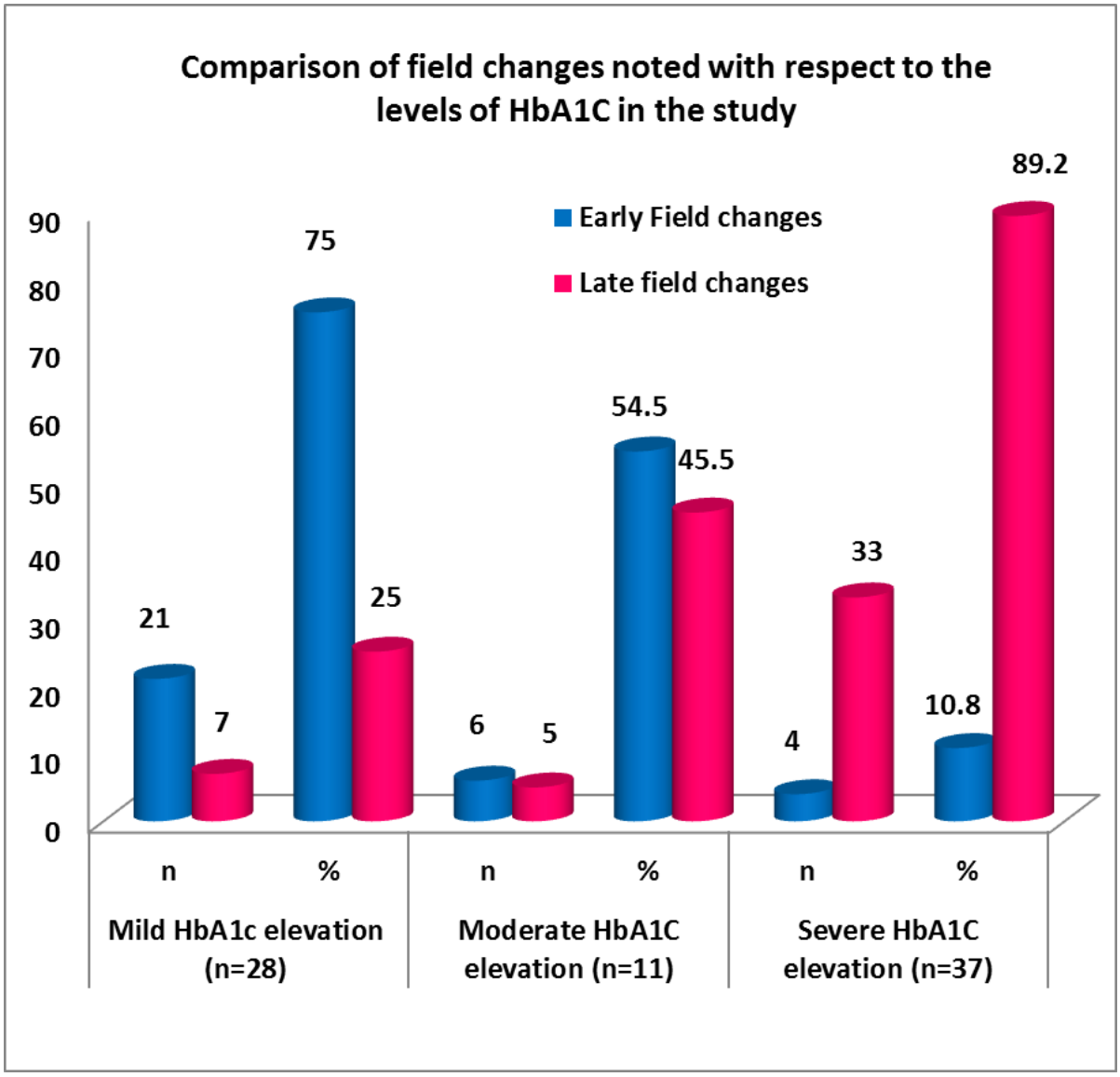

Fig 8.10. Comparison of field changes vs HbA1C levels

CUP-DISC RATIO AND HbA1c LEVELS

The relationship between cup-disc ratio and HbA1c levels were analyzed according to subgroups as detailed earlier. 54.1% of patients with severe HbA1c levels had a cup disk ratio greater than 0.8. 21.6% of patients in this category were also found to have glaucomatous optic atrophy. This correlation between HbA1c levels and cup-disc ratio was found to be statistically significant (p value <0.0001).

