Ultrasound Biomicroscopy and A- Scan Biometry Parameters in Hospital Based Primary Angle Closure Suspects Before and After Laser Peripheral Iridotomy – A Longitudinal Study.

Thesis

Submitted in Partial Fulfillment
of the requirements for the degree

Doctor of Philosophy

by

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Under the supervision of

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Pilani Rajasthan

Certificate

This is to certify the thesis entitled "Ultrasound Biomicroscopy and A- scan Biometry Parameters in Hospital Based Primary Angle Closure Suspects Before and After Laser Peripheral Iridotomy- A Longitudinal Study" submitted by R. Krishna Kumar ID No. 2001PHX F424 for the award of Ph.D. degree of the institute, embodies original work done by him under my supervision.

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Epidemiology:

Glaucoma affects 66.8 million people worldwide, with Asians accounting for almost half of the world's glaucoma population. (1) It is estimated that normal pressure glaucoma makes up anywhere from 40-75% of all Primary Open Angle Glaucoma (POAG). And POAG makes up 85-90% of all glaucoma in the Western world. Prevalence of POAG has been extensively studied by a number of well-designed clinical studies in different populations. In white populations, POAG is present in 0.3 to 4.0% of the older population. (Table 1-1) In Asian populations, POAG was present in 0.5 to 2.6% of the older population. In the population based study done at our institute (Chennai Glaucoma study) prevalence of 1.62% of POAG was documented. (2) In the Hispanic population in the United States, POAG was present in 2.0%; however, the number of studies on Hispanic populations was limited. In black populations, the prevalence of POAG was higher and ranged from 2.9 to 8.8% of the older population. Evidently the black population was at a higher risk of developing POAG as compared to others.

Primary Angle Closure Glaucoma (PACG) could account for 64% of all glaucomas in Mongolia, and 50% of all glaucomas worldwide. In the white, Hispanic, and black populations, angle-closure glaucoma was present in 0.1 - 0.6% of the older population (Table 1-2). However in Asian populations, angle-closure glaucoma was present in 0.3% (Japan) to 2.7% (Alaska) of the older population. (3)

Table 1-1: Prevalence of primary open-angle glaucoma in different world populations

Race / Location	Prevalence of POAG in older age population(> age 40)
White populations (US, Europe, Iceland, Australia)	0.3 – 4.0 %
Asian populations (Japan, Mongolia, Singapore, India)	0.5 – 2.6 %
Hispanic population (US)	2.0 %
Black populations (US, Caribbean, Africa)	2.9 – 8.8 %

Table 1-2: Prevalence of angle closure glaucoma in different world populations

Race / Location	Prevalence of PACG in older age population (> age 40)
White populations (Europe, Australia)	0.1 – 0.6 %
Asian populations (Alaska, Japan, Mongolia, Singapore, India)	0.3 – 2.7 %
Hispanic population (US)	0.1 %
Black populations (Africa)	0.5 – 0.6 %

Blindness can occur in angle closure glaucoma. In fact, the rate of blindness from angle closure glaucoma may be higher than that of open angle glaucoma. Blindness in one eye occurs in 10 –50% of Inuit and Chinese patients with angle closure glaucoma. In East Africa, blindness in both eyes occurs in 21% of angle-closure glaucoma patients. (3) According to the Chennai Glaucoma Study (CGS), the overall prevalence of primary angle closures (Primary Angle Closures and PACG) in a rural population of southern India was 1.58%.and Primary Angle Closure Suspects (PACS) was 6.27%(4), the Vellore Eye Study

(VES) showed prevalence of 4.32% of PACG and 10.3% of Occludable angles. An Andhra Pradesh Eye Disease Survey (APEDS) showed the prevalence was 0.32% of PACG and 1.41% of occludable angles. (5, 6)

India has higher prevalence of PACG compared to western population.(1) An estimated eight million Asian Indians were projected to suffer from glaucoma by 2000 with equal numbers of open angle and angle closure glaucoma.(1) Population based studies in India showed significant percentage (10.5%) of eyes with occludable angles. Occludable angles are known to be precursors to Angle closure Glaucoma.

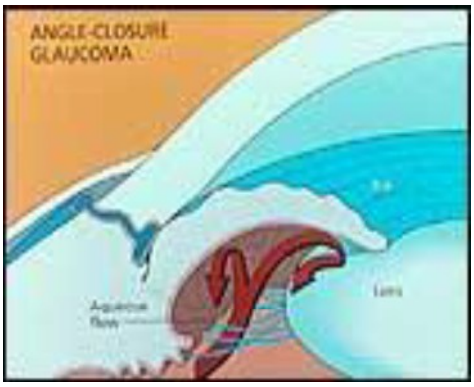

Fig. 1.1: Anterior chamber Angle and iris configuration in Angle closure glaucoma
(Courtesy: http://www.ophthalmic.hyperguides.com/)

***Primary Angle Closure Glaucoma (PACG)*:**

PACG is a condition in which the iris is apposed to the trabecular meshwork at the angle of the anterior chamber of the eye. When the iris is pushed or pulled anteriorly to block the trabecular meshwork, the outflow of aqueous substance from the eye is blocked, causing a rise in intraocular pressure (IOP). If closure of the angle occurs suddenly, symptoms are severe and dramatic. Immediate treatment is essential to prevent damage to the optic nerve

and loss of vision. If closure occurs intermittently or gradually, PACG may be confused with chronic open-angle glaucoma.

***Classification of Primary Angle Closure Glaucoma*:**

The traditional classification scheme for PACG is based on symptoms. This is not particularly helpful in understanding the mechanism underlying closure of the angle nor is it the appropriate method of management or the prognosis for vision. Primary Angle Closure (PAC) is a mechanical process within the anterior segment.

Staging the amount of tissue damage that has resulted from angle closure is essential in preventing further damage and arresting progression, or reversing visual impairment. PACG (7) can be classified into three stages of the disease process namely Primary Angle Closure Suspect (PACS), Primary Angle Closure (PAC) and Primary Angle Closure Glaucoma (PACG). Literature on the natural history of early stage of the PACG is not available. A PACS eye is that in which appositional contact between the peripheral iris and posterior trabecular meshwork is considered possible. PAC is the eye with an occludable drainage angle and features indicating that trabecular obstruction by the peripheral iris occurred, such as peripheral anterior synechiae, elevated intraocular pressure, iris whirling, glaucomflecken lens opacities or extensive pigment deposition on the trabecular surface. The optic disc does not have glaucomatous damage. PACG is an eye with PAC together with evidence of glaucomatous optic atrophy.

PACG is a disease with varied presentations. In the initial phase of the condition, anterior segment risk factor, namely, crowding of the anterior chamber will be the only sign with or without IOP increase either occasionally or constantly. Later there will be development of

posterior synechial changes accompanied by increased IOP but without any posterior optic disc cupping changes. Only in the later stage, anterior and posterior changes are noticed. Studies have shown that the angle closure glaucoma was caused by the apposition of the iris to the trabecular meshwork as a result of abnormal relationships of anterior segment structures or positions of anterior segment structures or posterior forces that altered anterior segment anatomy. The forces causing iris apposition to the trabecular meshwork may be viewed as originating at four successive anatomic levels: the iris (pupillary block), the ciliary body (plateau iris), the lens (Phacomorphic) and the posterior to the lens (malignant glaucoma).

General Risk Factors:

General risk factors for developing PACG include advanced age (8-10), female sex (11-14), hyperopia (15), family history (15), and diabetes.(15)The elderly have been noted to have an increased incidence of PACG presumably due to anterior chamber size decrease secondary to increased crystalline lens thickness and decreased pupillary diameter. Women have been reported to have an increased incidence of PACG, believed to arise from a shallower anterior chamber as compared to men. As decreased depth and volume of the anterior chamber correlate with the degree of hyperopia, an increased incidence of PACG is seen in hyperopic patients. In addition, a study has shown that 20% of 95 combined first- and second-degree relatives of patients with angle-closure glaucoma had potentially occludable angles.(15) Positive correlations calculated did suggest that type II diabetes mellitus or abnormal glucose-tolerance tests related to decreased anterior chamber depth.

Anatomical Risk Factors:

Previous studies (15) have shown the following anatomic configuration in primary angle closure glaucoma:

a) Shallow anterior chamber both centrally and peripherally. Both Lowe and Alsbirk found angle closure glaucoma to be uncommon in eyes with central anterior chamber depths of 2.5mm or greater.
b) Decreased anterior chamber volume
c) Short axial length of the globe
d) Small corneal diameter
e) Increased posterior corneal curvature
f) Decreased corneal height
g) Anterior position of the lens with respect to the ciliary body
h) Increased curvature of anterior lens surface
i) Increased thickness of the lens
j) More anterior insertion of the iris into the ciliary body, giving a narrower approach to the angle recess.

Clinical Picture:

Fig. 1.2: Angle Closure Glaucoma eye

Three different forms of pupillary block glaucoma have been described based on presenting symptoms and clinical findings (16)

Acute Angle-Closure Glaucoma

Patients with acute angle-closure glaucoma can appear markedly ill when they present. They may experience sudden severe pain in a trigeminal nerve distribution, blurred vision, nausea, vomiting, bradycardia, and diaphoresis. They may also show an extreme decrease in central visual acuity. Conjunctival hyperemia is present and consists of a ciliary flush and congestion in the conjunctiva. The cornea may be edematous and the pupil typically irregular, vertically oval, in a mid-dilated position, and fixed. This position of the pupil is believed to be due to ischemia and paralysis of the sphincter pupillae. As IOP increases, there is subsequent decrease in perfusion to the sphincter muscle. Slit lamp examination may reveal a shallow anterior chamber, aqueous flare, pigment dispersion, sector atrophy of the iris, and glaukomflecken in the anterior aspect of the lens. Acute angle-closure glaucoma is seen most often with the mid-dilated pupil as lens-iris contact is the greatest in this position of the pupil. This observation has been used to explain why dimly lit areas, emotional stress, and pharmacological dilatation can precipitate episodes of acute angle-

closure glaucoma. The rise in IOP can be dramatic, four- to five-fold, reaching values of 40 mm Hg to 60 mm Hg and higher in minutes

Subacute Angle-Closure Glaucoma

Subacute angle-closure glaucoma is often viewed to have the same mechanism as seen in AACG, but corresponding symptoms may be mild or absent. Patients may suffer from repeated subclinical episodes that precede an acute attack or predispose to chronic angle-closure glaucoma. Patients with subacute angle-closure glaucoma typically have few clinical indicators suggesting an attack of angle closure. Patients may experience episodes of blurred vision with a concurrent headache. Another symptom is the perception of seeing colored haloes around lights during an episode. Physical signs are typically absent except for a narrow angle in subacute angle-closure glaucoma.

Chronic Angle-Closure Glaucoma

Chronic angle-closure glaucoma is typified by closure of peripheral portions of the anterior chamber by synechiae that subsequently produce chronic elevations in IOP. Patients with chronic angle-closure glaucoma typically have an asymptomatic clinical course similar to that observed in patients with POAG and often present with glaucoma in an advanced state.

Instrumentation:

Apart from routine clinical procedures there are special tests for PACG. These are: Peripheral Anterior Chamber depth evaluation using van Herick method, Anterior chamber angle examination using Gonioscopy, Intraocular pressure measurement using Goldmann's Applanation tonometer, Central anterior chamber depth, Lens thickness and Axial length using A-scan biometry, documentation of crowding of the Anterior chamber angle using Ultrasound biomicroscopy (UBM), documentation of Optic disc changes using +90 DS lens and, in indicated cases, Central Visual field testing using Humphrey Filed Analyser.

Peripheral anterior chamber depth measurement (van Herick method – Fig 1.3 –1.7) is measured using Slit lamp biomicroscope. (17) The procedure involves projecting a narrow vertical beam of light from the slit lamp onto the more peripheral portion of the anterior chamber as close as possible to the limbus, with the patient looking straight ahead. The angle between the observation and lighting systems must lie between 50° to 60° so the beam of light strikes the peripheral cornea perpendicularly.

Fig 1.3: Estimation of the peripheral depth of the anterior chamber according to the van Herick test. **Level IV**

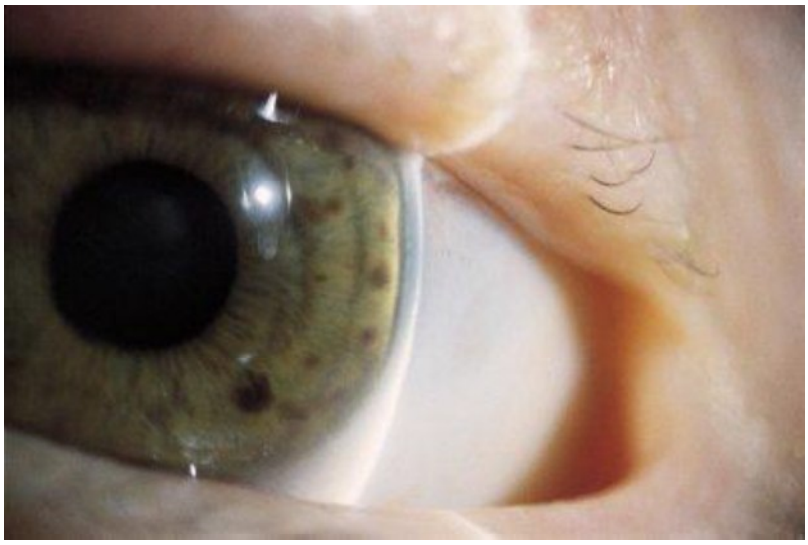

Fig 1.4: Estimation of the peripheral depth of the anterior chamber according to the van Herick test. **Level III**: the distance between the anterior surface of the iris and the rear surface of the cornea is equal to or greater than half of the corneal thickness. The angle is not liable to occlusion.

