"PREVALENCE OF PSEUDOEXFOLIATION SYNDROME IN PATIENTS WITH CARDIOVASCULAR DISEASE - ONE YEAR CROSS SECTIONAL HOSPITAL BASED STUDY"

By

REG. NO. BK0116004

Dissertation

Submitted to the KLE Academy of Higher Education and Research, Belagavi, Karnataka. In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY
IN
OPHTHALMOLOGY

DEPARTMENT OF OPHTHALMOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELAGAVI, KARNATAKA.

APRIL 2019

KLE Academy of Higher Education and Research, Belagavi, Karnataka.

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ABSTRACT

Background and objectives

Pseudoexfoliation (PXF) is an age-related systemic condition characterized by the production and accumulation of abnormal fibrillar extracellular material. Ocular pseudoexfoliation is now recognized as a systemic disease as these materials have been found in other parts of the body namely skin, vascular structures, and visceral organs such as the kidney, heart, lungs, and gall bladder as well as in the inner ear .

The objectives of our study are:

1. To find out prevalence of pseudoexfoliation syndrome in patient with cardiovascular disease.
2. To find out association of pseudoexfoliation syndrome with hypertension and diabetes.

Methodology

The present one year Cross Sectional Study of 125 patients was conducted on patients with cardiovascular diseases including myocardial infarction, angina, cardiomyopathies which, may or may not be associated with hypertension or diabetes to find out the prevalence and association with pseudoexfoliation. All patients were subjected to detailed ocular examination to diagnose pseudoexfoliation syndrome.

Results

The average age of these patients was 62.85 years but average age of 72 years was seen in subjects with PXF, with male predominance. 4 patients had unilateral pseudoexfoliation material of which 3 were males and 1 was female and 5 males

had bilateral involvement. No sex predilection was seen; however the prevalence was slightly higher in males. The mean IOP was 16.53 mm Hg and the mean IOP in subjects with PXF was 20.61 mm Hg which was higher than subjects without PXF. 10.39% patients diagnosed with pseudoexfoliation syndrome had hypertension, but 2.08% patients had no history of hypertension. Similarly 9.26 % of patients with diabetes mellitus were diagnosed to have pseudoexfoliation, but 5.64% patients had pseudoexfoliation syndrome but no history of diabetes.

Conclusion

The prevalence of pseudoexfoliation syndrome in cardiovascular diseases was 7.2%. The rates of arterial hypertension and diabetes in subjects with pseudoexfoliation were higher, however statistically it is not significant. Further, studies with larger populations are needed to clarify the relationship and systemic characteristics of pseudoexfoliation syndrome.

Keywords

Pseudoexfoliation syndrome, Cardiovascular diseases, Hypertension, Diabetes

LIST OF ABBREVIATIONS USED

PXF	Pseudoexfoliation Syndrome
LOXL1	Lysyl Oxidase Like 1
ECM	Extra Cellular Matrix
POAG	Primary Open Angle Glaucoma
IOP	Intraocular Pressure
PXFG	Pseudoexfoliative Glaucoma
RNFL	Retinal Nerve Fiber Layer
ONH	Optic Nerve Head
AAA	Abdominal Aortic Aneurysm
IHD	Ischemic Heart Disease
CAD	Coronary Artery Disease
HTN	Hypertension
DM	Diabetes Mellitus
AH	Arterial Hypertension
TDI	Tissue Doppler Imaging
CAE	Coronary Artery Ectasia

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INTRODUCTION

Pseudoexfoliation syndrome (PXF) is an age related systemic disease of extracellular matrix characterized by the multifocal production and progressive accumulation of a fibrillary extracellular material in intraocular and extraocular tissues that is either the result of an excessive production or insufficient breakdown or both.[1]

The etiology and pathogenesis of pseudoexfoliation syndrome is still unknown, but it is thought to be a systemic biochemical process. Molecular, biological and biochemical data support the pathogenetic concept of pseudoexfoliation as a type of stress induced elastic microfibrillopathy.[1]

Geographical clustering for pseudoexfoliation (PXF) and variable prevalence in same country suggests environmental and genetic risk factors. Single nucleotide polymorphisms in the coding region of the lysyl-oxidase-like 1(LOXL1) gene, that is responsible for cross-linking of elastin, have been identified as strong genetic risk factors for PXF syndrome and PXF glaucoma.[2, 3]

Prevalence of Pseudoexfoliation syndrome increases markedly with age. As very few studies have been done and very limited data is available, reported prevalence is 1.8 to 13.5%. India has significantly lower incidence.The prevalence of pseudoexfoliation syndrome in USA was found to be 0.6% for age range 52-64 years and 5% in age range 75-85years.[4]

Pseudoexfoliative material consists of central fibrillar component embedded in an amorphous ground substance. The fibrillar portion has been characterized as amyloid, laminin, oxytalan and various elastic tissue and basement membrane

components.The available histochemical data suggests a complex glycoprotein-proteoglycan structure and epitopes of the elastic fiber system.[4]

The definite clinical diagnosis of syndrome is based on slit lamp observation of the whitish flake like deposits on the anterior segment structure, particularly on the pupillary border of the iris and anterior lens surface. Ocular pseudoexfoliation has been associated with cataract progression and open angle glaucoma, pigment dispersion transillumination defect of iris and reduced response to mydriatics. Intra operative complications like zonular or posterior capsular rupture, vitreous loss, dislocation/subluxation of intraocular implant and corneal endothelial decompensation are common.[5]

In the last two decades, it has been shown that PXF material could be identified in several tissues. Pseudoexfoliation fibers are histologically found in conjunctival stroma, fibroblast, extraocular muscle and orbital connective tissue and also in other visceral organs like heart, lungs, liver, kidney, gallbladder as well as in wall of blood vessels, skin, cerebral meninges with unknown clinical significance. However, there is no consensus about the relationship between some vascular disorders and the PXF syndrome. [5]

Pseudoexfoliation has been associated with transient ischemic attacks (TIA), alzheimers disease, asymptomatic myocardial dysfunction, sensorineural hearing loss, stroke, myocardial infarction, systemic hypertension and aneurysm of abdominal aorta . [5, 6, 7, 8]

Pseudoexfoliation associated with ischemic heart disease (IHD) has been investigated. Elevated plasma homocysteine, lipoprotein (a), apolipoprotein-A, risk

factor for cardiovascular disease have been found more common in pseudoexfoliation than in healthy controls. [5, 9, 10]

Given the clinical implication of a shared pathogenesis of an ocular disorder diagnosed at the slit lamp and systemic vascular disease, we aimed to study the prevalence of pseudoexfoliation in cardiovascular disease.

AIMS AND OBJECTIVES

1. To find out the prevalence of pseudoexfoliation syndrome in patients with cardiovascular disease.
2. To find out the association of pseudoexfoliation syndrome with hypertension and diabetes.

REVIEW OF LITERATURE

HISTORY :

John G. Lindberg in 1917, a Finnish Ophthalmologist, for the first time ever described exfoliation. He wanted to execute Axenfeld's observations on iris changes in senile eyes. Two types of degeneration of the iris were described by Axenfeld: an atrophy of the iris pigment epithelium at the pupillary border and a hyaline degeneration of the pupillary margin of iris causing poor dilatation with mydriatics. He illustrated greyish flakes at the pupillary border of iris. Lindberg published his results on exfoliation as a thesis at the University of Helsinki in 1917. [11]

In 1918, Alfred Vogt, a Swiss Ophthalmologist gave the full description of this disorder. He described the film on the anterior lens capsule, as a remnant of the pupillary membrane. Later Vogt hypothesized that this material represented degenerative changes of the lens capsule followed by secondary desquamation. [3, 11]

The first comprehensive clinical description of pseudo-capsular exfoliation of the lens was published by Vogt (I923, 1925) under the name "superficial exfoliation of the anterior capsule of the lens". The appearance is described as a deposit of granular material likened to hoar frost or coarse white powder occurring on the anterior lens capsule, pupil margin, zonule, ciliary body, and persistent pupillary membrane, in the anterior chamber angle, and floating free in the aqueous [13]

In 1925, he recommended that exfoliation was as a consequence of degenerative changes of the lens capsule and it was associated with a new type of glaucoma. One year later he changed his opinion and was convinced that exfoliation resulted in glaucoma [3].

Vogt [3] named this condition as “capsular glaucoma” since it was assumed that the grayish flaky material originated from the peeling of the anterior capsule of lens. Vogt (1925) believed that the greyish frosting material lying on the anterior lens surface and on other structures bathed in aqueous was produced by vacuolation and exfoliation of the superficial capsule. A similar mechanism involving the zonular lamella has been proposed by Gifford (1957) and by Sugar (1976). [12]

Pseudoexfoliative material in sections stained in haematoxylin and eosin is seen usually as discrete, pink bush-like masses attached in either a sessile or pedunculated manner to the anterior lens surface but often without evidence of capsular dehiscence. This appearance led Busacca (1928) to interpret them as deposits of an unidentified material of unknown origin. An attempt to synthesize these somewhat divergent observations and to distinguish the disorder from true (thermal) exfoliation of the lens and capsule, resulted in the introduction by Dvorak- Theobold (1954) of the semantically confusing name 'pseudoexfoliation', which is in general use.[12]

Davanger and Pederson (1975) using transmission electron micrographic (TEM) and scanning electron microscopy (SEM) have likewise shown that the pseudoexfoliative excrescences rest on a 'basal lamina', which has a marked tendency to curl up. [12]

Ringvold (1973) observed that pseudoexfoliative material was also deposited in the walls of conjunctival capillaries, a finding confirmed and extended by Ghosh and Speakman (1976). Using iris fluorescence angiography, Vannas (1969) demonstrated abnormal vessels leaking fluorescein. Hence it was suggested that

pseudoexfoliative material is blood-borne, diffusing into the anterior chamber through walls of diseased vessels of the iris. [12]

Glenner et al. (1972) consider amyloid to result from enzymatic (lysozomal) fragmentation of long chain proteins (often immunoglobulins) into polypeptides, which polymerise spontaneously into an antiparallel beta-pleated sheet configuration, of which Congo red dichroism is probably the histochemical counterpart. They have thus suggested concept that under certain conditions, a pathogenic protein can be formed by proteolysis of an innocuous precursor. Histochemical and electron microscopic findings suggested that the pre-equatorial epithelial cells synthesis long-chain zonule-like proteins, which are then converted by lysozomal enzymes into small molecules capable of polymerizing both within the capsule and in relation to nearby aqueous-bathed structures. [12]

Ritch et al. [13, 42] had observed that a homogeneous ground-glass appearance of the lens surface in one eye compared to the other may represent a very early stage called as precapsular stage. In pregranular stage, authors postulated that a ring of about 80 faint, radial, non-granular striae may be seen on the mid-third of the anterior capsule behind the iris.

So clinically pre-granular stages were described .

CLINICAL APPEARANCE OF STAGE : (13)

- Stage I - Greyish radial non-granular striae are visible on the mid-third of the anterior capsular surface, entirely behind the iris. The striae are thin and slightly fusiform vary a little in length. These striae are difficult to see. They

are most easily seen when o.5 mm width slit beam is focused on the lens surface at an angle of 45' and the whole slit lamp is traversed from side to side

- Stage 2- They are more easily seen. They become slightly broader and thus lie closer together. The outer ends become a little longer while the inner ends become blunted and broader.
- Stage 3-These striae broaden and the blunted inner ends begin to touch one another, thus forming a continuous dentate line. No visible granular deposits seen.
- Stage 4 - With the addition of fine granular deposits.

Electron microscopic studies suggested that the anterior capsule of the lens was frequently affected in patients with exfoliation. The pre-equatorial lens epithelial cells produced the abnormal fibrillar substance and the term 'fibrillopathia epitheliocapsularis' was recommended.

One of the key changes proposed in pseudoexfoliation syndrome is overproduction of glycosaminoglycans coupled with abnormal metabolism. The proteineous element of pseudoexfoliation material is composed of both the epitopes of the elastic fiber system such as fibrillium and non-collagenous basement membrane components [(14)]. The name basement membrane exfoliation syndrome was derived due to abnormal secretions of basement membrane seen in this condition. The terms pseudoexfoliation syndrome (PXF) and exfoliation syndrome are generally used interchangeably to address this disorder.

EPIDEMIOLOGY AND GENETICS :

Pseudoexfoliation Syndrome has a global distribution. PXF syndrome's prevalence demonstrates considerable geographic, ethnic and racial variation. Low PXF syndrome rates (< 6% in patients older than 70 years) have been reported in Greenland, Eskimos, India, the eastern part of the United States, Germany, Britain, Australia, Japan, Austria, Denmark and Switzerland. In contrast, high PXF syndrome frequencies (>15%) have been reported in Iceland, Finland, Russia, Tunisia, Saudi Arabia, Sweden, Norway, Turkey and Greece. [(5)]

The prevalence of PXF syndrome in the USA was found to be 0.6% for those in the age range 52–64 years and 5% in the age range 75–85 years. Among Australian aborigines over age 60, Taylor et al. noted a 16.3% prevalence of pseudoexfoliative changes. Forsius had studied Finns, Lapps, Eskimos in Greenland, Canada and Alaska, Icelanders, populations in Tunis, India and Peru and four populations in the USSR. The prevalence vary from 0% in Eskimos to 21% in Finns over 60 years of age, and are at the same high level in Lapps, Finns, Russians in Novosibirsk and Icelanders, but significantly lower in all the others. [(7)]

The reported prevalence of PXF tends to increase with latitude in the Northern Hemisphere. Although scandinavian populations show high prevalence of the disease. The prevalence is as high as 20% in Finland and over 25% in Iceland. Though parts of Denmark and in Greenland, Eskimos the prevalence of PXF has been estimated as low as 5% and 0, respectively. In western European countries, such as England and Germany, a prevalence of 4.0 and 4.7% has been reported, respectively. [(15)]

It has been previously shown that the incidence of PXF increases with age. In a study of a Greek population, it was found that the prevalence increases from 1.2% in the 6th decade of life to about 34% in patients older than 80 years. (15)

A population-based study in the United States found a prevalence of 0.67% in people aged 52-64 years, 2.6% in people aged 65-74 years, and 5% in people aged 78-85 years.(15) Similarly in Reykjavik Eye Study, the prevalence of PXF in Iceland increased from 2.5% in those aged 50-59 years to 40.6% in those aged <80 years.(16)

Krishnadas. R et al. (17) conducted a study in southern districts of Tamil Nadu and concluded that concluded that the prevalence of pseudoexfoliation syndrome was 6.0% and prevalence increased with age and was greater in males.

A study conducted by Aalia R Sufi et al. (18) where the prevalence of pseudoexfoliation syndrome in patient scheduled for cataract surgery in Kashmir was 26.32%, with male predominance.

. The prevalence of PXF increased with increasing age, 3.01% in those 40 years of age or older, and 6.28% in those 60 years of age or older and the prevalence was higher among subjects who were involved in outdoor activities (19)

A study conducted in South India showed that the prevalence of pseudoexfoliation syndrome among the rural population aged 40 years and above is 3.8%. With increasing age the prevalence was considerably higher but no sex predilection. In a known population, the actual prevalence of pseudoexfoliation syndrome is most likely double than that is visible on clinical examination. (20)

A cross-sectional study was conducted in Central India which shows prevalence of PXF 1.49 ± 0.18%. Study concluded that pseudoexfoliation prevalence

was significantly associated with elderly age, lower body mass index and higher diastolic blood pressure and not significantly associated with gender [21]

Electron microscopic studies show pseudoexfoliative material in unaffected eye when other eye is diagnosed clinically with pseudoexfoliation. Approximately 25% of patients with clinically unilateral disease will develop pseudoexfoliation signs in the other eye within 10 years [22]

It is now recognized that pseudoexfoliation syndrome is essentially a bilateral condition and unilateral cases only represent an earlier period in the natural history of the disease. When only one eye is involved clinically, the other eye often has abnormal aqueous humour dynamics or glaucomatous damage.

Several lines of evidence, including regional clustering, familial aggregation, and genetic linkage analyses, have previously supported a genetic predisposition to PXF [23]. Both population-based and pedigree-based studies have suggested that PXF syndrome is inherited as an autosomal dominant trait with late onset and incomplete penetrance. [24] A simple inheritance model was not evident suggesting a complex inheritance pattern caused by the contributions of multiple genetic factors and/or environmental conditions [25]

Accordingly, several chromosomal regions have been tentatively associated with PXF, including the putative gene loci 2p16, 2q35-36, and 3q13-q21 as well as the loci 18q12.1-21.33, 2q, 17p, and 19q, which were identified by a genome-wide scan of 1000 microsatellite markers in a Finnish family. Recently, genetic studies have demonstrated a highly significant association between PXF and sequence variants in the gene coding for lysyl oxidase-like 1 (LOXL1). [25]

LOXL1 is currently the most significant genetic risk factor for glaucoma in general. LOXL1 is a key enzyme involved in elastic fiber synthesis and homeostasis supporting a role of elastogenesis and elastosis in the pathophysiology of PXF syndrome. [25]

Association between LOXL1 and PEX syndrome/ Glaucoma :

Recent genetic studies in multiple populations have identified the LOXL1 gene as a major contributor to the risk of developing PXF.[26] Performing a genome-wide association study, Thorleifsson and co-workers [27] first detected three common sequence variants or single nucleotide polymorphisms (SNPs) in the LOXL1 gene on chromosome 15q24 which was strongly associated with both PXF syndrome and PXF glaucoma, but not with POAG, in Scandinavians from Iceland and Sweden. A high-risk haplotype (G-G) formed by the two coding SNPs increased the risk for PXF by factor of 27. Individuals carrying two copies of this high risk haplotype would have a 700 times increased risk of developing PXF than those carrying the low-risk haplotype. However, compared with the general population, the risk of developing PXF is about 2.5-fold only, because approximately 25% of the unaffected controls were also found to carry the high risk haplotype in the homozygous state. [27]

Following this discovery, multiple replication studies in populations from the United States, Australia, Europe, Japan, China, and India confirmed genetic susceptibility of LOXL1 polymorphisms to PXF syndrome/glaucoma and verified the LOXL1 gene as a principal genetic risk factor for this condition worldwide accounting for almost all PXF cases. There were no significant differences between PXF syndrome and PXF glaucoma suggesting that the LOXL1 gene may contribute to disease onset rather than to IOP elevation and subsequent glaucoma. [25, 26]

Functional implications of LOXL1 for PEX pathophysiology :

LOXL1 is a member of the lysyl oxidase family of enzymes, copper-dependent amine oxidases that catalyze the covalent cross-linking of collagen and elastin in connective tissues through oxidative deamination of lysine or hydroxylysine side chains.[28]

They comprise five characterized members: lysyl oxidase (LOX) and lysyl oxidase-like 1 to 4 (LOXL1-4). LOXL1 seems to be specifically required for tropoelastin cross-linking and has been shown to be involved in elastic fiber formation, maintenance, and remodeling and to prevent age-related loss of tissue elasticity.[29]

In order to fulfill the cross-linking function, LOXL1 pro-peptide is selectively targeted to elastic microfibrils at sites of elasto-genesis by binding to both tropoelastin and fibulin. Following attachment to the scaffolding structure, the pro-peptide is cleaved off by the endo-metalloproteinase procollagen-C-terminal proteinase (bone morpho-genetic protein) for catalytic activation of the enzyme. Deamination of lysine residues causes spontaneous cross-linking of tropoelastin monomers and formation of elastin polymers. Mice deficient in LOXL1 exhibit massive elastic fiber defects resulting in pelvic organ prolapse, enlarged pulmonary air spaces, vascular abnormalities, and increased laxity of the skin. [29]

In PXF tissues, expression of LOXL1 was also found to be markedly dysregulated, and this dysregulation clearly depended on the stage of the fibrotic process.[30] The available data indicate that LOXL1 is transiently up regulated and activated at early stages of PXF fibrogenesis together with matrix components required for elastic fiber formation, such as tropoelastin, fibrillin-1, and fibulin-4, and

participates in the formation of the aberrant fibrillar aggregates accumulating in tissues of PXF patients.