Table 8.14. Comparison of disc-cup ratio category noted with respect to the levels of HbA1C in the study.

S. No	Disc cup ratio category	Mild HbA1c elevation (n=28)		Moderate HbA1C elevation (n=11)		Severe HbA1C elevation (n=37)		P value
		n	%	n	%	n	%	
1	0.5-0.7	23	82.1	6	54.5	9	24.3	<0.0001*
2	0.8-0.9	4	14.3	5	45.5	20	54.1	
3	GOA	1	3.6	0	0	8	21.6	
Statistic: Chi-square value: 23.4; df=4								

Data are expressed as n (%). Fisher's exact test was used to compare the proportions frequency between the groups. *indicates p<0.05 and considered statistically significant.

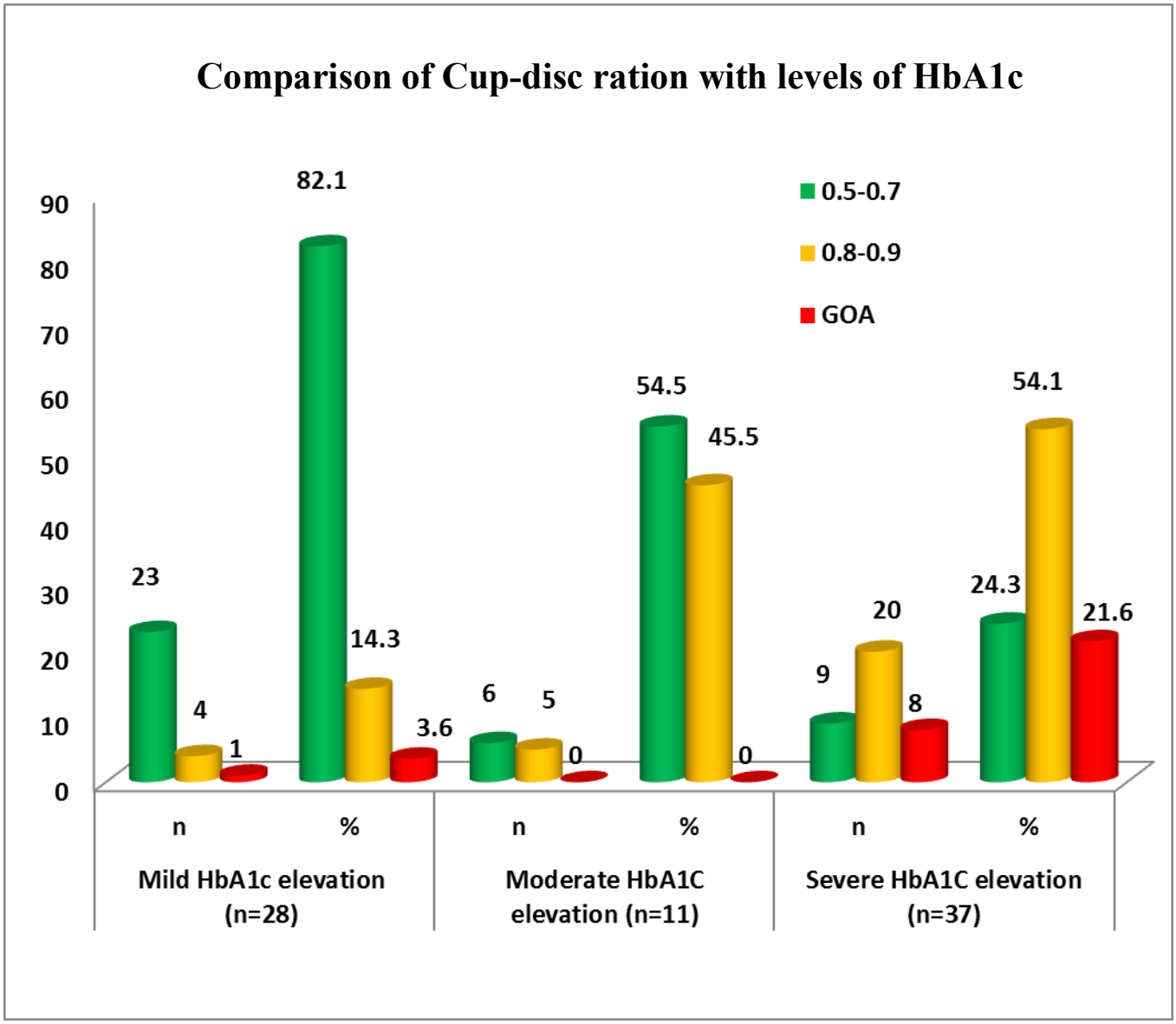

Fig 8.11. Comparison of Cup-Disc ratio vs HbA1C levels

CENTRAL CORNEAL THINNING AND HbA1c LEVELS

In this comparison, it was found that patients in the severe HbA1c level category had 62.2% central corneal thinning as opposed to mild HbA1c level in which 60.7% of patients did not have any central corneal thinning. This difference however, was not statistically significant.

Table 8.15. Comparison of CC thinning noted with respect to the levels of HbA1C in the study.

S. No	CC thinning	Mild HbA1c elevation (n=28)		Moderate HbA1C elevation (n=11)		Severe HbA1C elevation (n=37)		P value
