A Dissertation on

"A STUDY ON DIURNAL VARIATION OF CENTRAL CORNEAL THICKNESS AND INTRAOCULAR PRESSURE IN PATIENTS WITH PSEUDOEXFOLIATION"

Submitted in partial fullfilment of requirements of

M.S.OPHTHALMOLOGY

BRANCH III

REGIONAL INSTITUTE OF OPHTHALMOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI 600 -003

Submitted to

THE TAMIL NADU DR.M.G.R UNIVERSITY

CHENNAI

MAY 2022

REGISTER NO : 221913007

CERTIFICATE

This is to certify that **Dr. HEMA PRIYA.R**. Post Graduate in M.S. Ophthalmology, at Regional Institute of Ophthalmology and Government Ophthalmic Hospital attached to Madras Medical College , Chennai carried out this dissertation on **"DIURNAL VARIATION OF CENTRAL CORNEAL THICKNESS AND INTRAOCULAR PRESSURE IN PATIENTS WITH PSEUDOEXFOLIATION"** under our direct guidance and supervision during the academic period from MAY 2019 – MAY 2022.

This dissertation is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai for the fullfilment of award of M.S. Degree in Ophthalmology.

Prof.Dr.R. MALARVIZHI M.S, D.O
Director & Superintendent (I/C)
Regional Institute of Ophthalmology &
Government Ophthalmic Hospital,
Madras Medical College,
Chennai 600008.

Prof. Dr. E. THERANIRAJAN, MD., DCH., MRCPCH (UK)., FRCPCH(UK).,
DEAN,
Madras Medical College,
Rajiv Gandhi Government General Hospital,
Chennai 600003

CERTIFICATE BY THE GUIDE

This is to certify that Dr. HEMA PRIYA.R , Post Graduate (May 2019-May 2022) in the Department of Ophthalmology, at Regional Institute of Ophthalmology and Government Ophthalmic Hospital attached to Madras Medical College , carried out this dissertation work titled **"DIURNAL VARIATION OF CENTRAL CORNEAL THICKNESS AND INTRAOCULAR PRESSURE IN PATIENTS WITH PSEUDOEXFOLIATION"** under my direct guidance and supervision in partial fullfilment of the regulations laid down by The Tamil Nadu Dr.MGR Medical University, Chennai for **M.S.Ophthalmology,** degree examination to be held in May 2022

Prof. Dr. M.R.CHITRA M.S.,
Chief Glaucoma Services
Regional Institute of Ophthalmology
Madras Medical College & Research Institute
Govt General Hospital ,
Chennai - 600008

DECLARATION

I, Dr. HEMA PRIYA.R., solemnly declare that the dissertation titled **"DIURNAL VARIATION OF CENTRAL CORNEAL THICKNESS AND INTRAOCULAR PRESSURE IN PATIENTS WITH PSEUDOEXFOLIATION"** has been prepared by me. This is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai, in partial fulfillment of the requirement for the award of M.S. Ophthalmology (BRANCH -III), degree Examination to be held in May 2022.

Place :

SIGNATURE OF THE CANDIDATE

Date :

DR.HEMA PRIYA.R

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013/RR-16
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.HEMA PRIYA R,
MS Ophthalmology Post Graduate student,
Regional Institute of Ophthalmology (RIOGOH)
Madras Medical College,
Chennai-600008.

Dear Dr. HEMA PRIYA R,

The Institutional Ethics Committee has considered your request and approved your study titled **"A STUDY ON DIURNAL VARIATION OF CENTRAL CORNEAL THICKNESS AND INTRAOCULAR PRESSURE IN PATIENTS WITH PSEUDOEXFOLIATION"- NO.08122020.** The following members of Ethics Committee were present in the meeting held on **15.12.2020** conducted at Madras Medical College, Chennai 3.

1. Prof.P.V.Jayashankar :Chairperson
2. Prof.N.Gopalakrishnan,MD.,DM., FRCP, Director, Inst.of Nephrology,MMC,Ch : Member Secretary
3. Prof. K.M.Sudha, Prof. Inst. of Pharmacology,MMC,Ch-3 : Member
4. Prof. Alagarsamy Jamila ,MD, Inst. of Patholoy, Stanley Medical College, Chennai : Member
5. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai : Member
6. Prof.S.Lakshmi, Prof. of Paediatrics ICH Chennai :Member
7. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
8. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
9. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003.

Curiginal

Document Information

Analyzed document	diurnal variation of cct and iop in pseudoexfoliation.docx (D123558274)
Submitted	2021-12-23T04:30:00.0000000
Submitted by	Hema Priya
Submitter email	priyaram1209@gmail.com
Similarity	3%
Analysis address	priyaram1209.mgrmu@analysis.urkund.com

Sources included in the report

SA	**thesis pxf final.docx** Document thesis pxf final.docx (D30535412)	4
W	URL: https://www.slideshare.net/GloriaGeorge1/pseudoexfoliation-syndrome Fetched: 2021-12-23T04:31:59.9070000	2
W	URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4290197/ Fetched: 2020-12-09T08:07:42.6000000	2

CERTIFICATE –II

This is to certify that the dissertation titled **"DIURNAL VARIATION OF CENTRAL CORNEAL THICKNESS AND INTRAOCULAR PRESSURE IN PATIENTS WITH PSEUDOEXFOLIATION"** of the candidate **Dr. HEMA PRIYA.R**., for the award of **M.S. Degree of Ophthalmology** (BRANCH -III). I personally verified the urkund.com website for the purpose of plagiarism check, I found that the uploaded thesis file contains from the introduction to conclusion pages and result shows 3 (three) percentage of plagiarism in the dissertation.

Guide and Supervisor sign with Seal

ACKNOWLEDGEMENT

I express my sincere thanks to **Prof.Dr.E.THERANIRAJAN M.D., DCH., MRCPCH (UK).,FRCPCH (UK).,** Dean Madras medical college for permitting me to conduct this study.

I am very grateful to **Prof. Dr.R.MALARVIZHI M.S.,DO** Director and superintendent (I/C), RIO&GOH,Chennai, for helping me conduct the study.

I express my gratitude to **PROF Dr. M.R.CHITRA** Guide and Unit chief, Department of Glaucoma services who with her vast knowledge and experience assigned me the topic of study and provided me all the necessary facilities and guidance

I am grateful to **Prof Dr.M.R.CHITRA MS.** and **Prof Dr.SHARMILA.N MS FICO,** Assistant Professors **Dr.MOHAN.K MS, Dr.VIMALA.T MS, Dr.SARANYA.V MS** for rendering their valuable advice and guidance for the study.

I wish to express my sincere thanks to all the **Professors**, **Assistant Professors** and all my c**olleagues** and my **family** who helped me in bringing out this study.

Finally I am indebted to all my **patients** for their sincere co-operation for the completion of this study.

CONTENTS

PART I

INTRODUCTION

An Overview of Glaucoma

HISTORICAL BACKGROUND

Although our modern understanding of glaucoma dates back to the 19th century, this group of disorders was apparently recognized by the Greeks as early as 400 BC.Hippocrates described it as “Glaucosis” , in reference to the bluish-green hue of the affected eye [1].

SIGNIFICANCE OF GLAUCOMA

Glaucoma is one of the leading causes of irreversible blindness throughout the world. World Health Organization statistics, published in 1995, stated that glaucoma accounts for blindness in 5.1 million persons (13.5% of global blindness)[1].

Glaucoma is a large group of disorders, which is characterized by diverse clinical and histopathologic manifestations.

PSEUDOEXFOLIATION

Pseudoexfoliation syndrome (PXF) is the most common identifiable cause of open-angle glaucoma worldwide. It is an age-related, generalized disorder of the extracellular matrix, an elastic microfibrillopathy, characterized by progressive production and deposition of abnormal fibrillar material in many ocular and extraocular tissues.

Theobald called it pseudoexfoliation to distinguish from true exfoliation, which is the delamination of the lens capsule seen in glass blowers. Other names include senile exfoliation of the lens capsule, senile uveal exfoliation, fibrillopathia epitheliocapsularis and glaucoma capsulare (when associated with glaucoma).

Pseudoexfoliation glaucoma is a form of secondary open angle glaucoma which has increased resistance to medical management and has increased risk of intraoperative complications, hence making it a distinct entity from primary open angle glaucoma.The ocular findings are only the tip of the iceberg and the implications of this disorder are far more than what meets the eye.

AGE OF ONSET : There is an increase in prevalence of Pseudoexfoliation syndrome with increasing mean age, with maximum in the seventh to ninth decades of life.

GENDER : Women have predominated in some series of PXF without glaucoma. Others have found equal or greater prevalence in men.PXF increases the risk of glaucoma four fold in both sexes with no difference in mortality

PSEUDOEXFOLIATION AND GLAUCOMA

Pseudoexfoliation syndrome may be associated with open angle glaucoma, ocular hypertension and angle closure glaucoma. The prevalence of glaucoma in patients with pseudoexfoliation syndrome is reported to be 0 to 93 percent. The risk of developing glaucoma in patients with pseudoexfoliation syndrome is 5 to 10 times more, than in those without it. Elevated intraocular pressure is noted in about 25 percentage of patients with pseudoexfoliation syndrome. One-third of these patients develop glaucoma.It is important to distinguish POAG from pseudoexfoliation glaucoma as it has significant clinical implications. Worse prognosis and more serious course is expected out of eyes with pseudoexfoliation glaucoma, often requiring surgical intervention.

RISK OF GLAUCOMA WITH TIME : 5 percent of patients with pseudoexfoliation syndrome develop glaucoma within 5 years and 15 percent experience raised IOP after 10 years. Hence the presence of pseudoexfoliation may be a red flag for the development of glaucoma in

the future.There may be episodes of IOP spikes noted in pseudoexfoliation syndrome which may not be manifested on a single IOP record.

RISK FACTORS FOR CONVERSION FROM PSEUDOEXFOLIATION SYNDROME TO EXFOLIATION GLAUCOMA

- ✧ Increased intraocular pressure
- ✧ Presence of pseudoexfoliation material in the angle
- ✧ Presence of pseudoexfoliation material in the other eye
- ✧ Decreased pupillary dilatation
- ✧ Increased trabecular meshwork pigmentation.

THEORIES OF PATHOGENESIS :

Amyloid Theory : There was an initial positive labelling of pseudoexfoliation material (XFM). with crude antiamyloid serum suggesting of amyloid deposits.Other tests however yielded negative results. Thus this theory could not be substantiated.[1]

Basement Membrane Theory A frequent association of pseudoexfoliative material with basement membranes of various cell types was observed. This may suggest a disturbed basement membrane metabolism as a possible mechanism. Immunohistochemical studies revealed the presence of basement membrane epitopes like laminin,

heparin sulfate proteoglycan in the aggregates of pseudoexfoliation material.[1]

Elastic Microfibril Theory This theory was based on the frequent structural association of PXF with components of the elastin system like zonules. Marked localized elastosis of the elastic fibers in lamina cribrosa has also been seen. Immunohistochemical demonstration of epitopes of elastin further support this theory[1]. Both the basement membrane and elastic microfibril theories appear to describe part of the pathological process.The prevalence of infectious origin of pseudoexfoliation material in both the partners of married couples and reports of young patients developing pseudoexfoliation syndrome following intraocular surgery or ocular trauma suggested the possibility of an infectious origin.Increasing number of younger patients developing pseudoexfoliation syndrome after penetrating keratoplasty with grafts taken from elderly donors also suggested an infectious origin. However no conclusive evidence is available.

Current concept pseudoexfoliation syndrome is currently described as a type of stress induced elastosis. It is an elastic microfibrillopathy associated with excessive production of elastic microfibrils by a variety of elastogenic cells[1]. These microfibrils subsequently aggregate into typical pseudoexfoliative fibrils. A complex cross linking process is involved in the formation of the pseudoexfoliation material. Growth

factors especially TGF beta1 and oxidative stress factors are also involved. Other extracellular matrix components, e.g. basement membrane components and glycosaminoglycans may interact and become incorporated into the exfoliation material. Frequent association of XFM with defective basement membranes of various cell types and immunohistochemical evidence of basement membrane epitopes suggest disturbed basement membrane metabolism. An imbalance between MMP and TIMP may be responsible for the incomplete degradation of the newly formed material resulting in accumulation within tissues with deleterious effects over time.

ETIOLOGY AND PATHOGENESIS:

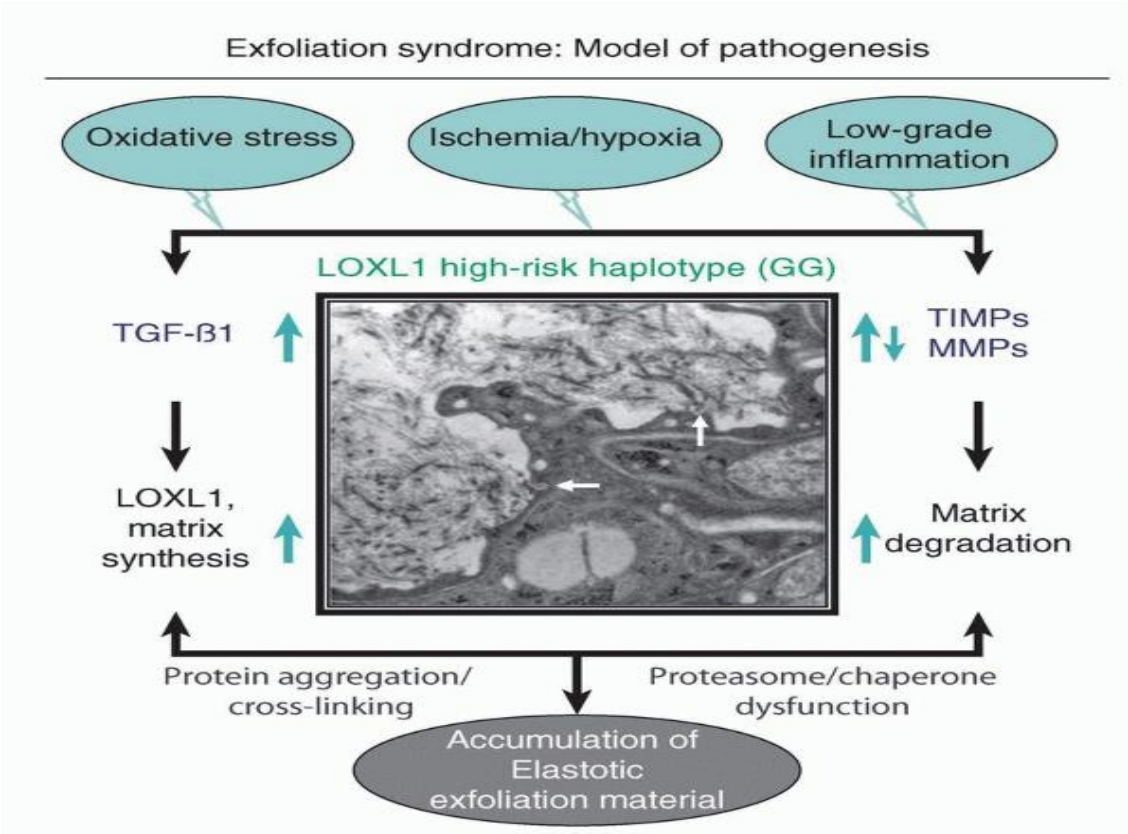


Fig 8 showing pathogenesis of PXF

The ultrastructural appearance of exfoliation syndrome is that of random 10 to 12 nm fibrils, arranged in a fibrillogranular matrix and occasionally coiled as spirals . Evidence supports the concept that exfoliation is an inherited microfibrillopathy involving transforming growth factor-1, oxidative stress, and impaired cellular protection mechanisms as key pathogenetic factors . In a landmark study in the Icelandic and Swedish populations, a common genetic variant was identified as a major risk factor for exfoliation syndrome and glaucoma . Polymorphisms in the coding region of LOXL1 located on chromosome

15q24 are associated with exfoliation syndrome and exfoliative glaucoma in these and other populations. The disease-associated polymorphisms are found in virtually all individuals with exfoliation syndrome in the studied populations. LOXL1 is one of many enzymes essential for the formation of elastin fibers: It plays a role in modifying tropoelastin, the basic building block of elastin, and catalyzes the process for monomers to cross-link and form elastin . Mice lacking LOXL1 protein have diffuse elastic tissue changes associated with tropoelastin accumulation, including pelvic organ prolapse, enlarged airspaces of the lung, loose skin, and vascular abnormalities .