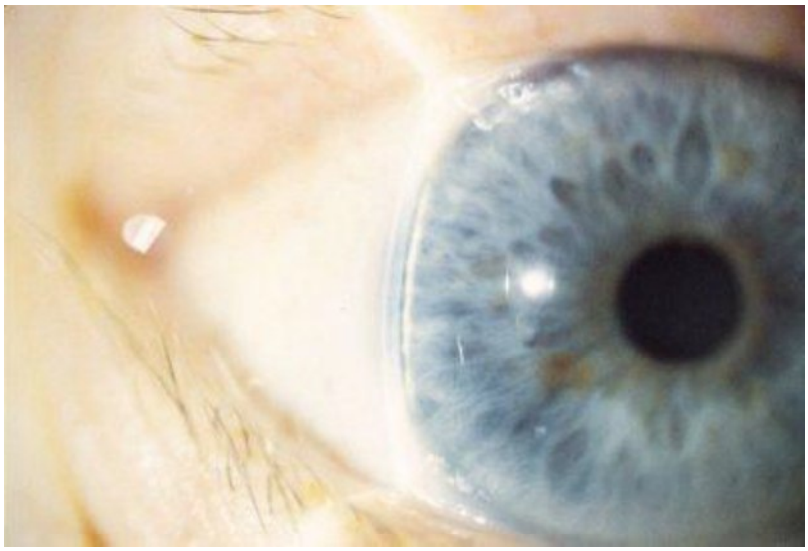

Fig 1.5: Estimation of the peripheral depth of the anterior chamber according to the van Herick test. **Level II**: the distance is equal to approximately 1/4 of the corneal thickness. There is a risk of occlusion.

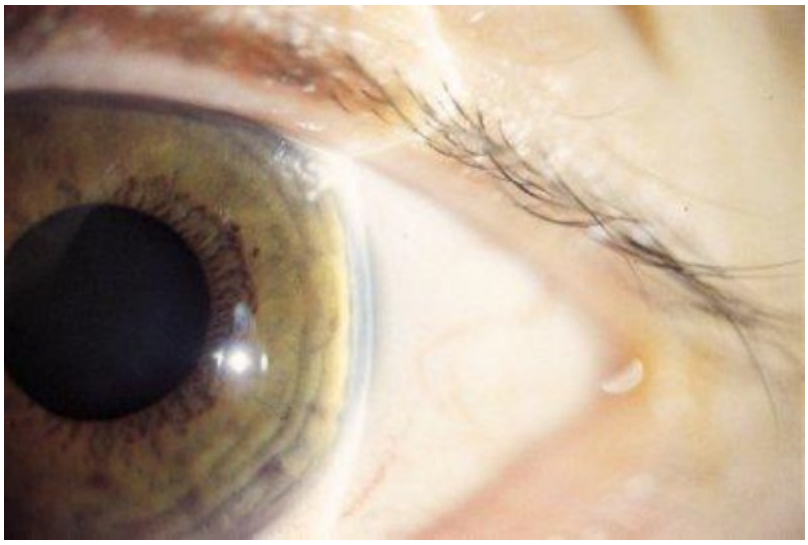

Fig. 1.6: Estimation of the peripheral depth of the anterior chamber according to the van Herick test. **Level I**: the distance is less than 1/4 of the corneal thickness. High risk of angle closure

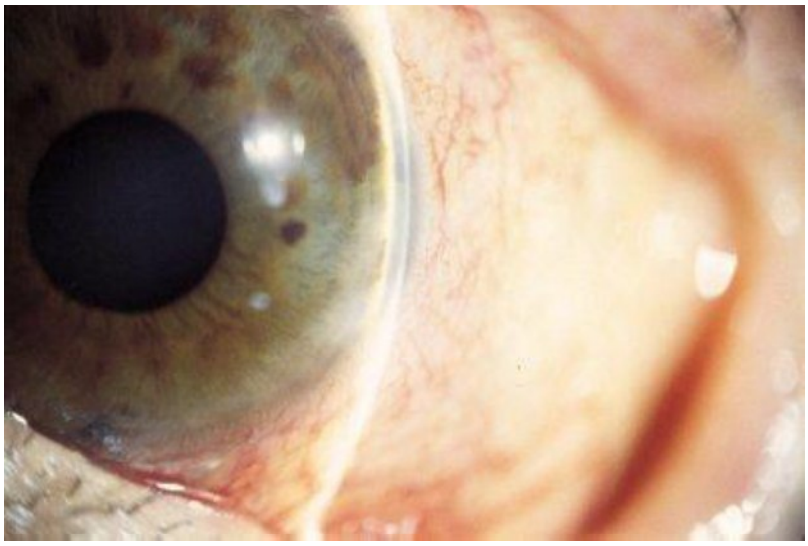

Fig. 1.7: Estimation of the peripheral depth of the anterior chamber according to the van Herick test. **Level 0**: contact between cornea and iris.

IOP measurement (Fig 1.8) using Goldman Applanation Tonometer (15): Intraocular pressure is most accurately measured by Goldmann applanation tonometry. The tonometer is a biprism mounted on a standard slit-lamp, which is used to applanate (flatten) the anaesthetized fluorescein stained cornea. The IOP calculation is based on the Imbert - Fick principle, whereby an external force (exerted by the tonometer) against a sphere (the eye) equals the pressure within the sphere times the area flattened by the force (3.06 sq. mm of the cornea). Unusually thick or thin corneas or irregular corneas can generate errors in IOP readings.

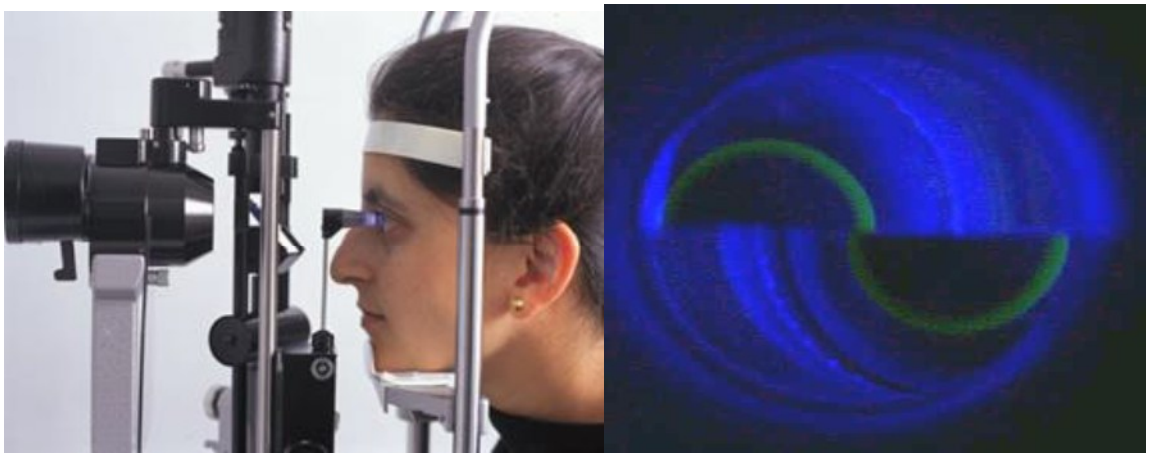

Fig 1.8: Applanation tonometry

It is not possible to view the structures of the anterior chamber angle (Fig 1.9) with direct observation. The scleral tissue projects anterior to the angle and the curvature of the cornea creates internal reflection when one attempts to view the angle obliquely. Gonio lenses (15) permit observation of the angle by eliminating the cornea as a refracting surface by placing a concave surface against the cornea.

There are six ocular structures normally available for observation. The appearance of the anterior chamber angle varies according to congenital individual differences and with acquired changes due to age, injury, or disease. From anterior to posterior the gonioscopic landmarks consist of cornea, Scwalbe's line, trabeculae, scleral spur, cilary body and the last roll of the iris (Fuch's roll).

Scwalbe's line forms the termination of Descemet's membrane and marks the transition from the transparent cornea to opaque scleral tissue. It also forms the anterior boundary of the trabeculae. It is a difficult structure to find and to observe.

The trabecular meshwork tends to be pale pink to pale brown in colour and is arbitrarily divided into anterior and posterior portions, the former usually paler. Schlemm's canal runs in the latter. Each of them occupies half the width of the trabecular band.

The scleral spur is a projection of the sclera beneath the trabeculae. It is whiter than any of the other structures making it the most easily recognised landmark.

The cilary body lies posterior to the scleral spur and varies in colour from pink to dark brown but is always more pigmented than the trabeculae.

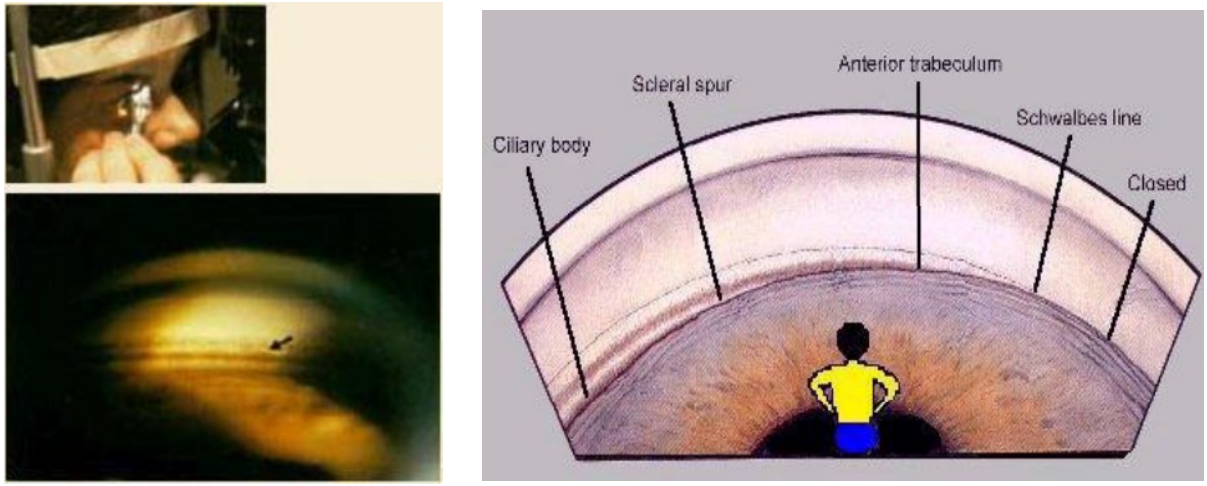

Fig. 1.9: Gonioscopy and angle structures

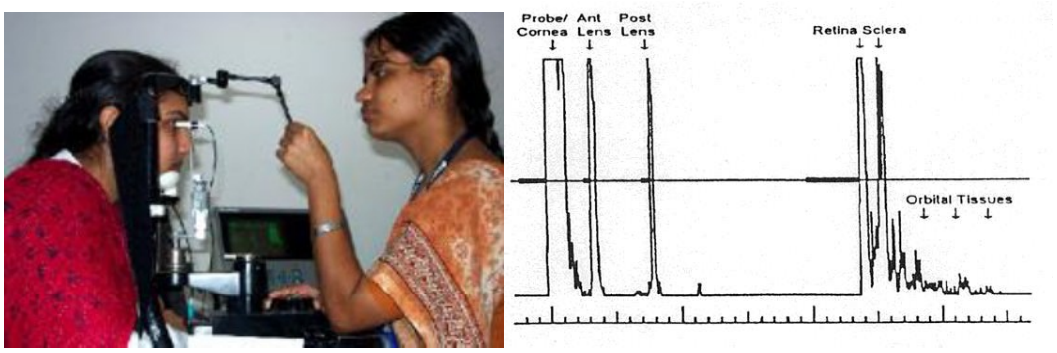

Fig 1.10: A scan biometry

With the sound beam properly aligned along the phakic patient's visual axis in contact scanning, 5 high-amplitude spikes will appear on display, as follows: (1) initial probe/corneal spike, (2) anterior lens spike, (3) posterior lens spike, (4) retinal spike, and (5) scleral spike. (Fig 1.10) Perpendicularity is achieved when all spikes are of high amplitude and the retinal spike is steeply rising from baseline at a 90° angle.

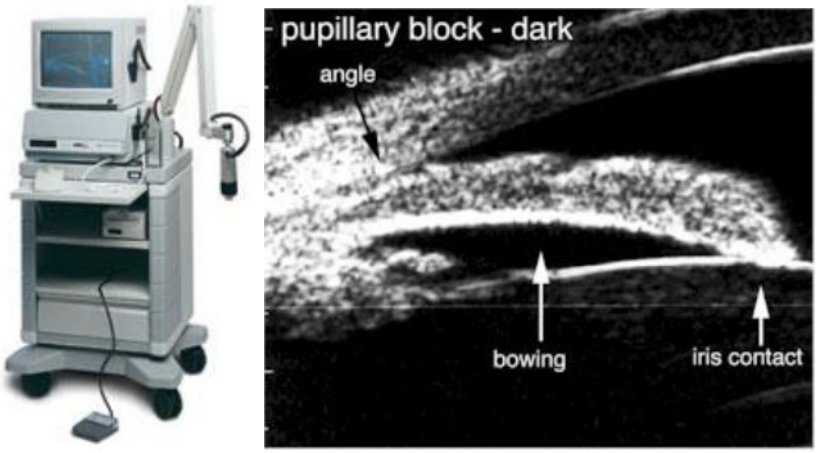

Fig 1.11: Ultrabiomicroscope (UBMP40, Paradigm, USA) and Angle closure glaucoma

Ultrasound Biomicroscopy (Fig 1.11) is a newly developed high resolution imaging method that uses high frequency ultrasound (50 MHz). Tissue penetration is about 5 mm. This method allows detailed observation of anterior and posterior chamber anatomy in the

living eye, and is thus a useful tool in both clinical assessment of glaucoma, and research into causes of various glaucoma types. (17)

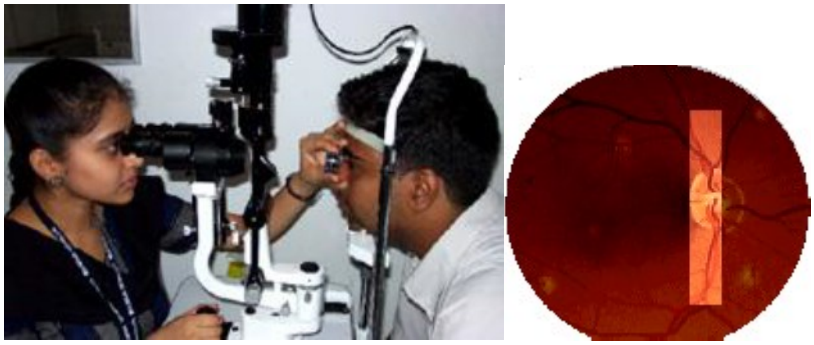

Fig 1.12: +90 DS optic disc evaluation

+ 90 DS lens (16) is used along with Slit lamp biomicroscope (Fig 1.12) to evaluate the Optic disc cupping and neural retinal rim.