		n	%	n	%	n	%	
1	Present	11	39.3	5	45.5	23	62.2	0.172 (NS)
2	Absent	17	60.7	6	54.5	14	37.8	
Statistic: Chi-square value: 3.516; df=2								

Data are expressed as n (%). Fisher's exact test was used to compare the proportions frequency between the groups. *indicates $p<0.05$ and considered statistically significant.

VISUAL ACUITY AND HbA1c LEVELS

Visual acuity was compared with HbA1c levels with respect to the subgroupings. It was noted that, in patients with severe HbA1c levels, 54.1% had poor vision whereas patients with mild HbA1c levels had only 25% poor vision. This difference was statistically significant (p value 0.04).

Table 8.16. Comparison of visual acuity with respect to levels of HbA1C observed in the study.

S. No	Quality of vision	Mild HbA1c elevation (n=28)		Moderate HbA1C elevation (n=11)		Severe HbA1C elevation (n=37)		P value
		n	%	n	%	n	%	
1	Poor vision	7	25	3	27.3	20	54.1	0.04*
2	Reduced vision	21	75	8	72.7	17	45.9	
Statistic: Chi-square value: 6.433; df=2								

Data are expressed as n (%). Fisher's exact test was used to compare the proportions frequency between the groups. *indicates $p<0.05$ and considered statistically significant.