Hence, LOXL1 was found to be a prominent component of fibrillar PXF aggregates in all intra- and extraocular locations, where it co-localized with elastic fiber constituents, particularly fibrillin-1, but not with its normal binding partner fibulin-5, suggesting a shift in substrate specificity for LOXL1 at sites of pathological matrix formation. As fibrillin-1 is a major component of PXF fibrils it is reasonable to speculate that SNP rs3825942 (G153D) of LOXL1 is involved in the abnormal processing, assembly, cross-linking, and aggregation of fibrillin-containing microfibrils into mature PXF fibrils. [25, 30].

In later stages of the disease, irrespective of the presence of glaucoma, LOXL1 expression is decreased below normal homeostatic levels required for elastin maintenance and stability .The resulting inadequate tissue levels of LOXL1 may in turn adversely affect elastin metabolism and lead to elastotic alterations, which have been previously described in tissues, such as lamina cribrosa, of patients with advanced PXF. [25]

In fact, lamina cribrosa tissue of PXF eyes reveals a disorganized elastic fiber network and a significant down regulation of LOXL1 in lamina cribrosa cells together with a reduction of elastic fiber proteins and elastin-specific desmosine cross-links. These elastotic alterations of laminar beams resulting from LOXL1 deficiency may have adverse effects on biomechanical properties of this critical structure and may predispose to glaucoma development in eyes with PXF syndrome. [25]

FUNCTIONAL CANDIDATE GENES FOR PEX SYNDROME :

Weaker evidence exists for the contribution of additionally associated genes which seem to differ among study populations indicating a modifying rather than a direct genetic effect. The contributing genes reported may modulate the risk of developing the PXF-specific matrix process, e.g. CLU and CNTNAP2, or the PXF associated neurodegeneration, e.g.APOE, GSTs, and TNFA. Several environmental conditions associated with PXF and other fibrotic disorders, including oxidative stress, hypoxia, and elevated levels of pro-fibrotic cytokines (interleukin-6) and growth factors (TGF-ß1), have been shown to regulate both LOXL1 and clusterin expression as well as synthesis of matrix molecules including elastin and fibrillin-1 in vitro and may therefore act as co-modulating external factors.[25]

HISTOCHEMISTRY:

Barbara streen et al. [32] described that in PXF disease, there are three characteristic zones of different morphology in the lens capsule. There are small bush like aggregates on the anterior capsule in its mid-periphery and over the whole zonular insertion region in advanced disease. They are composed of thick (20-55 nm) fibers banded at 25 to 50 nm and a small number of thin (6-8 nm) fibrils.

After reacting the lens capsule with zonular antisera without counter-stain, PXF vegetations stood out as black nodules, in light microscopy of the plastic thick section. Staining was always densest in the outer portion of stained areas. [32]

According to Davanger et al. [31] the material contains typical crossed-banded fibrils, distributed in random. Negative staining of dispersed pseudoexfoliative fibrils indicated that the fibrils have a core consisting of small number of filamentous

subunits the core is surrounded by a fuzzy material which protrudes from the fibrils at regular interval. This is the basis of the cross-bands of the fibrils. Staining with ruthenium red and alcian blue indicates that glycosaminoglycan are present, mainly on surface of fibrils. It is concluded that the pseudoexfoliative material is made up of filamentous proteoglycans. The fibrils represent relatively dense aggregates of such filaments, while the interfibrillar matrix is a gel of the same filamentous units in a loose, random arrangement.

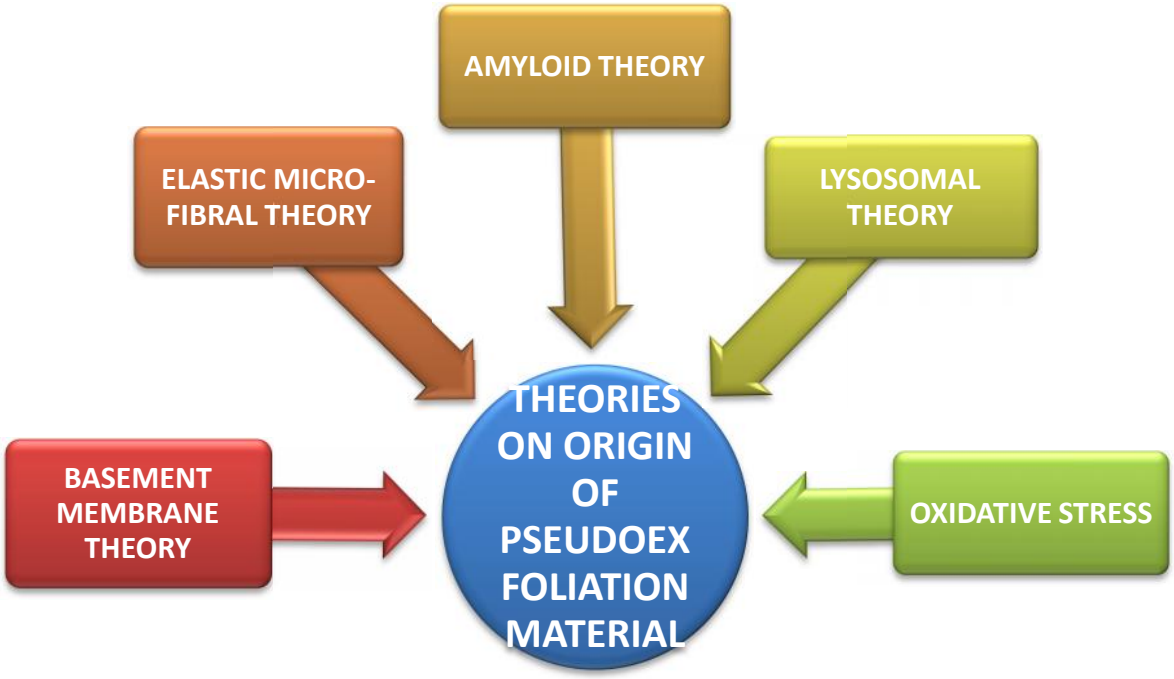
In haematoxylin and eosin preparations PXF material and the capsule proper, are stained pink while the striated band has a bluish tinge. Gomori's chrome haematoxylin colours the PXF material on the lens surface and the capsular shows dark blue. The striations are intensely stained as black lines in vertical sections but as black dots in tangential cuts. The zonular fibres are also blackened by this method. Congo red dichroism is not present in any of the sections examined. Sections stained with thioflavins T and S were examined by ultraviolet light. Green fluorescence is observed in PXF material on the anterior surface of the capsule and capsular inclusions and in the striated band. [(31)]

Light microscopy demonstrated this abnormally produced pseudoexfoliation material is Periodic acid Schiff positive, eosinophilic brush like feathery or nodular aggregate. These aggregates are composed of irregular tangle of fibrils as seen on electron microscopy. Transmission electron microscopy demonstrated focal condensations of fibrillogranular material along with cross banding where pseudoexfoliative material was present on the anterior lens capsule. [(33)]

Since the zonule is a member of the elastic microfibrillar system, PXF material on the lens capsule was tested for immunologic affinity to elastic using an

indirect immunoperoxidase electron microscopic method. Positive staining was obtained with all three antibodies on all components of lens PXF material, including the superficial aggregates, deep fibrogranular zone, and capsular inclusions. So it was suggested that PXF material derives from abnormal polymerization of glycoprotein associated with the zonular-elastic microfibrillar system. Similar staining of the abnormal material within the lens capsule indicates that the lens epithelial cell is involved in processing this protein. It might be suspected that other microfibrillar-secreting cells, even beyond the present range of suspected sources, could produce similar material. [32]

THEORIES ON ORIGIN OF PSEUDOEXFOLIATION MATERIAL :



1. BASEMENT MEMBRANE THEORY:

This theory was based on the close proximity of exfoliation material with basement membranes, and the extensive basement membrane changes associated with exfoliative deposion. These changes are particularly prominent in the basement membranes of the iris vasculature. [36]

PXF accumulation is result of both the factors, that is increased synthesis and incomplete degradation. Pseudoexfoliation syndrome is a disease of extra-cellular matrix characterized by abnormal breakdown and overproduction of basement membranes of ageing epithelial cells. Its origin is attributed to be basement membrane of the capsule of lens, iris, cilliary body and conjunctiva. The production of the exfoliation material may be related to disordered basement membrane metabolism. The fibrils contain basement membrane proteoglycan. [36]

Elhawy E et al. [34] studied immunohistochemical findings that suggested that pseudoexfoliation fibrils contain components of the elastic fiber and basement membrane system, such as elastin, tropoelastin, amyloid P, vitronectin, fibronectin, heparan sulfate proteoglycan, fibrillin-1, microfibril-associated glycoprotein, emilin, and latent transforming growth factor β binding proteins (LTBP-1 and LTBP-2) . Liquid chromatography coupled with tandem mass spectrometry has confirmed the presence of fibrillin-1, fibulin-2, vitronectin, and amyloid P-component. In addition, it allowed the identification of the basement membrane components laminin, serum amyloid protein and fibronectin, desmosomal cadherins (desmocolin-2), the proteoglycans syndecan-3, and versican metalloproteases of the 'A Disintegrin and Metalloprotease' (ADAM) family, (ADAMTS-8, 18, and 19), tissue inhibitors of

metalloprotinases (TIMP3) the extracellular chaperone clusterin, and complement factor 1q (C1q) as components of PXM microfibrils.

Schlotzer-Schrehardt U et al [(34)] in 1992 showed that the presence of all principal basement membrane components in precapsulardeposits of pseudoexfoliation on anterior capsule of lens by immunofluorescence and electron microscopic immunogold techniques. They have shown that heparin sulfate and chondroitin sulfate, proteoglycan, laminin, entactin /nidogen, fibronectinn and amyloid P protein to be integral constituent of PXF material. The type 4 collagen was restricted to a microfibrillar layer interposed between capsular surface and typical PXF material. They also concluded that presence of elastin epitopes indicates that the pseudoexfoliation material is a multicomponent expression of an abnormal extracellular matrix synthesis, including the incorporation of the non-collagenous basement membrane components. The extensive labelling of pseudoexfoliation material for chondroitin sulfate indicates there is an excessive production and irregular metabolism of glycosaminoglycans.

2. ELASTIC MICRO-FIBRAL THEORY:

Exfoliation material is immunologically related to the elastic tissue. There are histochemical and antigenic similarities between zonular elastic microfibrils and exfoliation material**.** Mature and intermediate micro-fibrils adjacent to fibroblasts resemble close proximity to the conjunctival elastic tissue.

Streenten and coworker et al. [(36)] postulated that exfoliation material was derived from abnormal polymerization of glycoproteins associated with the zonular elastic microfibrillar system in a type of elastosis. This postulate was based on histochemical and immunohistochemical similarities between exfoliation material,

the ocular zonules and elastic components.

Ludwisiak-Kocerba et al. [21] explained pseudoexfoliation as a type of elastosis, affecting especially elastic microfibrils. Pseudoexfoliation material is made up of complex composition of glycoprotein/proteoglycan, containing glycosaminoglycans (heparan sulfate, hyaluronic acid, chondroitin sulfate, dermatan sulfate). The presence of elastic fiber epitopes, mainly elastic microfibrillar components (elastin, amyloid P, vitronectin, fibrillin-1) support the theory that pseudoexfoliation syndrome is a type of elastosis, especially affecting elastic microfibrils.

Histochemical staining properties of pseudoexfoliation material deposited in the anterior segment of the eye and the zonules of the lens shows characteristics of the microfibrillar component of elastic tissue, oxytalan. [22]

A study conducted by Steenten et al. [37] suggested that pseudoexfoliative material found in the conjunctiva had a close relation with components of the elastic system. Pseudoexfoliation fibrils were present in clumps of oxytalan around small elastic fibers. Morphology of PXF here varied from typical to thicker fragmented and sometimes non-diagnostic fibers. This intertangled pseudoexfoliation material and elastotic fibres proposed that pseudoexfoliation fibrillopathy is a type of elastosis, due to abnormal aggregation of elements related to elastic microfibrils.

Schlotzer Schrehardt et al. [2] studied the matrix of the pseudoexfoliation material by light electron microscopy and demonstrated certain epitopes as fibrillin positive fibers, supporting the elastic microfibril theory of its production.

3. AMYLOID THEORY:

Glenner et al. [12] in 1972, consider amyloid to result from enzymatic (lysozomal) fragmentation of long chain proteins (often immunoglobulins) into polypeptides, which polymerize spontaneously into an antiparallel beta-pleated sheet configuration, of which Congo red dichroism is probably the histochemical counterpart. They have thus suggested the concept that under certain conditions, a pathogenic protein can be formed by proteolysis of an innocuous precursor.

J Berlau et al.[38] examined aqueous humour in eyes with pseudoexfoliation syndrome for protein composition. Aqueous humour of 43 PXF specimens and 32 non-PXF specimens were collected during cataract or glaucoma surgery was screened for amyloids. This screening was performed by Congo red staining coupled with polarised light microscopy. Findings of the aqueous sample suggested that the pseudoexfoliation syndrome was associated with amyloid of a serum protein.

4. LYSOSOMAL THEORY:

A J Dark et al.[12] suggested that the pre-equatorial epithelial cells synthesizes long-chain- zonule-like proteins, which are then converted by lysozomal enzyme into small molecules which are capable of polymerising both within the capsule and in relation to nearby aqueous-bathed structures. Peeling or exfoliation of capsule in PXF disease is not readily explained from the information available. The numerous organelles scattered over the anterior lens capsule in PXF disease suggest that lysozomal enzymes could also play a role in exfoliation.

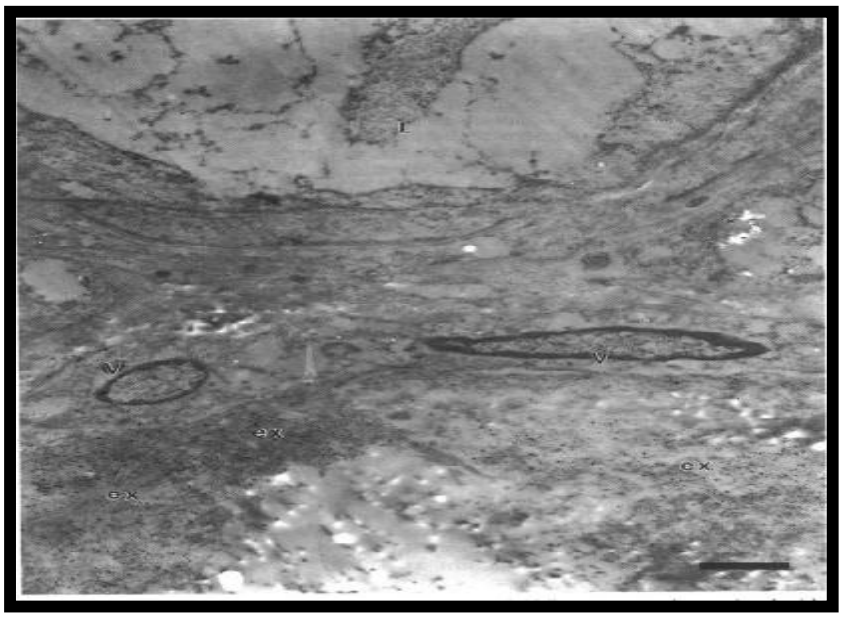
The immunohistochemical reports demonstrated lysosomal enzymes within pseudoexfoliation aggregates suggesting that zonular disintegration is facilitated by

proteolytic mechanisms. Histochemical evidence of high acid phosphatase activity was seen suggesting that lysozymes were involved in the production of exfoliation material. Proteolytic enzymes present in lyzosomes may facilitate granular disintegration. Immunochemical studies have revealed heparin sulphate, chondroitin sulphate proteoglycans in PXF material. [49]

5. OXIDATIVE STRESS:

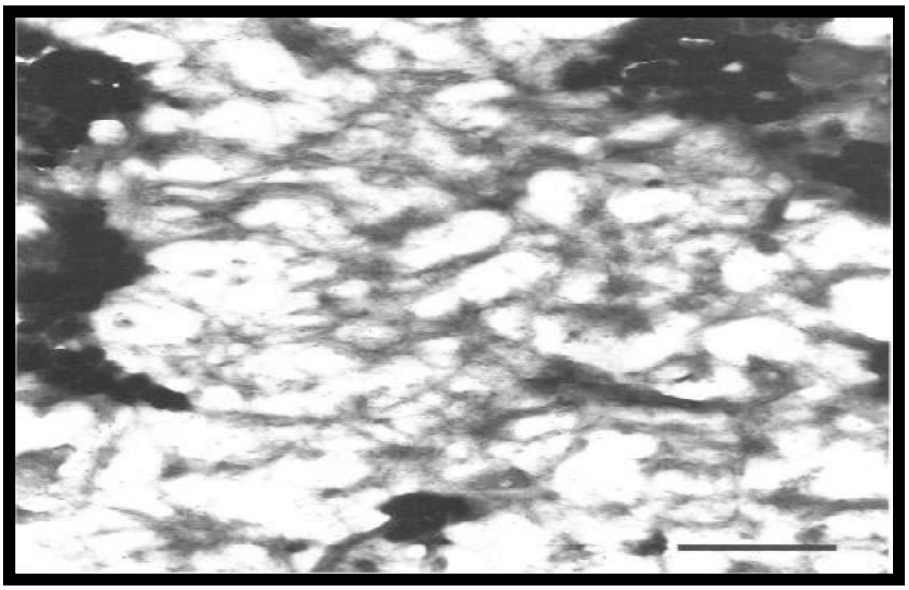
Elevated level of serum alpha-1 antitrypsin in PXF patients denotes the presence of inflammation. In a study conducted by Cumurcu T et al. [39] serum total antioxidant capacity (TAC) and total oxidant status (TOS) levels were determined. It is found that there is significant increase in serum TOS and significant decrease in serum TAC in PXF patients and concluded that role of oxidative stress in PXF.