***Pathophysiology*:**

Releative pupillary block underlies most cases of angle closure glaucoma. Resistance to transpupillary flow of aqueous humor from the posterior chamber to the anterior chamber is increased by iridolenticular contact. This creates relative pressure gradient between the two chambers and pushes the iris anteriorly, causing bowing of the iris and narrowing or closure of the angle. Relative pupillary block typically occurs in hyperopic eyes, which have a shorter than average axial length, a more anterior chamber, a thicker lens , a more anterior lens position, a smaller corneal diameter and a small radius of corneal curvature. In absolute pupillary block, there are posterior synechiae between the iris and lens. Laser iridotomy eliminates the pressure differential between the anterior and posterior chambers and the iris convexity. The iris configuration becomes planar and the angle widens. Studies

have shown deepening of the peripheral anterior chamber and increase in the volume of the anterior chamber after laser iridotomy. (6, 18) However a subset of patients in whom the angles open post peripheral iridotomy progress to next stage of the disease like optic disc or field changes is noticed and in some cases continue to show progressive closure even with a patent iridotomy. (18)

Laser Peripheral Iridotomy:

Laser Peripheral iridotomy (LPI) was introduced in 1956 but later gained popularity with the advent of argon laser and, more recently, with the neodymium: yttrium-aluminum-garnet (Nd: YAG) laser. Peripheral iridotomy involves creating a full-thickness defect in the peripheral iris and is most commonly performed to treat pupillary block angle closure. In pupillary block, a functional block develops between the lens and the iris, which causes pressure to build up posterior to the iris and makes the iris bow forward. In this manner, the peripheral iris closes the trabecular meshwork by apposition. (16)

Laser peripheral iridotomy (LPI) enables free passage of aqueous humor between the posterior and anterior chambers of the eye, equalizing the pressures in between and lets the peripheral iris rest in a natural position. (i.e., away from the angle). Laser peripheral iridectomy is the treatment of choice for angle-closure glaucoma when the mechanism involved is pupillary block.

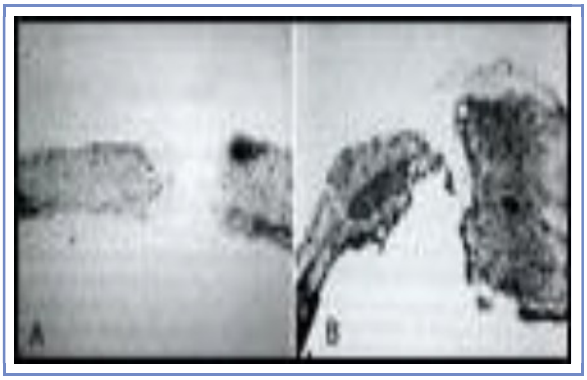

Fig 1.13: Iris disruption due to Laser Iridotomy

LPI may be performed using an argon laser or an Nd: YAG laser. Diode laser has also been used. Considerable differences are found among the laser-tissue interactions with the various technologies, and the Nd: YAG has proved to be the laser of choice for LPI.(Fig 1.13)

Nd: YAG is the most commonly used type of laser for LPI. The LPI closure rate is lower when Nd: YAG is used. Disruption of the iris pigment epithelium may occur with this type of laser. Pigment migration and plugging accounts for most cases of LPI closures, except in uveitis, where fibrin may close the LPI. (19-21)

In some instances Argon laser is used for LPI. The argon laser may be useful in combination with the Nd: YAG laser in some cases (e.g., in patients with dark brown irides that may be thick and difficult to perforate). In those situations, it may be convenient to pre-treat the intended iridotomy area with argon laser to thin it before full iris perforation with the Nd: YAG laser is attempted. After full explanation to a patient of what the procedure involves, what to expect (e.g., seeing a flash, hearing and feeling a "pop," electric shock sensation), and after informed consent is obtained from a patient, pilocarpine 2% drops are instilled every 5 minutes three times in the procedure eye. Adequate

constriction and akinesia of the pupil must be ensured. The goal is to stretch the iris to facilitate its perforation with the laser. A drop of apraclonidine or brimonidine is given. Proparacaine is instilled for anesthesia.

Fig 1.14: Abraham and Wise lenses

A patient and operator are adequately positioned for the laser treatment. A patient's head may be secured with a head strap if necessary. Laser energy is selected to be between 4 mJ and 6 mJ and single pulse mode is preferable. Generally, one to 10 single pulses are sufficient. The less energy used to perforate the iris, the better it is. A corneal contact lens with a plano-convex button (Abraham or Wise lens. Fig 1.14) is placed on the eye after filling it with a coupling solution.

The laser beam is focused on the iris along the superior peripheral iris, usually at 11 o'clock or 1 o'clock position. (Positions on the iris are described analogous to a clock face with the upper portion corresponding to 12 0'clock) The peripheral iridectomy should be placed in a location where it can be covered by the upper eyelid. Furthermore, location is influenced by the presence of iris crypts along the superior peripheral iris, in which the iris is already thinned and penetration may be easier.

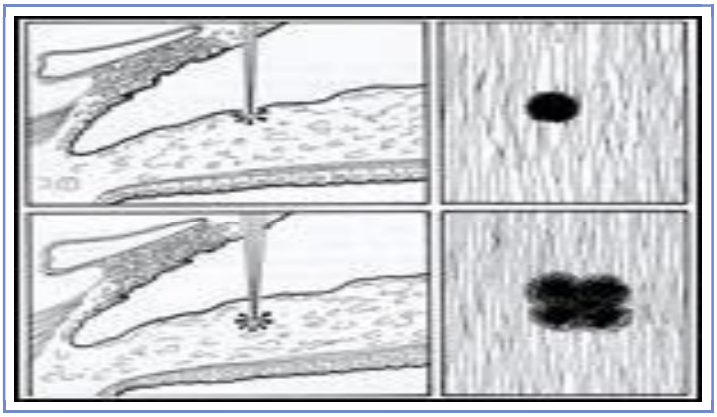

Fig 1.15: Laser delivery to disrupt Iris in Iridotomy

Once location for laser delivery is chosen and the beam is focused on the iris, the slit lamp is pushed forward toward the patient to defocus the beam slightly posteriorly (single spot separates into two or four spots, depending on the laser manufacturer), placing it deeper in the iris, in midstream. (Fig.1.15)

Laser energy is delivered until full thickness perforation is achieved. A "gush" of fluid and pigment may be seen once this is achieved. This represents aqueous passage from a higher pressure posterior chamber to a lower pressure anterior chamber, thus breaking the pupillary block. The iris should fall back away from the angle to a flat position because the pressures in the anterior and posterior chambers are now equalized.

Once a full thickness hole is created in the iris, it can be enlarged if necessary by directing the beam to the edges of the hole (avoid applying laser to underlying structures such as the lens). Before the contact lens is removed, patency of the PI is confirmed by disappearance of the aiming beam in the iridotomy and being able to see and focus on the lens capsule in the area of the PI. The contact lens is then removed; the patient is reassured and asked to wait for 1 hour for an IOP check.

In the absence of complications, the patient is instructed to use prednisolone acetate 1% drops four times a day for 4 days in the operated eye. Pre-laser medications are continued except for miotics (to avoid synechiae formation). Follow-up is usually in 1 week, at which time the PI patency is evaluated, IOP is rechecked and gonioscopy is performed to evaluate the angle for openness and occludability. Gonioscopy and dilation may be reserved for the patient's 6-week visit. In a study on acute primary angle closure in 44 Asian subjects, deepening of the angle after LPI was observed in the first 2 weeks and did not vary further in 1 year. (22)

A corneal contact lens with a plano convex button is used. Two main types are available: Abraham and Wise lenses. The Abraham iridectomy lens has a 66 D plano-convex button that is larger and easier to focus through than the Wise lens, especially when used with the Nd: YAG laser, which has a larger cone angle than the argon. On the other hand, the Wise lens has a plano-convex button of 103 D which although smaller, concentrates the laser energy more.

The corneal contact lens:

- Concentrates the energy by minifying the beam spot
- Magnifies the target site
- Acts as a heat sink, decreasing corneal burns (with photocoagulators)
- Helps in keeping the eye open

Complications from LPI are rare but can occur. (23)

Cornea

Corneal whitening at the LPI overlying site can occur secondary to unexpected energy absorption by the endothelium when using argon or diode laser or due to corneal edema secondary to disruption of the endothelium in case of using the Nd:YAG laser. Prompt discontinuation of laser application through this area is recommended. The corneal whitening will generally disappear with time.

Uveitis

Variable amounts of inflammation can be expected after LPI. It is usually a mild transient iritis that resolves in a few days. Prednisolone acetate 1% is routinely prescribed and seems to control the inflammation with low doses, namely 1 drop four times a day for 4 days.

IOP Spike

IOP is routinely checked 1 hour after the procedure. It is not rare to find an elevated IOP. All patients should be pre-treated with apraclonidine 0.5% or 1% or brimonidine 0.15% or 0.2% for prophylaxis. If the IOP spike is significant compared to the patient's baseline or appears hazardous given the patient's degree of glaucoma damage, adequate IOP lowering should follow.

Topical medications are tried first to control the spike in the majority of cases. Oral medications such as acetazolamide or glycerin may be needed in certain patients. IOP

elevation may persist for 1 month and this should be appropriately managed. Laser peripheral iridectomy is commonly performed in individuals who already have more susceptible optic nerves than healthy patients; hence, it is important to avoid any further damage from an untreated pressure spike.

Lens Injury

Lens injury is a potential complication of this procedure but to date no evidence of long-term consequences of LPI to the lens exists.

Pigment Dispersion

It is common to observe additional pigment in the angle after LPI. Consequences are not known.

Retinal Burn

This risk can be practically eliminated with the use of the contact lens and adequate caution.

Corectopia

The pupil can change its shape, elongating towards the quadrant lasered. This may happen with photocoagulation and usually does not persist.

Monocular Diplopia

Rarely patients may complain of diplopia or "ghost image" after LPI. This will be seen if the laser spot is small and in the right position for light refracted by the upper lid tear meniscus to enter and become focused on the retina.

Iris Atrophy

This was a complication when low-power photocoagulation was used, but is now rarely seen.

Malignant Glaucoma

LPI can precipitate malignant glaucoma, also known as aqueous misdirection syndrome. LPI is the treatment for angle closure caused by pupillary block and malignant glaucoma is mostly seen in patients with angle closure after an incisional or laser procedure. Shallowing of the anterior chamber is seen in pupillary block and malignant glaucoma but the pattern is different. In pupillary block, iris convexity may be observed, with the chamber remaining deep centrally and shallow peripherally. On the other hand, in malignant glaucoma, the chamber shallows centrally and peripherally.

Failure

Patency should always be confirmed after the procedure is done. Positive transillumination may not be enough proof of patency, given that with partial thickness Peripheral iridotomies may transilluminate as well. Visualization of structures beyond the iris, such as the lens capsule, may be more accurate in indicating patency. If full thickness

penetration is not achieved, then more laser applications are needed until this is accomplished.

Late Closure

Once the LPI is patent, it rarely closes and if it does, it happens during the first few weeks or during a bout of uveitis. Pigment migration is the most common cause of peripheral iridotomy closure. Nd: YAG laser has been proven to be more efficient than argon or diode in removing the iris pigment epithelium (24), presumably due to its shock wave. Peripheral iridotomy closure after Nd: YAG LPI is rare.

Posterior Synechiae

Use of miotics after LPI is to be avoided because they can contribute to synechiae formation. Posterior synechiae may form after anterior segment inflammation. If the inflammation persists, it may be wise to employ cycloplegia for the eye.

Hemorrhage

Blood vessels can be ruptured when using the Nd: YAG laser because it does not photocoagulate the tissue (as argon laser does). Bleeding during LPI is generally self-limited and can be treated by gentle pressure on the eye through the contact lens.

***Study Objectives*:**

(A) The Primary objective of the study was aimed at collecting baseline and follow-up examination data of PACS who underwent LPI and to know the course of the disease in

these study subjects following LPI. It was also aimed to look into the predictive factors for the progression of the disease among the study subjects.

(B) The Secondary Objectives were:

To find the inter and intra observer reliability of measurement of ultrasound biomicroscopy images in primary angle closure suspects

To look into the gender variation in ocular biometry and ultrasound biomicroscopy of primary angle closure suspects and normal eyes.

To develop new software for quantifying iris configuration among primary angle closure suspects and normal eyes.

Chapter 1 is the introductory chapter on Glaucoma.

Chapter 2 deals with inter and intra observer reliability of UBM measurements among PACS subjects.

Chapter 3 deals with gender variation of the A-scan biometry and UBM parameters among normal and PACS subjects

Chapter 4 deals with the two year follow up data of the PACS subjects after LPI among our hospital based Indian subjects, in particular.

Chapter 5 deals with the development of new software to quantify iris configuration, reliability of this quantification technique and its application to normal and PACS subjects.

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Chapter 2:

Inter and Intraobserver reliability of Measurement of Ultrasound Biomicroscopy Images in Primary Angle closure Suspects (PACS)

***Abstract*:**

Aim: To evaluate Inter and Intra-observer reliability of measurement of Ultrasound biomicroscopy (UBM) images of Primary Angle Closure Suspect (PACS) patients.