Although LOXL1 is a major risk factor for exfoliation syndrome and exfoliative glaucoma, strong evidence suggests that additional genetic or environmental factors will be identified that influence disease expression and severity. For example, despite similar prevalences of LOXL1 risk variants, the clinical prevalence of exfoliation syndrome is ninefold lower in a white population from Australia compared with whites in Iceland . Nevertheless, the finding of LOXL1 involvement will provide critical insights into the pathophysiology of exfoliation syndrome, providing an opportunity for novel treatment approaches. Since the disease-associated LOXL1 variant is commonly found in both affected and unaffected individuals, genetic testing is of limited clinical value at this time

OCULAR AND SYSTEMIC SOURCES

Exfoliative material is produced by many cell types in the anterior segment, including lens capsule epithelium, iris epithelium, vascular endothelium, corneal endothelium, and Schlemm canal endothelium. The material has also been found in extrabulbar tissue, including the conjunctiva , which appears to be another independent source of the material. This has been demonstrated in conjunctival biopsies of eyes that did not have the typical clinical appearance of exfoliative material on the anterior lens capsule but were suspected on the basis of other signs, such as pigment dispersion and iris transillumination defects . Other extrabulbar sites where exfoliative material has been identified include extraocular muscles, orbital septa, posterior ciliary arteries, vortex veins, and central retinal vessels passing through the optic nerve sheaths .

The exfoliative material has also been demonstrated in tissues throughout the body of patients with the exfoliation syndrome, including lung, heart, liver, gallbladder, skin, kidney, and cerebral meninges . LOXL1 is one of a family of lysyl oxidase enzymes essential for the formation of elastin fibers. It has an important role in modifying tropoelastin, the basic building block of elastin, and catalyzing process for monomers to cross-link and form elastin. TE, tropoelastin. suggesting a systemic process involving generalized abnormal elastin metabolism.

CLINICAL FEATURES

EARLY FEATURES: The classical picture of flakes or dandruff like deposits on the anterior surface of lens represents, the late stage of the disease, which is preceded by a chronic, preclinical course.Early subtle signs can be missed easily. They could be present in the absence of a raised IOP or full marked features and may be detected by careful evaluation of a dilated eye. One should keep in mind that pseudoexfoliation syndrome is essentially bilateral with marked amount of asymmetry.

The Most Striking Early Features

THE PUPILLARY MARGIN: Presence of pseudoexfoliation material on the pupillary margin giving the first clue, even before dilation . In a small pupil, the pseudoexfoliation material may be hidden behind the pupillary margin. It is detected by gonioscopy in such cases by looking under the pupillary margin.

THE LENS (PRECAPSULAR STAGE): Commonly a precursor of exfoliation deposits. A homogenous, uniform or ground glass appearance of the anterior surface of lens when compared to the other eye is seen.

These early changes can be visualised by direct illumination by placing a slit of beam at 45 degree to the axis of observation on slit lamp , with a dim light light source,focussing temporally to highlight the deposits on the lens surface.

The fellow eyes of unilateral cases are called ‘exfoliation suspects’, if there is signs of pigment dispersion and loss of pupillary ruff without any clinically detectable pseudoexfoliation material .

VASCULAR: The lumen of blood vessels in the iris is often narrowed and may become obliterated. In advanced stages, the vascular wall cells degenerate completely.

Fluorescein angiographic studies have shown partial occlusion of radial iris capillaries associated with hypoperfusion, microneovascularization, a reduced number of vessels, and diffuse, patchy fluorescein leakage, especially in the pupillary region. Indocyanine green angiography provides better recognition of iris hypoperfusion and anastomotic vessels.

Blood Aqueous Barrier Fluorescein angiography studies demonstrated impairment in the blood aqueous barrier[1]. This is primarily localized to the iris and to some extent to the ciliary body. The impairment has a direct bearing on the early postoperative period making these eyes more prone to a transitory fibrinoid reaction. It may also lead to formation of posterior synechiae, pupillary block glaucoma and neovascularization of the iris (NVI).

PUPIL : Eyes with PXF dilate poorly. The pupil might be smaller in the the involved eye as compared to the uninvolved eye. And the constriction with pilocarpine is also lesser. This can be attributed to fibrotic and degenerative changes in the iris sphincter and dilator muscles. This is

significant during the surgical management. The pseudoexfoliation material can be noted on the pupillary margin with loss of puplillary ruff.

PXF predisposes to the formation of posterior synechiae even in the absence of miotic therapy. This is due to an impaired blood aqueous barrier. A profuse pigment release from the posterior pigment epithelium followed by a marked IOP rise is seen 1 to 2 hours after pupillary dilatation. Thus it is an ideal practice to check intraocular pressure postdilatation especially in already compromised eyes with glaucomatous damage.

CORNEA : Flakes of exfoliative material and pigment accumulation may be seen on the corneal endothelium , scattered diffusely or in the form of a vertical spindle similar to the Krukenberg spindle in pigmentary glaucoma.The central corneal thickness is also increased in eyes with PXF reflecting early corneal dysfunction

Specular microscopy of the corneal endothelium has revealed a significantly lower-than-normal cell density in eyes with the PXF and changes in cell size and shape. These findings may also be observed in the unaffected eye of unilateral cases, leading to suggest that these corneal endothelial changes might serve as an early sign of the disorder.

Ultrastructural studies have revealed clumps of exfoliative material adhering to the corneal endothelium and incorporated into the posterior

Descemet membrane, which indicate that the exfoliative material was formed by degenerative endothelial cells . It has been suggested that corneal endotheliopathy in exfoliation syndrome can give rise to an appearance like guttata but is distinct from Fuchs endothelial corneal dystrophy or pseudophakic bullous keratopathy or aphakic bullous keratopathy. Exfoliation syndrome endotheliopathy differs from Fuchs endothelial corneal dystrophy in that the former typically has less and more diffusely distributed guttata like structures and is associated with more melanin dispersion in the anterior segment and peripupillary iris atrophy.There may be association with climatic droplet keratopathy has been observed and lattice degeneration of the cornea

Exfoliation Material and Pigment Flakes of exfoliation material may be present on the endothelium. A diffuse, nonspecific pigmentation of the central endothelium may be seen, having the pattern of a Krukenberg spindle. Corneal endothelial changes may help in early diagnosis, especially in fellow eyes of presumed ‘unilateral cases’ in asymmetric cases. It is also important to assess these endothelial changes preoperatively as they affect the outcome of the surgery

Clinical and histopathologic evidence of a distinct type of keratopathy in pseudoexfoliation syndrome, which is different from Fuchs' endothelial dystrophy has been observed. It is characterized by a diffuse, irregular thickening of Descemet's membrane, focal accumulations of exfoliation material on or within Descemet's membrane, and a pronounced melanin phagocytosis by the endothelial cells. Exfoliation material may also be produced by corneal endothelial cells.

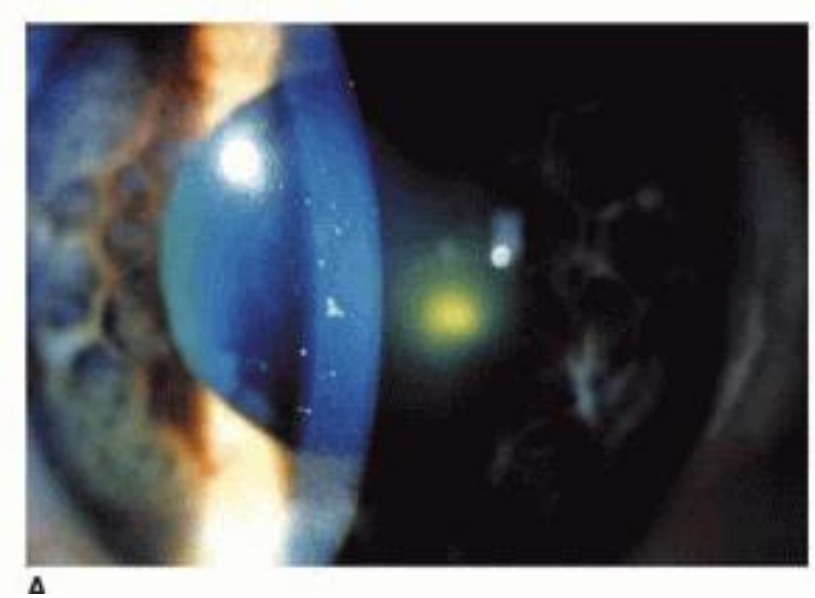


Fig 1 showing pseudoexfoliation flakes in cornea

LENS : The characteristic appearance of exfoliative material on the anterior lens capsule has three distinct zones. :

A translucent, central disc with occasional curled edges; a clear zone, probably corresponding to contact with the moving iris; and a peripheral granular zone, which may have radial striations. The central zone is absent in 20% of cases or more, but the peripheral defect is a

consistent finding, and the pupil must be dilated before the lens changes can be seen in some cases. A precapsular film has been noted on the anterior lens capsule of many older individuals, which has a ground-glass appearance and has been shown by ultrastructural studies to be a fibrillar layer similar to exfoliative material. The precapsular layer may be a precursor of the exfoliation syndrome . Cataracts occur frequently in eyes with exfoliation syndrome . This may be in part a function of the age of the patient population, cataracts in eyes with exfoliation syndrome have a higher percentage of nuclear opacities and smaller percentage of cortical and supranuclear opacities . In patients with uniocular exfoliation syndrome, the involved eye typically has the more advanced cataract. The resulting corneal endotheliopathy predisposes to early corneal endothelial decompensation at only moderate rises of IOP or after cataract surgery. Exfoliative material on the pupillary margin and the anterior lens surface seen after pupillary dilatation.

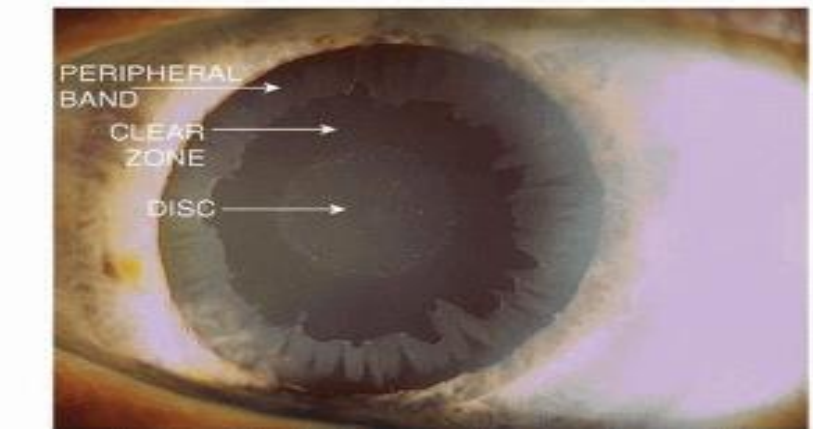


Fig 2 showing 3 zones of PXF over lens

ZONULES AND CILIARY BODY : Exfoliative material may be detected earliest on the ciliary processes and zonules . In patients with apparently unilateral exfoliation syndrome, cycloscopy reveals exfoliative material on the ciliary processes, zonules, or both in 77% of fellow eyes in which exfoliative material was not clinically visible on the lens surface or pupillary border . By using gonioscopy, exfoliative material can be observed on ciliary processes through a patent basal iridectomy. Involvement of the zonules can lead to lens subluxation and phacodonesis . This instability of the zonules can be understood by examining exfoliation aggregates at the origin and anchorage of the zonules between nonpigmented ciliary epithelial cells and at the insertion of the zonules on the preequatorial region of the lens . In these areas, exfoliation aggregates erupt through the basement membrane and involve the zonular lamellae, producing areas of weakness. Proteolytic enzymes in the exfoliative material may facilitate zonular disintegration. These changes, lead to lens instability, need to be kept in mind for all patients with exfoliation syndrome undergoing cataract surgery

XFM deposits are present on zonules which may be frayed or broken. This explains the tendency for lens subluxation. The process continues over time, even after cataract surgery and IOL implantation and may lead to late decentration, subluxation or dislocation of posterior chamber intraocular lens.