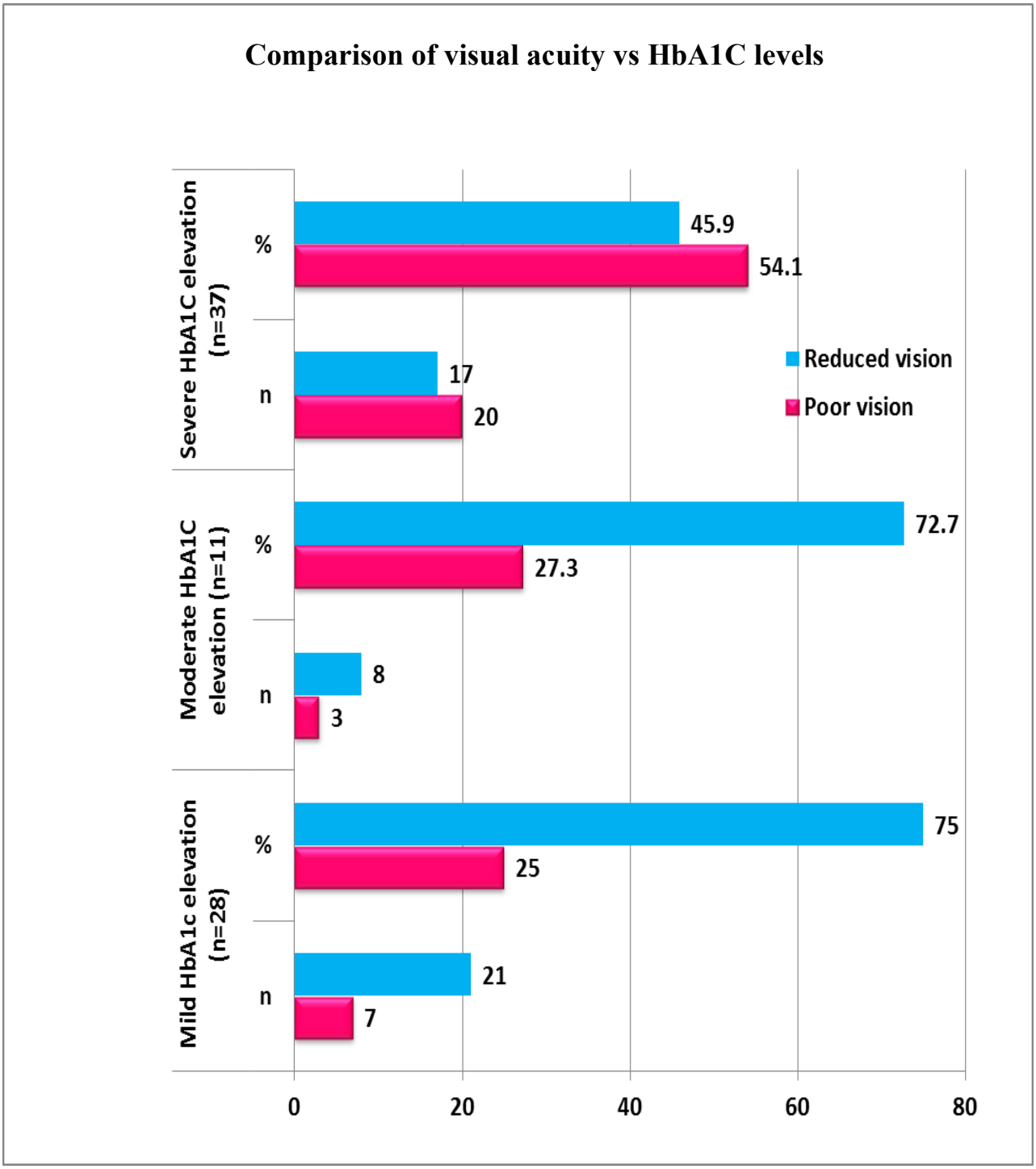

Fig 8.12. Comparison of visual acuity vs HbA1C levels

9. DISCUSSION

Glaucoma represents the leading cause of worldwide irreversible blindness. The aim of the study was to correlate glycemic control and various ophthalmological parameters in patients with primary open angle glaucoma in order to look for relationships between glycemic control and visual outcomes in this population. We analyzed data from 76 diabetics out of 120 POAG patients who were recruited during the study period.

On univariate analysis, 75% of our study population belonged to the 51-70 years age group with a 2:1 male: female ratio. Half of the patients had elevated IOP more than 30 mmHg. About 59.2% had neuroretinal rim thinning and 51.3% patients had central corneal thinning. Late field changes suggestive of advanced glaucomatous disease was found in 59.2%. 60.5% of patients had poor vision on testing for visual acuity. Majority of the population (48.7%) had severely elevated HbA1c levels (> 9 g%) as compared to mild or moderate groups. Urine glucose was positive in 89.5% of the population.

Comparative multivariate analysis between various ophthalmological parameters and glycemic control as assessed by HbA1c was done. This showed a statistically significant association between elevated IOP, presence of neuroretinal rim thinning, presence of late field changes, presence of higher cup-disk ratio and glaucomatous optic atrophy, poor vision and severely elevated HbA1c levels (> 9 g%). Central corneal thinning was found to be higher in this group, but the correlation was not statistically significant.

Recently, Hymowitz et al reported on the correlation between elevated IOP and hyperglycemia(55). This study showed a significant correlation between these two

parameters and also found that only less than 1% of patients with elevated HbA1c levels had normal IOP. Similar other studies have been done in the past which also show a similar correlation. Elevated glucose levels were associated with raised IOP in the Framingham study(11). Similarly the Rotterdam study(14) and the Beaver dam study(12) also showed higher IOP in diabetics as compared to non-diabetic population.