Methods: UBM images from all the quadrants were obtained from 57 PACS patients seen by two of the authors between March 2003 and July 2003 at the glaucoma clinic of a tertiary eye care center. For each patient, one good UBM image was selected. For the interobserver reliability measurement, two experienced examiners, masked to each other, measured 5 parameters of 20 randomly selected images using the calipers in the UBM software. Randomization was done by random clicking of the mouse pointer on the file names in the directory containing the 57 images. The parameters measured were Angle Opening Distance (AOD500), Trabecular Meshwork Ciliary Process Distance (TCPD), Iris Thickness (IT), Anterior Chamber Angle (ACA) and IridoCiliary Process Distance (ICPD). For intraobserver reliability measurement, a different set of 25 randomly selected images was measured for 5 parameters twice by one of these examiners. Based on the data obtained inter- and intraobserver reliability using coefficient of variation (CV) was measured.

Results: Interobserver reliability was good for Angle Opening Distance (AOD), Trabecular Meshwork Ciliary Process Distance (TCPD), and Iris Thickness (IT) (CV < 10%). Intraobserver reliability of all the parameters was good.

Conclusions: Follow up measurement of some UBM parameters of PACS subjects by different observers can be misleading. Good reliability of follow up measurement could be maintained if the same observer measures them all the time.

Review of Literature:

Ultrasound Biomicroscopy (UBM) has provided an opportunity to the clinicians and researchers to visualize at near microscopic resolution the areas not easily seen otherwise. This paves the way for diagnoses and reorienting therapeutic interventions in case of anterior segment disorders (1). Using the calipers provided in the UBM software, the anatomical variations of anterior segment could be quantified from the saved UBM images (2). However, for a parameter to be quantitatively useful, its measurement must be reproducible. The configuration and relative proportions of structures in images obtained by scanning depend on the plane of section, degree of tilt from the perpendicular in the scanning probe and the distance from the center of the anterior chamber (3). Thus, there is potential in an artifact to confound the interpretation of results, especially, the clinical relevance of follow up cases using UBM images as that depends on the ability of reproducibility of measured parameters. There have been studies on reproducibility of UBM parameters of normal angle eyes (3-6). In this study we have evaluated interobserver and intraobserver reliability in the measurement of UBM parameters from the images of PACS subjects (Figure 2.1). Previous studies on normal angle eyes (Figure 2.2) showed good intraobserver reliability of angle measurement (3-6). However, there

was no literature on the effect of anterior crowding on inter- and intraobserver reliability in measurements of parameters of UBM images of PACS patients.

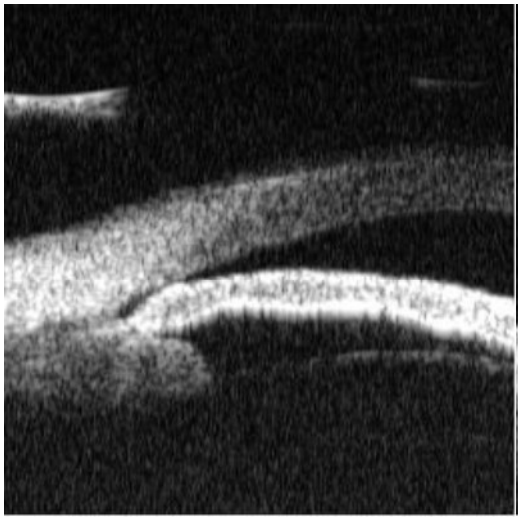

Fig 2.1: PACS eye

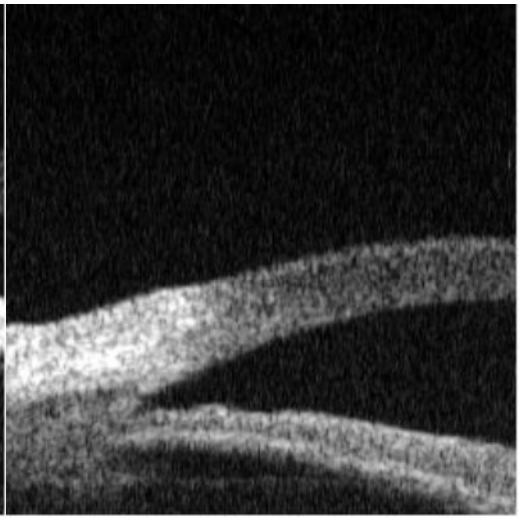

Fig 2.2: Normal angle eye

Materials and Methods:

UBM (UBMP40, Paradigm, USA) images (scanned under dim room illumination) from all the quadrants were obtained from 57 PACS patients seen by two of the authors between March 2003 and July 2003 at the glaucoma clinic of a tertiary eye care center. These images were stored in a computer in the internal data format of the accompanying software. The criterion for diagnosis of PACS was gonioscopically posterior trabecular meshwork not visible for at least 180 degrees (equivalent to modified Shaffer Grade 1 or less), without synechial changes, with normal intraocular pressure and normal disc features. We have included subjects who were asymptomatic PACS. The exclusion criteria were peripheral anterior synechiae, plateau iris and peripheral iridotomy. For each patient, one good UBM image was selected. Good quality images were selected on

the basis of clear demarcation of scleral spur and the limbal architecture in UBM image (3). From these 57 images, 20 UBM images and a different set 25 UBM images were randomly selected for inter- and interobserver analysis, respectively. Two independent observers measured the parameters using the calipers available in the UBM software (3).

UBM parameters could be classified into measurement of distance (TCPD, ICPD, IT, AOD) and measurement of angle (ACA, SCPA – Sclerociliary Process Angle). In this study we measured parameters that are commonly used in our clinical practice. These include:

1) Trabecular Meshwork Ciliary Process Distance (TCPD): Measured as the line extending from a point 500 microns anterior to the scleral spur along the corneal endothelium dropping perpendicularly through the iris to the most anterior ciliary process seen during scanning in that meridian.
2) Iridociliary Process Distance (ICPD): Measured from iris pigment epithelium to the ciliary process along the same line as TCPD.
3) Iris Thickness (IT): Measured along the same line as TCPD.
4) Angle Opening Distance (AOD): Measured on a line perpendicular to the trabecular meshwork 500 microns from the scleral spur to the iris stromal surface.
5) Anterior Chamber Angle (ACA): Measured with the apex in the iris recess and the arms of the angle passing through a point on the trabecular meshwork 500microns and a point on the iris perpendicularly opposite.

Interobserver reliability:

Two experienced examiners were asked to measure the above-mentioned 5 parameters from 20 images. These parameters were measured in a fixed order. The observers were masked to each other's measurements. Coefficient of variation of all the parameters between the two observers was obtained.

Intraobserver reliability:

One of the examiners was shown 25 images on screen and was asked to measure the 5 parameters twice. The interval between the first and the second measurements of the same image was more than 2 days. The order of presentation of the images for the second measurement was randomly varied using computer generated random numbers. Coefficient of variation of all the parameters between the two measurements was obtained.

The patients for inter and intraobserver studies were different. A coefficient of variation of less than 10 % was considered indicative of good reliability (3).

Results:

Interobserver reliability was good for AOD, TCPD, and IT (CV < 10%) parameters (Table2.1). ICPD and ACA showed higher values suggestive of poor agreement between the examiners. Intraobserver reliability was good (CV < 10%) for all the 5 parameters (Table 2.2). Using Altman and Bland analysis (7), the difference in the measurement of AOD and ACA by the two observers was calculated (Figure 2.3 and 2.4). It was found

that mean difference of AOD was 0.003 (95% CI 0.128,-0.121) and for ACA was -2.893 (95% CI 14.28,-20.66).

Table 2.1: Interobserver reliability of the measurement of UBM parameters:

Angle Opening Distance	Trabecular ciliary process distance	Iris ciliary process distance	Iris thickness	Anterior chamber angle
1.58	**3.73**	**13.21**	**3.92**	**13.02**

Coefficients of variation (%) are given for parameters measured by two observers.

Table 2.2: Intraobserver reliability of the measurement of UBM parameters:

Angle Opening Distance	Trabecular ciliary process distance	Iris ciliary process distance	Iris thickness	Anterior chamber angle
0.36	**0.24**	**0.30**	**3.42**	**4.78**

Coefficients of variation (%) are given for parameters measured by two observers

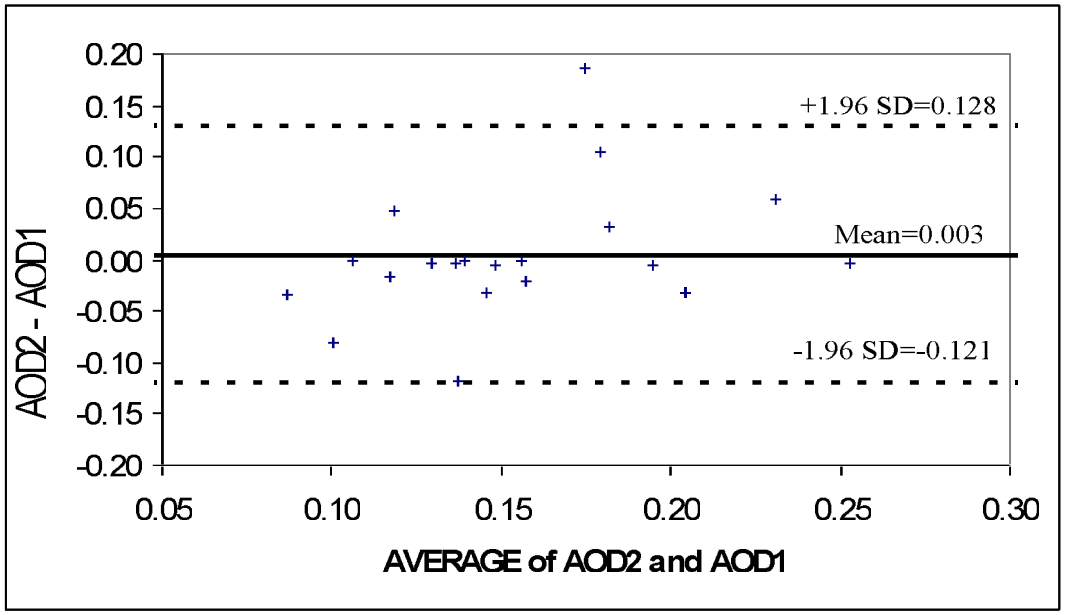

FIGURE 2.3: Bland and Altman graph of interobserver reliability for AOD

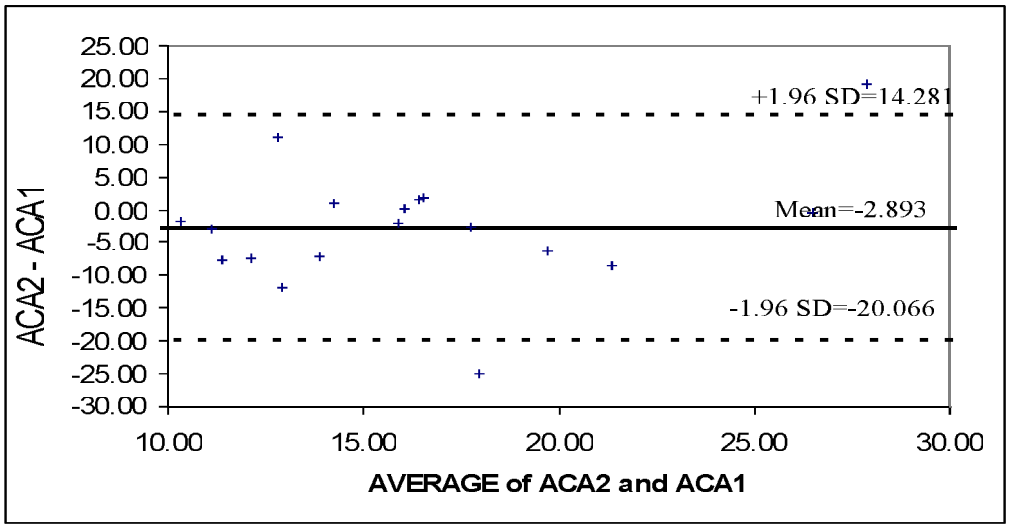

FIGURE 2.4: Bland and Altman plot of interobserver reliability for ACA

Discussion:

Quantitative measurements of the UBM image are useful for research purposes in evaluating the pathophysiology of angle-closure mechanisms. It can also be used for follow up of cases in narrow angle or angle closure glaucoma. Research studies involving angle-closure include anterior segment imaging and quantitative measurements (8-11). However the reproducibility of UBM parameters needs to be assessed before using it reliably in clinical practice.

Inadequate reproducibility or excessive variability between one measurement and the other can arise from systematic differences between observers or instruments of measurement or physiological changes in the parameters measured (3). Studies (3-6) have shown good reliability of measurement for most of the parameters in the UBM images with a single observer. However, interobserver reliability was variable. The qualities of images were suggested as the major reason for this variability; but when good quality images were chosen the variability remained. All the previous studies used UBM images of normal eyes for evaluating inter- and intraobserver reliability of UBM parameters.

In this study, the reliability of measurement of five parameters of good quality UBM images of PACS subjects was studied. To our knowledge, this was the first study to find out the interobserver and intraobserver reliability in the measurement of UBM parameters in PACS subjects. Some of the parameters (AOD500, IT, TCPD) had well-defined landmarks for measurement while others (ICPD, ACA) had ambiguity in the landmarks.

It was found that the intraobserver measurements (repeated measurements by the same individual) for all of the parameters of the UBM images were reliable. Interobserver

measurements (measurements repeated by different observers) of some parameters such as ICPD and ACA of these images were not reliable.However, Altman and Bland analysis showed good agreement between two observers for AOD and ACA measurements. A report by Ritch et al. also showed similar results in normal eyes (3). The variability in measurements between individuals may be due to the variations in anatomical identification of scleral spur and the assumed endpoint of the measurements. If only one examiner measured the image, there might not be a variation in the reference point, which could explain the good intraobserver reproducibility. As seen in this study, where ICPD involved both the beginning and endpoints, which were ill defined, or ACA, which involved more than 2 points for measurement can introduce an error in measurement. The parameters such as AOD500, TCPD and IT have defined landmarks to start with, which could explain the good reliability.