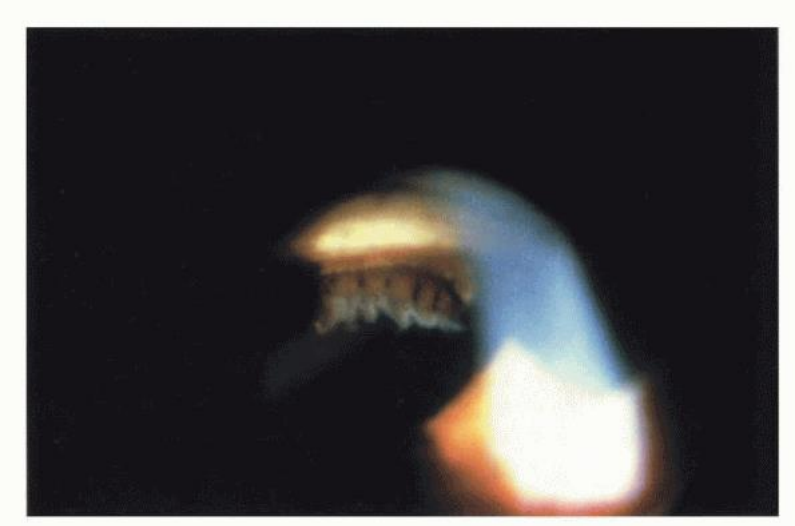


Fig 3 showing pxf material over cilairy process viewed by gonioscopy

IRIS : Exfoliative material may also be seen as white flecks on the pupillary margin of the iris, with loss of pigment at the pupillary ruff. Iris transillumination typically reveals a moth-eaten pattern near the pupillary sphincter, and many patients also have diffuse midperipheral transillumination defects. Light and scanning electron microscopy demonstrate exfoliative material on the posterior surface of the iris. Fluorescein angiographic studies of the iris have revealed hypoperfusion, peripupillary leakage, and neovascularization. These findings are more pronounced with increasing age of the patient, longer duration of the disease, and the presence of glaucoma, and they may represent secondary features of the disease. Ultrastructural studies suggest that vascular abnormalities or abnormal extracellular matrix production causes tissue hypoxia.Conversely, it has been observed that eyes with transient ischemic attacks have an increased incidence of abnormal iris

transillumination and exfoliative material, suggesting that hypoperfusion may be a contributory factor in the development of the exfoliation syndrome .Whether a primary or secondary feature, the iris hypoxia is associated with atrophy of the iris pigmentepithelium, stroma, and muscle cells . Atrophy of the pigment epithelium may be associated with anterior chamber melanin dispersion, which may be seen as a whorl-like pattern of pigment particles on the iris sphincter and pigment deposition on the peripheral iris, whereas atrophy of the muscle cells may account for the poor mydriasis, which is also a typical finding in the pseudoexfoliation syndrome .

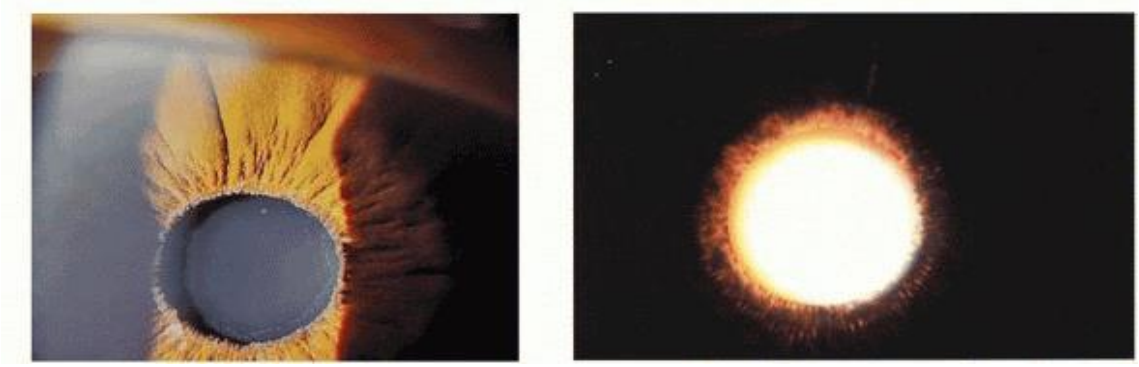


Fig 4 showing PXF material over pupillary border and transillumination defect

ANTERIOR CHAMBER ANGLE : The exfoliation syndrome is associated with excessive pigment dispersion, which leads to increased trabecular meshwork pigmentation. Increased trabecular pigmentation is a prominent sign seen on gonioscopy. The pigmentation is typically patchy in contrast to the homogeneous mascara line seen in pigment dispersion

syndrome and may be associated with flecks of XFM. It may be an early diagnostic sign preceding the development of XFM on the lens or iris. It is denser in the involved eye in unilateral cases. A strong correlation appears to exist between elevated IOP and the degree of trabecular meshwork pigmentation.. XFM may be seen in the angle. An accumulation of pigment may also be seen along the Schwalbe line, which has been termed the Sampaolesi line . In eyes with marked asymmetry of trabecular meshwork pigmentation, glaucoma is more common in the more pigmented eye. However, increased pigmentation of the trabecular meshwork has also been observed in the fellow eye without apparent exfoliation syndrome, and it has been suggested that this may be the earliest detectable sign of exfoliation syndrome. Although the anterior chamber depth is normal in most eyes with the exfoliation syndrome, the anterior chamber angle is occludable in a high percentage of cases . The latter cases typically have a shallow central and peripheral anterior chamber depths. Narrow angle is present in some patients

Ultrastructural studies indicate that there is active exfoliation production in the trabecular meshwork, Schlemm canal, and collector channels, as well as passive deposition of exfoliative material within intertrabecular spaces. The progressive accumulation of the exfoliative material leads to swelling of the juxtacanalicular meshwork and gradual narrowing and disorganization of the Schlemm canal architecture in

advanced cases. Occasionally, proliferating and migrating corneal endothelial cells produce a pretrabecular sheet of abnormal extracellular matrix that covers the inner surface of the uveal meshwork.

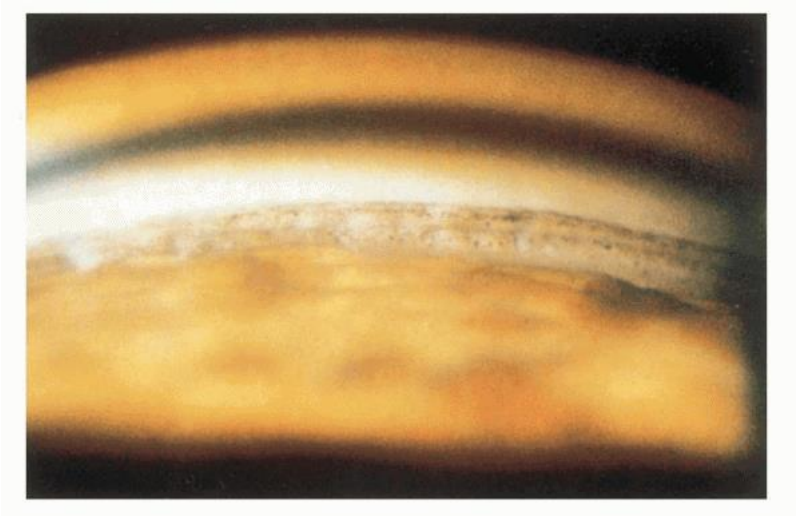


Fig 5 : showing PXM over angle structures viewed by gonioscopy

OPTIC NERVE HEAD AND RETINAL NERVE FIBER LAYER : The mean optic disc area has been reported to be smaller in eyes with PXF and pseudoexfoliative glaucoma. In eyes with pseudoexfoliative glaucoma, cupping tends to be more diffuse as compared to POAG. The percentage area of optic disc pallor in PXF patients may be greater than controls. A relatively smaller disc is diagnostically important as early changes may be easily overlooked. The RNFL has been found to be significantly thinner in PXF eyes.

OTHER SLITLAMP FINDINGS

Exfoliative material may also be seen after cataract surgery on the anterior hyaloid in aphakic eyes and on a posterior chamber intraocular lens in pseudophakic eyes.

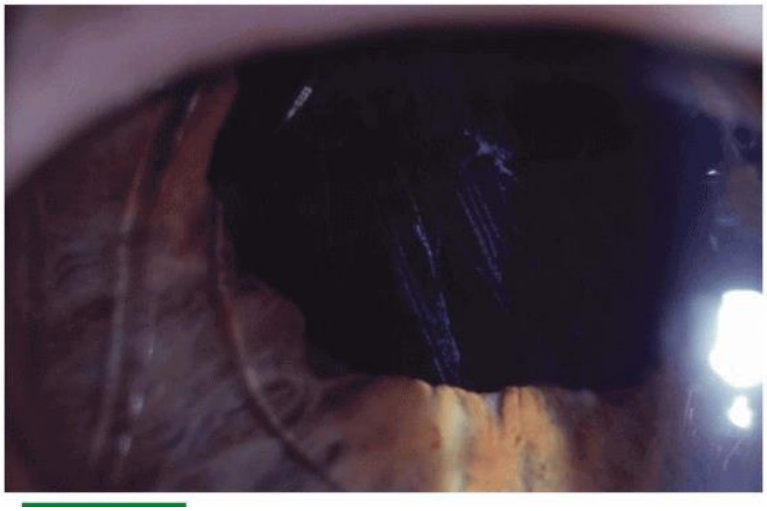


Fig 6 showing PXM in anterior hyaloid phase

ULTRASOUND BIOMICROSCOPIC FINDINGS

Ultrasonographic biomicroscopy can be a useful tool to look for the presence of exfoliation syndrome material on zonules or the peripheral lens capsule, particularly when the pupil cannot be easily dilated and the diagnosis of exfoliation syndrome is uncertain

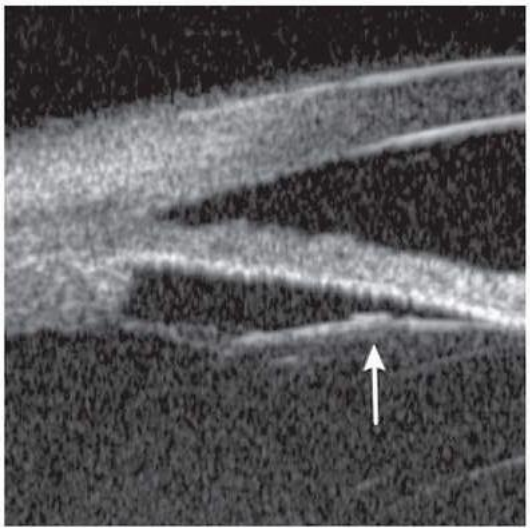


Fig 7 UBM showing zonular weakness and breakage

CLINICAL FEATURES OF ESTABLISHED PXF :

Exfoliation material (XFM): The hallmark of exfoliation syndrome is the appearance of a white, flaky dandruff like material on the anterior lens capsule in a characteristic pattern. XFM can be seen on the iris, corneal endothelium, anterior lens surface, lens zonules and ciliary processes.

EXFOLIATION GLAUCOMA :

Studies indicate about 40% of exfoliation syndrome patients will develop glaucoma

Exfoliation glaucoma (XFG) is a secondary open angle glaucoma occurring due to the deposition of exfoliative material in the trabecular meshwork. It mimics primary open angle glaucoma in many forms and may go undetected many times. Yet it is a distinct entity and it is

important to differentiate the two. Recognition requires a meticulous examination. It is a systemic disorder with important eye manifestations, including development of open- and closed angle glaucoma and of cataract with zonular instability . It may also be associated with increased systemic risk of cardiovascular disorders

Exfoliation syndrome is the most common identifiable cause of open-angle glaucoma worldwide . It is a systemic disorder with important eye manifestations, including development of open- and closed angle glaucoma and of cataract with zonular instability .It may also be associated with increased systemic risk of cardiovascular disorders

When open angle glaucoma is encountered with considerable cupping, elevated IOP, field loss in one eye with no evidence of glaucoma in the other eye, the most common finding is exfoliative material in the affected eye. The clinical importance is that exfoliative open angle glaucoma is more likely to go out of control, with more inter visit spikes and requires faithful and frequent follow ups. Early failure of medical therapy and late failure of laser trabeculoplasty is common . PXF glaucoma is more aggressive with worse prognosis .Shows higher mean IOP associated with more diurnal fluctuations with marked pressure spikes ,Marked optic nerve damage, Rapid visual field loss and poor

response to medications ,Frequently needing surgical intervention . Postmydriasis IOP spikes is also present.

HISTOLOGICAL: TM essentially normal except for the deposition of XFM . Surgery is associated with an increased risk of intra and early postoperative complications. 'Normal Tension' Exfoliation Glaucoma Pressure-independent risk factors may contribute to glaucomatous changes of the optic nerve head. A higher maximum IOP level, a greater IOP fluctuation within normal range could be significant risk factors for development of glaucomatous optic nerve head(ONH) changes in eyes with exfoliation in the presence of a normal pressure. Non-IOP dependant factors include impaired ocular and retrobulbar perfusion and abnormalities of elastic tissue of the lamina cribrosa. This is supported by the ultrastructral and immunohistochemical demonstration of the exfoliation fibers in the vortex veins, ophthalmic artery, central retinal vein and iris stroma. Iris neovascularization and patchy occlusion of normal iris vasculature has been observed. Significant hemodynamic alterations in retrobulbar, ONH and peripapillary vasculature have been noted. In addition, a widespread elastosis of the vessels has been seen. The disturbed autoregulation related to microvascular alterations or changes in lamina cribrosa might result in an increased vulnerability with minor pressure changes within normal IOP ranges. The exfoliative

process as a risk factor for optic disc changes independent of IOP Normotensive eyes with exfoliation should also be followed up on a regular basis .Higher maximum IOP levels and greater IOP fluctuations may be valuable indicators for upcoming glaucomatous damage. Acute Open Angle Glaucoma, Dispersion of pigment granules and XFM in the anterior chamber is common after diagnostic pupillary dilation and may lead to marked rise in IOP sometimes causing diffuse corneal edema producing a deceptive clinical picture of acute primary angle closure glaucoma. Such pressure peaks may even mimic acute pupillary block with a red eye, corneal edema, pressure rise of more then 50 mm Hg in spite of an open angle. There is a positive correlation between the degree of IOP rise and pigment release, both reaching a maximum two hours following mydriasis and going back to normal after 12 to 24 hours. It is important to distinguish it from acute angle closure as a peripheral iridotomy may worsen the situation by increasing the pigment load. In rare cases, spontaneous subluxation of the lens into vitreous may induce a phacolytic glaucoma.

PXF AND ANGLE CLOSURE GLAUCOMA:

A less-common mechanism of glaucoma in patients with the exfoliation syndrome is acute or chronic angle-closure glaucoma . A number of mechanisms may create a tendency toward pupillary block and

angle closure, including zonular weakness, causing anterior movement of the lens;lens thickening from cataract formation; increased adhesiveness of the iris to the lens (occasionally with posterior synechiae) due to exfoliative material, sphincter muscle degeneration, and uveitis; and iris rigidity from hypoxia. Patients with exfoliation syndrome predisposed to angle closure may have a relatively small anterior segment despite normal axial length. These eyes as mentioned earlier may have a narrow anterior chamber angle, smaller anterior chamber volume, especially in prone position along with a minimal subluxation of lens which predisposes to pupillary block. A rigid iris also contributes to the development of angle closure glaucoma. These eyes tend to be more myopic in the presence of a normal axial length due to a forward shift in the lens or a progression of nuclear sclerosis. Other mechanisms for angle closure glaucoma include formation of posterior synechiae due to a deranged blood aqueous barrier leading to pupillary block and neovascularization of the iris. In rare cases, aqueous misdirection syndrome can occur due to marked zonular laxity and anterior subluxation of lens and marked contraction of the ciliary muscles.