Hyperglycemic conditions induce excess extracellular matrix (ECM) synthesis by trabecular meshwork cells. The ECM components include fibronectin, laminin and collagen IV which are essential for maintaining the ultrastructure of the trabecular meshwork and hence plays a vital role in its function of aqueous outflow. This may lead to ECM accumulation in the trabecular meshwork, contributing to blockage of aqueous outflow.

As elevated IOP is an important risk and prognostic factor for glaucoma, reduction of intraocular pressure is paramount in reducing the deleterious glaucomatous changes and hence retarding poor visual outcomes. A strict glycemic control may help in reduction of IOP and subsequently reduce the exposure of the optic nerve to elevated IOP and hence delay the poor visual outcomes in glaucoma patients who are diabetic. With diabetics at the risk of diabetic retinopathy due to chronic hyperglycemia, tight glycemic control not only prevents this dreaded complication but also delays the effect of glaucoma. HbA1c monitoring may also serve as a potential tool to screen for glaucoma in diabetic patients.

10. CONCLUSION

- As p-values are statistically significant, HbA1c correlates with poorer visual outcomes in POAG
- Quality glycaemic control over a period of time may retard the progression of visual loss.
- Glaucomatous patients with higher blood glucose values may require more rigid control.
- Though central corneal thinning was found to be associated with POAG, the correlation was not statistically significant.

PART III

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12. PROFORMA

NAME OF THE PATIENT:

AGE/SEX:

DATE:

HOSPITAL NO.:

ADDRESS:

OCCUPATION:

PRESENTING ILLNESS:

PAST MEDICAL HISTORY:

- Diabetes mellitus
- Hypertension
- bronchial asthma
- epilepsy/others

PAST SURGICAL HISTORY:

DRUG HISTORY:

PERSONAL HISTORY:

DIET HISTORY:

OCULAR HISTORY:

- H/O defective vision yes no
- H/O Headache yes no
- H/O Pain yes no
- H/O previous spectacle yes no
- H/O frequent spectacle changing yes no
- H/O contact lens use for refractive errors yes no
- H/O ocular trauma yes no
- H/O ocular surgeries in the past yes no

GENERAL EXAMINATION:

BP: PULSE:

SYSTEMIC EXAMINATION:

Cardiovascular system:

Respiratory system:

Abdominal examination:

Central nervous system:

OCULAR EXAMINATION:

	OD	OS
VISION UNAIDED		
NEAR VISION		
CORRECTED VISION		
LID		
CONJUNCTIVA		
CORNEA		
IRIS		
ANTERIOR CHAMBER**:**		
PUPIL		
LENS		

INVESTIGATIONS:

FUNDUS DIRECT OPHTHALMOSCOPY:

NRM

C/D RATIO

OPTIC DISC SIZE

VESSELS

MACULA

FOVEAL REFLEX

FUNDUS INDIRECT OPHTHALMOSCOPE:

NRM

C/D RATIO

OPTIC DISC SIZE

VESSELS

MACULA

FOVEAL REFLEX

GONIOSCOPY

PACHYMETRY

IOP(AT)