Some of the limitations in our study were: we did not study all the UBM parameters found in the literature. We included five sample parameters. We utilized the software available in the UBM instrument itself and did not explore the variability using the UBM Pro 2000 software available for measuring other parameters such as Angle Recess Area (ARA). Measurement of ARA with UBM Pro 2000 is semi-automated and is found to be a useful parameter for assessing angle configuration (12). Semi-automation for imaging tools could be a solution to inter-observer variability.

Conclusion:

To sum up, in interpreting quantitative differences of the images when measured by different individuals caution should be exercised. Our study highlights the subjective nature of measurement of some of the parameters of UBM images of PACS subjects. It is therefore suggested that interpretations of same image or follow up images by more than one observer should be avoided until acceptable and reliable objective alternatives are found. Alternatively, the parameters chosen for follow up studies should have well defined beginning and end points such as for AOD500, TCPD and IT. However, we reiterate that similar results in PACS subjects as in normal eyes (3-6) show that the reliable measurements of UBM parameters are possible even with narrow angle configuration and that this reliability is good when a single observer makes all follow up measurements of a single UBM image.

Specific Contribution:

In narrow angle subjects, the anterior chamber angle was difficult to measure because of anterior crowding of the anterior chamber. The only way to quantify the angle is with the help of UBM software. However the limitation of identifying the reference point and measuring the angle remains a challenge clinically. This perception about the reliability of measurement among the narrow angle subjects was not tested by anyone. The existing knowledge on the inter and intraobserver reliability of the measurement of the UBM parameters among normal angle eyes was documented and it was extrapolated wrongly to

be the same for the narrow angle eyes. Our contribution was that through this study we have first time documented the significance of intra observer reliability of measurement of UBM parameters among narrow angle eyes.

Future scope of study:

A prospective parallel documentation of the normal angle and narrow angle eyes using both UBM inbuilt software, and UBMpro2000 software can be done to compare the two software for their reliability. Also the newly developed software by us (Chapter 5) could be applied along with other UBM parameters.

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Chapter 3:

Gender Variation in Ocular Biometry and Ultrasound biomicroscopy of Primary Angle Closure Suspects and Normal eyes

Abstract:

Purpose: To compare A- scan biometry and Ultrasound biomicroscopy in Primary Angle Closure Suspects with age-matched normal Indian eyes.

Patients and Methods: Subjects with Primary Angle Closure Suspects (PACS; n = 57 eyes) and normal eyes (n = 57 eyes) underwent A scan biometry and Ultrasound biomicroscopy. Anterior chamber depth (ACD), anterior chamber angle (ACA), axial length, lens thickness (LT), relative lens position (RLP), central corneal thickness (CCT), angle opening distance 500 (AOD500), trabecular–ciliary process distance (TCPD), iris-ciliary process distance (ICPD), iris thickness (IT) and scleral-ciliary process angle (SCPA) were measured. The subjects were divided into males, females and combined groups for analysis. The parameters were compared using independent sample't' test with Bonferroni correction for multiple comparisons.

Results: In combined group, the PACS subjects presented a significantly lesser ACD, AXL, CCT, AOD500, TCPD, ACA ($p<0.001$) and RLP ($p=0.04$). In males, the RLP was anterior ($p=0.002$) and in females, the LT ($p<0.001$) was significantly thicker among the PACS group.

Conclusion: ACD, AXL, CCT, TCPD, ACA and AOD500 were significantly less in PACS group than in Normals. In females, the lens was thicker in PACS than in Normals. Lens was anterior-placed in PACS group than in Normals among males.

***Review of literature*:**

Compared to normal eyes, eyes with "occludable angles" and primary angle closure glaucoma present with smaller anterior chamber depth, a thicker lens, a more anterior lens position, and a shorter axial length. (1-8)Ultrasound biomicroscopic (UBM) parameters show relatively lesser values in primary angle closure glaucoma than in normals. (4,9,10) Most of the biometric and UBM studies have concentrated on the severe forms of glaucoma. (1-5,6-9) The so-called "precursor" for the severe stages i.e. PACS has been studied in a few (2,4,5) but a detailed comparison of the parameters with age-matched controls using both A-scan biometry as well as UBM is not available to our knowledge. There is little information available on the differences between PACS and normal eyes with gender differences in the Indian population. In this study, we analysed the ocular biometry and UBM measurements in PACS and normal eyes in both female and male subjects of hospital based Indian subjects.

Patients and Methods:

Primary Angle Closure Suspect (PACS) subjects were recruited from the Glaucoma service of a tertiary eye care hospital from March 2003 to December 2003. The criterion for diagnosis of PACS is posterior trabecular meshwork not visible for at least 180 degrees (equivalent to Modifies Shaffer Grade 1 or less), without synechial changes, with normal intraocular pressure and normal disc features. We have included subjects who were asymptomatic PACS. The exclusion criteria were peripheral anterior synechiae,

secondary angle closure, glaucoma, history of intraocular surgery, history of significant retinal pathology and nuclear sclerosis defined as LOCS II more than Grade 2 (NC2, NO2).

The institutional review board of Vision Research Foundation approved the study and written informed consent was obtained from all subjects. The study was conducted as per the tenets of declaration of Helsinki.

All subjects underwent a complete ocular examination that included refraction, slit lamp biomicroscopy, applanation tonometry, indentation gonioscopy using Zeiss four mirror gonioprism, stereobiomicroscopic examination of optic disc using +90 D lens, dilated examination for LOCS II grading. A-scan ultrasonic biometry (Alcon Labs, Fortworth, TX, USA), Keratometry (Aravind Engineering Industrial Unit, Pondicherry, India) and Ultrasound biomicroscopy (Paradigm Medical Industries, Inc, USA) were also done in all the subjects.

Normal Control Subjects**:**

We selected age matched normal angle subjects (defined as Shaffer grade 3 or more) from previously collected normative data for UBM. A trained ophthalmologist performed the UBM and gonioscopy for all the normal subjects using the same protocol. (10) The demographics and ocular biometry data were taken from the medical records except for UBM measurements. UBM images of 57 age matched normal subjects were retrieved and parameters were measured by the same examiner (RKK).

Gonioscopy**:**

Gonioscopy was done by a senior optometrist (RKK), using a Zeiss four mirror gonioprism (Ocular Instruments Inc, USA). The procedure was done under dim room illumination with shortest and narrowest beam width. The angle structures visible were noted and Shaffer grading system was used to grade angles.

A-Scan Ultrasonic Biometry**:**

A standardized Ocuscan instrument (Alcon Labs, Fortworth, TX, USA) with a 10 MHz ±10% transducer probe was used for measurements. Examination was done under topical anesthesia. Ten automatic measurements were taken and saved. An average of consistent readings was considered for measurement purposes. .

Parameters measured were as follows:

1) Anterior Chamber Depth (ACD): from the cornea to the anterior lens spike. True ACD was measured by subtracting corneal thickness from ACD measured.
2) Lens Thickness (LT): from the anterior lens spike to the posterior lens spike.
3) Axial length (AXL): the sum of ACD, LT and vitreous chamber length.
4) Relative Lens Position (RLP) was calculated as follows (11): (ACD + ½ LT) ÷ AXL

Ultrasound Biomicroscopy**:**

The examinations were performed using the UBM 840 model (Paradigm Medical Industries, Inc,USA) with a 50 MHz transducer probe, which facilitates 4 to 5 mm of tissue penetration and has a resolution of 50µm. UBM imaging of all PACS subjects was done by the same optometrist (RKK) and the examination was performed with subject in

supine position. Under topical anesthesia, an ocular cup of special design filled with 2% methylcellulose as a coupling solution was used. Radial scan images at the 12, 3, 6 and 9 o'clock positions centered over the limbal region and perpendicular scans centered over the pupil were obtained under dark room condition. Using special caliper in the instrument, the following parameters were measured:

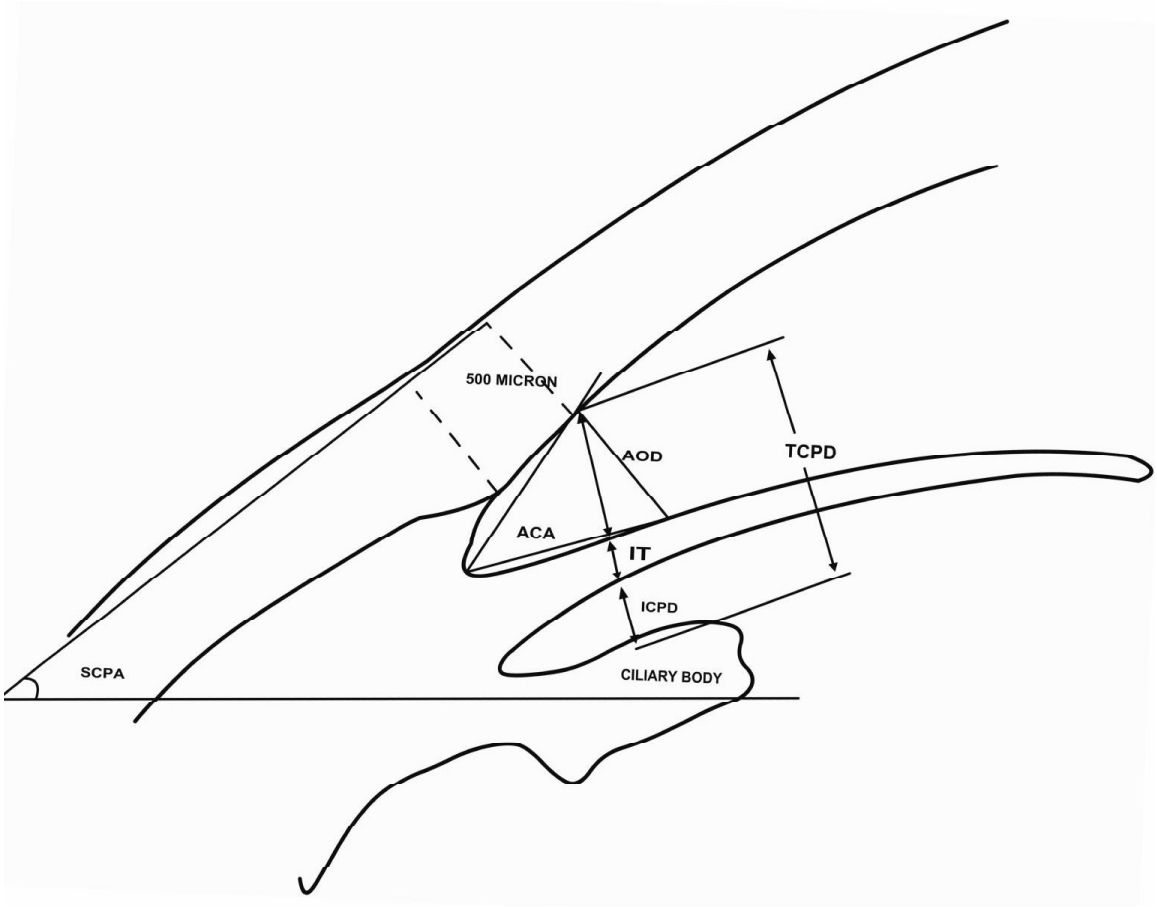

Fig 3.1: Diagrammatic representation of a UBM image with parameters

1) UBM-Anterior Chamber Depth (UACD): from the corneal endothelium to the anterior lens surface.
2) UBM-Central Corneal Thickness (CCT): from the corneal endothelium to the corneal epithelium.

3) The Angle Opening Distance 500 (AOD500): by taking a point on the internal ocular wall 500µm anterior to the scleral spur and extending a line perpendicular to the plane of the trabecular meshwork from that point to the apposing iris.
4) The Trabecular Ciliary Process Distance (TCPD): on a line extending from the corneal endothelium at 500µm from the scleral spur perpendicularly through the iris to the ciliary process.
5) The Iris Ciliary Process Distance (ICPD): from the posterior iris surface to the ciliary process along the same line as the TCPD.
6) The Iris Thickness (IT): along the same line as the TCPD.
7) Anterior Chamber Angle (ACA): measured with the apex in the iris recess and the arms of the angle passing through a point on the trabecular meshwork at 500µm from the scleral spur.
8) The Scleral Ciliary Process Angle (SCPA): between the tangent to the scleral surface and the axis of the ciliary process.

One randomised eye of each subject was used for analysis.

Statistical Analysis:

All the data were entered into the Microsoft Excel sheet and analysis was done using SPSS 13 (SPSS, Inc., Cary, NC, USA.). Descriptive statistics of all the patient data was obtained. Independent samples't' test was done to compare the parameters of PACS and normals. Comparison was done between male and female subjects. Statistical tests were performed using the level of significance 0.05. We performed Bonferroni corrections by

adjusting the significance (12) showed in the independent student's't' test for UBM parameters and $p < 0.0023$ was kept statistically significant.

***Results*:**

57 subjects each of normal angle eyes (32 females, 25 males) and of PACS eyes (34 females, 23 males) were studied. The mean age of the subjects with normal angles was 52.40±10.88 yrs and 52.48± 10.32 yrs in PACS subjects (p=0.968). The mean age of males with PACS was 52.84± 8.41 and in normals was 55.80±8.39 (p=0.229). The mean age of females with PACS was 52.06 ±12.61 and in normals was 50.41±10.98 yrs (p=0.572). In each group, both males and females were age matched (Normals: p =0.792, PACS: p=0.06).

Ocular biometry:

In Table 3.1, the biometry data of both sexes in the normal and PACS groups were compared separately. Females had significantly shorter AXL (p=0.018), thicker lens (p=0.013) and relatively more posterior placed lens (p=0.002) than males in PACS group. There was no gender variation among normals.