PXF AND NEOVASCULAR GLAUCOMA:

Neovascular Glaucoma CRVO is more common in patients with exfoliation. Thus neovascular glaucoma can occur . Patients with

diagnosed exfoliation glaucoma and open angle may develop a superimposed angle closure with the passage of time as the zonular weakness increases. This emphasizes the need for a regular gonioscopy especially if the glaucoma is progressing. A laser iridotomy may be useful in such a situation.

PXF AND PIGMENTARY GLAUCOMA :

Exfoliation glaucoma has been known to occur in patients with pigmentary glaucoma and cause a rapid progression in these cases.

COURSE OF GLAUCOMA

The presence of exfoliative material in the eye is a major risk factor for conversion to glaucoma in patients with ocular hypertension. Exfoliation syndrome is also a risk factor for progression in patients with established glaucoma. Not all patients with the exfoliation syndrome develop glaucoma, and reports vary considerably regarding the frequency of glaucoma in eyes with this condition. In one study of patients with the exfoliation syndrome without glaucoma on initial examination, one third developed glaucoma during a 1.5-year follow-up. Some patients with bilateral exfoliation syndrome have glaucoma in both eyes, but others have a pressure rise in only one of the eyes with exfoliation. Less commonly, a patient with unilateral exfoliation may have open angle

glaucoma in both eyes. Most eyes with exfoliative glaucoma have an open-angle mechanism, although acute angle-closure glaucoma also occurs in a small number of cases. It is not uncommon for patients with the exfoliation syndrome to have an acute onset of high intraocular pressure (IOP) in the presence of open angles. The observation that glaucoma does not develop in all eyes with the exfoliation syndrome but may develop in both eyes of a patient with unilateral exfoliation has led to the theory that exfoliative glaucoma and chronic open-angle glaucoma (COAG) may share similar mechanisms of aqueous outflow obstruction . However, the much greater incidence of glaucoma in eyes with exfoliation syndrome is thought to indicate a causal relationship between the abnormal material and the elevated IOP. Patients with exfoliation syndrome do not have the same response to topical corticosteroids as patients with COAG do . Furthermore, although some lysyl oxidase-like 1 gene (LOXL1) variants predispose to exfoliative glaucoma, they do not appear to be associated with COAG . It therefore appears that exfoliative glaucoma represents a distinct form of glaucoma, but it may be superimposed on COAG in some patients. Mechanisms of IOP elevation in exfoliative glaucoma associated open angles may include local production of exfoliative material, endothelial cell damage of the trabecular meshwork, and passive deposition of exfoliative material and pigment originating from elsewhere in the anterior segment.Once open-

angle glaucoma has developed in an eye with exfoliation, the IOP tends to run higher and may be more difficult to control than in cases of COAG . It has also been observed that the probability of developing glaucomatous optic neuropathy is higher in eyes with exfoliative glaucoma than in other forms of glaucoma at similar IOP levels , suggesting an intrinsic vulnerability in the optic nerve in the former group. Although disc area and other morphometric features of the optic nerve head do not differ between nonglaucomatous eyes with and without exfoliation , glaucomatous neuroretinal rim damage tends to be more diffuse with exfoliative glaucoma

ACUTE INCREASES IN INTRAOCULAR PRESSURE

Patients with exfoliation syndrome and open angles may present with acute glaucoma mimicking angle closure glaucoma (i.e. a red eye, corneal edema, and IOP often >50 mm Hg) . In a study of 139 cases of "acute" glaucoma, comprising 25% of a series of patients with exfoliation syndrome and glaucoma, 86 had open-angle glaucoma, 21 had neovascular glaucoma, and 18 had acute angle-closure glaucoma . In all the latter eyes, the anterior chamber depth was less than 2.2 mm.

MANAGEMENT

GLAUCOMA

Glaucoma associated with exfoliation syndrome can be particularly challenging to manage. IOP can fluctuate considerably, and care should be taken when setting the target pressure range. Because of higher IOP fluctuation, some choose to set a lower target IOP and follow up these patients more closely. Patients with exfoliative glaucoma typically have an excellent response to prostaglandin analogues and laser trabeculoplasty, particularly argon laser trabeculopexy. When incisional surgical intervention becomes necessary, filtering surgery is generally advocated. One study suggested that exfoliative glaucoma has a poorer response to medical therapy than COAG but that it has a better response to trabeculectomy. Cataract surgery may also decrease the IOP in patients with exfoliation syndrome and exfoliative glaucoma

CATARACT

Although lens extraction is not advocated for the management of exfoliative glaucoma, cataract extraction for improvement of visual acuity is frequently indicated and requires special consideration in these patients. With traditional extracapsular cataract surgery and with phacoemulsification, patients with the exfoliation syndrome have a higher-than-average risk of zonular and capsular breaks. This is most likely caused by degeneration of the zonular fibrils, but it may also be

associated with a thin posterior lens capsule . Other factors that may complicate cataract surgery in these patients are poor pupillary dilatation and occasional synechiae between the iris pigment epithelium and the peripheral anterior lens capsule . Preoperatively, the surgeon should look for evidence of zonular dialysis, such as phacodonesis and asymmetric anterior chamber depth , the corneal endothelium should also be evaluated carefully for compromise. Ultrasonographic biomicroscopy can be very helpful when trying to decide if significant zonular dialysis is present, and also to detect the presence of stretched zonules.Helpful tips for cataract surgery are to make the capsulorrhexis large so as to enable the nucleus or pieces of the nucleus to prolapse into the anterior chamber, thus minimizing zonular stress; a large capsulorrhexis also helps prevent capsular phimosis, which is common in eyes with exfoliation syndrome. During hydrodissection, care should be taken to tap on the center of the nucleus from time to time to decompress fluid pressure on a weak posterior capsule. If zonular weakness is evident intraoperatively, a capsule tension ring or capsule tension segments can be helpful. In addition to taking special care to minimize zonular stress during nucleus manipulation and removal of the cortex, if the pupil size is small, the surgeon should consider mechanically dilating and maintaining pupil dilatation.The use of a posterior chamber intraocular lenses is well

tolerated in patients with the exfoliation syndrome, although there may be a greater risk for fibrinoid reaction in these patients .

KEY POINTS

Exfoliation syndrome is an inherited microfibrillopathy associated with polymorphisms in LOXL1. It is generally recognized by the typical appearance of exfoliative material on the anterior lens capsule and is a relatively common disorder in older individuals among many populations worldwide. It is characterized by a protein-like material on the lens, iris, and various other ocular and extraocular structures. It is a major risk factor for development of open-angle glaucoma and, in some cases, angle-closure glaucoma. The condition may be unilateral or bilateral, and about 40% of patients with exfoliation syndrome may have associated glaucoma. Early recognition and appropriate management are essential to good outcomes. Early signs of exfoliation syndrome include a light frosting of material on the lens capsule best seen with a dilated pupil, heavy (often irregular) pigment in the trabecular meshwork, and visualization of exfoliative material on the zonules or ciliary body. Ocular manifestations associated with exfoliation syndrome include glaucoma, cataract, zonular and lens capsule weakness, poor pupillary dilatation, blood-aqueous barrier breakdown, corneal endothelial decompensation, and retinal vein occlusion.

Any patient with exfoliation and a shallow peripheral and central anterior chamber depth should have gonioscopy and be evaluated for a prophylactic peripheral iridotomy.

When contemplating cataract surgery in a patient with exfoliation syndrome, check the status of the lens zonules (i.e., examine for presence of phacodonesis or lens subluxation).

GOLDMANN APPLANATION TONOMETER

PRINCIPLE :

Goldmann modified Maklakoff-Fick law, referred as the Imbert-Fick law . This law states that an external force (W) against a sphere equals the pressure in the sphere (Pt) multiplied by the area flattened (applanated) by the external force (A) [1]

W=Pt X A

SOURCES OF ERROR :

Tonometry has potential sources of error .

- ✧ The appropriate amount of fluorescein is important because the width of the semicircle meniscus influences the reading.
- ✧ Wider menisci cause falsely higher pressure estimates.
- ✧ Improper vertical alignment (one semicircle larger than the other) will also lead to a falsely high IOP estimate .

RELATION BETWEEN IOP AND CCT

The mathematical calculation for Goldmann applanation tonometry is based on a presumed average CCT of 520 µm. Deviations from the average CCT are a source of error with cornea edema underestimating the true IOP, whereas variations of CCT in normal corneas can lead to falsely higher pressure readings with thicker corneas and falsely lower ones with thinner corneas. Individuals in the Ocular Hypertension Treatment Study (OHTS) had a mean CCT of 573.0 ± 39.0 µm, and 24% of the OHTS cohort had a CCT greater than 600 µm . Patients with normal-tension glaucoma have thinner mean CCTs of 514 to 521 µm.This variance of CCT and its effect on the accuracy of IOP measurements raised questions as to what correction factor for the adjusted IOP measurement should be used when the CCT deviates from the assumed average, 520 µm.

Ehlers and colleagues have published a table in which the average error is 0.7mm Hg per 10 µ of deviation from the mean of 520 µ. Another study, however, revealed a smaller error, of 0.19 mm Hg per 10 µ, which is consistent with findings of a direct cannulation study. IOP measurements with the Tono-Pen are also affected by CCT, with reported errors of 0.29 mmHg per However, there is a lack of general agreement on the correction factor that should be used for adjusting the IOP

measured by Goldmann tonometry, when the CCT deviates from the normal.

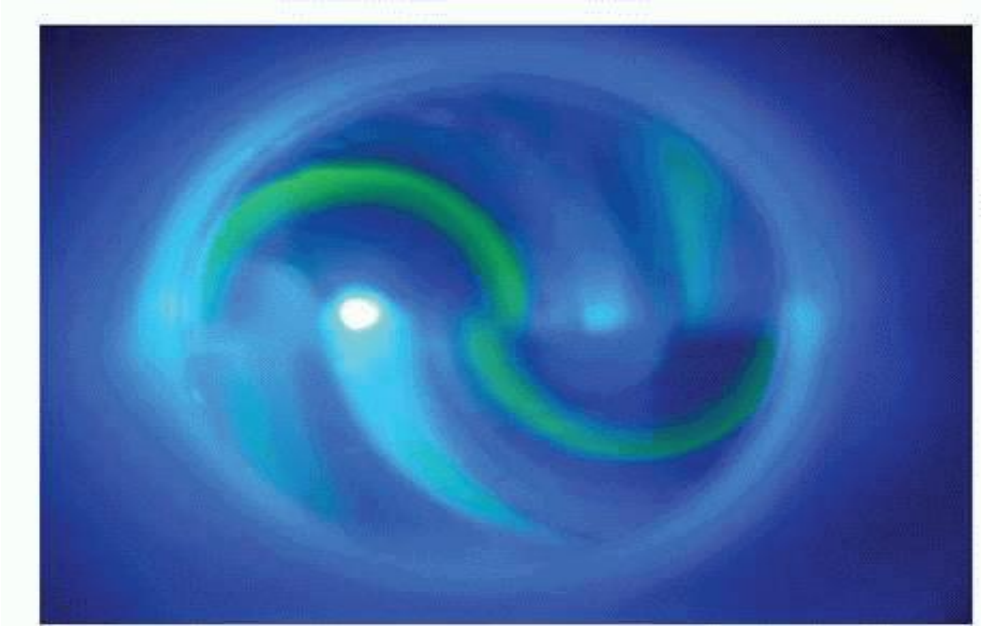


Fig 9 showing Applanation tonometer mires

DESCRIPTION OF TONOMETER

The instrument is mounted on a standard slitlamp in such a way that the examiner's view is directed through the center of a plastic biprism, which is used to applanate the cornea. Two beam-splitting prisms within the applanating unit optically convert the circular area of corneal contact into semicircles. The prisms are adjusted so that the inner margins of the semicircles overlap when 3.06 mm of cornea is applanated. The biprism is attached by a rod to a housing, which contains a coil spring and series of levers that are used to adjust the force of the biprism against the cornea

Technique

- ✧ The cornea is anesthetized with a topical preparation
- ✧ tear film is stained with sodium fluorescein.
- ✧ the cornea and biprism illuminated by a cobalt blue light from the slitlamp
- ✧ biprism is brought into gentle contact with the apex of the cornea .
- ✧ The fluorescence of the stained tears facilitates visualization of the tear meniscus at the margin of contact between cornea and biprism.
- ✧ The fluorescent semicircles are viewed through the biprism, and the force against the cornea is adjusted until the inner edges overlap .
- ✧ The influence of the ocular pulsations is seen when the instrument is properly positioned, and the excursions must be averaged to give the desired endpoint.
- ✧ The IOP is then read directly from a scale on the tonometer housing.

The staining of the tear film may be accomplished by instilling a drop of topical anesthetic and touching a fluorescein impregnated paper strip to the tears in the lower cul-de-sac or using a commercial fluorescein solution combined with a topical anesthetic. With the commercial preparations, there is potential concern with bacterial contamination . When contaminated with Pseudomonas or Staphylococcus, a fluorescein preparation with the anesthetic, benoxinate, and the preservative, chlorobutanol (Fluress), regained

sterility in the solution in 1 minute and on the dropper tip in 5 minutes, whereas sterility in preparations with proparacaine and thimerosal took at least 1 hour

SOURCES OF ERROR WITH GOLDMANN TONOMETRY

Tonometry has potential sources of error .

- ✧ The appropriate amount of fluorescein is important because the width of the semicircle meniscus influences the reading.
- ✧ Wider menisci cause falsely higher pressure estimates.
- ✧ Improper vertical alignment (one semicircle larger than the other) will also lead to a falsely high IOP estimate

DIURNAL VARIATION IN IOP

Glaucoma is especially challenging to control in patients with exfoliation syndrome. Care should be taken to set the target pressure range and follow carefully, because there is greater diurnal IOP fluctuation in exfoliative glaucoma patients, and IOP can spike out of control in a short period.Patients may require aggressive treatment and frequent, close follow-up.Various studies have shown that eyes with PXS display thinner central corneal thickness as compared to normal eyes and thin corneas are now considered as a significant risk factor for glaucoma independent of IOP. A thin cornea is an independent risk factor for glaucoma progression due to underestimation of intraocular pressure.