FIGURE 2 :



Immunogold labelling of the extracellular matrix - Exfoliation aggregates (ex) labeled for amyloid P component, is associated with vascular supporting cells (V) of an exfoliative iris vessel. [36].

FIGURE 3 :



Exfoliation fibres are labeled with antibodies against elastin associated glycoprotein [36]

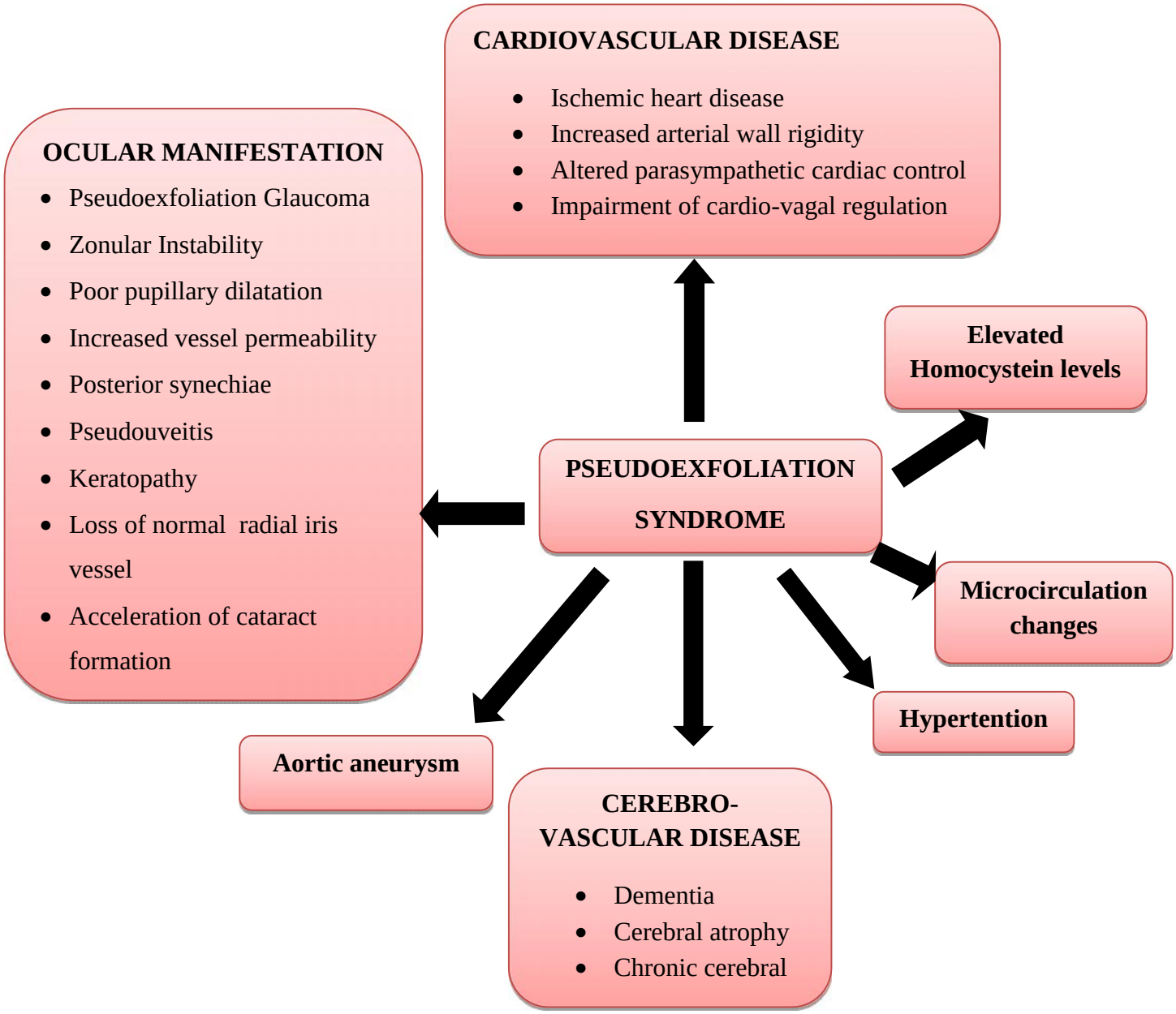
CLINICAL FEATURES OF PSEUDOEXFOLIATION SYNDROME :

Can be described under 2 categories:

A. Ocular manifestations

B. Systemic manifestations

FIGURE 4 :



Clinical features of pseudoexfoliation syndrome

OCULAR MANIFESTATIONS :

1) CONJUNCTIVA : (40, 41, 42, 43)

Clinically the conjunctiva appears normal. But tear secretion and film stability seems to be influenced by pseudoexfoliation syndrome. On electron microscopy, typical peudoexfoliation filaments were found in the connective tissue of the conjunctiva. PXF seems to alter basic feature of goblet cell morphology, thus affecting tear film stability. Further remarkable changes of mucin pockets, irregular distribution, various forms of size and appearance and even complete collapse seen. Also there is loss of regular limbal vascular pattern as seen in fluorescein angiography. [40]

PXF material is almost invariably found in association with fibroblasts of the Tenon's capsule, not only in the involved eye, but also in the fellow eye. Tear osmolality is higher and tear film breakup time lower in PXF compared with controls, suggesting that PXF predisposes to dry eye syndrome. Increased levels of the inflammatory marker MMP-9 was reported elevated by immunoassay. [41]

In an electron microscopic study, Parekh et al. [42] reported that 26 of 32 patients (81%) with clinically unilateral PXF had pseudoexfoliation material on conjunctival samples of the clinically unaffected eyes.

Tasha T et al. [22] suggested that patients presenting in one eye will definitely show pseudoexfoliation material in the other eye on conjunctival biopsy. Exfoliative material (PXM) has been found in the conjunctiva of fellow eyes in unilateral PXF. It has been postulated that the conjunctival changes may precede the development of

PXF material on the lens surface, this idea has led Prince et al [43] to define a category of patients that they refer to as PXF suspects.

2) CORNEA: (44, 45, 46, 47)

The corneal endothelium is essential for maintenance of normal corneal hydration, thickness, and transparency. This cellular monolayer is highly vulnerable and has only limited regenerative capacity. In patients with pseudoexfoliation syndrome, quantitative and qualitative morphological changes of the corneal endothelium have been demonstrated in specular and electron microscopic studies. It has been postulated that these changes represent an abnormal or unstable endothelium, predisposing to an endotheliopathy.

A study conducted by K Miyake et al. [44] using specular microscopy and computer-assisted morphometry, showed significantly lower cell density than endothelium from control eyes. There may be even nonspecific changes of the corneal endothelial cells like thinning of the cells, cytoplasmic vacuolization, phagocytosis of melanin granules and abnormal extracellular matrix production. This leads to increase in central corneal thickness, reflecting early corneal dysfunction.

By transmission electron microscopy, large clumps of typical pseudoexfoliation material were found adhering to the corneal endothelium and masses of pseudoexfoliation material were incorporated into the posterior Descemet's membrane. In the affected areas, the endothelial layer appeared irregular and discontinuous, with loosely adherent, degenerating cells producing pseudoexfoliation fibers and fibroblastic cells spreading to cover denuded Descemet's membrane. [46]

Pseudoexfoliation associated corneal damage is likely multifactorial in etiology. Several theories exist, including the penetration of pseudoexfoliation material towards Descemets membrane breaking the hexagonal connections and signaling of the endothelial layer, promoting apoptosis, hypoxia to the anterior chamber with increased antioxidant stress and reduced ascorbic acid levels, changes in the blood-aqueous barrier, vascular endothelial dysfunction, compression of endothelial cells from elevated IOP, changes in levels of transforming growth factors (increased TGF- α1 and TGF- β) and ratios of MMPs (Matrix metalloproteinase) and TIMPs (Tissue inhibitor of metalloproteinases) promoting matrix accumulation in the affected tissues, and changes in cytokine/chemokines in the anterior chamber and cornea [47]

3) AQUEOUS HUMOR AND ANTERIOR CHAMBER :

It has also been demonstrated that an impairment of the blood-aqueous barrier is frequently associated with PXF [5, 8] leading to an altered composition of aqueous humour. Increased aqueous protein concentrations were reported as compared to age-matched controls as well as changes in the levels of alpha1-lipoprotein and caeruloplasmin, transferrin and fibronectin. Electrophoretic analyses of aqueous proteins demonstrated either a prominent band at 12.5 kDa or at 16.3 kDa in aqueous humour of PEX patients. [38]

4) IRIS AND PUPIL :

The other ocular structure commonly affected is the iris, involvement of which can be evidenced by poor dilatation, transillumination defects and exfoliative deposits at the margin of iris vessels demonstrated on electron microscopy. Pseudoexfoliative material is frequently observed on both the anterior and posterior surface of the iris.

Due to the movement of iris against the lens there is deposition of grayish flakes over the pupillary margin making it appear irregular. It is usually associated with poor pupillary mydriasis due to atrophic and fibrotic changes in sphincter muscle of iris because of tissue hypoxia. Also reduced stromal elasticity by accumulation of flaky material causes poor mydriasis. Iris appears more rigid. Pseudoexfoliation syndrome leads to formation of synechiae between iris and the anterior capsule of lens. There is iris ischemia and neovascularisation due to deposition of pseudoexfoliative material on the vascular endothelium of the iris. Histological changes in the dilator muscle showed disorganized and degenerative muscle fibres. [42]

Loss of pigment from the iris sphincter area and the pigment deposition in the anterior chamber structures is characteristic feature of pseudoexfoliation syndrome. The material on the lens causes dispersion of pigment epithelial cells of iris at the pupillary margin and sphincter area with deposition of pigment into anterior chamber. This loss of iris pigment and its deposition throughout the anterior segment structures is manifested in various ways as loss of pupillary ruff, increased trabecular pigmentation, sphincter region transillumination defect and pigment deposition on the iris surface. Extensive depigmentation of iris is seen all over the sphincter region, which gives a moth eaten appearance on transillumination at the pupillary area. [42]

Virtually all iris cell types are involved in PXF material production and deposition. Clinically iris is characteristically rigid with reduced dilating properties. Dispersion of melanin granules, after pharmacological dilation, due to rupture of degenerative posterior pigment epithelial cells, may result in acute rise in IOP. [47]

Iris stromal vessels, because of deposition of fibers in the adventitia, may become obliterated resulting in hypoperfusion and iris microneovascularization.

Neovascularization may result in microhyphema after pharmacologic dilation. Pseudoexfoliative ocular ischemia may play a role in cataract formation too. Iris vasculopathy may be associated with a chronic breakdown in the aqueous barrier, that may manifest as pseudouveitis with posterior synechiae and elevated aqueous flare.(47)

Posterior synechiae are common in PXF eyes due to adherence of the posterior pigment epithelium to the PXF coated anterior lens capsule or to miotics that inhibit iris movement. A combination of PXF material deposition in the stroma and muscle tissue with vascular disorders leads to hypoxia (Repo et al.1995) and tissue degeneration that result in reduced dilating properties of iris (Asano et al. 1995). Even the pupil in PXF eyes may be smaller (suggesting a defective dilator muscle or reduced sympathetic innervation). (47)

Parodi et al. (42) observed that eyes affected by PXF glaucoma showed signs of microneovascularisation (marked stromal tufts and marked plexi), and anastomotic vessels (peripheral loop, lesser circle and oblique vessels). The microvascular abnormalities at a microscopic level may be responsible for the different phenotypes representing areas of anastomic tufts or different patterns of neovascularization at different locations giving rise to the diverse pattern of deposits in this entity. These would therefore suggest that the source of the deposits in the eye to be the iris blood vessels (explaining why this is a systemic disease with vascular ischemic episodes) while different ocular features or pattern of deposits are due to different epigenetic influences. (42)

5) CILIARY BODY AND ZONULES : (49)

A weak zonular apparatus has been postulated to account for the high incidence of phacodonesis, lens dislocation, and vitreous complications during

cataract surgery in eyes with pseudoexfoliation syndrome. The production of pseudoexfoliation material by both the nonpigmented ciliary epithelium and the pre-equatorial lens epithelium resulted in typical alterations of the zonules at three levels.

1) At their origin and anchorage in the ciliary body, the zonular bundles were separated from the disrupted basement membrane of the nonpigmented epithelium by intercalating pseudoexfoliation fibers.
2) In the pars plicata of the ciliary body, pseudoexfoliation material infiltrated the zonular bundles passing alongside the ciliary processes leading to zonular rupture.
3) At their attachment to the anterior lens capsule, the zonular lamella was focally lifted and subsequently ruptured by pseudoexfoliation masses erupting through the capsular surface

The immunohistochemical demonstration of lysosomal enzymes within pseudoexfoliation aggregates indicates that proteolytic mechanisms facilitate zonular disintegration.

6) LENS : (42)

Accumulation of whitish material deposits is seen on the lens capsule. Typical the bull's eye pattern of deposition is due to the rubbing movement of the iris on the surface of lens, producing a concentric double ring pattern. Three areas are observed. The inner central zone, equal to the pupil diameter (almost can be absent in 20% of cases). The intermediate clear zone, due to the rubbing of iris on the anterior surface of lens, peripheral area containing radial striations. It has been observed that these patients have higher percentage of nuclear sclerosis. Weakening of the zonules predisposes to phakodonesis.. Lens dislocation is more common inferiorly.

A radial pattern of deposits as seen in this disease signifies deposits arising from the iris vessels due to breakdown of blood aqueous barrier or may indicate chronic rubbing of the iris against an ageing lens. The pattern of these deposits is uniquely seen as peripheral, fine and radially oriented. In later stages, the peripheral lines were observed to coalesce indicating that the radial pigmentary may denote an earlier stage of the disease process along with pupillary ruff atrophy. So the possibility that the classical PXF deposit arises from chronic rubbing of two surfaces with exudation from vascular structures in close apposition between the two surfaces.

Based on study and observations, Aparna Rao et al [(42)] suggest clinical PXF stages :

1.Radial Pigmentary Form (RP Form) (Earlier Described Pregranular Form) :

Here the altered blood aqueous barrier would be disturbed which would cause pigment deposition by iris friction with the anterior lens surface evident as radial pigment with normal IOP. The only clinical feature pointing to PXF in these eyes would be pupillary ruff atrophy. While glaucoma is not very common, secondary lens induced glaucoma may be seen at this stage. The RP form had peripherally arranged fine radial pigmentary lines on the anterior lens surface extending from the periphery to the centre and sparing the pupillary area. There was intervening clear space between the pigmentary lines with occasional rounded pin-point pigment collections interspersed between the radial lines with no curling of the capsule seen in any eye.

B) RP With Classical Or Combined Form :

In this stage there is early coalescence of deposits into classical form of peripheral ring. The exudation of low molecular weight proteins caused by loss of

chaperone effect of certain proteins with chronic rubbing causes alteration in the pattern. There is pseudoexfoliative deposits with slow and gradual trabecular dysfunction by ECM remodeling and/or mechanical damage. These features may be bilaterally asymmetric. Combined (CR) form of pseudoexfoliation showed features of classical peripheral or central ring with radial pigmentary pattern in the same eye.

C) Classical PXF :

In this stage, there is iris stromal hyalinization with severe iris vessel hyalinization due to precipitation of large molecular weight protein The trabecular damage evidenced by raised IOP and optic nerve damage. In these eyes, poor dilatation and curling of the anterior capsular membrane may indicate early glaucoma.

Pragya Parmar et al. [(50)] described a case report in which 134 consecutive eyes with exfoliation and senile cataract undergoing cataract surgery were included in study. Of these, 5 eyes (3.7%) were noted to have anterior "lenticonus". All 5 eyes had a central conical bulge in the anterior capsule associated with exfoliation material on the anterior lens capsule, pupillary border and the corneal endothelium. They concluded that it might represents either a thick central disc of heaped up exfoliation material or a genuine conical protrusion of the anterior capsule due to lax zonules.

7) ANGLE CHARACTERISTICS : (51, 52, 53)

Gonioscopy should be performed in all eyes with pseudoexfoliation syndrome. Pigment and flecks of greyish material are seen over the structures of the angle, usually along the Schwalbe's line, where the pigment dispersion pattern is named as "Sampaolesi's line".

Angle characteristics in pseudoexfoiation syndrome are:

- Hyperpigmentation of trabecular meshwork, mostly in the inferior angle. The pigment has a patchy distribution. It increases in eyes with pseudoexfoliative glaucoma.
- A scalloped wavy band of pigment running on to or ahead of Schwalbe line (Sampaolesi line) which is an early sign.
- Flecks of pseudoexfoliation deposits on the trabeculum result in 'dandruff-like' appearance.
- Narrow angles if present, there is an increased risk of angle closure, possibly due to zonular laxity.

8) TRABECULOPATHY : (52, 53, 54)

One of the commonest causes of secondary open-angle glaucoma or ocular hypertension is Pseudoexfoliation Syndrome. It is usually asymmetric and bilateral. As compared to primary open angle glaucoma prognosis is generally worse due to higher fluctuations in IOP levels, more severe optic nerve and visual field damage.

Patient present with higher levels of IOP compared to those affected by primary open angle glaucoma. Usually failure of medical management is seen in these patients. The incidence of pseudoexfoliation glaucoma increases with age and prevalence is higher in 60 and 70 years of age, affecting men more than women. Probable causes of elevation of IOP include trabecular blockage possibly due to trabecular cell dysfunction due to a combination of blocking of the trabeculum by pseudoexfoliation material and/or pigment released by iris causes increased resistance in the aqueous outflow.

A patient with unilateral pseudoexfoliation glaucoma and only pseudoexfoliation in the other eye is at high risk (50% in 5 years) of developing glaucoma in the other eye.

Pseudoexfoliation syndrome accounts for 15-20% of cases of open angle glaucoma. In patients with pseudoexfoliation syndrome, at the time of diagnosis 20% have glaucoma and increased IOP. Patients who have pseudoexfoliation syndrome but not glaucoma should be considered to have increased risk to glaucoma, as 15% of such patients develop increased IOP within 10 years. At the time of diagnosis glaucomatous damage is more severe and it progresses more rapidly in eyes with Pseudoexfoliation.