FBS

PPBS

HBA1C

URINE SUGAR

CLINICAL IMPRESSION

KEY TO MASTERCHART

DM – Diabetes Mellitus

RE – Right eye

LE – Left eye

VA – Visual acuity

AS – Anterior segment

DISC – Cup-Disc ratio

NRR – Neuroretinal rim thinning

NASAL – Nasalisation of vessels

GONIO – Gonioscopy

CC THINNING – Central corneal thinning

AT – Applanation tonometry

FBS – Fasting blood sugar

PPBS – Postprandial blood sugar

HBA1C – Glycated haemoglobin

s.no	name	age	sex	his DM	VALVE	LE	AS XO	AS LG	PUPIL XO	LE	LENS CHAN	LR	DISC	NRR	NASAL	early fold-cha	lace	GONIO	CC THICKNESS	MET XO	AC LG	PRS	IPHIL	SMEAR SC	SMEAR C	
1	sreenivi	82	F	PRESENT	PL	2/60	N	N	N	ABNORMAL	A	A	GOA	P	P		P	N	P		24	32	120	230	P	69
2	manisc	65	F	PRESENT	6/12	PL	N	ABNORMAL	N	ABNORMAL	A	P		0.6	A	P		N	P		35	28	78	110	A	7
3	dharmavi	75	F	PRESENT	6/12	6/18	N	N	N	ABNORMAL	A	A		0.7	A	P	P	N	P		23	30	190	260	P	9.2
4	nagarjun	60	M	PRESENT	6/9	6/60	N	N	N	N	P	P		0.9	P	P		P	N	P	26	32	140	250	P	9
5	karunath	58	M	PRESENT	6/60	6/60	N	N	ABNORMAL	N	A	A		0.3	A	P	P		N	P	42	26	70	190	P	9.2
6	vasuluc	64	F	PRESENT	6/36	HM	N	N	N	N	P	A		0.8	P	P		P	N	A	32	28	110	180	A	69
7	mukthodi	63	F	PRESENT	6/36	6/18	ABNORMAL	N	N	ABNORMAL	P	P		0.5	A	P	P		N	P	35	34	140	210	P	9.2
8	natarajn	53	M	PRESENT	NO PL	HM	N	N	ABNORMAL	N	P	P		0.8	P	P		P	N	P	24	31	220	260	P	10
9	rajata	50	F	PRESENT	NO PL	HM	N	N	ABNORMAL	N	P	P	GOA		P	P		P	N	A	24	18	70	130	P	9.2
10	subhasc	63	F	PRESENT	PL	3/60	ABNORMAL	N	N	N	A	P		0.9	P	P		P	N	A	40	18	280	390	P	13
11	grace	43	F	PRESENT	2/60	PL	N	N	N	ABNORMAL	P	P		0.8	P	P		P	N	P	26	31	68	102	A	6.8
12	sunthara	69	M	PRESENT	NO PL	6/12	ABNORMAL	N	ABNORMAL	N	A	A	GOA		P	P		P	N	P	28	12	72	105	A	7
13	vasanthal	60	F	PRESENT	NO PL	6/36	N	N	ABNORMAL	N	P	A		0.8	P	P		P	N	A	32	32	72	102	A	9.2
14	velayuth	60	M	PRESENT	5/60	5/60	N	N	N	N	P	P		0.5	A	P	P		N	P	35	28	92	140	P	9
15	poojaku	53	M	PRESENT	CFCF	PL	N	N	N	N	P	A		0.9	P	P		P	N	P	38	30	97	122	A	9.6
16	sasidhri	60	F	PRESENT	6/60	PL	N	N	N	ABNORMAL	P	P		0.8	P	P		P	N	P	22	42	130	200	P	12
17	dhanagir	50	M	PRESENT	6/60	6/60	N	N	N	N	P	P		0.6	A	P		P	N	P	36	35	140	220	P	11
18	dhanapl	48	M	PRESENT	HM	6/36	N	N	N	N	A	A	GOA		P	P		P	N	P	48	35	172	480	P	14
19	chinnu	40	M	PRESENT	2/60	6/24	N	N	N	N	P	P		0.5	A	P	P		N	A	35	20	70	140	A	9.5
20	mani	65	M	PRESENT	6/60	6/36	N	N	N	N	P	P		0.6	A	P	P		N	P	35	35	70	130	P	7
21	mayavat	70	M	PRESENT	6/60	3/60	N	N	N	N	A	P		0.7	A	P	P		N	A	34	28	89	233	P	9.6