DIURNAL VARIATION IN CENTRAL CORNEAL THICKNESS

Diurnal variation in central corneal thickness (CCT) exists in eyes with no patholog and Keel *et al* showed this variation was higher in PXS eyes. Studies report that CCT is thickest in the morning upon awakening and decreases as the day progresses. To date, no study is reported to find the diurnal variation of CCT and IOP in PXS eyes without glaucoma in India. Assessing this variation in CCT would help in earlier detection of individuals at risk of developing pseudoexfoliation glaucoma (PXG) as a variation in CCT during the day would cause a false IOP reading. We have therefore investigated whether there is a significant CCT fluctuation among PXS eyes without evidence of glaucoma and whether this CCT fluctuation has a linear relationship with variations in IOP. This study could suggest the correct timing of IOP and CCT measurement in diagnosis of PXG and the need for a regular CCT measurement in an outpatient setting while screening PXS.

The consensus in the literature is that CCT is thickest in the morning upon awakening and gradually thins as the day progresses, with the greatest proportion of this variation occurring in the 3 h after awakening. More recent studies on individuals with no ocular pathology, and those with glaucoma, who have explored daytime (circadian) variations in CCT and its relationship to the circadian variations in IOP have not been in agreement of the importance of regular CCT

examination. To date, no study has assessed the diurnal variation of CCT in PXF eyes without glaucoma which could prove pivotal so that the timing of glaucoma diagnosis for an individual is not overlooked.

REVIEW OF LITERATURE

Syed *et al* conducted a study on patients with pseudoexfoliation syndrome without glaucoma. IOP by Goldmann Applanation Tonometer and CCT by ultrasonic pachymetry was measured during working hours of the day. The results showed a diurnal variation in IOP and CCT and there is a gradual drop in CCT and IOP by evening. The study also showed there existed a correlation between CCT and IOP. And its ideal to measure CCT along with IOP each time[4]

Keel *et al* ,on comparing pseudoexfoliation patients without glaucoma with normal subjects stated that ,there was significantly higher diurnal variation of CCT and IOP in pseudoexfoliation patients. Pseudoexfoliation patients also had thinner corneas thus leading to underestimated IOP hence it is important to measure CCT along with IOP[6]

PART II

AIM OF THE STUDY

1. To analyse the diurnal central corneal thickness (CCT) and Intraocular Pressure (IOP) variation in patients with Pseudoexfoliation without glaucoma.
2. To study the effect of central corneal thickness (CCT) on Intraocular Pressure (IOP).

METHODOLOGY

Design of study :

Prospective Observational study

Study Population :

70 eyes

Study centre :

Regional Institute of Ophthalmology, Government Ophthalmic Hospital, Chennai

Subject selection :

All patients above 40 years of age with pseudoexfoliation syndrome without glaucoma attending RIOGOH services are taken up for study after consent.

Inclusion criteria :

1. Patients > 40 years
2. Patients with Pseudoexfoliation Syndrome without glaucoma

Exclusion criteria :

1. Patients with elevated IOP
2. Corneal Injuries
3. Corneal Ectasia
4. Severe Dry eye and
5. Post Keratorefractive surgeries

Methods :

1. All patients attending Glaucoma Services at RIOGOH will be screened for Pseudoexfoliation.
2. The following parameters are taken: Ophthalmic history, Best corrected Visual Acuity, Slit lamp examination, Intraocular pressure by Goldmann Applanation Tonometry, and Fundus examination using 90D lens.
3. A complete glaucoma investigation (Optic nerve head exam, IOP and reliable visual fields) will be done to rule out glaucoma.
4. Patients presenting with pseudoexfoliation syndrome but with no evidence of glaucoma were included in the study.
5. A written informed consent is obtained from subjects which matched the inclusion criteria.

6. The central corneal thickness by using Ultrasonic Pachymetry and intraocular pressure by Goldmann Applanation Tonometer is measured 4^{th} hourly i.e 8 AM, 12 PM, 4 PM, 8 PM, 12 AM ,4 AM.

RESULTS

Table 1 showing mean age

	Mean Age	SD
Age (years)	62.63	6.359

In my study the mean age of presentation of the patients was 62 years (mean 62.63 years) with a variation of +/- 6 years.

Table 2 showing Gender

GENDER	NUMBER	PERCENTAGE
MALE	31	44.3
FEMALE	39	55.7
TOTAL	70	100

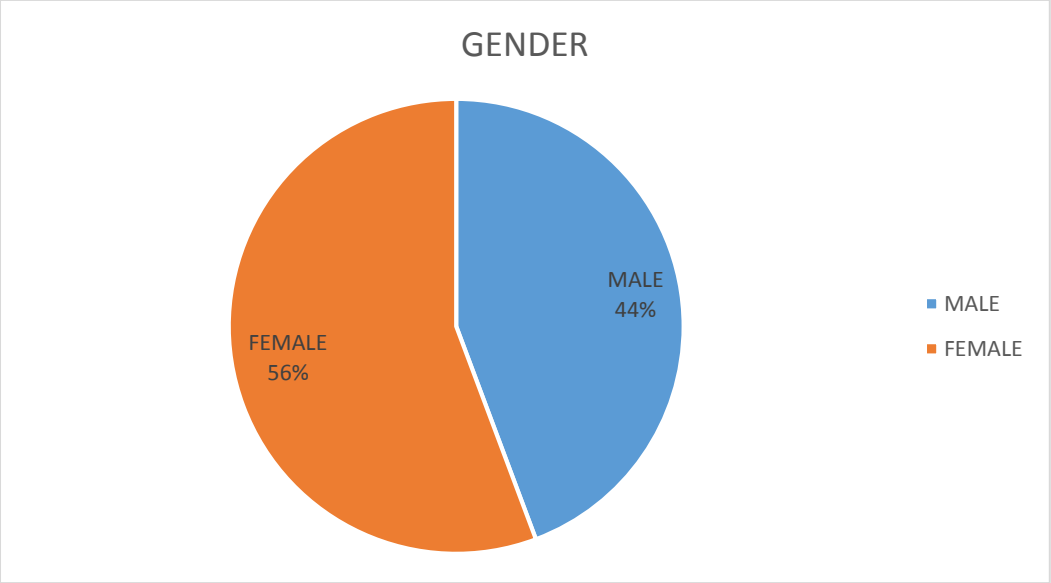


Chart 1 showing Gender

In my study 39 females were affected which constituted about 59 % showing that females are more affected by the condition.

Table 3 showing mean IOP

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
						Lower Bound	Upper Bound
IOP8AM	RE	40	16.08	2.464	0.39	15.29	16.86
	LE	30	16.07	2.196	0.401	15.25	16.89
IOP12PM	RE	40	15.3	2.151	0.34	14.61	15.99
	LE	30	15.2	2.455	0.448	14.28	16.12
IOP4PM	RE	40	13.68	2.505	0.396	12.87	14.48
	LE	30	13.9	2.339	0.427	13.03	14.77
IOP8PM	RE	40	12.8	2.604	0.412	11.97	13.63
	LE	30	12.93	2.377	0.434	12.05	13.82
IOP12AM	RE	40	11.83	2.308	0.365	11.09	12.56
	LE	30	11.8	2.172	0.397	10.99	12.61
IOP4AM	RE	40	16.65	2.537	0.401	15.84	17.46
	LE	30	16.53	2.285	0.417	15.68	17.39

From this table we infer that among a total of 40 samples of right eye we examined, the mean IOP was 16.08 at 8 AM, 15.3 at 12 PM, 13.68 at 4 PM, 12.8 at 8 PM, 11.83 at 12 AM, 16.65 at 4 AM.

Among a total of 30 samples of left eye we examined, the mean IOP was16.07 at 8AM, 15.2 at 12PM, 13.9 at 4 PM, 12.93 at 8 PM, 11.8 at 12 AM and 16.53 at 4AM.

Table 4 showing mean CCT

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
						Lower Bound	Upper Bound
CCT8AM	RE	40	532.13	10.186	1.611	528.87	535.38
	LE	30	532.4	9.547	1.743	528.84	535.96
CCT12PM	RE	40	529.42	10.31	1.63	526.13	532.72
	LE	30	529.33	9.408	1.718	525.82	532.85
CCT4PM	RE	40	526.23	10.144	1.604	522.98	529.47
	LE	30	526.87	9.786	1.787	523.21	530.52
CCT8PM	RE	40	523.5	10.368	1.639	520.18	526.82
	LE	30	524.37	9.686	1.768	520.75	527.98
CCT12AM	RE	40	521.73	10.051	1.589	518.51	524.94
	LE	30	521.97	9.817	1.792	518.3	525.63
CCT4AM	RE	40	533.95	9.915	1.568	530.78	537.12
	LE	30	534.5	9.965	1.819	530.78	538.22

From this table we infer that among a total of 40 samples of right eye we examined, the mean CCT was 532.13 at 8 AM, 529.42 at 12 PM, 526.23 at 4 PM, 523.5 at 8 PM, 521.73 at 12AM, 533.95 at 4 AM.

Among a total of 30 samples of left eye we examined, the mean CCT was 532.4 at 8 AM, 529.33 at 12 PM, 526.87 at 4 PM, 524.37 at 8 PM, 521.97 at 12 AM, 534.5 at 4 AM.

‘Table 5 showing mean IOP at various times right eye

RE	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P value
				Lower Bound	Upper Bound	
IOP8AM	16.08	2.464	0.39	15.29	16.86	0.000
IOP12PM	15.3	2.151	0.34	14.61	15.99	
IOP4PM	13.68	2.505	0.396	12.87	14.48	
IOP8PM	12.8	2.604	0.412	11.97	13.63	
IOP12AM	11.83	2.308	0.365	11.09	12.56	
IOP4AM	16.65	2.537	0.401	15.84	17.46	

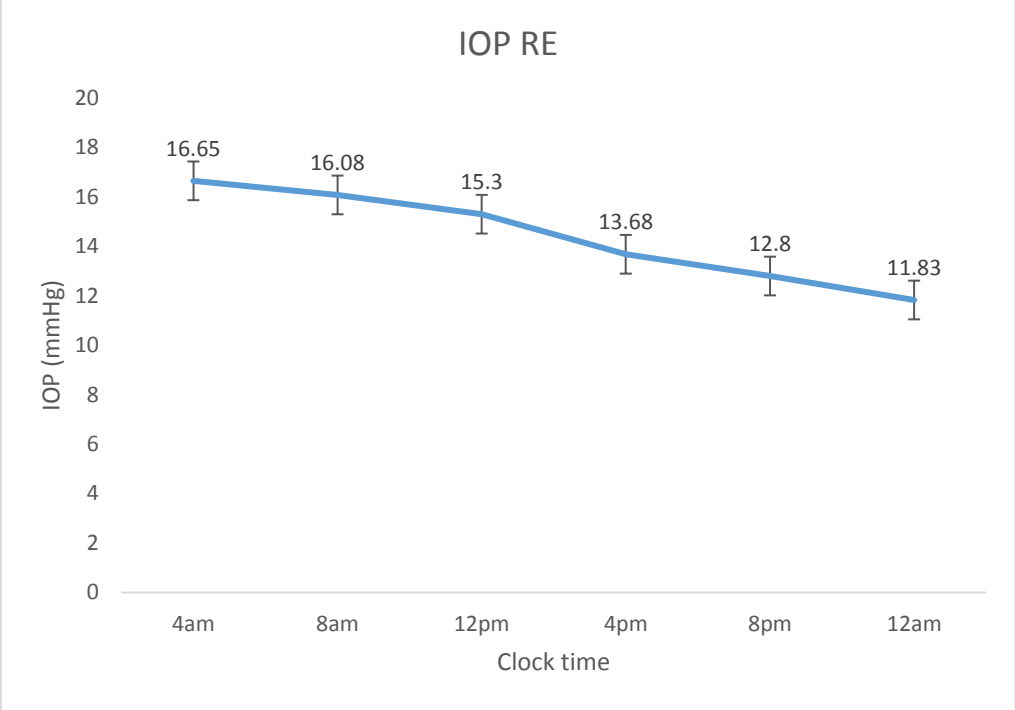


Chart 1 showing IOP at various times right eye

The study shows a gradual decrease in IOP from 16.08 at 8 AM to 11.83 at midnight 12 AM and again peaking of 16.65 early in the morning at 4 AM in the right eye.

Table 6 showing CCT at various times right eye

RE	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P value
				Lower Bound	Upper Bound	
CCT8AM	532.13	10.186	1.611	528.87	535.38	0.000
CCT12PM	529.42	10.31	1.63	526.13	532.72	
CCT4PM	526.23	10.144	1.604	522.98	529.47	
CCT8PM	523.5	10.368	1.639	520.18	526.82	
CCT12AM	521.73	10.051	1.589	518.51	524.94	
CCT4AM	533.95	9.915	1.568	530.78	537.12	

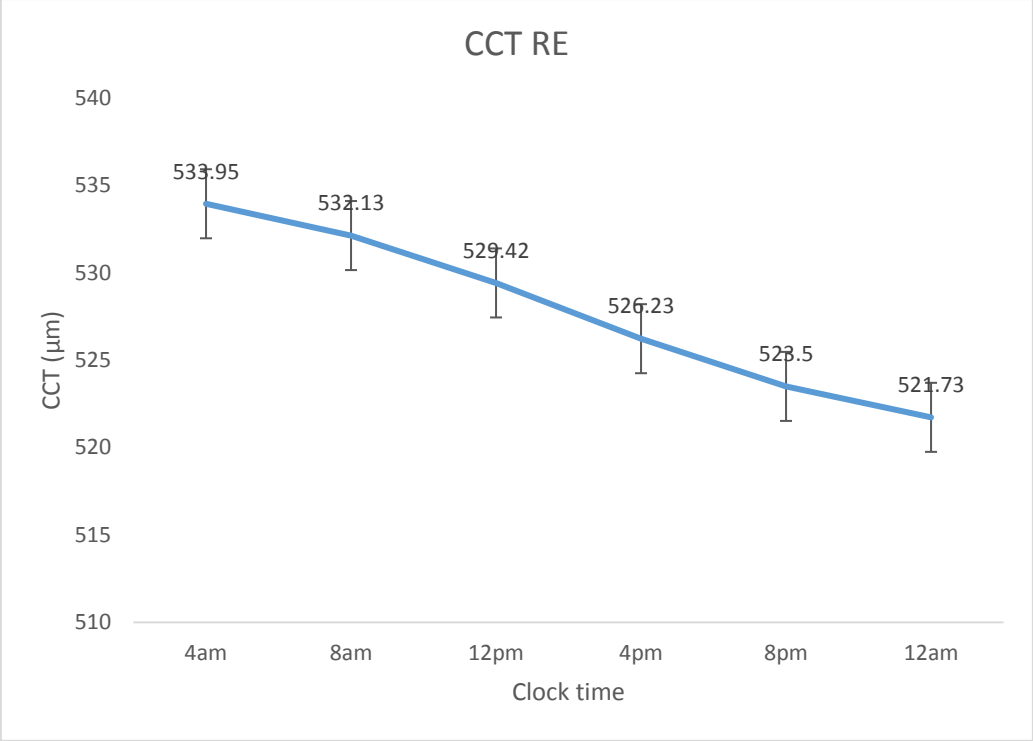


Chart 2 shows CCT at various times RE

The study shows a gradual decrease in CCT from 532.13 at 8 AM to 521.73 at midnight 12 AM and again peaking of 533.95 at early morning 4 AM in the right eye.