Pseudoexfoliation Syndrome may also lead to development of angle closure glaucoma. Pupillary block may be caused by combination of miotic-induced circular posterior synechiae, increased thickness of iris or iris rigidity or anterior subluxation and dislocation of lens due to zonular weakness or dialysis.

Electron microscopy shows pathologic changes in trabecular meshwork and deposition of pseudoexfoliative material in the juxtacanalicular tissue adjacent to Schlemm's canal. This suggests local production of pseudoexfoliative material in the juxtacanalicular portions of the meshwork, particularly by the Schlemm's canal endothelium. Progressive accumulation of pseudoexfoliative material in the advanced stages leads to edema of the juxtacanalicular tissue and a marked disorganization of Schlemm's canal architecture like tightening of the canal lumen, disruption of the endothelial lining, fragmentation into smaller channels, collapsing of both walls of the canal, and degenerating and partial obliteration endothelial cells.

Trabecular meshwork obstruction by pseudoexfoliative material and degenerative changes in the area of greatest outflow resistance seems to be contributory factors for the chronic raised pressure and glaucoma. Also there is increased aqueous protein levels due to defective blood-aqueous barrier and dispersion of melanin pigment from the iris pigment epithelium.

Corneal endothelial proliferation seen ahead of Schwalbe's line above the trabecular meshwork further contributes to ocular hypertension. Sometimes the trabeculum is covered by a pretrabecular layer of abnormal extracellular matrix, including pseudoexfoliative material produced by proliferating endothelial cells of cornea. This is consistent with the finding that, decreased oxygen content increases the corneal endothelial cell proliferation in tissue culture and also with the hypoxia measured in the anterior chamber in eyes with pseudoexfoliation.

A study determined whether severity of the glaucoma correlates with gonioscopic features of the anterior chamber angle in patients with pseudoexfoliation syndrome. It demonstrated that there was no obvious association between severity of glaucoma and angle characteristics. Hence the mechanism of damage is similar to that seen in open angle glaucoma.

8) VITREOUS :

Vitreous changes are routinely seen in pseudoexfoliation Syndrome since hyaluronic acid and pseudoexfoliation material are both acid mucopolysaccharides. A change in composition of aqueous in pseudoexfoliation syndrome deranges metabolism of hyalocytes causing impaired production of hyaluronic acid and liquefaction of vitreous. Vitreous prolapse from zonular defect may be present before surgery or occur during surgery.

9) RETINA : (47, 55, 56)

Linner et al. [47] found increased optic nerve pallor in PXF patients versus control patients despite statistically equal IOP measurements. Pulsatile ocular blood flow has been shown to be reduced in unilateral PXF compared to the unaffected fellow eye, in addition to reduced laminar blood flow with progression of PXF glaucoma (PXFG)..

More recently, PXF and PEXG eyes have been found to have significantly lower posterior choroidal thicknesses, thought to be related to increased vascular resistance, compared to fellow unaffected eyes and healthy control eyes. Even central retinal vein occlusion seems to be more commonly seen in eyes with PXF.

PXF patients with normal IOP and visual fields have thin RNFL. Eltutar et al. [56] compared pseudoexfoliation syndrome with control subjects. Macular NFL, ganglion cell layer and inner plexiform layer, total peripapillary nerve fiber layer and ONH parameters were compared. They showed that inferior, temporal, nasal and total peripapillary nerve fiber layer thickness thinner than control subject.

SIGNS RELATED TO EXFOLIATION SYNDROME :

- **Diagnostic signs**
    - Exfoliative material on lens surface, pupillary margin
- **Suggestive signs**
    - Loss of papillary ruff
    - Iris sphincter region transillumination
    - Pigment whorl on iris surface at sphincter

- Pigment dispersion in anterior chamber following dilation in elderly patients
- Heavy trabecular pigmentation of trabecular meshwork in the elderly

- **Alerting signs**
  - Phacodonesis in the absence of trauma in elderly patients
  - Posterior lens subluxation in elderly patients
  - IOP rise after pharmacological dilatation
  - Marked asymmetry of IOP (33%) in the absence of other obvious cause in the elderly

EXTRAOCULAR SYSTEMIC MANIFESTATIONS:

Recent studies have demonstrated the presence of PXF material in a variety of tissues; such as lung, heart, brain, and vessels. These findings have led to the hypothesis that PXF is more likely a systemic disorder with multiple clinical manifestations. Focally these pseudoexfoliation deposits are present in the interstitium of fibrovascular connective tissue septa of various organs. The deposition of pseudoexfoliation material in heart muscle cells and extraocular muscle cells suggest, muscle cells are also involved. Ultrastructural and immune-histochemical studies shows similarities both in intraocular and extraocular sites.

1) CEREBROVASCULAR DISEASE :

Blood flow velocities of the middle cerebral artery have been found to be decreased in patients with PXF-related glaucoma and this could predispose to cerebrovascular disease. Also, total cerebral perfusion in these patients is lower than normal and previous imaging studies have demonstrated diffuse cerebral ischemic changes and cerebral infarcts. Another study showed that chronic cerebral diseases

such as senile dementia, cerebral atrophy, and chronic cerebral ischemia are more common in patients with PXF-glaucoma. In the same study, patients with PXF-glaucoma had higher probability of developing acute cerebrovascular events compared to patients with non-PXF related glaucoma. Alzheimer's disease has also been linked to PEX syndrome. [5, 15]

In 1995 Repo et al. [4] determined 42% of patients who have had the transient ischaemic attack also have pseudoexfoliation syndrome. In that study, Color Doppler imaging in the ophthalmic artery blood flow spectra of patients who have had transient ischaemic attack and PEX showed an increasing index of resistance in the ophthalmic artery.

Janciauskiene et al. [4] examined the presence of Alzheimer's disease related proteins, such as Alzheimer's peptide and serine proteinase inhibitor, α-1-antichymotrypsin in cataractous PXF eyes. Alzheimer's peptide was found in 38% of all cases. Similarly Li et al.[4] studied the amyloid P protein in pseudoexfoliative patients. Amyloid P protein was demonstrated by immunostaining in ocular and conjunctiva tissue.

2) AORTIC ANEURYSM AND PERIPHERAL VASCULAR DISEASE :

A high frequency of abdominal aortic aneurysm (AAA) has been reported in patients with PXF syndrome. In a prospective study by Schumacher et al. where 55 patients that required surgery for aneurysm of the abdominal were examined and 44% of them were having ocular manifestations of PXF. Diffuse fibrosis and elastosis of the tunica intima and accumulation of PXF deposits in the adventitial and subendothelial connective tissue were the most common histopathological findings in patients with coexistence of AAA and PXF. [5, 15]

Similar study conducted to show the association between abdominal aortic aneurysms and pseudoexfoliation syndrome. Histological samples of aortic-wall was obtained in patients with ocular pseudoexfoliation material and showed focal accumulation of pseudoexfoliation material in the subendothelial connective tissue and adventitia. Also there were elastosis of the tunica intima and pronounced fibrosis. These findings suggested that there is an association between abdominal aortic aneurysms and pseudoexfoliation syndrome. [39]

Schumacher S et al. [52, 58] examined 55 patients with aneurysms of abdominal aorta and 41 controls with carotid artery occlusion. 24 of 55 patients with aortic aneurysm showed signs of manifest or early-stage pseudoexfoliation syndrome. 8 of 41 control patients showed manifest or early ocular pseudoexfoliation . These findings including histopathological examinations, suggested an association between aneurysms of the abdominal aorta and PXF.

On the other hand, in a study conducted by Jaana Hietanen et al. [57, 59] where total 77 patients who recently got operated for abdominal aortic aneurysm were examined for pseudoexfoliation and concluded that no proposed connection between PXF and abdominal aortic aneurysm.

3) HYPERTENSION : (5, 15)

Several studies have correlated PXF syndrome with arterial hypertension. The Australian Blue Mountains Eye Study, a large study including a total of 3,654 patients, showed that PXF is significantly associated with a history of hypertension, angina, or both. In another large cross-sectional study in Japan, which included 1,884 patients, the prevalence of arterial hypertension was high and significantly associated with PXF.

Endothelial dysfunction, oxidative stress, elastosis, and impaired autonomic regulation are some of the proposed mechanisms that may account for the high prevalence of arterial hypertension in patients with PXF syndrome.

Cross-sectional study conducted by Miyazaki et al. in 2005 where, age-adjusted and multivariate-adjusted logistic regression analyses found significant AH association with PXF. Another possible cause has recently been described by Gonen et al. who depicted a high incidence of renal artery stenosis in PXF individuals.

4) ELEVATED HOMOCYSTEINE: (5, 9, 60, 61, 62, 63)

Homocysteine is an independent risk factor for cardiovascular disease. It is associated with vascular injury and, thus increases risk for stroke, CAD and venous thrombosis. Possible mechanisms of action include endothelial dysfunction, platelet aggregation and perturbation of clotting factors. In addition, alteration of the extracellular matrix of several tissues (mainly vessels), elastolysis and oxidative stress may be implicated.

Vessani RM et al. [(9)] tested 25 patients with exfoliation syndrome and 50 with exfoliative glaucoma and 25 with normal tension glaucoma and 24 control subjects. Fasting plasma homocysteine concentrations were measured by fluorescence polarization immunoassay. And concluded that elevated plasma homocysteine a risk factor for cardiovascular disease, is more common in exfoliation syndrome and exfoliative glaucoma.

Hyperhomocysteinemia has been suggested as a possible cause for increased vascular risk, because of the potential to trigger the abnormal matrix accumulation in PXF patients. High levels of plasma homocysteine have been found in patients with

PXF syndrome and PXF glaucoma. Homocysteine concentration has been found to be elevated or unaffected in aqueous humor of patients with PXF glaucoma, but increased in PXF glaucoma patients tears.

A study conducted by Roedl JB et al [(62)] showed that Vitamins B6, B12 and folate, which are involved in homocysteine metabolism and negatively correlated with total plasma homocysteine levels, have been reported to be decreased in PXF glaucoma patients, though not differing between PXF and control groups in another study. On the contrary, Turacli et al. [(62)] did not confirm the relationship between plasma homocysteine and PXF syndrome.

Raposo B et al. [(63)] suggested that homocysteine in a pathophysiological range, significantly inhibits LOX-1 in endothelial cells by a complex mechanism involving LOX inhibition together with a transcriptional – mediated decrease of LOX-1 expression. Also it has been suggested that the inhibition of LOX-1 could promote alterations of ECM composition contributing to the pathological changes observed in the vascular wall of hyperhomocysteinemic patients. This could partially explain the higher prevalence of Vitamin B deficiency in other diseases that have been linked to PXF, such as Alzheimer's disease.

5) EFFECT ON MACROCIRCULATION AND MICROCIRCULATION :

Functional changes in systemic macrocirculation and microcirculation have been found in PXF patients. PXF deposits have been associated with many endothelial cell markers, collagen, fibroblasts, and elastin. Moreover, it has been shown that patients with PXF demonstrate impaired endothelial function.

Also, PXF patients have been found to have raised inflammatory markers, cytokines, and markers of endothelial dysfunction such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), high sensitivity C-reactive protein (hsCRP). However, the fact these findings have not been consistent in all studies suggests that the pathogenesis of PXF is more complex and likely multifactorial. [5, 15]

In a study conducted by Z Visontsi et al. [64] in order to investigate systemic arterial function in patients with PXF and PXF glaucoma, using the ultrasound wall tracking system they measured end diastolic diameter and pulsatile distension of the common carotid artery, and calculated baroreflex sensitivity (BRS). And found that characterizing arterial distensibility were significantly lower and stiffness, a parameter which characterizes arterial rigidity, was significantly higher in PXF and PXF glaucoma than in the control group. These results suggest that the arteries become more rigid as a result of PXF.

Praveen M R et al. [8] in his study used an Ankle Brachial Index (ABI) to diagnose peripheral vascular diseases. The mean least ABI value was lower in cases with established PXF as compared to control, suggested that peripheral vascular disease are more common in patients with pseudoexfoliation syndrome.

6) AUTOMONIC DYSFUNCTION :

Baroreflex sensitivity (BRS) is significantly reduced in patients with PXF and PXF glaucoma, indicating a altered parasympathetic cardiac control. Effects of PXF material on autonomic dysfunction have not been thoroughly addressed, but evidence to support that the parasympathetic system is also affected in these patients.

Hollo et al. [15] identified decreased cutaneous capillary blood flow and diminished cutaneous flow reactions to cold and warmth provocation, without any change in plasma endothelin-1 levels. The same research group showed that baroreflex sensitivity was significantly reduced in patients with PXF, suggesting a pathologically altered parasympathetic vascular control. The above findings are supported by another study by the same group which reported statistically significant impairment of cardio-vagal regulation and increased pulse wave velocity in PXF.

7) HEARING:

The inner ear is a complex organ. The tectorial and basilar membranes of the inner ear similar to like the anterior segment structures of the eye, and are derived from the neural ectoderm. PXF material has been found on the tectorial and basilar membrane of the inner ear. Accumulation of pseudoexfoliative material on these structures will interfere in normal hearing threshold levels due to dysfunction of the mechanoreceptors of the ear, resulting in hearing loss. Also these PXF material may cause alteration in the vibration induced by sound and can affect the hearing in an individual.

In a study conducted by Nandini VS et al. [65] showed bilateral sensory-neural hearing loss was more prevalent among the pseudoexfoliation group. According to the severity of the hearing loss, most of the patients had mild sensory-neural hearing loss. There was no significant difference between the laterality of the hearing loss. Similar results were shown by a study conducted by Yazdani et al.[65] where sensory-neural hearing loss (SNHL) in pseudoexfoliation syndrome (PXF) patients was more common (88.4%) than in controls (53.6%).

Similarly study conducted by Tatjana S et al.[70] where hearing loss, as a concomitant sign of PXF was present in all patients in comparison with control group.

8) EFFECT ON CARDIOVACULAR SYSTEAM :

- **SYSTEMIC ARTERIAL ENDOTHELIAL DYSFUNCTION :**

Arterial endothelial dysfunction is an independent predictor of future cardiovascular events. Vascular endothelium has a major role in the control of blood flow by releasing factors which may act either to contract the vascular smooth muscle, such as endothelin-1, or to relax it, such as nitric oxide. Atalar et al. [5] found an impaired endothelial function in the brachial artery of patients with PXF syndrome, which wasassessed by vascular response to reactive hyperemia and sublingual nitroglycerin using high-resolution ultrasound. Endothelial dysfunction was attributed to the pseudoexfoliative fibrillar accumulation in the vessel wall.

A major theory of atherosclerosis is based on lesions that results from an excessive fibroproliferative response to various forms of insult to the endothelium and smooth muscle of the vascular wall. Endothelial exfoliation has been defined as thin, friable, mobile and translucent tissue, loosely adherent to the vascular wall that may play a functional role in thrombus formation. [7]

In a study conducted by M citirik et al. [4] 50 patients with CAD proven by coronary angiography, and controls with normal coronary angiographic findings were compared in terms of PXF, other vascular diseases, and retinal vascular findings. The number of patients with PXF among CAD patients was substantially larger than controls.

Dustin D et al.[6] conducted a study where various stages of ischemic heart disease, cardiomyopathy, and aortic aneurysm were significantly associated with ocular pseudoexfoliation, Similar study was done French et al. [6] reported significant associations of PXF and PXF glaucoma with a variety of cardiovascular disorders.

Mitchell et al. [7] investigated the relation of pseudoexfoliation to systemic vascular history. They found the history of either angina or hypertension was significantly associated with presence of PXF. The purpose of this study was to determine possible relationships between coronary artery disease (CAD) and PXF. In addition, Sainz Gomez C et al. [10, 57] showed higher prevalence of heart failure in PXF individuals.

Siordia JA et al. [10] reviewed the literature and 18 studies were selected for analysis and concluded that the association between ischemic heart disease and PXF was stastistically significant.

A study conducted by Ulus, Taner et al. [67] where, myocardial TDI measurements (Tissue Doppler Imaging), the mean carotid intima thickness (IMT), total carotid plaque area data were obtained. The peak systolic TDI velocities at the septal and lateral annuli and isovolumic contraction velocity at lateral annulus were significantly lower in patient with PXF, whereas IMT, total carotid plaque area and number were significantly higher.

Similar study conducted by N Demir et al. [68] aimed to investigate the association between PXF syndrome and subclinical myocardial ischaemia using tissue doppler echocardiography. Peak systolic velocities at septal, lateral, anterior and inferior annuluses were significantly lower in patient with PXF. The early diastolic velocity at septal annulus and the ratio of early /late diastolic velocity at lateral

annulus were significantly lower in study group. So they have concluded that there may be an association between PXF syndrome and subclinical myocardial ischaemia in patients who have no signs and syndromes of ischaemia.

Bojic L et al. [(69)] conducted a study to investigate the frequency of asymptomatic left ventricular dysfunction in patient with pseudoexfoliation. A significant difference was found, regard to diastolic filling parameters, so they concluded that possibility of an association between patients with PXF and discrete asymptomatic myocardial diastolic dysfunction.

A study conducted by Tatjana S et al. [(70)] suggested that ischemic heart disease was statistically significantly present in the PXF syndrome and PXF glaucoma patient groups, in comparison with those of the control group also aortic aneurysm was statistically significantly present in patients with PXF syndrome.

MO Akdemir et al. [(71)] conducted a study to determine whether pseudoexfoliation syndrome is associated with coronary artery ectasia or not. Coronary artery ectasia (CAE) is a form of atherosclerotic coronary artery disease that is defined as dilation of an arterial segment to a diameter at least 1.5 times that of the adjacent normal coronary artery. There are several histopathological similarities between CAE and atherosclerosis. The presence of pseudoexfoliation material was more common in patients with coronary ectasia compared with controls.

Sekeroglu et al. [(72)] also showed the relationship between ischemic heart disease and PXF. They investigated 1480 patients who were scheduled for cataract surgery. The patients underwent a comprehensive systemic and eye examination. They found that 242 (16.4%) patients had PXF syndrome and the only systemic disease associated with PXF was ischemic heart disease.

Nilgun Yildirim et al. [73] conducted a study where he found that patients using drugs for cardiac and psychiatric diseases were higher in patients with PXF.

But many studies have failed to show association with cardiovascular diseases A study conducted by Martynas S et al. [1] where association of ocular pseudoexfoliation syndrome with ischemic heart disease, arterial hypertension and diabetes mellitus was studied. In this population based study 1065 participants aged 45-72 years examined. The AH rate was higher in PXF subjects than in non-PXF subjects and the rates of IHD, DM, and cholesterol levels did not differ statistically significantly. And concluded that PXF did not increase risk for IHD, AH or DM.