22	palaivel	70	M	PRESENT	6/60	CFCF	N	N	N	N	P	A		0.8	P	P		P	N	P	22	36	180	240	P	9
23	sebasin	69	M	PRESENT	6/60	6/60	N	N	N	N	P	P		0.7	A	P		P	N	A	32	18	178	220	P	9.2
24	manimegh	56	F	PRESENT	PL	6/60	ABNORMAL	N	ABNORMAL	N	A	A		0.9	P	P		P	N	P	44	34	92	140	P	9.4
25	devanandh	68	M	PRESENT	6/36	6/36	N	N	N	ABNORMAL	P	P		0.8	P	P		P	N	A	35	30	90	189	P	9.2
26	sinlamal	57	F	PRESENT	6/36	PL	N	N	N	ABNORMAL	P	P		0.9	P	P		P	N	A	38	38	130	172	P	7
27	velamal	72	F	PRESENT	5/60	6/36	N	N	N	N	P	P		0.8	P	P		P	N	A	34	22	182	240	P	10
28	ijunayuth	60	M	PRESENT	3/60	6/60	N	N	N	N	P	P		0.6	A	P	P		N	A	22	22	96	189	P	9.8
29	mayan	60	M	PRESENT	6/36	6/12	N	N	N	N	P	A		0.6	A	P	P		N	A	22	24	118	162	P	7
30	manimthi	50	M	PRESENT	6/18	6/36	N	N	N	N	A	A		0.5	A	P	P		N	A	22	20	120	190	P	9.5
31	shanmugan	67	M	PRESENT	6/60	6/60	N	N	N	N	ABNORMAL	P		0.7	A	P	P		N	P	22	23	149	220	P	9.6
32	harichndra	60	M	PRESENT	2/60	6/36	N	ABNORMAL	ABNORMAL	N	P	A		0.7	P	P		P	N	P	32	22	130	240	P	10
33	sivanandhan	67	M	PRESENT	6/18	6/36	N	N	N	N	A	P		0.8	P	P		P	N	A	20	30	127	222	P	9.2
34	panneerselvam	60	M	PRESENT	3/60	6/36	N	N	N	N	A	A		0.9	P	P		P	N	A	34	24	127	202	P	9.8
35	swati	66	M	PRESENT	6/12	6/24	ABNORMAL	ABNORMAL	N	N	P	A		0.5	A	P	P		N	P	35	35	84	120	P	7
36	lindra	82	F	PRESENT	6/12	6/12	N	N	N	N	P	P		0.6	A	P	P		N	A	35	28	130	220	P	9.6
37	ponnumal	45	F	PRESENT	6/36	6/36	N	N	N	N	A	A		0.7	P	P		P	N	P	24	28	115	240	P	9.2
38	nagarajan	73	M	PRESENT	3/60	6/36	N	N	ABNORMAL	N	P	P		0.8	P	P		P	N	A	28	24	184	240	P	9.4
39	devamani	60	F	PRESENT	6/60	6/36	N	N	ABNORMAL	N	P	P		0.8	P	P		P	N	A	40	34	190	400	P	13
40	thangam	60	F	PRESENT	3/60	6/36	N	N	ABNORMAL	N	P	P		0.7	A	P	P		N	A	32	24	160	140	P	9
41	rajkumar	64	M	PRESENT	PL	PL	N	N	ABNORMAL	ABNORMAL	P	P	GOA		P	P		P	N	P	32	48	310	370	P	12
42	samyagan	60	M	PRESENT	6/18	6/60	N	N	N	N	A	A		0.6	A	P	P		N	A	38	28	80	120	P	7.5
43	krishnamthy	70	M	PRESENT	6/60	6/60	N	N	N	N	A	A		0.5	A	P	P		N	A	34	35	120	180	P	9.5
44	sivasusan	60	M	PRESENT	6/12	6/12	N	N	ABNORMAL	N	A	A		0.7	P	P	P		N	A	42	23	176	280	P	8
45	jayapal	64	M	PRESENT	6/18	HM	N	N	N	ABNORMAL	A	A		0.9	P	P		P	N	P	32	40	120	190	P	7.8
46	kasthuri	68	F	PRESENT	6/60	6/60	N	N	N	N	P	P		0.7	A	P	P		N	A	26	32	110	180	P	7
47	durairaj	53	M	PRESENT	6/18	6/18	N	N	N	N	P	P		0.6	A	P	P		N	A	22	23	121	182	P	6.5
48	jayaraj	53	M	PRESENT	6/6		E	N	N	N	P	P		0.8	A	P	P		N	A	30	22	72	124	P	9.5