Table 7 showing mean IOP various times left eye

LE	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P value
				Lower Bound	Upper Bound	
IOP8AM	16.07	2.196	0.401	15.25	16.89	0.000
IOP12PM	15.2	2.455	0.448	14.28	16.12	
IOP4PM	13.9	2.339	0.427	13.03	14.77	
IOP8PM	12.93	2.377	0.434	12.05	13.82	
IOP12AM	11.8	2.172	0.397	10.99	12.61	
IOP4AM	16.53	2.285	0.417	15.68	17.39	

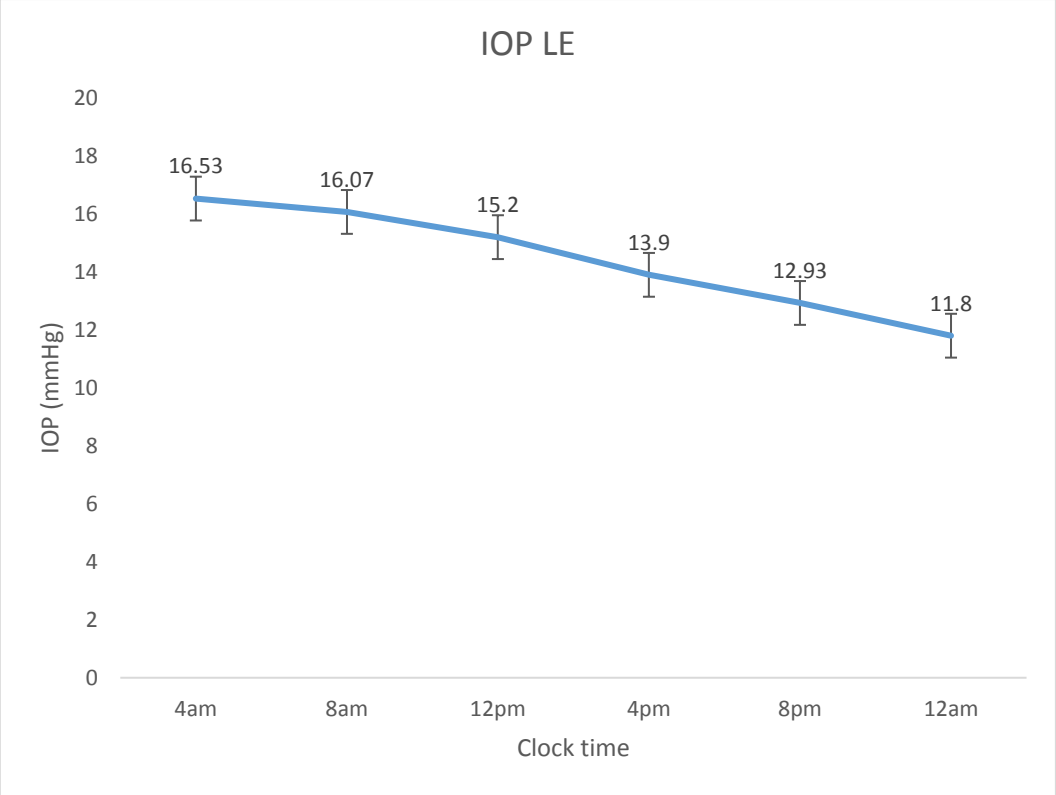


Chart 3 shows IOP at various times left eye

The study shows a gradual decrease in IOP from 16.07 at 8AM to 11.8 at midnight 12 AM and again peaking of 16.53 at early morning 4 AM in the left eye.

Table 8 showing mean CCT various times left eye

LE	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P value
				Lower Bound	Upper Bound	
CCT8AM	532.4	9.547	1.743	528.84	535.96	0.000
CCT12PM	529.33	9.408	1.718	525.82	532.85	
CCT4PM	526.87	9.786	1.787	523.21	530.52	
CCT8PM	524.37	9.686	1.768	520.75	527.98	
CCT12AM	521.97	9.817	1.792	518.3	525.63	
CCT4AM	534.5	9.965	1.819	530.78	538.22	

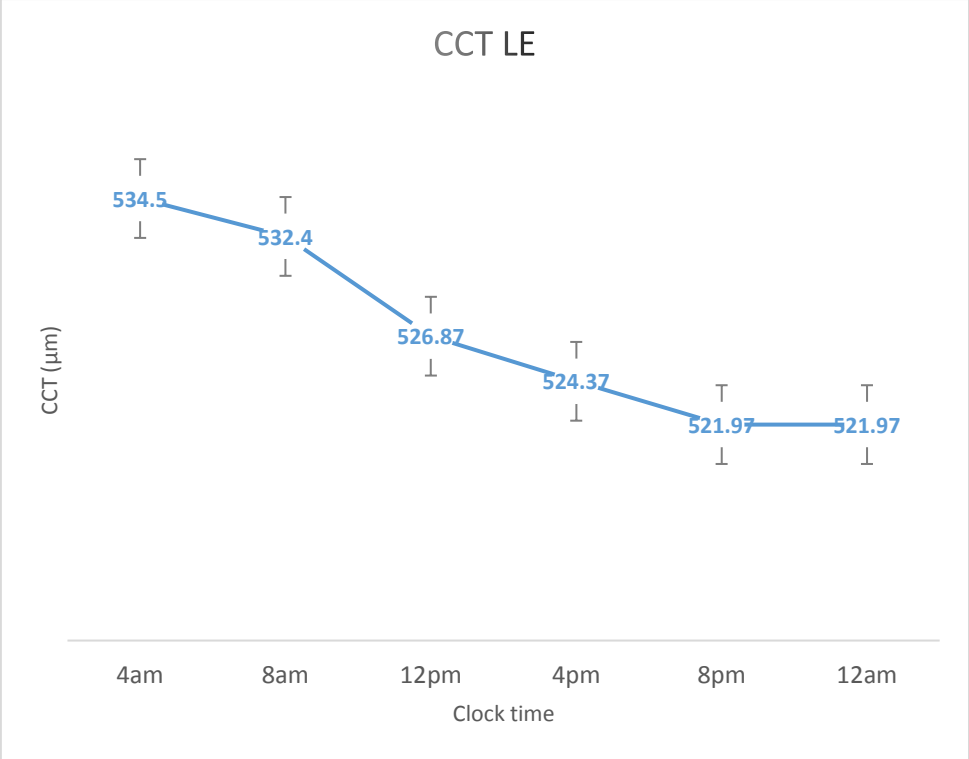


Chart 4 showing mean CCT various times left eye

The study shows a gradual decrease in CCT from 532.4 at 8AM to 521.97 at midnight 12AM and again peaking of 534.5 at 4 AM in the left eye.

Thus there exists a diurnal variation of IOP and CCT throughout the day with a $P<0.001$ (by using ANOVA test)- which is STATISTICALLY SIGNIFICANT.

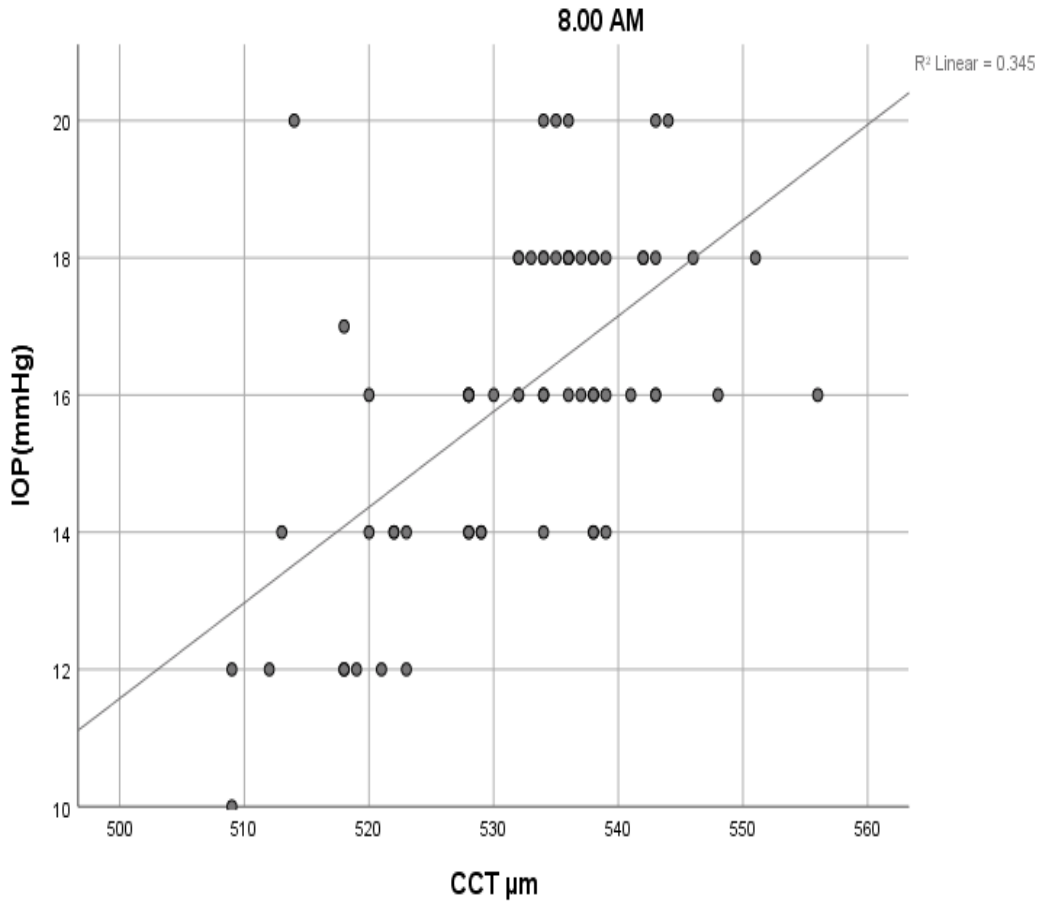


Chart 5 linear regression graph between CCT and IOP 8AM

The graph shows a positive regression line which shows a positive correlation exist between IOP and CCT at 8 AM.

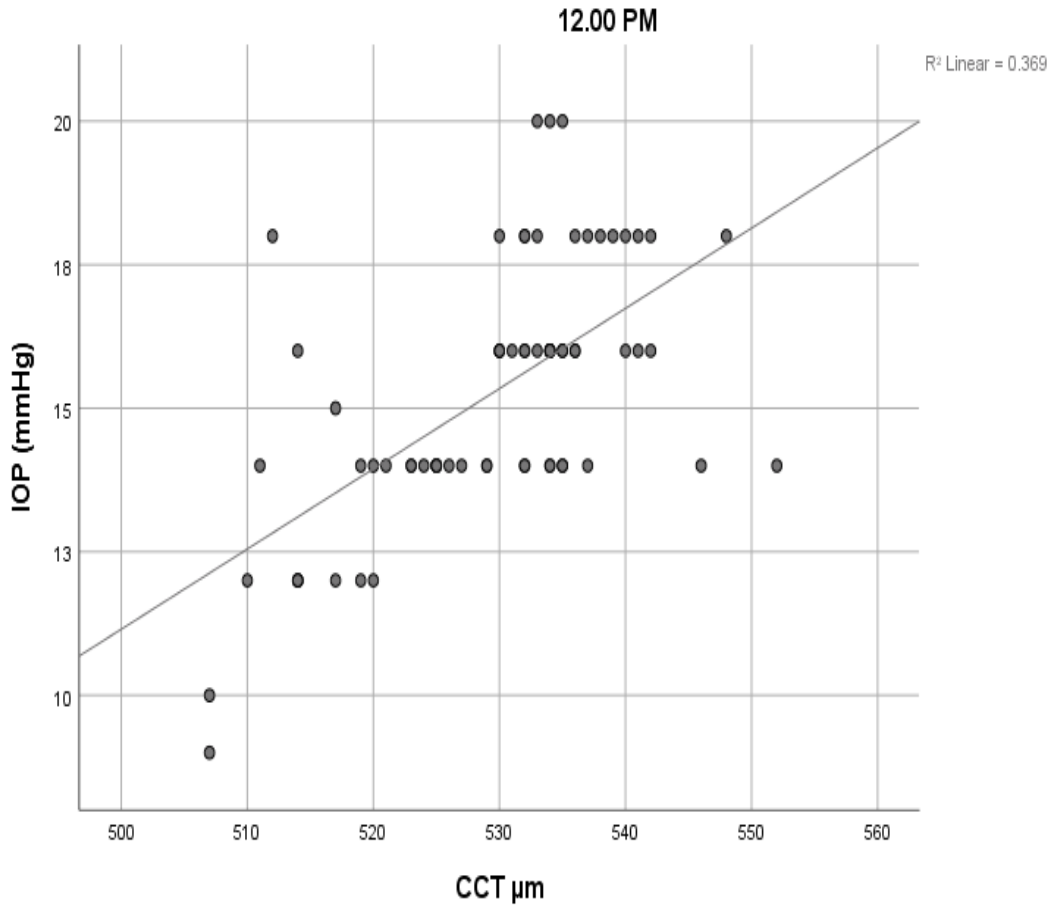


Chart 6 :linear regression graph between IOP and CCT at 12 PM

The graph shows a positive regression line which shows positive correlation exist between IOP and CCT at 12 PM.