A study conducted by Emiroglu et al. [5, 74] showed no significant relationship between PXF and aortic aneurysm or peripheral artery disease. Similarly, Tarkkanen et al. [10, 75] failed to show any significant difference in the frequency of hypertension or ischemic heart disease between patients with primary open-angle glaucoma (POAG) and PXF glaucoma.

In the Thessaloniki Eye Study [5, 76] no association was found between PXF and the history of specific or any systemic cardiovascular diseases. Avsar et al .[5,77] found no significant differences in time domain heart rate variability parameters (a measure of cardiac autonomic function) between patients with PXF syndrome and control subjects.

In case of association between PXF and IHD higher mortality in PXF subjects would be expected. In Sweden and Norway, where PXF prevalence is high, no association between PXF and cardiovascular cause for mortality was found. Similarly in Minnesota no association was found between PXF and specific cardiovascular mortality. [66]

METHODOLOGY

The present study was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi to find the prevalence of pseudoexfoliation syndrome in patients with cardiovascular disease and its association with hypertension and diabetes during the period of 1st January 2017 to 31st December 2017. The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belagavi.

SOURCE OF DATA:

The source of data for the present study was drawn from patients attending the outpatient, inpatient and referrals to department of ophthalmology from the cardiology department at KLES. Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

METHOD OF COLLECTION OF DATA

Study Design: A Cross Sectional Study

Study Period: One year – 1st January 2017 to 31st December 2017.

Sample Size:

Sample size of 125 cases.

Sampling Procedure :

Sample size for the study is calculated by following formula:

$n = z_{\alpha}^2 pq \div d^2$

Where, n = sample size

Z_α = for 95% confidence

p = 50%

q = (100-p)

d = 15(error rate)

Selection criteria:

Inclusion criteria –

- All patients with cardiovascular diseases including ischemic heart disease (IHD), myocardial ischemia (MI), angina, congestive cardiac failure, cardiomyopathy diagnosed by 2D Echo, ECG which may or may not be associated with hypertension or diabetes.

Exclusion criteria:

- History of ocular surgery
- History of ocular trauma
- History of uveitis, Glaucoma
- Ophthalmic disease preventing the view of the anterior segment

METHODOLOGY PROPER

All the patients who satisfy the inclusion criteria were included in the study. The patients were enrolled into the study and written informed consent was taken from them by the investigator.

Data regarding demographic parameters such as age, sex, occupation and address were noted on a predesigned proforma by the investigator at the time of first visit.

Detailed history of following symptoms was noted:

- H/O Diminution of vision RE/LE
    - ✓ Duration
    - ✓ Gradual/Sudden
    - ✓ Progression/static
    - ✓ Distant/Near vision
    - ✓ Visual improvement with bright light or dim light
    - ✓ Painful/ Painless
- Diplopia / Polyopia
- Photophobia
- Flashes of light
- Coloured halos
- Floaters
- Watering
- Redness
- Discharge

- Black spots in front of the eye
- H/O Curtain falling sensation in front of the eyes
- H/O wearing glasses
- H/O Diabetes Mellitus, Hypertension or other chronic systemic illness.
- H/O Cardiovascular diseases.

History was followed by ocular examination that included:

1. Visual acuity testing for distance and near using Snellen's distant chart and Jaeger's near vision chart respectively, both unaided and aided.
2. External ocular examination.
3. The pupils were then dilated with a combination of Phenylephrine 5% and Tropicamide 0.8 %. 1 drop was instilled every 15 minutes for one hour.
4. Slit lamp biomicroscopic examination for evidence of the following findings.
    - Pseudoexfoliation material at the pupillary margins.
    - Examination of lens capsule for pseudoexfoliation material deposition.
    - Evaluation of lens for the type of cataract.
    - Phacodonesis or dislocation of lens / frank subluxation.
    - Pseudoexfoliation material on the cornea
    - Anterior chamber depth
    - Iridodonesis.
5. Tonometry using applanation non-contact tonometer
6. Fundoscopy.

STATISTICAL ANALYSIS

- The data was tabulated on Microsoft excel spread sheet.The data was analyzed using SPSS version 20.0. Categorical data was expressed as rates , ratios and percentages.

- Categorical data was compared using Chi Square Test / Fisher Exact Test.

- Significance level of the test was kept at 0.05 at 95% confidence interval.

- Percentage of prevalence of pseudoexfoliation syndrome in cardiovascular disease was computed.

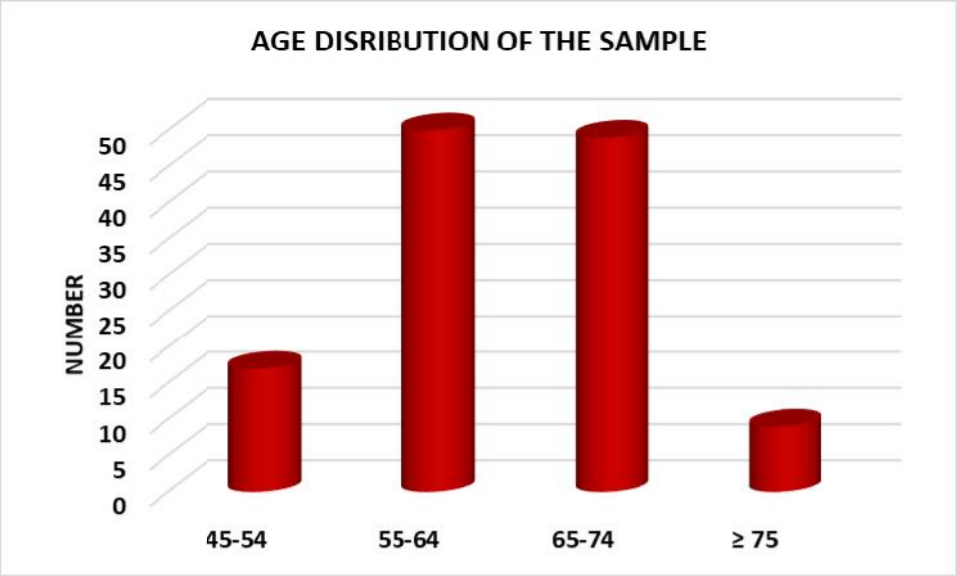
RESULTS

The present study was conducted on 250 eyes of 125 patients with cardiovascular diseases diagnosed by 2D Echo, ECG and underwent ocular examination at Department of Ophthalmology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belagavi. The data obtained was tabulated as below.

TABLE 1: AGE DISTRIBUTION:

AGE	NUMBER	%
45-54	17	13.6
55-64	50	40
65-74	49	39.2
≥ 75	9	7.2
TOTAL	125	100

GRAPH 1: AGE DISTRIBUTION:



As shown in table 1, in our study there were 17(15.6%) patients in the age group of 45-54 years, 50(40%) patients were in the age group of 55-64 years, 49 (39.2 %) in the age group of 65-74 , 9 (7.2%) of above 75 age group .The mean age in our study was 62.86 years .The minimum age was 48 years and maximum age was 85 years .

TABLE 2: SEX DISTRIBUTION :

GENDER	NUMBER	%
FEMALE	22	17.6
MALE	103	82.4
TOTAL	125	100

2 : SEX DISTRIBUTION GRAPH :

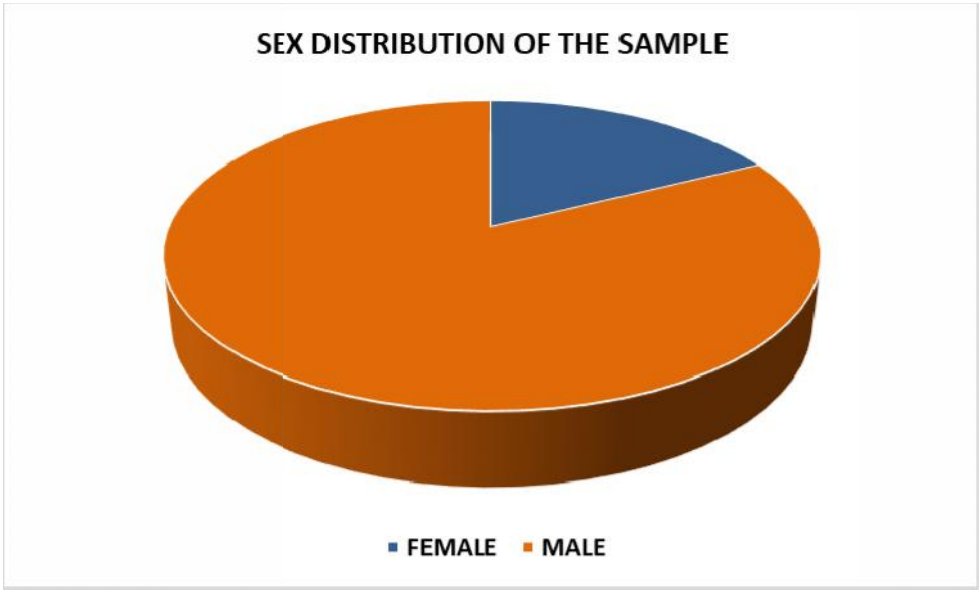
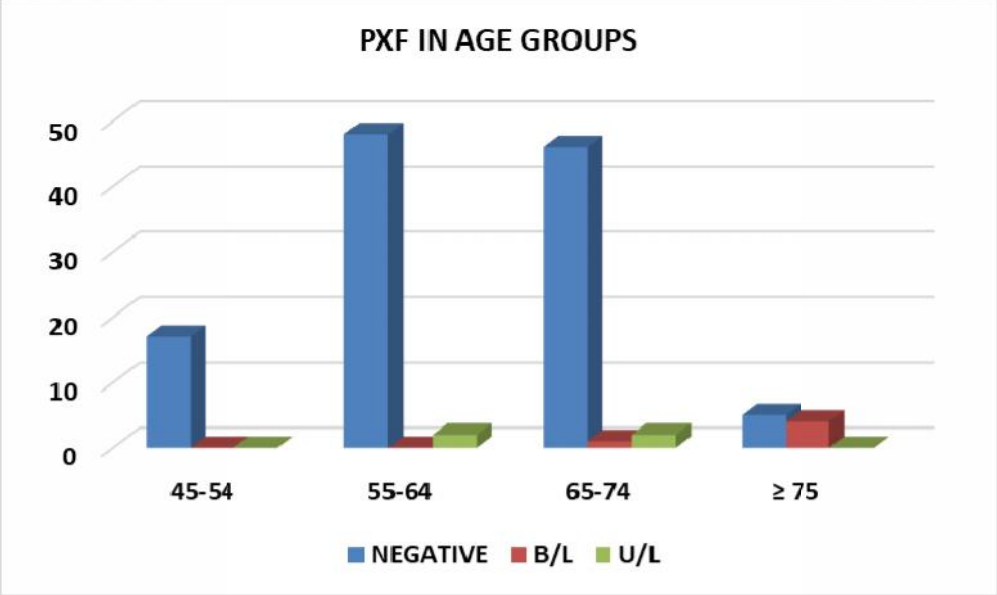


Table 2 shows that in our study 22 (17.6%) patients were female and 103 (82.4%) patients were male.

TABLE 3: LATERALITY :

	AGE				
PXF	**45-54**	**55-64**	**65-74**	**≥ 75**	**TOTAL**
NEGATIVE	17	48	46	5	116
B/L	0	0	1	4	5
U/L	0	2	2	0	4
TOTAL	**17**	**50**	**49**	**9**	**125**

GRAPH 3: LATERALITY:

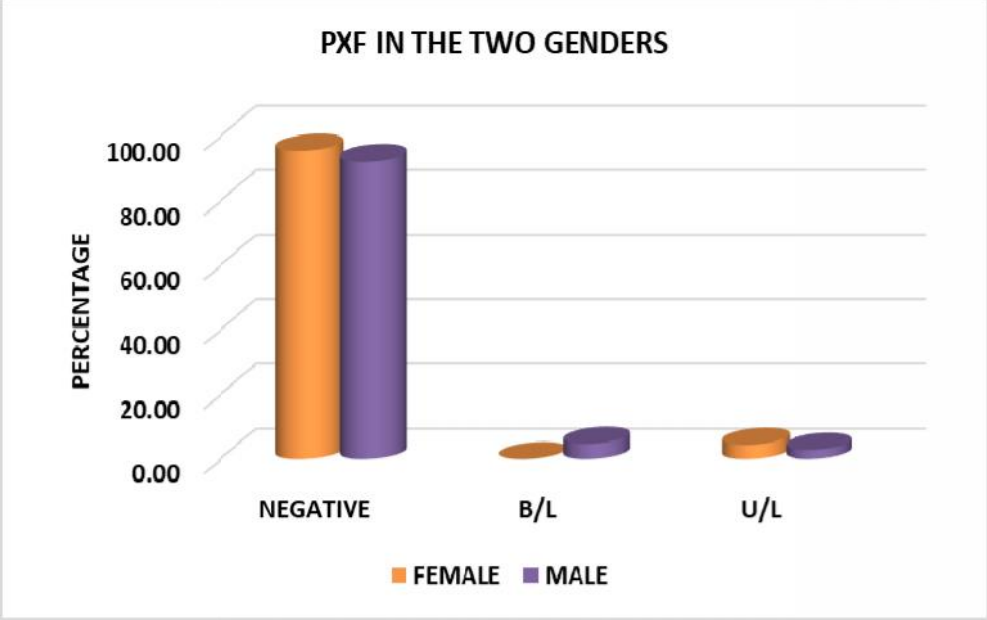


As shown in table 3, in our study 4 (44.44.%) patients had clinical unilateral pseudoexfoliation material and 5 (55.56%) had bilateral involvement

TABLE 4: PXF WITH GENDER:

PXF	FEMALE	%	MALE	%	TOTAL
NEGATIVE	21	95.45	95	92.23	116
B/L	0	0.00	5	4.85	5
U/L	1	4.55	3	2.91	4
TOTAL	22	100.00	103	100.00	125

GRAPH 4: PXF WITH GENDER :

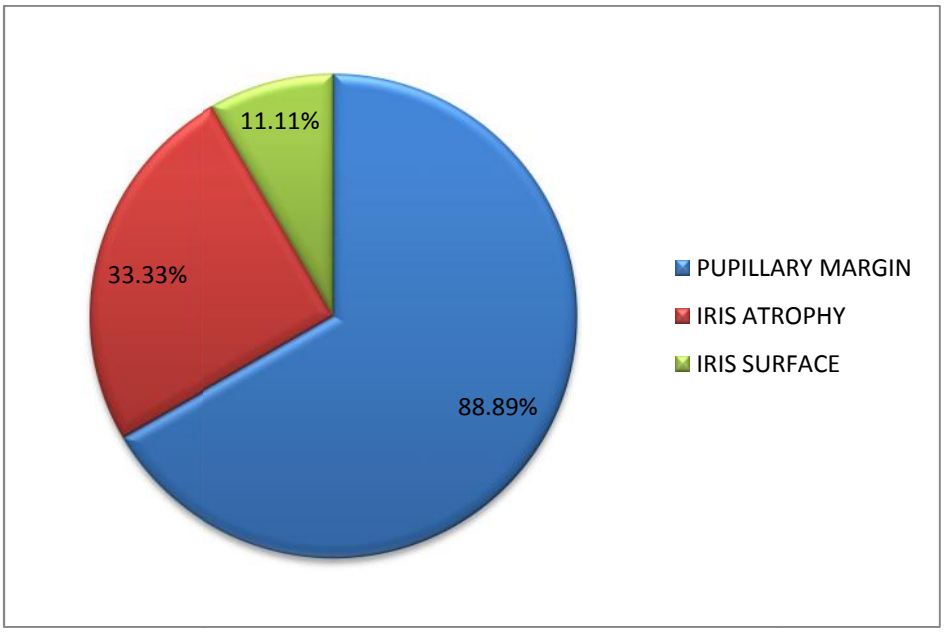


As shown in table 4, in our study 1 (4.55.%) of female patients had clinical unilateral pseudoexfoliation material and 5 (4.85%) male patients had bilateral involvement and 3 (2.91) had unilateral involvement. Using chi-square test the p value is 0.5381 which is not significant. PXF is not associated with gender.

TABLE 5: IRIS CHARACTERISTICS:

PXF	NO OF CASES	%
PUPILLARY MARGIN	8	88.89
IRIS SURFACE	1	11.11
IRIS ATROPHY	3	33.33

GRAPH 5 - IRIS CHARACTERISTICS :



In present study, 88.89% of patients had pseudoexfoliation material on the pupillary margin, 11.11% on the iris surface and 33.33% had iris atrophy as depicted in table 5.

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TABLE 6 : PXF MATERIAL ON LENS :

PXF	NO OF CASES	%
YES	7	77.77
NO	2	22.23

GRAPH 6 : PXF MATERIAL ON LENS :

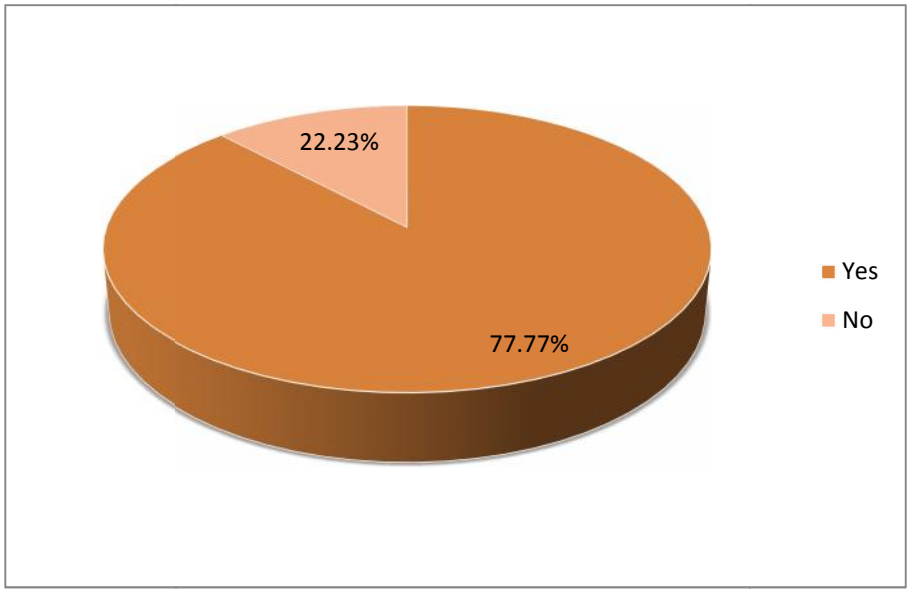
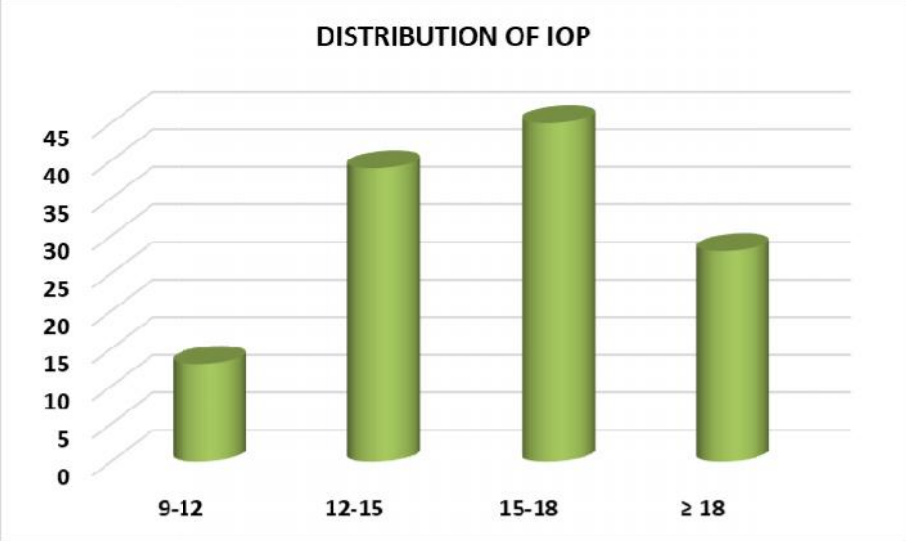


Table 6 showed that in our study, 77.77 % of the patients had PXF material deposited on the anterior lens capsule and 22.23% patients had no PXF deposition on lens capsule.