Table 3.1. Comparison of ocular biometric data in the Normal group and Primary Angle Closure Suspects between Males and Females

Group	Parameter	Males Mean (SD)*	Females Mean(SD)	95% CI† difference in means	p value
Normal Males : n=25 Females: n=32	AXL (mm)	23.41 (1.25)	22.91 (1.78)	(-0.34 ,1.34)	0.241
	ACD (mm)	3.01 (0.27)	2.90 (0.38)	(-0.067, 0.29)	0.217
	LT(mm)	4.17 (0.40)	3.98 (0.54)	(-0.063, 0.45)	0.136
	RLP	0.22 (0.02)	0.21 (0.02)	(-0.007, 0.02)	0.440
PACS Males : n=23 Females : n=34	AXL (mm)	22.59 (0.98)	21.9 (0.79)	(0.11 , 1.09)	0.018**
	ACD (mm)	2.35 (0.43)	2.50 (0.24)	(-0.34 ,0.04)	0.109
	LT(mm)	3.96 (0.96)	4.47 (0.47)	(-0.91, -0.11)	0.013**
	RLP	0.19 (0.03)	0.22 (0.02)	(-0.04, -0.01)	0.002**

*** SD-Standard Deviation; †CI – Confidence Intervals**

*** Significant difference, by independent student's't' test using $p<0.05$ level*

Ocular biometry values were significantly different between the groups (Table 3.2). Mean AXL and ACD were significantly ($p < 0.0001$) less and RLP was significantly ($p=0.04$) anterior in the PACS group than in the normal group. In both the genders, it was found that PACS group had significantly shorter AXL ($p=0.01$), shorter ACD ($p<0.001$). In addition, females had thicker lens ($p<0.001$) and males ($p=< 0.001$) had relatively anterior-placed lens in PACS than in normal group.

Table 3.2: Comparison of ocular biometric data in the Normal and Primary Angle Closure Suspects groups among Combined, Female and Male subjects, showing variation among genders.

Group	Parameter	Normals Mean (SD)† n=57	PACS Mean(SD) n=57	95% CI difference in means	p value
Combined	AXL (mm)	23.13 (1.58)	22.23 (0.91)	(0.41 , 1.39)	0.0001*
	ACD (mm)	2.94 (0.34)	2.44 (0.34)	(0.38 ,0.65)	0.0001*
	LT (mm)	4.06 (0.34)	4.27 (0.74)	(-0.45 ,0.03)	0.081
	RLP	0.22 (0.02)	0.21 (0.03)	(0.0001 ,0.019)	0.039*
Females	AXL (mm)	22.91 (1.78)	21.99 (0.79)	(0.11 , 1.09)	0.010*
	ACD (mm)	2.89 (0.38)	2.50 (0.24)	(-0.34 , 0.04)	0.0001*
	LT (mm)	3.98 (0.54)	4.47 (0.47)	(-0.91 , -0.11)	0.0001**
	RLP	0.21 (0.02)	0.22 (0.02)	(-0.04 , -0.01)	0.734
Males	AXL (mm)	23.4 (1.25)	22.59 (0.98)	(0.14 , 1.50)	0.010*
	ACD (mm)	3.01 (0.27)	2.35 (0.43)	(0.45 , 0.87)	0.0001*
	LT (mm)	4.17 (0.40)	3.96 (0.96)	(-0.22 , 0.63)	0.331
	RLP	0.22 (0.02)	0.19 (0.03)	(0.01 , 0.04)	0.002*

**Significant difference by independent student's t' test using $p < 0.05$ level*

† SD – Standard Deviation

Table 3.3: Comparison of ocular Ultrasound biomicroscopic data between Primary Angle Closure Suspect group and normal group among Combined, Female and Male subjects

	Combined Group				Females				Males	
Parameters	**Normal Mean(SD) n=57**	**PACS Mean(SD) n=57**	**95% CI of the difference of the means**	***p* value**	**Normal Mean(SD) n=32**	**PACS Mean(SD) n=34**	**95% CI of the difference of the means**	***p* value**	**Normal Mean(SD) n=25**	**PACS Mean(SD) n=23**
UACD	2.74(0.30)	2.09(0.29)	(0.54,0.76)	0.0001*	2.74(0.34)	2.11(0.24)	(0.48,0.77)	0.0001*	2.75(0.25)	2.06(0.36)
CCT	0.50(0.03)	0.48(0.04)	(0.01,0.04)	0.0001*	0.49(0.03)	0.47(0.03)	(0.00,0.04)	0.0001*	0.52(0.03)	0.48(0.04)
AOD -S	0.26(0.08)	0.08(0.08)	(0.14,0.21)	0.0001*	0.25(0.08)	0.09(0.09)	(0.12,0.21)	0.0001*	0.27(0.09)	0.08(0.08)
AOD -T	0.32(0.10)	0.12(0.07)	(0.16,0.23)	0.0001*	0.32(0.12)	0.13(0.08)	(0.15,0.25)	0.0001*	0.31(0.08)	0.11(0.06)
AOD- I	0.30(0.09)	0.09(0.07)	(0.18,0.25)	0.0001*	0.32(0.10)	0.08(0.07)	(0.19,0.28)	0.0001*	0.28(0.08)	0.10(0.07)
AOD- N	0.32(0.11)	0.11(0.07)	(0.17,0.24)	0.0001*	0.32(0.11)	0.12(0.07)	(0.16,0.26)	0.0001*	0.31(0.10)	0.11(0.06)
TCPD- S	0.89(0.16)	0.75(0.18)	(0.06,0.21)	0.001*	0.90(0.18)	0.74(0.19)	(0.05,0.27)	0.005*	0.87(0.13)	0.77(0.17)
TCPD- T	0.91(0.13)	0.66(0.20)	(0.18,0.32)	0.0001*	0.91(0.14)	0.67(0.20)	(0.15,0.34)	0.0001*	0.92(0.12)	0.66(0.19)
TCPD- I	0.89(0.11)	0.72(0.16)	(0.11,0.23)	0.0001*	0.88(0.12)	0.70(0.15)	(0.10,0.25)	0.0001*	0.90(0.11)	0.74(0.19)
TCPD- N	0.92(0.14)	0.67(.21)	(0.18,0.33)	0.0001*	0.94(0.14)	0.69(0.19)	(0.15,0.34)	0.0001*	0.90(0.15)	0.64(0.23)
ICPD -S	0.20(0.13)	0.21(0.18)	(-0.07,0.07)	0.951	0.22(0.14)	0.18(0.19)	(-0.06,0.14)	0.408	0.19(0.13)	0.26(0.15)
ICPD -T	0.15(0.13)	0.15(0.14)	(-0.04,0.07)	0.614	0.17(0.14)	0.13(0.16)	(-0.03,0.13)	0.252	0.13(0.12)	0.16(0.12)
ICPD -I	0.14(0.09)	0.16(0.15)	(-0.08,0.03)	0.372	0.12(0.09)	0.14(0.12)	(-0.07,0.05)	0.688	0.15(0.08)	0.19(0.18)
ICPD -N	0.18(0.14)	0.14(0.17)	(-0.02,0.11)	0.141	0.19(0.14)	0.13(0.18)	(-0.04,0.15)	0.238	0.18(0.15)	0.14(0.15)
IT -S	0.44(0.07)	0.42(0.07)	(0.02,0.05)	0.339	0.46(0.09)	0.42(0.08)	(-0.01,0.09)	0.133	0.42(0.06)	0.43(0.06)
IT-T	0.46(0.07)	0.42(0.07)	(0.01,0.07)	0.006	0.45(0.06)	0.42(0.07)	(-0.01,0.06)	0.221	0.48(0.07)	0.42(0.05)
IT- I	0.46(0.09)	0.43(0.08)	(-0.01,0.07)	0.095	0.46(0.09)	0.43(0.09)	(-0.03,0.08)	0.373	0.46(0.09)	0.42(0.06)
IT- N	0.43(0.08)	0.41(0.07)	(-0.02,0.05)	0.372	0.43(0.08)	0.41(0.08)	(-0.02,0.07)	0.342	0.42(0.07)	0.42(0.05)
ACA -S	23.48(9.0)	4.21(7.42)	(15.90,22.66	0.0001*	23.30(9.42	4.44(8.03)	(14.13,23.57)	0.0001*	23.68(8.73)	3.77(6.39)
ACA- T	32.09(13.34)	5.09(6.67)	(22.85,31.15)	0.0001*	32.11(15.40)	5.46(6.79)	(20.63,32.67)	0.0001*	32.07(10.5)	4.46(6.58)
ACA- I	27.32(11.70)	5.55(7.90)	(17.80,25.75)	0.0001*	28.94(13.10)	4.11(6.48)	(19.50,30.16)	0.0001*	25.14(9.36)	7.78(9.45)
ACA -N	29.56(11.81)	6.30(8.43)	(19.12,27.39)	0.0001*	30.24(12.82)	6.66(8.96)	(17.80,9.35)	0.0001*	28.69(10.68)	5.67(7.62)

**Significant difference, Student's''t' test using Bonferroni corrected at p<0.0023 level*

S- Superior, T- Temporal, I- Inferior, N- Nasal Quadrants

Ultrasound biomicroscopy – Overall comparison:

Anterior segment measurements by UBM were significantly different between the groups after Bonferroni corrections (Table 3.3).

Mean UACD and CCT were significantly ($p<0.0001$) less, mean AOD500, mean TCPD, mean ACA in superior, temporal, inferior and nasal quadrants of PACS group were significantly ($p< 0.0001$) less compared to the corresponding quadrants of normal group. There were no significant difference in mean ICPD and IT between PACS group and normal group. Out of 57 normal subjects, SCPA was measured only for one image in superior quadrant; six in temporal quadrant, five in inferior quadrant and ten in nasal quadrant. In PACS group, SCPA was measured only for 8, 24, 16 and 24 images of superior, temporal, inferior and nasal quadrants respectively. In other images, the scleral structures were not imaged for measurement of SCPA.

The mean Corrected ACD of A-scan biometry was 2.44 ± 0.34 for normals and 1.97 ± 0.34 in PACS. On comparing ACD measured with UBM (UACD), the difference was found to be 0.30 ± 0.24 in normals and 0.14 ± 0.24 in PACS group.

Comparison of UBM between genders:

Anterior segment measurements were significantly different between the groups among females (Table 3). There was significant difference ($p <0.0001$) between PACS and normals in both the genders for mean UACD, AOD500 and ACA. TCPD (except superior quadrant) among females and mean CCT, TCPD (except superior and inferior quadrants) among males showed significant difference. In both the gender, all the UBM parameters showed lesser value in PACS than in normals. (Table 3).

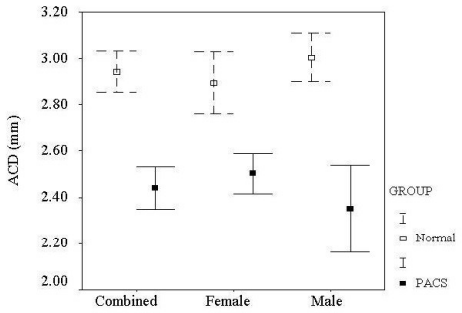

Fig 2a.

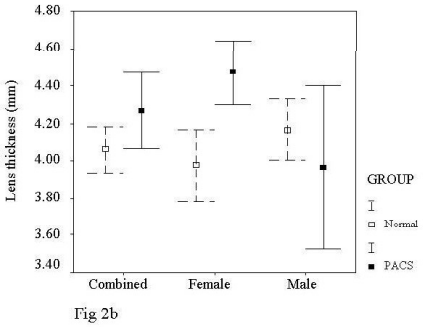

Fig 2b

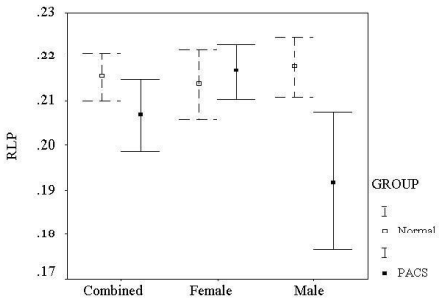

Fig 2c

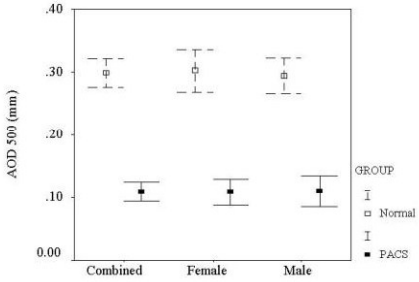

Fig 2d.

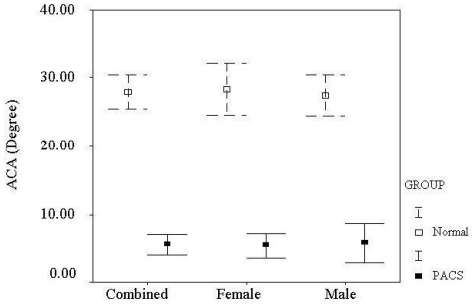

Fig 2e.

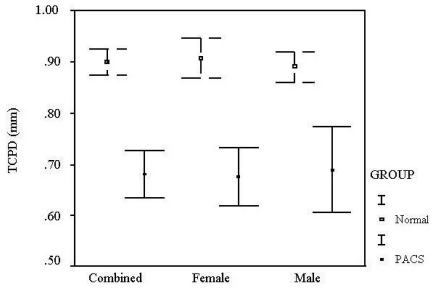

Fig 2f.

Figure 2: Comparison of Ocular Ultrasound biomicroscopic parameters between Primary Angle Closure group and Normal group subjects in Combined group, Females and Males. Anterior chamber depth (ACD; Fig 2a), Lens thickness (LT;Fig 2b), Relative lens position (RLP;Fig 2c), Angle Opening distance (AOD500;Fig 2d), Anterior chamber angle (ACA;Fig 2e), Trabecular ciliary process distance (TCPD;Fig 2f) were compared between groups. Data represented as Mean ±2 Standard error.

In Fig 2, on comparing mean of various parameters between PACS and normal eyes among combined, female and male groups, it was found that the following parameters namely ACD, AOD500, ACA and TCPD were significantly different. LT among females and RLP among males were also significantly different.