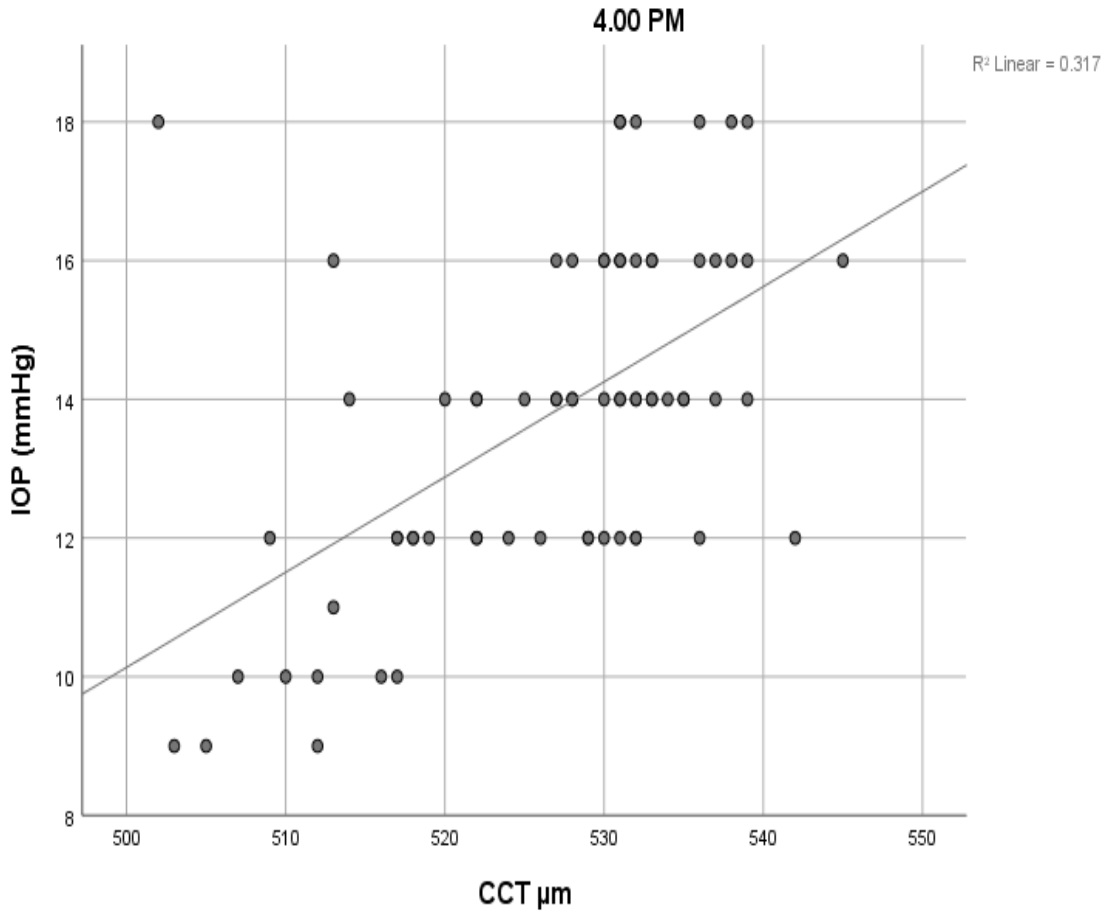


Chart 7 linear regression graph between IOP and CCT at 4 PM

The graph shows a positive regression line showing positive correlation exist between IOP and CCT at 4 PM.

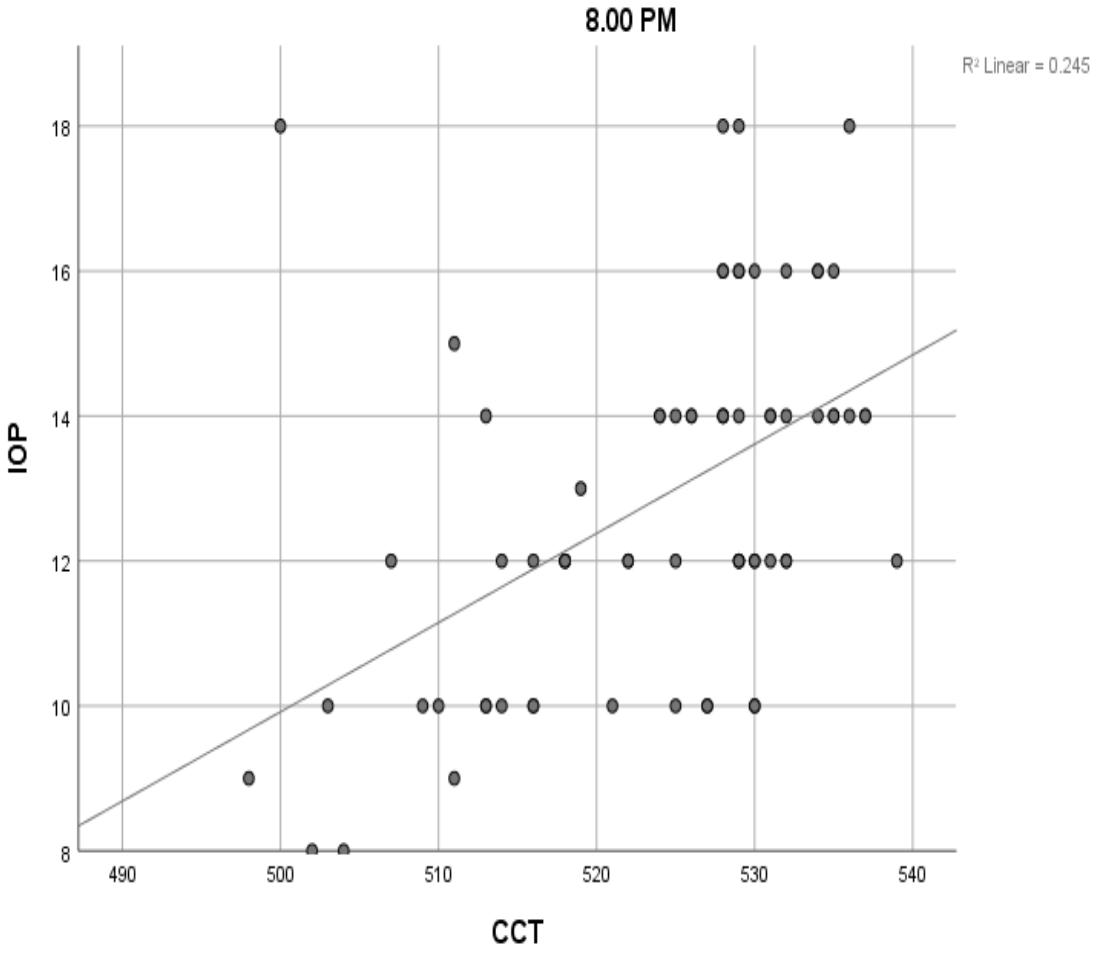


Chart 8 linear regression graph between IOP and CCT at 8 PM

The graph shows positive regression line showing positive correlation exist between IOP and CCT at 8 PM.

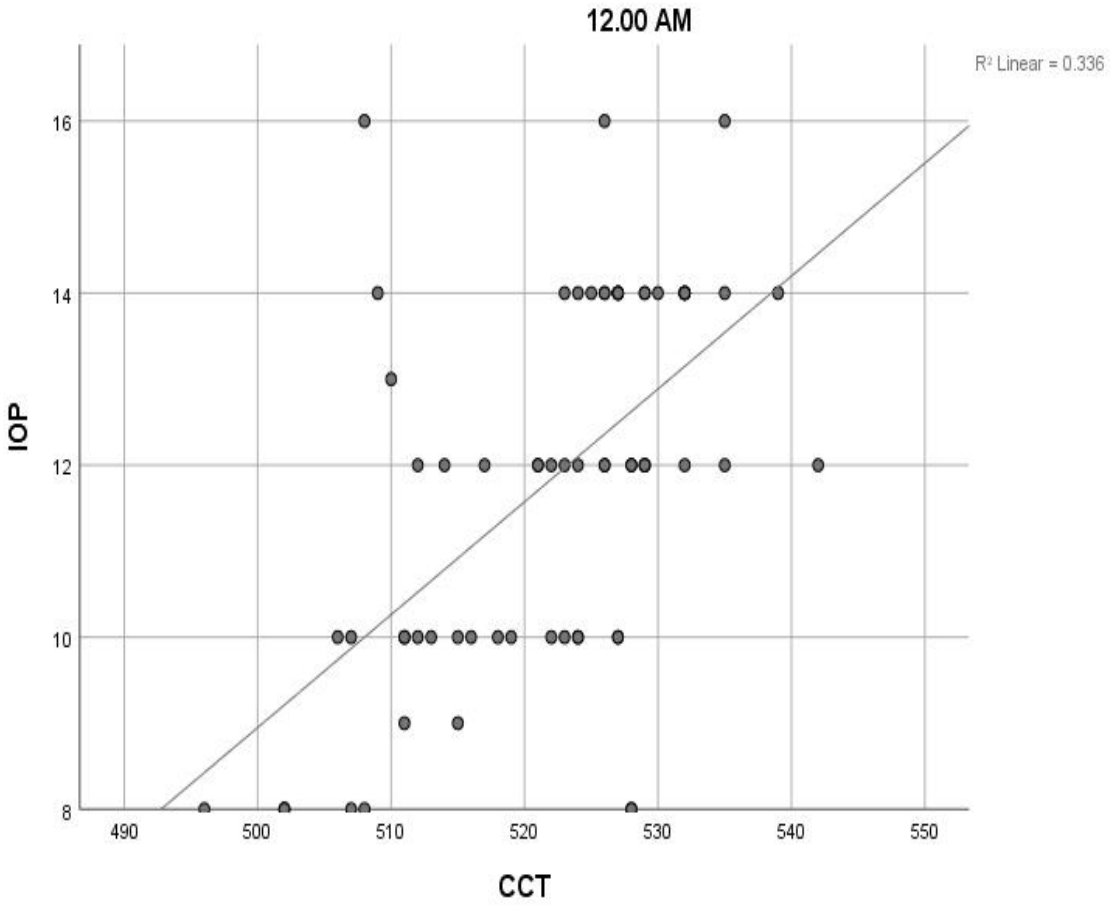


Chart 9 linear regression graph between IOP and CCT at 12 AM

The graph shows a positive regression line showing positive correlation exists between IOP and CCT at 12 AM

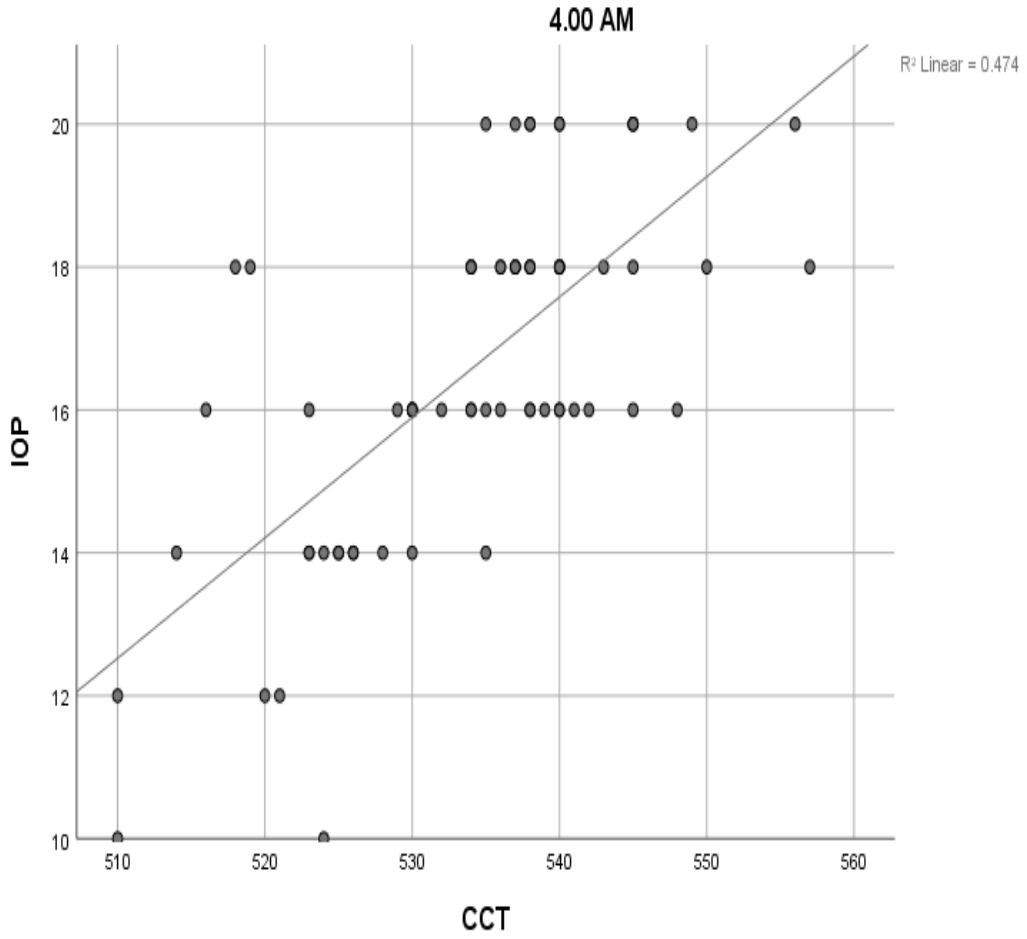


Chart 10 linear regression graph between IOP and CCT at 4 AM

The graph shows a positive regression line showing positive correlation exists between IOP and CCT at 4 AM.

DISCUSSION

AGE : In this study the mean age of presentation of patients with pseudoexfoliation syndrome is 62 years with variation of +/- 6 years.Previous studies conducted by Syed *et al* showed similar results.According to Framinghem study there is an increased incidence of pseudoexfoliation with increasing age[4].

GENDER : In this study out of 70 samples we examined , 39 (55.7 %) patients were female and 31 (44.3%) patients were male, thus showing a female preponderance.Previous studies conducted by Syed et *al* and Luntz MH showed a male preponderance[4,5].

DIURNAL VARIATION OF IOP : In this study there is significant variation in IOP in both the eyes throughout the day.The statistical test used was ANOVA test which showed a P value of 0.001 which was statistically significant.The IOP decreases gradually by the evening and is the least by midnight 12 AM.The IOP again spikes up early in the morning by 4 AM.Previous studies conducted by Syed *et al*, Keel *et al* and Altintas *et al* also showed a similar results of diurnal variation of intraocular pressure in pseudoexfoliation syndrome with minimum IOP at midnight and maximum IOP at early morning while waking up and PXF eyes showed a larger fluctuation in IOP than normal eyes[4,6,7].Altintas *et al* concluded that diurnal variation of IOP is less than 5mmHg in normal individuals and variation of more than 5 mmHg in pseudoexfoliation patients[7].

DIURNAL VARIATION OF CCT : In this study there was diurnal variation in CCT throughout the day with thickest CCT early in the morning while waking up and thinnest CCT at midnight which is similar to previous studies conducted by Syed *et al*,Keel *et al* , Du Toit *et al* which showed similar results of diurnal variation in CCT[4,6,8].Statistical test used was ANOVA test which showed a P value of 0.001 which is statistically significant.PXF eyes have shown to have thinner corneas which is an added risk factor for progression to glaucoma[7].