TABLE 7 - IOP RANGE :

IOP	NUMBER	%
9-12	13	10.40
12-15	39	31.20
15-18	45	36.00
>18	28	22.40
TOTAL	125	100

GRAPH 7 - IOP RANGE :

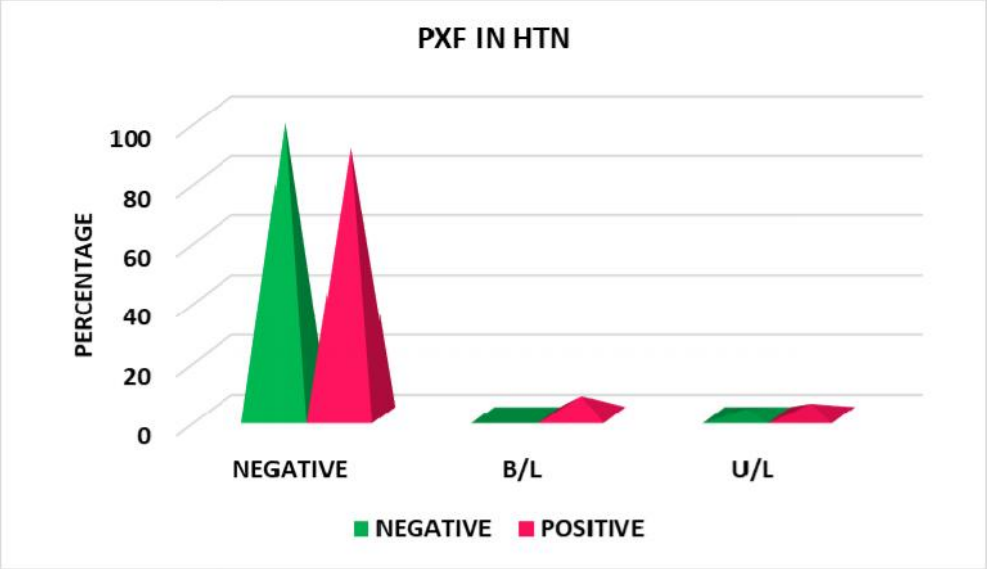


In our study, 13(10.40%) patients had IOP in the range of 9-12 mm Hg, 39 (31.20%) in range of 12-15 mm Hg, 45 (36%) in range of 15-18 mm Hg and 28 (22.40%) patients in range of above 18 mm Hg as shown in Table 5.

TABLE 8 - PXF AND HTN :

	HTN				
PXF	**POSITIVE**	**%**	**NEGATIVE**	**%**	**TOTAL**
B/L	5	6.49	0	0.00	5
U/L	3	3.90	1	2.08	4
NEGATIVE	47	97.92	69	89.61	116
TOTAL	77	100	48	100	125

GRAPH 8 - PXF WITH HTN :

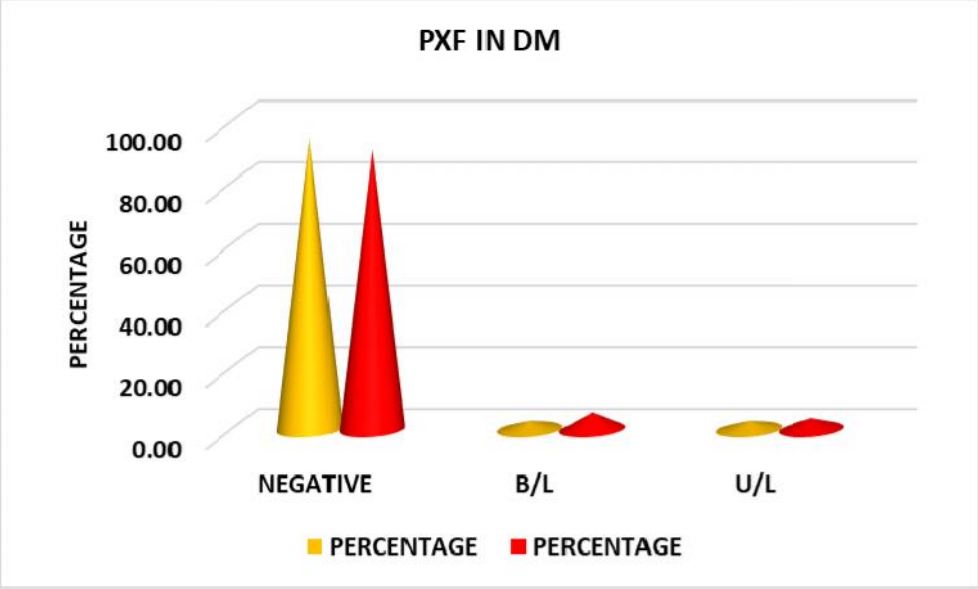


As shown in table 8, in our study 5 (6.49.%) patients had clinical bilateral pseudoexfoliation material and 3 (3.90%) had unilateral involvement with history of hypertension, but 1 (2.08%) patient was having unilateral PXF with no history of hypertension. Using chi-square test the p value is 0.1620 which is not Significant. PXF is not associated with HTN

TABLE 9 - PXF WITH DM :

	DM				
PXF	**POSITIVE**	**%**	**NEGATIVE**	**%**	**TOTAL**
B/L	3	5.56	2	2.82	5
U/L	2	3.70	2	2.82	4
NEGATIVE	49	90.74	67	90.74	116
TOTAL	71	100	54	100	125

GRAPH 9 - PXF WITH DM :



As shown in table 9 , in our study 3 (5.56.%) patients had clinical bilateral pseudoexfoliation material and 2 (3.70%) had unilateral involvement with history of diabetes but 4 (5.64%) patients had clinical pseudoexfoliation but no history of diabetes . Using chi-square test the p value is 0.7068 which is not Significant . PXF is not associated with DM.

TABLE 10 - TYPE OF CARDIAC DISEASE :

TYPE OF MI	NUMBER	PERCENTAGE
LBBB	1	0.8
AWMI	50	40
AWMI+CARDIOMYOPATHY	1	0.8
AWMI+RBBB	2	1.6
CARDIOMYOPATHY	1	0.8
IWMI	49	39.2
IWMI+TVD	3	2.4
RBBB	1	0.8
TVD	15	12
TVD+ STABLE ANGINA	2	1.6
TOTAL	125	100

As shown in table 10, 50 (40%) cases were diagnosed as anterior wall MI and 49 (39.2%) cases of inferior wall MI, 15 (12%) cases were of TVD and 3 (2.4%) cases of combined inferior wall MI and TVD and 2 (1.6%) cases of TVD had stable angina , 2 (1.6%) cases of cardiomyopathy out of which 1 has anterior wall MI. There were 3 (2.4%) cases of RBBB out of which 1 has anterior wall MI also and 1(0.8%) case was of LBBB.

DISCUSSION

The present study was conducted on 250 eyes of 125 patients with cardiovascular diseases including ischemic heart disease (IHD), myocardial ischemia (MI), angina, congestive cardiac failure and cardiomyopathy diagnosed by 2D Echo, ECG, which was or was not associated with hypertension/diabetes at Department of Ophthalmology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belagavi during study period of 1 year from 1st January 2017 – 31st December 2017.

Pseudoexfoliation (PXF) syndrome is an age related disease that is rarely seen under the age of 50 years and is characterized by deposition of fibrillar material in the anterior segment of the eye and in some other tissues such as skin and in the connective tissue portions of various visceral organs. Moreover, molecular, biological, and biochemical evidence showed that it is a type of stress induced elastic microfibrillopathy.(1)

It is a very important entity for ophthalmology in which PXF material accumulates on the lens epithelium and capsule, pupillary margin, ciliary epithelium, iris pigment epithelium, iris stroma, iris blood vessels and subconjunctival tissue.(5)

PXF syndrome causes chronic open-angle glaucoma, angle-closure glaucoma, blood aqueous barrier impairment, lens subluxation and increased complications during cataract surgery. (1)

Its prevalence varies from 0.0% (in Eskimos) to 38% (in Navaho Indians) in different races. The reasons for this variation and the exact etiology of PXF are not totally clear. (1)

At the beginning, PXF material was thought to accumulate only in ocular tissues, but then some reports revealed that it could be a systemic disorder. PXF material was found in the heart, lungs, liver, kidney, gallbladder and walls of blood vessels, as well as in the skin and cerebral meninges. [5, 6, 7, 8]

Our study is one of the pioneer studies in the contribution to correlate pseudoexfoliation with cardiovascular disease. National and International studies have been done to correlate the systemic association of pseodoexfoliation, but the results are variable. The results in the studies that are analyzing the associations of pseudoexfoliation syndrome with other chronic non-ophthalmological diseases are sensitive to diagnostic capabilities of these diseases.

In the present study, we studied 125 patients of which, 17 (15.6%) patients in the age group of 45-54 years, 50 (40%) patients were in the age group 55-64 years, 49 (39.2 %) in the age group 65-74 , 9 (7.2%) in above 75 age group. The average age of patients was 62.85 years in the study. And average age of 72 years was seen in PXF positive patients. The minimum included age was 48 years and maximum age was 85 years in the study. In our study, prevalence of pseudoexfoliation syndrome in cardiovascular diseases is 7.2%. In our study, 4 (44.44%) cases of pseudoexfoliation are from age group above 75 years, 3 (33.33%) from 65-74 and 2 (22.22%) from 55-64 age group. So prevalence of pseudoexfoliation increases with age but p value is not significant in our study.

A similar study conducted to study the profile of pseudoexfoliation in a south Indian population by H Arvind et al.[20] in which they studied 2850 subjects, out of which 108 (3.8%) were found to have PXF syndrome. According to study the prevalence of pseudoexfoliation syndrome in rural population was 3.8%.

A study conducted by Rao RQ et al. [80] found the prevalence of pseudoexfoliation syndrome was 6.45% in Pakistan. Also quite similar results were found in hospital based study in India by Lamba et al. [81] which showed a prevalence of 7.4 and 6% in south Indian population based study by Krishnadas R et al. [17]

These could reflect true variations arising from racial, genetics and geographical differences. Some of the variability could be explained by differences in the techniques of assessment and whether pseudoexfoliation was actively looked for with a dilated pupil. However, they could also be accounted for by many other factors including differences in study design, sampling methods, population size, and age distribution in the sampled population.

In present study 22 (17.6%) were females and 103 (82.4%) were males, out of which 1 (4.55%) female patient had clinical unilateral pseudoexfoliation material and 5 (4.85%) males had bilateral involvement and 3 (2.91%) male patients had unilateral involvement. Using chi-square test the p value is 0.5381, which is not significant. We did not notice any gender predilection; however the prevalence was slightly higher in males.

Similar results were found in study conducted by Martynas Speckauskas et al.[1] in which 1,065 participants were examined, among them 419 (39%) were males and 646 (61%) females. No statistically significant difference in occurrence of PXF was found between males and females, even in this study.

Also study conducted by H Arvind et al. [20] women constituted 54.6% of subjects with PXF and men constituted 45.4% of them. There was no significant difference in gender distribution.

In our study 4 (44.44%) patients had clinical unilateral involvement and 5 (55.56%) had bilateral involvement. Similar results were seen in a study conducted by H Arvind et al [(20)] where 53(49%) cases had unilateral involvement and 55(50.9%) cases had bilateral involvement.

But study conducted by Nilgun Y et al [(73)] showed rate of bilateral involvement is more than unilateral involvement, while there are studies that report unilateral involvement is more common.

Clinically most patients presents only with unilateral involvement but subclinical involvement of the other eye is always present. Clinical bilateral involvement often present after 5-10 years of unilateral involvement.

In present study 8 (88.89%) patients had pseudoexfoliation material on the pupillary margin, 1 (11.11%) on the iris surface and 3 (33.33%) had iris atrophy and 7(77.77%) of the patients had PXF material deposited on the anterior lens capsule and 2 (22.23%) patients had no PXF deposition on lens capsule.

Our results are similar with the study conducted by Sufi AR et al.[(18)] where 73% patients showed PXF on papillary border only and 27% showed PXF both on papillary magin and anterior lens capsule.

In our study 13 (10.40%) patients had IOP in the range of 9-12 mm Hg, 39 (31.20%) in range of 12-15 mm Hg, 45 (36%) in range of 15-18 mm Hg and 28 (22.40%) patients had IOP of 18 mm Hg or above. In our study the mean IOP was 16.53 mm Hg. The mean IOP in subjects with PXF was 20.61 mm hg which was higher than subjects without PXF .Almost all studies focusing on PXF in the past

have shown an association with raised IOP and glaucoma. And there is no significant correlation between age and IOP.

A Study conducted by Krishnadas et al. [17] in 2003, where mean IOP in patients without PXF was 15.9 mmHg by applanation tonometry which is similar to our study.

In our study 13 patients had history of MI in the past, 3 patients had history of stroke, 4 patients were known cases of asthma, 8 patients were found to have elevated lipid profile, 4 cases were having chronic renal diseases and 1 patient was known case of carcinoma of bladder, 1 with liver cirrhosis, 4 patients are on treatment for hypothyroidism and 2 patients were diagnosed with raised homocysteine levels.

In our study, 50(40%) cases were diagnosed as anterior wall MI and 49 (39.2%) cases of inferior wall MI, 15 (12%) cases were of TVD and 3 (2.4%) cases of combined inferior wall MI and TVD, 2 (1.6%) cases of TVD had stable angina , 2 (1.6%) cases of cardiomyopathy out of which 1 had anterior wall MI. There were 3 (2.4%) cases of RBBB out of which 1 had anterior wall MI and 1(0.8%) case was of LBBB.

Studies, that analyzed IHD and PXF association, provided conflicting results. Our data agree with some studies, which found no statistically significant association between PXF and IHD.

Study conducted by Tarkkanen et al in 2008 and Ritland et al in 2004 did not prove any difference in IHD rates. [75]

Two hospital based studies also support the view that PXF and IHD are not associated, although study conducted by Praveen et al [8] had small sample size of 160 and study conducted by Brajkovic et al [78] included relatively young 50 years aged

subjects. Similar results are seen in study conducted by Allingham et al in 2001 in which Icelandic families containing three or more members aged 70 years or older with at least one member with PXF, did not find any PXF association with IHD. [1, 78]

Shrum KR et al. [78, 79] conducted a study to determine the association between ocular pseudoexfoliation and cardiovascular causes, cerebrovascular causes and all other causes of mortality. No association was found between ocular pseudoexfoliation and cardiovascular or cerebrovascular mortality.

Brajkovic et al. [78] investigated the relationship between PXF and hypertension, CAD, arrhythmia, diabetes and cerebrovascular accidents. No relationship was found between PXF and mortality or other risk factors.

A study conducted by Mehmet YE et al. [74] where 490 patients who underwent coronary angiography were included in the study, 20 (5.2%) of CAD patients and 4 (3.9%) of normal CAG patients were found to have PXF. There was no significant relationship between CAD and the presence of PXF

More recent study conducted by Emiroglu et al.[74] failed to show any significant relationship between PXF and CAD, aortic aneurysm or peripheral vascular diseases.

In study conducted by Citirik et al. [4] there was comparison of 50 patients with CAD proven by coronary angiography and 50 gender and age matched controls showed higher PXF rates in the study group. When all patients were regrouped according to the presence of PXF, patients with PXF did not differ from patients without PXF in terms of age and gender, but the prevalence of CAD was higher.

Sekeroglu et al. in 2008 also studied 1480 patients, scheduled for cataract surgery, subjects with PXF were 1.49 times statistically significant that is more likely to have coronary heart disease.[1]

In Greece a hospital-based study conducted by Andrikopoulos et al.[5] where 2140 cataract patients, were found to be positively associated with PXF and the risk for CAD.

In our study 5 (6.49%) patients had clinical bilateral pseudoexfoliation material and 3 (3.90%) had unilateral involvement with history of hypertension and 1 (2.08%) patient was having unilateral PXF with no history of hypertension. Using chi-square test the p value is 0.1620 which is not significant. PXF is not associated with HTN according to the observations.

In our study 3 (5.56%) patients had clinical bilateral pseudoexfoliation and 2 (3.70%) had unilateral involvement with history of diabetes and 4 (5.64%) patients had pseudoexfoliation syndrome but no history of diabetes. Using chi-square test the p value is 0.7068 which is not significant. Therefore, PXF is not associated with DM .

Similar results are also seen in a study conducted by Jonas and Grundler et al. on pseudoexfoliative glaucoma and age matched control group, where they found lower rate of AH in the first group (18.8% vs. 30.2%, p=0.04). Also other study conducted by Shingleton et al. found lower rate of AH in cataract patients with PXF than in those without PXF (38% vs. 50%, p<0.01). [1]

Also similar results seen in study conducted by the Martynas S et al. [1] showed that differences between rates of IHD and DM were not statistically significant in PXF and non-PXF groups.

But study conducted by Praveen et al. [8] in which Ankle brachial index (ABI) was used to determine the risk of peripheral vascular disease in PXF cases and found mean low ABI in PXF cases, which indicates the presence of peripheral vascular diseases.