The TCPD is governed by the position of the ciliary body and since the zonules and lens can have a bearing on the ciliary process position due to their anatomical attachment, we analyzed the correlation between TCPD and RLP in both normal and PACS groups. The nasal quadrant in males ($r = 0.47$, $p=0.042$) and superior quadrant in females ($r=0.41$, $p=0.035$) among the normal group and nasal quadrant in males ($r=0.60$, $p=0.011$) and inferior quadrant in females ($r=0.49$,$p=0.020$) in PACS group showed a significant positive correlation. Rest of the quadrants showed no such correlation between TCPD and RLP. In combined group, it was found that the nasal quadrant in PACS group showed significant correlation between TCPD and RLP ($r=0.33$, $p=0.033$).

***Discussion*:**

To our knowledge, this is the first study where both A- scan biometric measurements and UBM measurements were done on PACS and compared with age matched normal Indian population. Previous studies concentrated on A- scan biometry findings between primary angle closure glaucoma (1 -4, 6-8, 11, 13 -19) or PACS (2, 4, 5, 7) or only UBM study among primary angle closure glaucoma. (4,9,10,15,16) Comparison among the genders in

PACS using A - Scan biometry readings alone was done before in the Chennai Glaucoma Study (8), which was a population based study.

*A scan ultrasound biometry***:**

The biometric features in our series of subjects with PACS were similar to other study reports (1 -3, 8, 9). Compared to normal group, a distinctly shallower axial length, anterior chamber depth and relatively anterior placed lens characterized the PACS group in males. However females had posterior placed lens. This may suggest that the lens thickness is not predominantly responsible for the angle configuration in the PACS group among males. The A scan biometric findings from Chennai Glaucoma Study (8) showed that the ACD and AXL were significantly smaller and lens thickness greater for severe forms of angle closure but the difference in lens thickness disappeared when age-matched controls were analyzed. We also found that the normal eyes had lesser mean age than the PACS eyes in that study. It may be possible that the lens contributes to the severity in later stages of the disease process or hastens the disease process. This is evident from the work done by Marcini et al (16) in a group of PACG, Chronic Angle Closure Glaucoma (CACG) and normal subjects where they concluded that there was a gradual shift in ocular biometric parameters as the severity of glaucoma increased. However, these are cross-sectional studies and we need to have longitudinal biometry data on PACS subjects to have conclusive evidence.

In our study, the ocular biometric data did not show statistically significant gender variation among normals. This was different from the results of Chennai Glaucoma Study (8). This might be due to the large sample size in the population-based study compared to this sample. However the tendency of shorter axial length, shallower anterior chamber

and lesser lens thickness were found among the females than the males in the normal subjects. Compared to this, there was gender variation in PACS group, showing significantly shorter axial length, thicker lens and relatively more posterior-placed lens in females compared to males. In Chennai glaucoma study, there was significant difference in axial length and no difference among genders for other biometric parameters in PACS group. We noted that only the female subjects in this study population showed increased LT in PACS group than age matched normal group. This can be new evidence showing such variation among PACS in different genders**.**

*Ultrasound biomicroscopy***:**

The differences between the mean A-scan and mean UBM measurements were 0.20 mm in normal group and 0.35mm in PACS group. The ACD measurement using UBM was always lesser than the ACD measurement using A-scan biometry. Similar results were reported in other studies. (15,16, 20) The reason may be due to the difference in selected techniques. On correcting for the corneal thickness for A scan biometry, the differences were 0.30$\pm$0.24mm in normal group and 0.15 $\pm$0.24mm in PACS group. We could not account for this difference.

AOD500, TCPD and ACA showed significant variation between normal group and PACS group. This is similar to a previous study by Garudhari et al on South Indian population but in subjects with primary angle closure glaucoma after peripheral iridotomy. (9) Sihota et al showed that primary angle closure glaucoma eyes presented with thinner iris, shorter AOD and TCPD.(4) There was no gender difference, except that in males the TCPD in superior and inferior quadrants did not show significant variation between normal group and PACS group in our study. All the UBM parameters showed

higher values among normal group compared to PACS group, although not all were statistically significant.

TCPD may be a parameter of primary importance since it indicates the width of the space available for the iris insertion. The variation in TCPD will have effect on both ACA and AOD. Previous studies (4,9,16) have shown decreased TCPD in severe forms of glaucoma and the presence of such a difference in the early stages such as PACS itself may give a clue to the pathogenesis of the disease in the absence of a thicker lens. Though we could show such a finding among combined group, we were unable to demonstrate a uniform difference in each of the quadrants on analyzing the data from male and female group separately.

Conclusion:

In conclusion, AXL, ACD, CCT, TCPD, ACA and AOD500 were significantly less in PACS group than in normal group. The lens was more anterior-placed in PACS than in normal group among males. In females, lens was thicker in PACS group compared to normal group. The findings of gender variation may be important while analyzing parameters from imaging studies of the angle.

Specific Contribution:

There were studies that have documented gender variation of ocular A-scan biometry parameters namely AXL, ACD, LT and RLP, but this was the first study that attempted to

study the gender variation in UBM parameters. For the first time, this study documented the very useful clinical information that relative lens position among PACS was anterior compared to normals in males. And in females, the lens was thicker in PACS group than normals. This hints at the possibility of different pathogenesis in male and female PACS subjects.

***Future scope of study*:**

We expect the thicker lens would have shorter TCPD in females than in males and therefore the lens position will be more anteriorly placed in females than in males. However this relation was not noticed in this study subjects except in the nasal quadrant. PACS, being less severe than other stages of angle closure, may have a relatively similar TCPD to that of normal group or it may be possible that the Indian population exhibits more of a non-lenticular process in the pathogenesis of angle closure. We need more evidence through longitudinal studies to prove such a hypothesis among different stages of the disease and with age matched and gender matched sample subjects.

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Chapter 4:

Follow up of Primary angle closure suspect (PACS) subjects after Laser Peripheral iridotomy using Ultrasound biomicroscopy and A - scan biometry for a period of two years

Abstract:

Aim: To collect baseline and follow-up examination data of Primary Angle Closure Suspects who underwent LPI and to know the course of the disease in these subjects following LPI. Another aim was to look into the predictive factors for the progression of the disease among the study subjects.

Patients and Methods: Subjects with Primary Angle Closure Suspects (PACS; n = 82 eyes) underwent A-scan biometry and Ultrasound biomicroscopy. Anterior chamber depth (ACD), Anterior Chamber Angle (ACA), Axial Length (AXL), Lens Thickness (LT), Relative Lens Position (RLP), Central Corneal Thickness (CCT), Angle Opening Distance 500 (AOD500), Trabecular–Ciliary Process Distance (TCPD), Iris-Ciliary Process Distance (ICPD), Iris Thickness (IT) and Scleral-Ciliary Process Angle (SCPA) were measured. Subjects who came for the 1 week, 6 months, 1 year, 1 ½ year and 2 year follow –ups underwent all evaluation as above. All the subjects underwent gonioscopy, peripheral anterior chamber depth measurement, and LOCS – II documentation during all the visits. Analysis was done to look into the variation in the parameters before and after LPI, progression of PACS to PAC, progression of cataract, and trend of different ocular

parameters measured and using logistic regression analysis, Risk factors for the progression of cataract and PACS were documented. $p < 0.05$ was considered statistically significant.

Results: Fifteen (15) eyes out of 52 eyes (28.85%) developed into PAC with synechial changes. Five (5) developed within 6 months, 4 between 6 months and 1 year, 5 between one and 11/2 years and one developed between 11/2 and 2 years. Univariate analysis showed that the Risk Ratio for PAC for TCPD was significant in the study subjects (Risk ratio, 1.18; 95% CI, 0.94 to1.49). No significant association was found for age, gender, and narrow angle, ACA, ACD, AOD, ICPD, IT and VCDR. Nearly 37 % of the posts –LPI PACS subjects were found to have progression of cataract at the end of first year and 13% between first year and second year follow-up. ICPD, ACA, LT and AOD500 were the parameters that varied significantly ($p<0.05$) between "before LPI group" and all "after LPI groups".

Conclusion: In this hospital based study on the course of PACS subjects after LPI, as many as 28% progressed to PAC but none progressed to PACG. TCPD was the predictive factor for the progression of PACS to PAC. ICPD, ACA and LT parameters varied significantly between the "Before LPI group" and "After LPI group". Cataract progression was noticed after Laser LPI in this study subjects.There was no increase in IOP, history or symptoms of acute attack of glaucoma after LPI.

Review of Literature:

Primary angle closure glaucoma is common in Indian population. (1, 2)Laser Iridotomy (LPI) is now the standard first line intervention in both acute and chronic forms of primary angle closure glaucoma. It is successful in preventing recurrence of acute attacks. (3) LPI eliminates pupillary block, allowing the convex iris to flatten and wideneing the anterior chamber angle. (4, 5)

There are few Indian studies done to find the effect of LPI on the angle closure glaucoma. (6, 7) These studies lack in the baseline UBM data for comparison. Tiedman (8) analysed iris configuration in relative pupillary block in terms of vector forces acting on the iris. Before iridotomy, the forces acting within the iris are produced by the dilator and sphincter muscles and the iris root, which stabilise the iris at the root and the pupillary border. In relative pupillary block, the greater hydrostatic pressure in the posterior chamber results in anterior displacement of the iris, which assumes a convex configuration. Laser Iridotomy relives pupillary block by allowing aqueous fluid to pass unimpeded from the posterior to the anterior chamber and causes the convex iris to flatten and the anterior chamber angle to increase. A few studies showed that iridotomy had no effect on central anterior chamber depth. (9, 10, 11) High rates of progression to chronic primary angle closure glaucoma after successful initial treatment with Laser peripheral iridotomy have been described in Asians. (12) Studies have demonstrated increased anterior chamber angle opening after Laser peripheral iridotomy. (13) In one study (14) the five year risk of primary angle closure suspects (PACS) progressing to primary angle closure (PAC), it was shown that 11 of the 50 PACS (22%; 95%CI 9.80 to 34.2) were

progressing to PAC. Seven of the of synechial type and four of appositional type. The relative risk for progression of PACS to PAC was 24% (95%CI; 3.2 to 182.4). None of these patients had laser peripheral iridotomy before developing PAC. Another study of follow up of Eskimos reported 8% of normal and 35% of PACS progressed to PAC or PACG over 10 years. (15) Long term results of Nd: YAG laser iridotomy in treatment of PACG and occludable angles showed significant effect on intraocular pressure. (16) A study on Angle closure glaucoma suspects by Wilensky (17) reported that 25 (19.5%) patients progressed to Angle closure glaucoma after a mean of 2.7 years follow up. A recent study by Kaushik et al. (18) showed that LPI significantly widened the anterior chamber angle on UBM in the quadrant with LPI and the quadrant furthest away in patients of chronic angle closure glaucoma.

However, no single study reported the effect of LPI on all the ocular parameters measured using A-scan Biometry and Ultrasound biomicroscopy among Primary Angle closure suspects (PACS) from an Indian population. An attempt was made to see the effect of LPI on A-scan biometry and UBM parameters among the hospital based Indian subjects for a follow up period of two years, and then follow the course of the PACS after LPI. The study also looked into any specific predictive factor for the progression of PACS to next stage of the disease.

***Patients and Methods*:**

Primary Angle Closure Suspect (PACS) subjects were recruited from the Glaucoma service of a tertiary eye care hospital from March 2003 to December 2003. The criterion for diagnosis of PACS was non visibility of the posterior trabecular meshwork for at least 180 degrees (equivalent to Modified Shaffer Grade 1 or less), without synechial changes, with normal intraocular pressure and normal optic disc features. We have included subjects who were asymptomatic PACS. The exclusion criteria were peripheral anterior synechiae, secondary angle closure, glaucoma, history of intraocular surgery, history of significant retinal pathology and nuclear sclerosis defined as LOCS II higher than Grade 2. The institutional review board of Vision Research Foundation approved the study and written informed consent was obtained from all the subjects. The study was conducted as per the Tenets of the Declaration of Helsinki.

All subjects underwent a complete ocular examination that included refraction, slit lamp biomicroscopy, applanation tonometry, indentation gonioscopy using Zeiss four mirror gonioprism, stereobiomicroscopic examination of optic disc using +90 D lens, dilated examination for LOCS II grading. A-scan ultrasonic biometry (Alcon Labs, Fortworth, TX, USA), Keratometry (Aravind Engineering Industrial Unit, Pondicherry, India) and Ultrasound biomicroscopy (Paradigm Medical Industries, Inc,USA) were also done.

All the subjects underwent the above tests, once before LPI, and one-week, six-month, one year, 11/2 years and 2 years after LPI.

Gonioscopy**:**

Gonioscopy was done by a senior optometrist (RKK), using a Zeiss four mirror gonioprism (Ocular Instruments Inc, USA). The procedure was followed under dim room illumination using short and narrow slit beam that did not fall on the pupil. The angle structures visible were noted and Modified Shaffer grading system was used to grade angles. Agreement of gonisocopic findings (angle structures) was done for the examiner with a glaucoma consultant (MB). The Glaucoma consultant did baseline gonioscopy and confirmation of peripheral anterior synechiae. Any amount of PAS (including pinpoint PAS) was considered significant. The angle structures, Modified Shaffer's grading, iris configuration and trabecular pigmentation were documented during each of the scheduled visits.

A-Scan Ultrasonic Biometry**:**

A standardized Ocuscan instrument (Alcon Labs, Fortworth, TX, USA) with a 10 MHz 10MHz transducer probe was used for measurements. Examination was done under topical anesthesia. Ten automatic measurements were taken and saved. An average of consistent readings was considered for measurement purposes. A scan biometry was standardized as per the institutional protocol and standard deviation below 0.03 was taken as the acceptable reading for individual parameters.

Parameters measured were as follows:

1) Anterior Chamber Depth (ACD): from the cornea to the anterior lens spike. True ACD was measured by subtracting corneal thickness from the ACD measured.

2) Lens Thickness (LT): from the anterior lens spike to the posterior lens spike.

3) Axial length (AXL): the sum of ACD, LT and vitreous chamber length.