RELATION BETWEEN IOP AND CCT : This study shows a positive correlation between IOP and CCT at all times we measured in a day.With increase in CCT the IOP increases and with decrease in CCT the IOP decreases.In previous studies by Keel *et al* and Fogagnolo *et al* also showed correlation between IOP and CCT[4,9].According to the Ocular hypertension treatment study central corneal thickness influences the measurement of intraocular pressure by Goldmann Applanation tonometer and thus the intraocular pressure may be overestimated or underestimated [10].

SUMMARY

- Pseudoexfoliation syndrome is most commonly prevalent in 6^{th} and 7^{th} decade of life .
- Increased prevalence of pseudoexfoliation syndrome with increasing age.
- Pseudoexfoliation syndrome is common in females.
- There is a diurnal variation in intraocular pressure in individuals with pseudoexfoliation.
- The maximum intraocular pressure was at early in the morning while waking up and lowest at midnight.
- There existed a diurnal variation in central corneal thickness in individuals with pseudoexfoliation .
- The thickest central corneal thickness was at early morning and thinnest was at midnight.
- There was a positive correlation between central corneal thickness and intraocular pressure measured by Goldmann Applanation Tonometer at all times of the day.

CONCLUSION

Pseudoexfoliation is mostly prevalent with increasing age with a female preponderance. Normal individuals also show diurnal variation in intraocular pressure and central corneal thickness. But there is more variation in individuals with pseudoexfoliation syndrome. Hence its essential to evaluate all patients with pseudoexfoliation thoroughly throughout the day. It is ideal to measure the central corneal thickness and intraocular pressure fourth hourly a day to assess the risk of developing glaucoma in these patients. Pseudoexfoliation patients are at higher risk of developing glaucoma earlier due to thinner corneas. Hence patients with pseudoexfoliation should be followed up regularly. There is also positive correlation between IOP and CCT. Hence its ideal to measure CCT each time we measure IOP by Goldmann Applanation Tonometer to avoid overestimated or underestimated IOP.

PART III

BIBLIOGRAPHY

1. Shields, Textbook of Glaucoma, 6th edition, 2011,section II, chapter 15.
2. Becker-Shaffers, Diagnosis and Treatment of glaucoma, 8th edition, 2009, chapter 18.
3. Kanski JJ, Bowling B. Clinical Ophthalmology: A Systematic Approach. 7th Edition.
4. Syed Z, Srikanth K, Nagarajan S. Diurnal variation of central corneal thickness and intraocular pressure in eyes with pseudoexfoliation. Indian J Ophthalmol. 2019 Oct;67(10):1607-1609. doi: 10.4103/ijo.IJO_1899_18. PMID: 31546490; PMCID: PMC6786200.
5. Luntz MH. Prevalence of pseudo-exfoliation syndrome in an urban South African clinic population. Am J Ophthalmol. 1972 Oct;74(4):581-7. doi: 10.1016/0002-9394(72)90816-1. PMID: 5075128.
6. Keel S, Malesic L, Chan SP. Diurnal variation in central corneal thickness and intraocular pressure in eyes with pseudoexfoliation syndrome without glaucoma. Indian J Ophthalmol. 2014 Nov;62(11):1072-1076. doi: 10.4103/0301-4738.146755. PMID: 25494249; PMCID: PMC4290197.

7. Altintas O, Yuksel N, Karabas VL, Caglar Y. Diurnal intraocular pressure variation in pseudoexfoliation syndrome. Eur J Ophthalmol. 2004 Nov - Dec 2004;14(6):495-500. doi: 10.5301/EJO.2008.5057. PMID: 28221657.

8. du Toit R, Vega JA, Fonn D, Simpson T. Diurnal variation of corneal sensitivity and thickness. Cornea. 2003 Apr;22(3):205-9. doi: 10.1097/00003226-200304000-00004. PMID: 12658083.

9. Fogagnolo P, Rossetti L, Mazzolani F, Orzalesi N. Circadian variations in central corneal thickness and intraocular pressure in patients with glaucoma. Br J Ophthalmol. 2006 Jan;90(1):24-8. doi: 10.1136/bjo.2005.079285. PMID: 16361661; PMCID: PMC1856876.

10. Gordon MO, Kass MA. What We Have Learned From the Ocular Hypertension Treatment Study. Am J Ophthalmol. 2018 May;189:xxiv-xxvii. doi: 10.1016/j.ajo.2018.02.016. Epub 2018 Mar 1. PMID: 29501371; PMCID: PMC5915899.

11. Syed, Zeeshan; Srikanth, Krishnagopal; Nagarajan, Swathi Diurnal variation of central corneal thickness and intraocular pressure in eyes with pseudoexfoliation, Indian Journal of Ophthalmology: October 2019 - Volume 67 - Issue 10 - p 1607-1608

12. Read, Scott A.*; Collins, Michael J.* Diurnal Variation of Corneal Shape and Thickness, Optometry and Vision Science: March 2009 - Volume 86 - Issue 3 - p 170-180

13. Inoue K, Okugawa K, Oshika T, Amano S. Morphological study of corneal endothelium and corneal thickness in pseudoexfoliation syndrome. Jpn J Ophthalmol. 2003 May-Jun;47(3):235-9. doi: 10.1016/s0021-5155(03)00022-4. PMID: 12782156.

14. Harper CL, Boulton ME, Bennett D, Marcyniuk B, Jarvis-Evans JH, Tullo AB, Ridgway AE. Diurnal variations in human corneal thickness. Br J Ophthalmol. 1996 Dec;80(12):1068-72. doi: 10.1136/bjo.80.12.1068. Erratum in: Br J Ophthalmol 1997 Feb;81(2):175. PMID: 9059272; PMCID: PMC505705.

PROFORMA FOR PSEUDOEXFOLIATION SYNDROME

NAME **AGE**

SEX **IP NUMBER**

CHIEF COMPLAINTS

SYSTEMIC ILLNESS

H/O OCULAR SURGEY

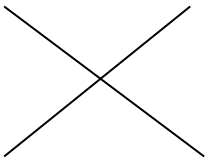
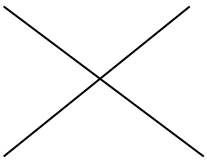
H/O OCULAR TRAUMA

FAMILY HISTORY

VITALS

1. ANTERIOR SEGMENT

RE	Examination	LE
	Best Corrected Visual Acuity	
	Lids	
	Conjuctiva	
	Cornea	
	Anterior Chamber	
	Iris	
	Pupil	

	Lens	
	Gonioscopy	
	Fundus	
	OCT RNFL	
	Fields	

2. CCT and IOP Measurement

	Central Corneal Thickness (µm)		**Intraocular Pressure (mmhg)**	
	RE	**LE**	**RE**	**LE**
8:00 am				
12:00 pm				
4:00 pm				
8:00 pm				
12:00 am				
4:00 am				

KEY TO MASTER CHART

S. No - serial number

M - male

F -female

PXF - pseudoexfoliation syndrome

RE -right eye

LE -left eye

CCT -central corneal thickness

IOP -intraocular pressure

S.No	NAME	AGE	SEX	IP NUM	PXF	IOP & CCT											
						8am		12pm		4pm		8pm		12am		4am	
						CCT	IOP	CCT	IOP	CCT	IOP	CCT	IOP	CCT	IOP	CCT	IOP
1	TYRIN	52	M		RE	514	20	512	18	502	18	500	18	508	16	518	18
2	MUTHAYE	60	F		RE	548	16	546	14	536	12	532	12	524	10	550	18
3	MUTHAYE	60	F		LE	543	16	540	16	539	14	537	14	535	12	548	16
4	KUPPAN	72	M		RE	556	16	552	14	542	12	539	12	542	12	557	18
5	KUPPAN	72	M		LE	551	18	548	18	545	16	537	14	539	14	556	20
6	BANU	56	F		RE	536	18	534	14	530	12	529	12	530	14	537	20
7	PADMINI	62	F		RE	536	20	535	20	531	18	528	18	527	14	540	20
8	PADMINI	62	F		LE	534	18	533	18	530	16	528	16	527	14	540	20
9	KARUNAKARAN	50	M		RE	528	14	524	14	517	12	514	10	515	10	526	14
10	AMARAVATHI	70	F		RE	512	12	510	12	507	10	503	10	502	8	514	14
11	AMARAVATHI	70	F		LE	509	10	507	9	505	9	502	8	502	8	510	10
12	ETHIRAJULU	62	M		RE	538	18	536	18	532	16	528	16	527	14	540	18
13	ETHIRAJULU	62	M		LE	537	16	532	16	530	14	528	14	526	14	538	18
14	RAJA	67	M		LE	522	14	519	14	517	12	516	10	511	10	523	14
15	SAROJA	68	F		RE	518	12	514	12	512	9	504	8	502	8	520	12

S.No	NAME	AGE	SEX	IP NUM	PXF	IOP & CCT											
						8am		12pm		4pm		8pm		12am		4am	
16	SAROJA	68	F		LE	520	14	517	12	513	11	511	9	508	8	524	14
17	VASANTHA	70	F		RE	543	18	540	18	539	16	535	14	532	14	545	18
18	NATARAJ	65	M		RE	528	14	525	14	522	12	518	12	513	10	528	14
19	NATARAJ	65	M		LE	530	16	526	14	525	14	522	12	522	12	532	16
20	PRABU	56	M		RE	546	18	542	16	538	16	536	14	535	14	549	20
21	PRABU	56	M		LE	543	16	541	16	537	14	535	14	532	14	545	16
22	SIVA	69	M		RE	521	12	519	12	516	10	513	10	511	9	524	10
23	SIVA	69	M		LE	523	12	520	12	517	10	516	10	515	9	525	14
24	RAMAN	70	M		RE	536	18	532	18	530	16	528	14	527	14	537	18
25	LALITHA	63	F		RE	538	16	536	16	535	14	534	14	532	12	540	18
26	LALITHA	63	F		LE	535	18	533	16	531	16	530	16	527	14	537	18
27	MALAR	60	F		RE	518	17	514	16	513	16	511	15	509	14	519	18
28	MALAR	60	F		LE	520	16	517	15	514	14	513	14	510	13	523	16
29	FATHIMA	55	F		RE	534	20	533	20	531	18	529	18	526	16	535	20
30	FATHIMA	55	F		LE	533	18	532	18	531	16	529	16	523	14	534	18
31	JANAKI	62	F		RE	534	16	532	16	531	14	529	14	526	14	535	16
32	JANAKI	62	F		LE	537	18	534	16	533	16	528	14	525	14	538	16
33	MOHAN	58	M		RE	544	20	542	18	539	18	536	18	535	16	545	20
34	MOHAN	58	M		LE	538	18	535	16	533	16	531	14	529	14	540	18

S.No	NAME	AGE	SEX	IP NUM	PXF	IOP & CCT											
						8am		12pm		4pm		8pm		12am		4am	
35	SUMATHY	74	F		RE	528	16	523	14	522	14	519	13	517	12	530	16
36	SUDAR	54	F		RE	532	18	530	16	527	14	524	14	521	12	534	18
37	SUDAR	54	F		LE	536	16	534	16	533	14	532	14	529	12	538	16
38	VILASAM	63	F		RE	523	14	521	14	518	12	514	12	512	10	525	14
39	VILASAM	63	F		LE	528	16	525	14	522	14	518	12	512	12	530	16
40	MANI	58	M		RE	519	12	514	12	510	10	509	10	507	10	523	14
41	PRAKASAM	67	M		RE	539	18	537	18	536	16	534	16	532	14	540	18
42	PRAKASAM	67	M		LE	535	20	534	20	532	18	529	16	527	14	538	20
43	PUGAZH	70	M		RE	532	18	530	16	528	16	526	14	524	14	534	18
44	PUGAZH	70	M		LE	536	18	534	16	533	14	531	14	528	12	538	18
45	SELVI	60	F		RE	538	16	536	16	534	14	531	12	529	12	540	18
46	SELVI	60	F		LE	534	18	530	18	527	16	524	14	521	12	536	18
47	MAARAN	63	M		RE	513	14	511	14	509	12	507	12	506	10	516	16
48	MAARAN	63	M		LE	509	12	507	10	503	9	498	9	496	8	510	12
49	VALLI	58	F		RE	529	14	525	14	522	12	521	10	518	10	530	16
50	VALLI	58	F		LE	532	16	529	14	527	14	525	12	522	10	534	16
51	MURUGAN	64	M		RE	536	18	534	16	532	14	530	12	527	10	538	20

S.No	NAME	AGE	SEX	IP NUM	PXF	IOP & CCT											
						8am		12pm		4pm		8pm		12am		4am	
52	MURUGAN	64	M		LE	538	16	534	14	532	12	530	10	528	8	537	18
53	MULLAI	71	F		RE	538	14	535	14	532	12	530	10	528	8	540	16
54	MULLAI	71	F		RE	541	16	537	14	535	14	532	12	529	12	542	16
55	NARMATHA	69	F		LE	539	14	535	14	531	12	529	12	527	10	541	16
56	MUNI	70	M		RE	534	16	532	14	529	12	527	10	524	10	536	18
57	MUNI	70	M		LE	538	14	529	14	526	12	525	10	523	10	539	16
58	SENTHIL	58	M		RE	539	16	535	16	531	14	530	12	528	12	540	16
59	PANKAJAM	61	F		RE	534	14	532	14	529	12	527	10	526	12	535	14
60	PANKAJAM	61	F		LE	532	16	530	16	528	14	526	14	524	12	534	16
61	SIVAGAMI	48	F		RE	536	18	534	16	532	14	529	12	526	12	538	18
62	LATHA	52	F		RE	522	14	520	14	518	12	513	10	511	10	526	14
63	LATHA	52	F		LE	528	16	525	14	519	12	516	12	514	12	529	16
64	BABU	70	M		RE	518	12	514	12	512	10	510	10	507	8	521	12
65	BABU	70	M		LE	528	16	523	14	520	14	518	12	516	10	530	16
66	MEENA	68	F		RE	543	20	541	18	538	18	534	16	532	14	545	20
67	MEENA	68	F		LE	542	18	538	18	536	18	532	16	529	14	545	20
68	KOMALA	57	F		RE	534	16	531	16	528	14	525	14	523	12	536	16
69	DAMU	50	M		RE	529	14	527	14	524	12	522	12	519	10	530	14
70	LAKSHMI	60	F		LE	530	18	527	18	523	16	519	14	516	14	529	18