Similar results are also seen in the study conducted by Citirik et al. [4] where both DM and HTN were more prevalent but these differences did not reach to statistical significance.

Mitcell P et al. [7] investigated the association of pseudoexfoliation to systemic vascular history. A history of either angina or hypertension or combined history of angina, acute myocardial infarction and stroke was significantly associated with presence of PXF.

Another study showed high prevalence of pseudoexfoliation in patients with coronary artery ectasia [71]. A population based randomized trial in turkey conducted by Nilgum Yildirim et al. [73] where 2356 subjects were randomly chosen and investigated and showed that cardiac ischemic disease, history of previous angioplasty and the use of anti-hypertensive and cardiac agents were significantly higher in their PXF cases, but failed to reach a statistical significance.

Also similar results were seen in a study where, AH was found more in subjects with PXF in comparison with no PXF ($p=0.017$). χ^2 linear-by-linear association test found higher AH rate in unilateral PXF cases and even higher AH rate in bilateral cases than in non-PXF group ($p=0.014$)[1].

Miyazaki et al. [1] conducted a cross-sectional study of 1844 participants in Japan, they concluded that arterial hypertension is associated with PXF.

Tatjana S et al. [70] also showed that there was no statistical significance regarding presence of hypertension in patients with pseudoexfoliation but IHD was statistically significant in patients with pseudoexfoliation.

Two studies Tarkkanen et al. and Jonas & Gründler et al. after comparison of pseudoexfoliative Glaucoma group with POAG or normal control groups found lower trend of DM rate in the first group, but statistically borderline (p=0.05) difference was identified. In six other studies DM rates did not vary between patients with and without PXF (Praveen et al. 2011; Sekeroglu et al. 2008; Brajković et al. 2007; Citirik et al. 2007; Miyazaki et al. 2005; Allingham et al. 2001). [1,4,8,74]

In our study, correlation of pseudoexfoliation syndrome and its association with hypertension and diabetes was evaluated on the basis of information obtained from medical record which did not reach the significance.

CONCLUSION

From our study we conclude that:

1. We found the prevalence of pseudoexfoliation syndrome in cardiovascular diseases to be 7.2%.
2. The rates of arterial hypertension and diabetes in subjects with pseudoexfoliation (PXF) were higher, however statistically it is not significant because of smaller sample size.
3. We recommend that, no matter what sex and age; patients that present with PXF should be screened for detrimental cardiovascular disorder.
4. Further studies with larger populations are needed to clarify the relationship and systemic characteristics of pseudoexfoliation syndrome.

SUMMARY

The present study titled " Prevalence of pseudoexfoliation syndrome in patients with cardiovascular disease - One year cross sectional hospital based study" 250 eyes of 125 patients with diagnosed cases of cardiovascular diseases were included . The aim of the is to find prevalence of pseudoexfoliation syndrome in cardiovascular diseases and its association with hypertension, diabetes .The average age of these patients was 62.85 years but average age of 72 years was seen in subjects with PXF in our study .

In present study 22 were females and 103 were males . In our study 4 patients had unilateral pseudoexfoliation material of which 3 were males and 1 was female and 5 males had bilateral involvement. Using chi-square test the p vale is not significant for gender so we did not notice any sex predilection; however the prevalence was slightly higher in males.

In present study 88.89% patients had pseudoexfoliation material on the pupillary margin, 11.11% on the iris surface and 33.33% had iris atrophy . Also in our study 77.77% of the patients had PXF material deposited on the anterior lens capsule and 22.23% patients had no involvement of lens capsule.

In our study the mean IOP was 16.53 mm Hg. The mean IOP in subjects with PXF was 20.61 mm Hg which was higher than subjects without PEX. And also there was no significant correlation between age and IOP.

In our study majority of included subjects were of anterior wall MI and inferior wall MI. Other cases included were of TVD, stable angina, cardiomyopathy and bundle branch block.

In present study 10.39% patients were diagnosed with pseudoexfoliation syndrome had hypertension but 2.08% patients had no history of hypertension in the past.Similarly 9.26% of patients with known case of diabetes mellitus were diagnosed to have pseudoexfoliation but 5.64% patients had pseudoexfoliation syndrome but no history of diabetes .

In present study the association of pseudoexfoliation with hypertension and diabetes was statistically not significant.

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ANNEXURE-I- CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

ID NO. | | | |

Mr/Mrs/Ms_____

You are invited to participate in our research study titled **"** PREVALENCE OF PSEUDOEXFOLIATION SYNDROME IN PATIENTS WITH CARDIOVASCULAR DISEASE - ONE YEAR CROSS SECTIONAL HOSPITAL BASED STUDY **"** conducted by Dr.Madhura Patil, Post Graduate in M.S. Ophthalmology under the guidance of **Dr. _____, M.S(ophtho),FGO,** Professor & Head of the department of Ophthalmology, J.N. Medical College, Belagavi.

Respected Sir/Madam we request you to enroll yourself in our study as you are eligible for doing so.Your participation in the study is voluntary. Your decision whether or not to participate in the study will not affect your relationship with the hospital. If you decide to participate you are free to withdraw at any time.

Objective and Purpose of the study :- The purpose of the research is to assess prevalence of pseudoexfoliation syndrome in patients with cardiovascular disease.

Procedure Involved :- If you agree to enroll yourself in this study, you will be asked to give detailed history. Then you will be clinically examined in detail by slit-lamp examination, fundoscopy, Tonometry for measurement of intraocular pressure and blood pressure measurement,

Risks and Benefits :- As such no risks are involved.Your participation may benefit you and others suffering from same ailment in future, by helping us learn more about the disease process and better treatment modalities.

Alternatives:- If you are not willing to participate you will be treated according to the existing protocol & it will not affect your relationship with this hospital.

Costs for participating in this research :- There will not be any extra cost incurred by the participant. The participant will however have to pay for the investigations which are the part of the existing management protocol for this ailment. There is no commitment for any reimbursement or any other compensation for the participant.

Privacy and Confidentiality:- The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to others without your written permission.

Authorization to Publish Results :- When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Compensation :- In the event of injury related to the study, treatment will be made available through KLES Dr. Prabhakar Kore Hospital & MRC, Belagavi. There is no compensation or payment for such medical treatment by law. The doctors and the staff will provide facilities and medical attention to you.

Questions :- If you have any questions about the research you may please contact:

1) Chief Investigator, Dr_____ P.G,

   Department of Ophthalmology,

   JNMC, Belagavi.

2) Dr._____, Professor and Head, Guide,

   Department of Ophthalmology, JNMC, Belagavi.

If you need any further information regarding your rights as a study participant contact

3) Dr.GANGA S. PILLI, CHAIRPERSON, JNMC, Belagavi and Chairman of Institutional Ethics Committee. Contact No. 08312471350

Consent for participation in research trial

I, Mr./Ms./Mrs _____ voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name: _____

Signature or the Left Thumb Print of Subject: _____

Witness Name: _____

Signature of Witness: _____

Investigators Name: _____

Signature of Investigator: _____

Date: _____

Place: _____

ANNEXURE-II - PROFORMA

DATE:

NAME

(FIRST NAME) (MIDDLE NAME) (SURNAME)

AGE: ☐ Years

SEX: ☐ (1-Male; 2-Female)

ADDRESS: _____

_____

_____

CONTACT NUMBER :- ☐☐☐☐☐☐☐☐☐☐

OP NUMBER: ☐☐☐☐☐☐☐☐

IP NUMBER: ☐☐☐☐☐☐☐☐

CARDIOVASCULAR INVESTIGATION:

1. ECG :

2. 2D ECHO:

DIAGNOSIS :

IS THE PATIENT ELIGIBLE FOR STUDY? (1-YES; 2-NO) ☐

HAS INFORMED CONSENT BEEN GIVEN? (1-YES; 2-NO) ☐

PAST HISTORY: [1.Yes 2. No (If 1, then duration)]

	RE	LE
Intra-ocular Surgery		
Trauma		
Other		

DIABETES: [1- Present 2- Absent] ☐

Duration: ☐☐ months/years

HYPERTENSION: [1- Present 2- Absent] ☐

Duration: ☐☐ months/years

ANY OTHER MEDICAL DISORDERS: _____

FAMILY HISTORY: [1.Significant 2. Insignificant] ☐

If 1 ; specify _____

GENERAL PHYSICAL EXAMINATION:

Pulse: ☐☐☐ /minute

BP: ☐☐☐ / ☐☐☐ mm of hg

OCULAR EXAMINATION:

1 . Head posture: [1- Erect 2- Tilted] ☐

If 2, specify; _____

2 . Visual Axis: [1- Parallel 2- Deviated] ☐

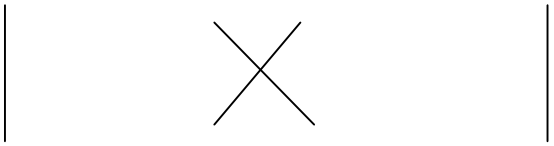
If 2, specify; _____

3 . Facial Symmetry: [1- Symmetrical 2- Asymmetrical] ☐

If 2, specify; _____

4 . Extra-ocular movements

OD BINOCULAR OS



5 . Visual Acuity:

H/O wearing glasses [1- Present 2 – Absent] ☐

Duration: months/years

	RE	LE
Distant		
Pinhole		
Near		
Aided		

6 . Anterior segment examination

	RIGHT EYE	LEFT EYE
1. Adnexa (1- Normal; 2-Abnormal) If 2 , specify		
2. Sclera (1- Normal; 2- Abnormal) If 2 , specify		
3. Conjunctiva (1-normal; 2- Abnormal) If 2 , specify		
4. Cornea (1- normal; 2- Abnormal) If 2 , specify		

5. Anterior chamber (1- normal depth; 2-shallow; 3-deep; 4- any other)		
6. Iris (1-normal colour& pattern; 2-Abnormal) • PXF material on pupillary margin • PXF material on surface • Atrophy • Iridodonesis (1-Yes ; 2-No)	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐
7. Pupil: • Size ✓ Undilated ✓ Dilated • Reactions: ✓ Direct ✓ Indirect (1=present; 2=absent;3=sluggish)		
8. Lens (1=Clear; 2=Cataract) if 2 then specify the type • PXF on lens • Phacodonesis • Zonular dehiscence (1-Yes ; 2-No)	☐ ☐ ☐	☐ ☐ ☐

- **POSTERIOR SEGMENT EXAMINATION:**

	RIGHT EYE	LEFT EYE
Glow		
Media		
Disc		
C:D ratio		
Blood vessels		
Background		
Macula		

- **INVESTIGATIONS:**

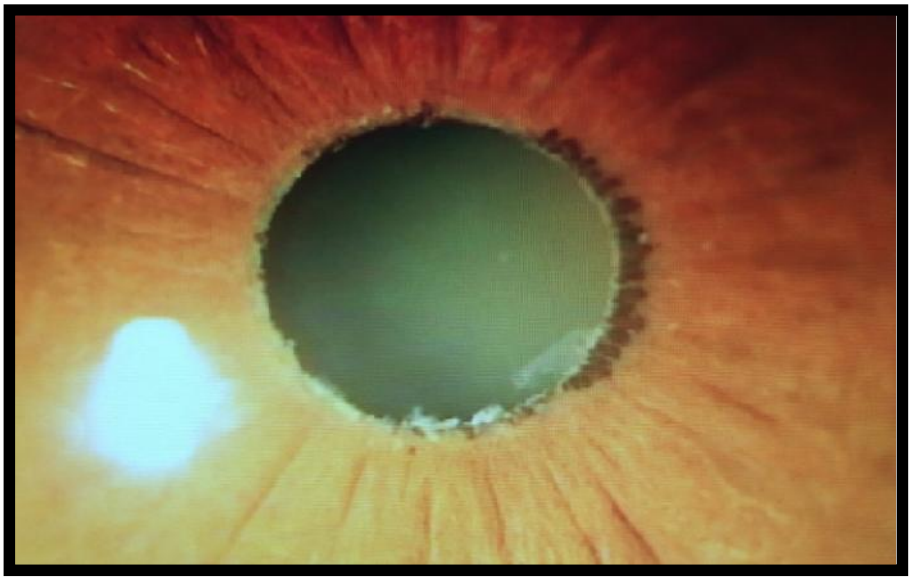
1.Tonometry

	RE	LE
IOP (mm Hg)		

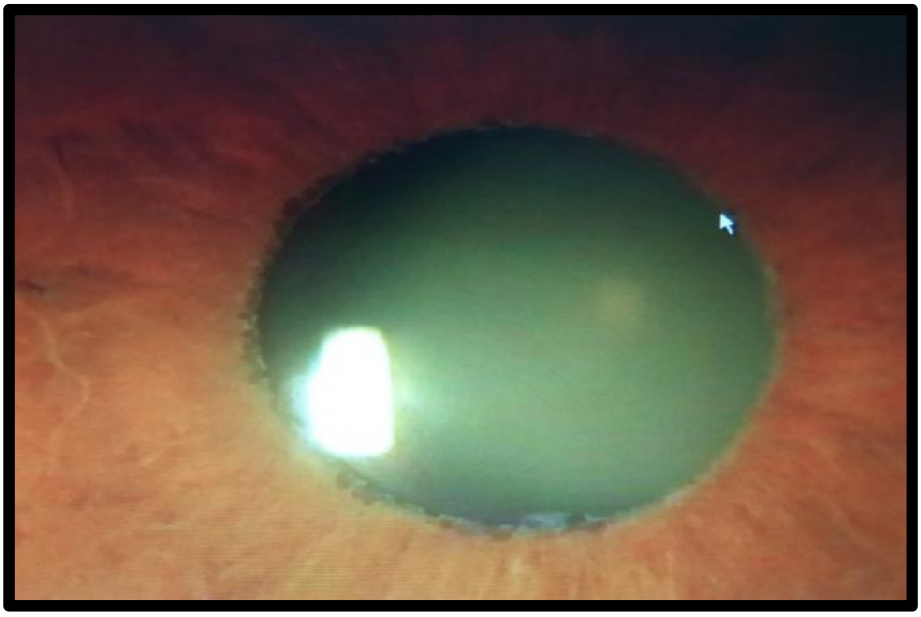
- **DIAGNOSIS:-**

- **COMMENTS:**

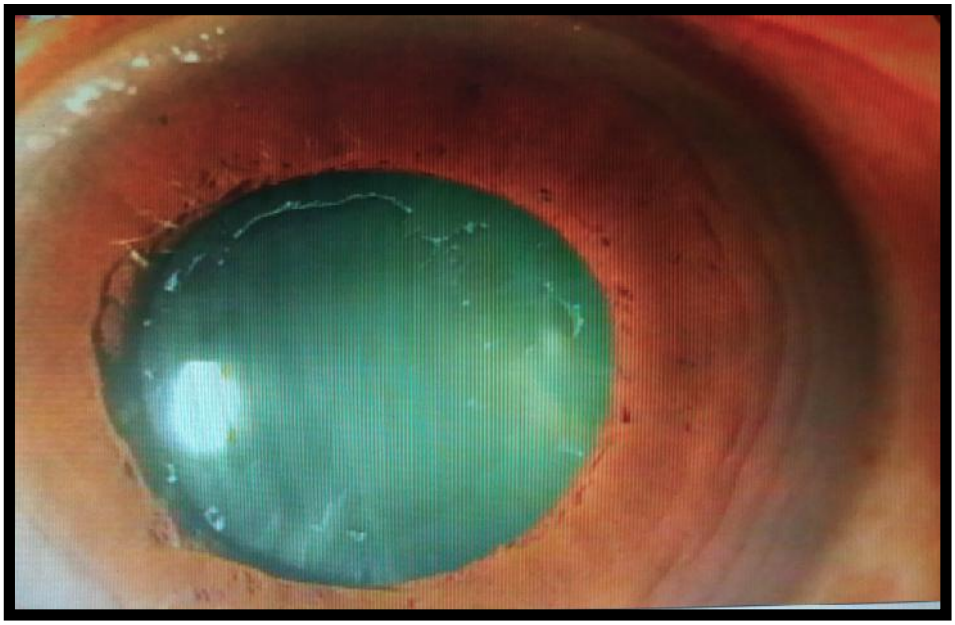
ANNEXURE III – PHOTOGRAPHS



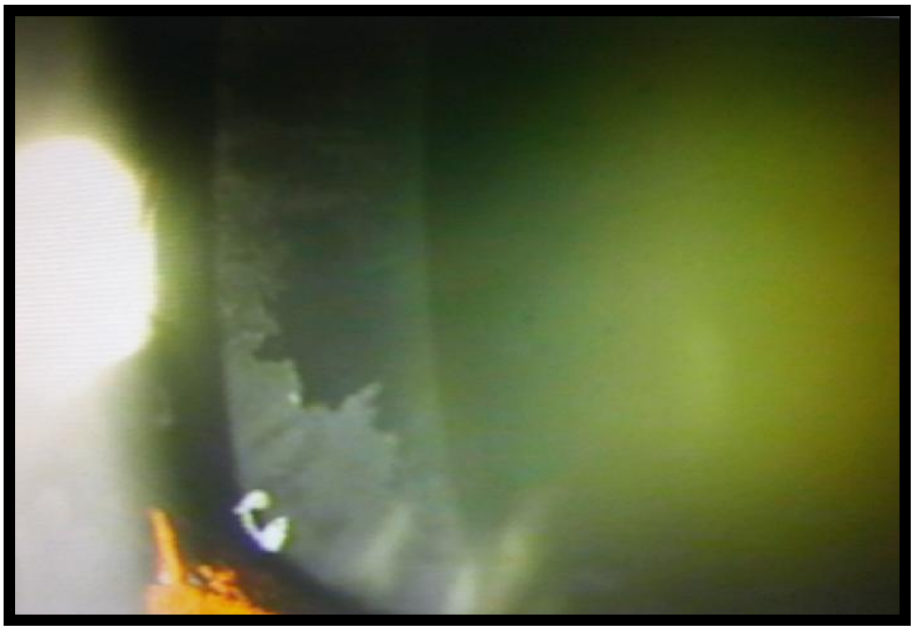
Photograph 1 – Slit lamp photograph showing pseudoexfoliation material on pupillary margin and lens