49	rajkumar	64	M	PRESENT	PL	PL	ABNORMAL	ABNORMAL	ABNORMAL	ABNORMAL	P	P		0.8	P	P		P	N	P	36	38	210	340	P	10
50	viswanthar	59	M	PRESENT	6/12	6/12	N	N	N	N	P	P		0.6	A	P	P		N	A	30	38	87	132	P	7
51	gayasm	69	M	PRESENT	6/60	HM	N	N	N	N	P	P		0.7	P	P		P	N	A	20	22	134	168	P	9.8
52	rani	67	F	PRESENT	6/60	6/12	N	N	ABNORMAL	N	P	P		0.7	P	P	P		N	P	22	34	132	166	P	9.8
53	ravi	67	M	PRESENT	pl	6/12	N	N	ABNORMAL	N	P	P		0.8	P	P		P	N	P	40	20	260	290	P	10
54	kasilhan	55	M	PRESENT	CFCF	6/36	N	N	ABNORMAL	N	P	P	GOA		P	P		P	N	P	36	26	160	295	P	10.2
55	perusamy	74	M	PRESENT	6/60	6/60	N	N	ABNORMAL	ABNORMAL	A	A		0.8	P	P		P	N	P	32	40	210	290	P	11
56	gowri	52	F	PRESENT	6/60	6/60	N	N	N	N	P	P		0.8	P	P		P	N	A	28	35	170	230	P	9.2
57	dharmaraj	58	M	PRESENT	6/36	6/36	N	N	N	N	P	P		0.8	P	P		P	N	P	35	31	186	280	P	9.4
58	murugaiyat	65	M	PRESENT	PL	6/60	N	N	ABNORMAL	N	P	A	GOA		P	P		P	N	A	46	32	176	290	P	9.6
59	kalaselvi	57	F	PRESENT	6/12	HM	N	N	N	ABNORMAL	A	P		0.9	P	P		P	N	P	35	26	138	198	P	7
60	dasamakkan	69	M	PRESENT	6/12	6/12	N	N	N	N	A	A		0.7	P	P	P		N	A	28	34	110	160	P	7
61	sekar	55	M	PRESENT	6/60	6/60	N	N	N	N	P	P		0.6	A	P	P		N	A	32	35	123	152	P	6.8
62	murgan	61	M	PRESENT	6/36	HM	N	N	N	ABNORMAL	P	P		0.8	P	P		P	N	P	38	32	204	300	P	10
63	sanjeevj	49	M	PRESENT	5/60	3/60	N	N	N	N	P	P		0.5	A	P	P		N	P	38	28	110	159	P	7
64	pakkirmal	63	F	PRESENT	6/60	6/60	N	N	N	N	P	P		0.6	A	P	P		N	A	22	18	115	169	P	6.5
65	krishani	53	F	PRESENT	6/36	3/60	N	N	N	N	P	P		0.6	A	P	P		N	A	38	20	160	180	P	6.5
66	abdulwahab	59	M	PRESENT	HM	HM	N	N	N	ABNORMAL	P	P		0.8	P	P		P	N	P	20	40	260	266	P	10
67	thirunavuk	68	M	PRESENT	NO PL	6/36	N	N	ABNORMAL	N	A	A	GOA		P	P		P	N	P	40	34	160	280	P	9.6
68	chandhirbo	40	M	PRESENT	5/60	5/60	N	N	N	N	P	P		0.6	A	P	P		N	A	35	34	166	142	P	9.5
69	murugaiyat	61	M	PRESENT	6/12	6/60	N	N	N	N	P	P		0.5	A	P	P		N	A	38	20	160	142	P	9.5
70	sivalenchezan	75	M	PRESENT	PL	6/60	N	N	ABNORMAL	N	P	P		0.9	P	P		P	N	A	38	38	226	310	P	9.8
71	selvaprakash	60	M	PRESENT	3/60	3/60	N	N	N	N	P	P		0.7	P	P		P	N	P	32	34	200	240	P	10.2
72	durairaj	68	M	PRESENT	PL	PL	N	N	ABNORMAL	ABNORMAL	P	P		0.9	P	P		P	N	P	30	34	160	190	P	8
73	chinnaponnu	60	F	PRESENT	6/36	6/12	N	N	N	N	A	A		0.8	A	P	P		N	A	38	38	110	156	P	7
74	sobarani	47	F	PRESENT	PL	CFCF	N	N	ABNORMAL	N	P	P	GOA		P	P		P	N	P	36	38	120	180	P	9.2
75	seelavath	55	M	PRESENT	6/60	6/60	N	N	N	N	P	P		0.3	A	P	P		N	P	20	22	92	126	P	6.5
76	mani	80	M	PRESENT	4/60	PL	N	N	ABNORMAL	N	A	P		0.8	P	P		P	N	P	35	28	72	128	A	7