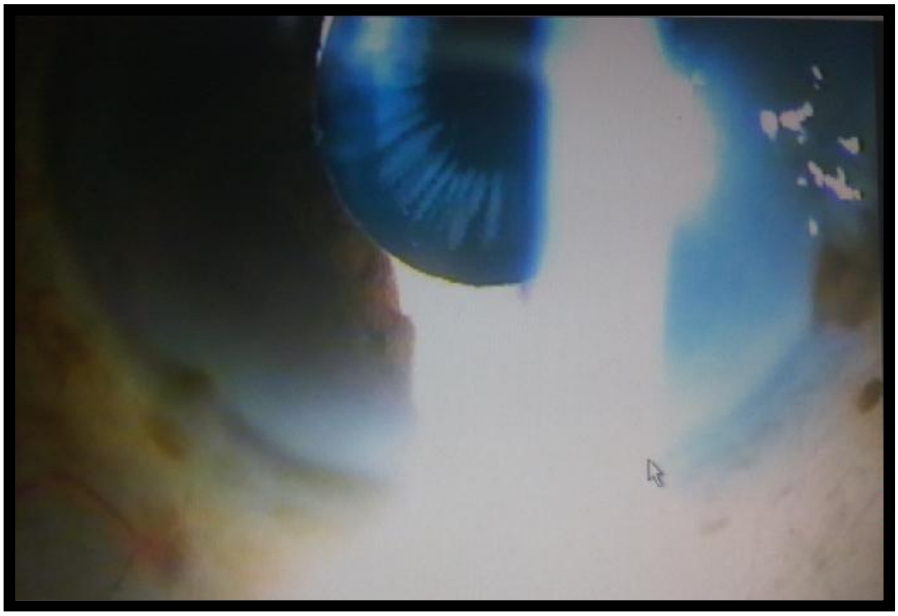
Photograph 2 – Slit lamp photograph showing pseudoexfoliation material only on pupillary margin



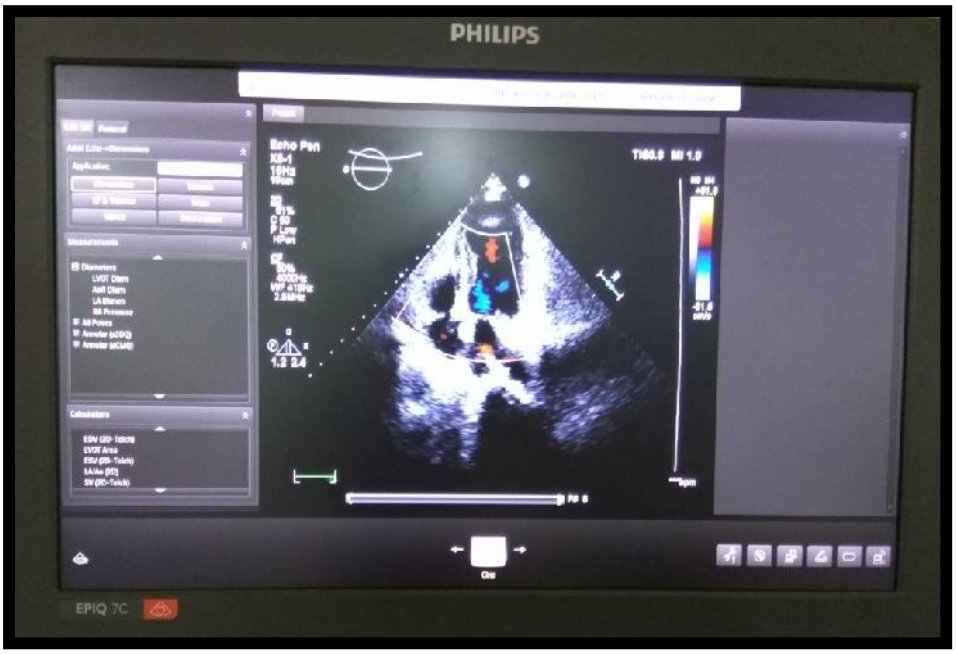
Photograph 3 – Figure showing features of classical pseudoexfoliation, anterior curling of the exfoliation sheet with iris pattern loss



Photograph 4 – Slit lamp magnified photograph showing classical peripheral pseudoexfolative ring



Photograph 5 – . Slit lamp photograph showing radial pigmentary pattern of deposits with adjacent pupillary ruff atrophy



Photograph 6 - 2D echo of a patient who had AWMI ,with grade 1 mitral regurgitation .

ANNEXURE IV – KEY TO MASTER CHART

U/L	Unilateral
B/L	Bilateral
RE	Right Eye
LE	Left Eye
PXF	Pseudoexfoliation Syndrome
IOP	Intraocular Pressure
MI	Myocardial Infarction
HTN	Hypertension
DM	Diabetes Mellitus
TVD	Triple Vessel Disease
AWMI	Anterior Wall MI
IWMI	Inferior Wall MI
RBBB	Right Bundle Branch Block
LBBB	Left Bundle Branch Block
NONSTMI	Non-ST- Segment Elevation MI
ARF	Acute Renal Failure
RA	Rheumatoid Arthritis
CKD	Chronic Kidney Disease
Ca	Carcinoma
COPD	Chronic Obstructive Pulmonary Disease

SR NO	IP/OP NO	AGE	SEX	HTN	DM	OTHER SYSTEMIC DISEASE	TYPE OF MI	PRESENSE OF PXF			PRESENSE OF PXF ON IRIS				PRESENSE OF PXF ON LENS			IOP	
									RE	LE	PUPILLARY MARGIN	IRIS SURFACE	IRIDODONESIS	ATROPHY	CAPSULE	PHACODONESIS	ZONULAR DEHISCENCE	RE	LE
1	774667	60	M	+	+	H/O MI	TRIPPLE VESSEL DISEASE	-	-	-	-	-	-	-	-	-	-	14.3	11.5
2	788580	57	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	11.7	12
3	785699	63	F	+	+	H/O MI	IWMI	U/L	-	+	+	-	-	+	-	-	-	20.4	22.6
4	2697442	65	M	-	+	H/O MI	DOUBLE VESSELE DI+ IWMI	-	-	-	-	-	-	-	-	-	-	11.1	15.3
5	1258014	60	M	-	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	18	18.8
6	784023	65	F	+	+	ASTHMA	AWMI+APICAL SEPTUM	-	-	-	-	-	-	-	-	-	-	9.4	11.8
7	789675	67	M	-	+	ARF	IWMI	-	-	-	-	-	-	-	-	-	-	18.9	20.9
8	794790	76	F	+	+	H/O MI	IWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.3
9	788405	62	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	14.7	15.6
10	788046	70	M	-	-	-	IWMI	U/L	-	+	+	+	-	+	+	-	-	22	20.9
11	894203	65	M	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	19	21.2
12	818274	56	M	-	-	-	AWMI+RBBB	-	-	-	-	-	-	-	-	-	-	15.9	17.3
13	895964	62	F	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	22	20
14	796324	85	M	+	+	H/O MI	AWMI+CARDIOMYOPATHY	-	-	-	-	-	-	-	-	-	-	17.3	17.5
15	818687	50	M	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	14.6	14.6
16	818465	58	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	13.4	13.4
17	818716	51	F	+	-	H/O MI	IWMI	-	-	-	-	-	-	-	-	-	-	15.9	15.9
18	815673	58	M	+	-	ELEVATED HOMOCYSTEINLEVELs	TVD+ STABLE ANGINA	-	-	-	-	-	-	-	-	-	-	15.9	15.9
19	817914	65	M	-	+	ELEVATED HOMOCYSTEINLEVELs	TVD+ STABLE ANGINA	-	-	-	-	-	-	-	-	-	-	17.3	17.3
20	792595	68	M	+	-	H/OSTROKE	IWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.3
21	795110	66	M	+	+	-	AWMI+RBBB	-	-	-	-	-	-	-	-	-	-	18.9	17.3
22	789322	74	M	+	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	19.6	20
23	790993	70	M	+	+	-	IWMI	B/L	+	+	+	-	-	-	+	-	-	20.4	19.7
24	788462	67	F	+	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	13.8	14.1
25	802106	48	M	+	-	-	TVD	-	-	-	-	-	-	-	-	-	-	17.3	17.3
26	787959	58	M	+	-	-	NON STEMI	-	-	-	-	-	-	-	-	-	-	21.9	19.5
27	788510	75	M	+	-	ASTHMA+RA	IWMI+STABLE ANGINA	B/L	+	+	+	-	-	-	+	-	-	19.9	22
28	892452	48	M	+	+	-	IWMI	-		-	-	-	-	-	-	-	-	18.9	17.3
29	828929	65	M	-	-	-	IWMI+ LBBB	-	-	-	-	-	-	-	-	-	-	12.3	14.3
30	824133	67	F	-	-	HYPERLIDEMIA	IWMI	-	-	-	-	-	-	-	-	-	-	14	14
31	823808	62	F	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	13.2	12
32	831259	55	M	-	-	HYPERLIDEMIA	AWMI	-	-	-	-	-	-	-	-	-	-	14	13.5
33	828621	60	M	-	-	HYPERLIDEMIA	AWMI	-	-	-	-	-	-	-	-	-	-	12	13.5
34	831256	62	M	-	-	HYPERLIDEMIA	AWMI	-	-	-	-	-	-	-	-	-	-	11.5	15.6
35	831259	57	M	+	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	13.8	15.8
36	831025	70	M	+	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	17.2	16
37	831610	59	F	+	+	HYPOTHYROIDISM	IWMI	-	-	-	-	-	-	-	-	-	-	14.5	14.5
38	831463	59	M	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	18.5	17.5
39	831357	65	M	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	10.5	13.5
40	831447	54	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	12.5	17
41	830475	61	F	-	-	-	IWMI+TVD	-	-	-	-	-	-	-	-	-	-	17.5	14.5
42	831578	68	M	-	-	H/O MI	AWMI	-	-	-	-	-	-	-	-	-	-	14.5	14.5
43	824131	67	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.5	17.5
44	820790	70	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	10.3	10.3
45	821123	58	M	-	-	-	DILATED CARDIOMYOPATHY	-	-	-	-	-	-	-	-	-	-	17.5	17.5
46	821159	60	M	+	+	CKD	AWMI	-	-	-	-	-	-	-	-	-	-	14.5	14.5
47	820681	56	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.5
48	821557	52	m	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	17.8	16
49	819493	65	M	+	+	H/O MI	TVD+AWMI	-	-	-	-	-	-	-	-	-	-	13	13.2
50	820394	50	M	-	+	H/O MI	AWMI	-	-	-	-	-	-	-	-	-	-	17	17.5
51	820937	66	M	+	-	-	TVD+UNSTABLE ANGINA	-	-	-	-	-	-	-	-	-	-	19.5	20.5
52	820027	62	M	+	+	RA	AWMI	-	-	-	-	-	-	-	-	-	-	9.5	9.5
53	819520	78	M	+	-	-	IWMI	B/L	+	+	+	-	-	-	+	-	-	19	19.2
54	823981	78	M	+	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	17.5	17.5

SR NO	IP/OP NO	AGE	SEX	HTN	DM	OTHER SYSTEMIC DISEASE	TYPE OF MI	PRESENSE OF PXF			PRESENSE OF PXF ON IRIS				PRESENSE OF PXF ON LENS			IOP	
									RE	LE	PUPILLARY MARGIN	IRIS SURFACE	IRIDODONESIS	ATROPHY	CAPSULE	PHACODONESIS	ZONULAR DEHISCENCE	RE	LE
55	824191	62	M	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	9.7	8.5
56	822912	67	M	-	-	CA BLADDER	IWMI	-	-	-	-	-	-	-	-	-	-	19.4	22
57	824330	56	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.5	17.5
58	824320	69	M	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.5	17.5
59	833050	51	F	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	11.3	12.5
60	832494	69	F	+	-	-	TVD+AWMI	-	-	-	-	-	-	-	-	-	-	11.3	12.5
61	833115	65	F	-	-	HYPOTHYROIDISM	AWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.3
62	833173	60	M	+	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	13.5	13.5
63	833292	70	M	+	-	COPD	AWMI	U/L	+	-	+	-	-	+	-	-	-	19.9	20.5
64	833037	48	M	+	-	-	IWMI+TVD	-	-	-	-	-	-	-	-	-	-	19.5	19.5
65	832742	51	M	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	173	11.2
66	840364	73	M	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	11.3	10.5
67	839961	54	M	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	20.3	20.3
68	839109	65	M	-	-	-	IWMI+TVD	-	-	-	-	-	-	-	-	-	-	19.3	17.5
69	840060	74	M	+	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	14.3	14.5
70	840709	69	M	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	12.5	12
71	840918	58	M	+	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	17.5	17.5
72	839480	64	M	+	+	-	IWMI	U/L	+	-	-	-	-	-	+	-	-	19.7	19.9
73	833645	80	M	+	+	-	AWMI+RBBB	-	-	-	-	-	-	-	-	-	-	16.5	17.2
74	831907	65	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.5	17.3
75	832971	60	M	+	+	-	IWMI+TVD	-	-	-	-	-	-	-	-	-	-	17.3	17.3
76	840146	81	M	+	+	-	AWMI+LATERAL WALL	B/L	+	+	+	-	-	-	+	-	-	22	24.5
77	839185	49	M	+	+	EPILEPSY	TVD+IWMI	-	-	-	-	-	-	-	-	-	-	17.2	17.5
78	891878	60	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	12.5	10.3
79	892099	72	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	11.5	11.5
80	892621	57	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	10.3	13.5
81	890992	70	M	+	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	10.3	10.3
82	878893	58	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.3
83	876863	67	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.3
84	879081	70	M	-	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.3	17
85	878878	65	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	14.6	13.4
86	877224	77	M	+	+	-	IWMI	B/L	+	+	+	-	-	-	+	-	-	18.6	19.8
87	878566	73	M	+	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	15.3	12.8
88	853351	69	M	+	+	CKD	AWMI	-	-	-	-	-	-	-	-	-	-	13	14.5
89	853290	70	M	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	14.7	15.3
90	853166	59	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	16	17.5
91	853252	64	M	+	+	-	TVD+AWMI	-	-	-	-	-	-	-	-	-	-	14	18
92	853301	66	M	+	-	H/O MI	AWMI	-	-	-	-	-	-	-	-	-	-	13.6	14
93	853153	59	M	-	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	18	17.5
94	852899	54	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	16	15.7
95	852968	67	M	+	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	15.3	17.5
96	853517	63	F	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	16.2	17
97	892264	59	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	18.9	20.8
98	892705	66	F	+	+	HYPOTHYROIDISM	AWMI	-	-	-	-	-	-	-	-	-	-	13.5	15
99	892018	62	M	+	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	15	13.7
100	891374	60	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	16	14.9
101	873819	60	M	-	+		IWMI	-	-	-	-	-	-	-	-	-	-	18	18.8
102	899941	65	F	+	+	ASTHMA	AWMI+APICAL SEPTUM	-	-	-	-	-	-	-	-	-	-	9.4	11.8
103	872191	67	M	-	+	ARF	IWMI	-	-	-	-	-	-	-	-	-	-	18.9	20.9
104	845677	76	F	+	+	H/O MI	IWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.3
105	848476	67	F	-	-	HYPERLIDEMIA	IWMI	-	-	-	-	-	-	-	-	-	-	14	14
106	845407	62	F	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	13.2	12
107	845443	55	M	-	-	HYPERLIDEMIA	AWMI	-	-	-	-	-	-	-	-	-	-	14	13.5
108	846103	60	M	-	-	HYPERLIDEMIA	AWMI	-	-	-	-	-	-	-	-	-	-	12	13.5

SR NO	IP/OP NO	AGE	SEX	HTN	DM	OTHER SYSTEMIC DISEASE	TYPE OF MI	PRESENSE OF PXF			PRESENSE OF PXF ON IRIS				PRESENSE OF PXF ON LENS			IOP	
									RE	LE	PUPILLARY MARGIN	IRIS SURFACE	IRIDODONESIS	ATROPHY	CAPSULE	PHACODONESIS	ZONULAR DEHISCENCE	RE	LE
109	816893	62	M	-	-	HYPERLIDEMIA	AWMI	-	-	-	-	-	-	-	-	-	-	11.5	15.6
110	814598	57	M	+	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	13.8	15.8
111	816502	70	M	+	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	17.2	16
112	814206	59	F	+	+	HYPOTHYROIDISM	IWMI	-	-	-	-	-	-	-	-	-	-	14.5	14.5
113	812523	59	M	+	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	18.5	17.5
114	813953	50	M	-	-	-	IWMI+LAT MI	-	-	-	-	-	-	-	-	-	-	14.6	14.6
115	813600	58	M	-	-	-	AWMI	-	-	-	-	-	-	-	-	-	-	13.4	13.4
116	811679	51	F	+	-	H/O MI	IWMI	-	-	-	-	-	-	-	-	-	-	15.9	15.9
117	809141	58	M	+	-	ARF	TVD+ STABLE ANGINA	-	-	-	-	-	-	-	-	-	-	15.9	15.9
118	893158	65	M	-	+	CIRRHOSIS	TVD+ STABLE ANGINA	-	-	-	-	-	-	-	-	-	-	17.3	17.3
119	892807	68	M	+	-	H/O STROKE	IWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.3
120	893604	67	F	+	+	-	IWMI	-	-	-	-	-	-	-	-	-	-	13.8	14.1
121	736651	48	M	+	-	-	TVD	-	-	-	-	-	-	-	-	-	-	17.3	17.3
122	786434	58	M	+	-	-	NON STEMI	-	-	-	-	-	-	-	-	-	-	17	19.5
123	735884	56	M	+	+	-	AWMI	-	-	-	-	-	-	-	-	-	-	17.3	17.5
124	894496	52	m	-	-	-	IWMI	-	-	-	-	-	-	-	-	-	-	17.8	16
125	893408	65	M	+	+	H/O MI	TVD+AWMI	-	-	-	-	-	-	-	-	-	-	13	13.2

86	877224	77	M	+	+	-	IWMI	B/L
76	840146	81	M	+	+	-	AWMI+LAT	B/L
72	839480	64	M	+	+	-	IWMI	U/L
63	833292	70	M	+	-	COPD	AWMI	U/L
53	819520	78	M	+	-	-	DOUBLE VE	B/L
27	788510	75	M	+	-	ASTHMA+R	IWMI+STAI	B/L
23	790993	70	M	+	+	-	IWMI	B/L
10	788046	70	M	-	-	-	IWMI	U/L
3	785699	63	F	+	+	H/O MI	IWMI	U/L

+	+	+	-	-	-	+	-	-
+	+	+	-	-	-	+	-	-
+	-	-	-	-	-	+	-	-
+	-	+	-	-	+	-	-	-
+	+	+	-	-	-	+	-	-
+	+	+	-	-	-	+	-	-
+	+	+	-	-	-	+	-	-
-	+	+	+	-	+	+	-	-
-	+	+	-	-	+	-	-	-

18.6	19.8	
22	24.5	
19.7	19.9	
19.9	20.5	
19	19.2	
19.9	22	
20.4	19.7	
22	20.9	
20.4	22.6	
20.21111	21.01111	20.61111