4) Relative Lens Position (RLP) was calculated as follows (11): (ACD + ½ LT) ÷ AXL

Ultrasound Biomicroscopy**:**

Examinations were performed using the UBM 840 model (Paradigm Medical Industries, Inc, USA) with a 50 MHz transducer probe, which facilitated 4 to 5 mm of tissue penetration and had a resolution of 50µm. UBM imaging of all PACS subjects was done by the same optometrist (RKK) and the examination was performed with the subject in the supine position in dim light illumination. Examination was done under topical anesthesia. An ocular cup of special design filled with 2% methylcellulose as a coupling solution was used. Radial scan images at the 12, 3, 6 and 9 o'clock positions centered over the limbal region and perpendicular scans centered over the pupil were obtained under dark room condition. Using special caliper in the instrument, the following parameters were measured:

1) UBM-Anterior Chamber Depth (UACD): from the corneal endothelium to the anterior lens surface.

2) UBM-Central Corneal Thickness (CCT): from the corneal endothelium to the corneal epithelium.

3) The Angle Opening Distance 500 (AOD500): by taking a point on the internal ocular wall 500µm anterior to the scleral spur and extending a line perpendicular to the plane of the trabecular meshwork from that point to the apposing iris.

4) The Trabecular Ciliary Process Distance (TCPD): on a line extending from the corneal endothelium at 500µm from the scleral spur perpendicularly through the iris to the ciliary process.

5) The Iris Ciliary Process Distance (ICPD): from the posterior iris surface to the ciliary process along the same line as the TCPD.

6) The Iris Thickness (IT): along the same line as the TCPD.

7) Anterior Chamber Angle (ACA): measured with the apex in the iris recess and the arms of the angle passing through a point on the trabecular meshwork at 500μm from the scleral spur.

8) The Scleral Ciliary Process Angle (SCPA): between the tangent to the scleral surface and the axis of the ciliary process.

One eye of each subject was randomly selected for analysis.

Laser peripheral iridotomy:

After obtaining an informed consent for the procedure, all the patients received 4% pilocarpine to constrict the pupil and stretch the iris. Apraclonidine 1% was instilled 1 h before the procedure. Nd:YAG LPI was performed in each eye using Abrahams lens and 2-4 mJ/shot energy, with minimum 5-10 shots depending upon the thickness of the iris, aiming for the minimum iridotomy size of 150 microns. All iridotomies were carried out in superior half (superior temporal or superior nasal) by single Glaucoma specialist (MB) Post operative Acetazolamide and topical steroid drops were prescribed in the absence of systemic contraindications

***Statistical Analysis*:**

All the data were entered into the statistical database and analysed using SPSS 10.5 statistical software, analysis was done. Descriptive statistics of all the patient data and clinical findings were gathered. Student "t" test was done to compare parameters of PACS before and after Nd:YAG Iridotomy. Progression to primary angle closure was

defined as the presence of the synechiae in eyes, classified to be Primary angle closure suspects during the follow up after LPI, this excluded synechiae noted during first week after LPI. The Wilcoxon signed rank test was used to compare the mean gonioscopy grades, and mean van Herick grades, before and after LPI. Using Kruskal- Wallis non-parametric test the gonioscopy gradings and UBM parameters (AOD500 and ACA) were compared. Using Chi square test, LPI location and gonioscopy grading, were analysed. Similarly using Mann Whitney test, LPI location and UBM parameters (AOD500 and ACA) were analysed. Cataract progression was defined as one grade progress in any region using LOCS II from pre LPI baseline to 1st and/or 2nd year follow-up. The significance of progression of cataract for each region for each year was assessed by Wilcoxon signed rank test. Logistic regression analysis was used to assess the association of age > 60 years, average angle width < Modified Shaffer grade 1 by gonioscopy at baseline, anterior chamber depth < 2 mm, Lens thickness < 4.5 mm and presence of peripheral anterior synechiae at each year with progression of cataract. Logistic regression analysis was done to find any risk association for cataract progression. Student "t" test was used to compare ocular parameters of cases progressed to PAC and those not progressed. Predictive factors for the progression from PACS to PAC were estimated using Univariate analysis.

Results:

A total of 82 eyes of 82 patients with PACS fulfilled the eligibility criteria. The mean age was 52.1 ±10.0 years. Out of this, 28 were male and 54 were female patients. After LPI

56,44,48,37 and 52 subjects came for one week, six month, one year, one and half year and two year follow up respectively. The reasons for dropouts were illness, distance from the hospital, location (other state), unwillingness to continue with the project due to personal reasons, undergoing cataract surgery and developing post LPI uveitis. Analyses were done for data of respective subjects who came for each follow up. The baseline refractive status of the study population was +0.94 (1.10) D.

The basic clinical data before and after LPI are given in Table 4.1.

Table 4.1: Basic clinical data of before and after LPI in PACS subjects

Variable	Mean (SD) Pre	Mean (SD) 1 week	Mean (SD) 6 month	Mean (SD) 1year	Mean (SD) 11/2 years	Mean (SD) 2 years
IOP (mm Hg)	15.77 (4.06)	14.85(3.65)	14.52(3.15)	15.24(3.63)	14.94(3.10)	15.17(3.39)
3Keratometry (D)	44.53(1.65)	44.54(1.81)	44.52(1.82)	44.54(1.65)	44.45(1.62)	45.24(1.96)
Keratometry (D)	44.44(1.73)	44.40(1.86)	44.46(1.77)	44.69(1.97)	44.46(1.81)	44.91(1.88)
van Herick	1.67(0.50)	2.89(0.63)	2.80(0.88)	2.80(0.71)	2.61(0.77)	2.69(0.68)
Gonio U	0.99(0.75)	3.42(0.70)	3.11(1.12)	3.18(0.10)	2.96(1.10)	3.00(1.13)
Gonio N	1.04(0.78)	3.34(0.85)	3.11(1.09)	3.15(0.96)	2.89(1.07)	3.00(1.04)
Gonio I	0.99(0.78)	3.34(0.75)	3.08(1.11)	3.15(0.96)	2.82(1.06)	2.91(1.12)
Gonio T	1.15(1.36)	3.36(0.85)	3.08(1.11)	4.15(0.96)	2.79(1.07)	3.00(1.04)
LD 90 D	0.40(0.14)	0.43(0.15)	0.45(0.16)	0.45(0.16)	0.45(0.15)	0.43(0.11)

S- Superior, T- Temporal, I- Inferior, N- Nasal Quadrants

The IOP, keratometry, ocular biometry and ultrasound biomicroscopy details of the Pre LPI group and the follow up groups (1 week, 6 months, 1 year, 11/2 year and 2 years) of PACS are given in Tables 4.2 and 4.3.

Pre LPI Versus 1 week follow up Group:

Keratometry, LT, AOD (Inferior Temporal quadrants and average of all quadrants), ICPD (all quadrants and average of all quadrants) and ACA (all quadrants and average of all

quadrants) were significantly different between the groups ($p<0.001$).95% confidence intervals for the difference in mean AOD values however overlapped zero. IOP, Vertical Cup Disc Ratio, ACD, RLP, AXL, CCT, TCPD, AOD (superior and nasal quadrants), and IT were found to be similar in both groups.

Pre LPI Versus 6 month follow up Group:

IOP, ACD, and ICPD (Superior, Temporal quadrants and average of all quadrants) showed significant difference between the groups ($p<0.001$).The 95% confidence intervals for the difference in mean ACD and ICPD values however overlapped zero. The other parameters did not show significant difference between the two groups.

Pre LPI Versus 1 year follow up Group:

LT, ICPD (Superior, Nasal, Temporal quadrants and average of all quadrants), ACA (Nasal and average of all quadrants) were significantly different between the groups ($p<0.001$). The other parameters did not show difference between the two groups.

Pre LPI Versus 1 ½ year follow up Group:

LT, ICPD (Superior, Temporal quadrants and average of all quadrants), ACA (Superior, Nasal, Temporal and average of all quadrants) were significantly different between the groups ($p<0.001$). The other parameters did not show differences between the two groups

Pre LPI Versus 2 year follow up Group:

ICPD (Temporal quadrant and average of all quadrants), ACA (Superior, Nasal quadrants and average of all quadrants) were significantly different between the groups ($p<0.001$). The other parameters did not show difference between the two groups

Table 4.2: Ocular parameters of Pre LPI compared with 1 week, and 6 months post LPI of PACS subjects

Variable	Pre Mean(SD) (n=82)	Post Mean (SD) (1week) (n=56)	95% CI difference in means	Post Mean (SD) (6months) (n=44)	95% CI difference in means
IOPmm Hg	15.77 (4.06)	14.85(3.65)	-0.14,1.92	14.52(3.15)	**0.49,2.23**
Keratometry (D)	44.53(1.65)	44.54(1.81)	0.01 ,0.21	44.52(1.82)	-0.02,0.23
Keratometry (D)	44.44(1.73)	44.40(1.86)	0.01,0.24	44.46(1.77)	-0.09,0.22
LD 90 DS	0.40(0.14)	0.43(0.15)	-0.03,0.00	0.45(0.16)	-0.05,0.01
Anterior chamber Depth(mm)	2.43 (0.37)	2.46(0.31)	-0.05,0.02	2.52(0.35)	-0.14,-0.00,
Lens Thickness(mm)	4.23 (0.74)	4.30(0.74)	**-0.06,-0.01**	4.24(0.78)	-0.06,-0.01
Relative Lens Position	0.21(0.03)	0.21(0.03)	-0.002,0.00	0.20(0.03)	-0.005,0.00
Axial Length(mm)	22.10(1.01)	22.12(1.10)	-0.06,0.02	22.14(1.14)	-0.11,0.01
UACD(mm)	2.10(0.29)	2.14(0.30)	-0.04,0.00	2.18(0.26)	-0.06,0.00
CCT(mm)	0.48(0.04)	0.49(0.03)	-0.01,0.01	0.46(0.91)	-0.01,0.06
AOD U(mm)	0.10(0.08)	0.11(0.10)	-0.03,0.03	0.12(0.88)	-0.05,0.02
AOD N(mm)	0.13(0.07)	0.16(0.11)	-0.06,0.00	0.12(0.10)	-0.02,0.05
AOD I(mm)	0.10(0.07)	0.14(0.09)	-0.06,-0.00	0.12(0.09)	-0.05,0.04
AOD T(mm)	0.12(0.07)	0.16(0.92)	**-0.07,-0.01**	0.13(0.91)	-0.04,0.02
AOD(mm)	0.11(0.06)	0.14(0.08)	**-0.05,-0.01**	-0.03(0.03)	-0.05,0.03
TCPD U(mm)	0.60 (0.25)	0.63(0.26)	-0.12,0.04	0.59(0.26)	-0.12,0.11
TCPD N(mm)	0.57(0.24)	0.56(0.24)	-0.08,0.08	0.53(0.26)	-0.07,0.14
TCPD I(mm)	0.63(0.23)	0.65(0.24)	-0.06,0.03	0.65(0.18)	-0.07,0.07
TCPD T(mm)	0.62(0.25)	0.63(0.21)	-0.10,0.05	0.63(0.16)	-0.15,0.04
TCPD(mm)	0.61(0.62)	0.62(0.14)	-0.08,0.03	0.60(0.15)	-0.08,0.07
ICPD U(mm)	0.14(0.14)	0.09(0.12)	**0.02,0.09**	0.09(0.11)	**0.007,0.10**
ICPD N(mm)	0.11(0.14)	0.08(0.11)	**0.005,0.07**	0.07(0.10)	-0.00,0.09
ICPD I(mm)	0.13(0.14)	0.10(0.11)	**0.01,0.08**	0.10(0.11)	-0.01,0.07
ICPD T(mm)	0.14(0.15)	0.07(0.11)	**0.02,0.11**	0.08(0.11)	**0.006,0.12**
ICPD(mm)	0.13(0.09)	0.09(0.08)	**0.03,0.08**	0.09(0.07)	**0.01,0.03**
IT U(mm)	0.42(0.07)	0.40(0.08)	-0.01,0.03	0.41(0.08)	-0.00,0.43
IT N(mm)	0.42(0.07)	0.42(0.06)	-0.01,0.02	0.44(0.07)	-0.04,0.02
IT I(mm)	0.42(0.08)	0.42(0.08)	-0.03,0.02	0.41(0.07)	-0.02,0.02
IT T(mm)	0.41(0.07)	0.39(0.06)	-0.00,0.03	0.40(0.06)	-0.02,0.03
IT(mm)	0.42(0.05)	0.41(0.05)	-0.00,0.02	0.42(0.04)	-0.02,0.01
ACA U (degree)	5.13(6.76)	8.22(7.49)	**-4.51,-0.64**	6.60(7.15)	-2.22,1.64
ACA N(degree)	5.68(6.84)	9.98(10)	**-5.67,-1.33**	8.47(7.46)	-4.66,0.68
ACA I (degree)	6.28(7.93)	9.62(8.83)	**-5.66,-0.56**	8.34(7.12)	-4.71,1.61
ACA T(degree)	7.07(7.93)	9.50(8.14)	**-4.94,-0.05**	9.12(7.46)	-4.65,0.22
ACA(degree)	6.05(5.19)	9.04(5.58)	**-4.26,-1.15**	8.09(5.75)	-3.28,0.48
SCPA U(degree)	41.23(5.09)	40.47(4.98)	-2.20,7.64	40.07(5.24)	-6.94,8.98
SCPA N(degree)	40.38(5.42)	39.10(5.93)	-1.44,5.76	39.70(5.78)	-3.17,6.58
SCPA I(degree)	41.07(7.01)	44.63(9.05)	-4.16,6.77	40.65(3.16)	-1.01,11.57
SCPA T(degree)	43.52(6.98)	44.55(6.76)	-5.32,3.50	41.83(5.01)	-5.90,14.09

S- Superior, T- Temporal, I- Inferior, N- Nasal Quadrants

Table 4.3: Ocular parameters of Pre LPI compared with 1 year, 11/2 year and 2 year Post LPI of PACS subjects

S- Superior, T- Temporal, I- Inferior, N- Nasal Quadrants

Parameters	Pre Mean (SD)	Post Mean (SD) (1 year)(n= 48)	95% CI difference in means	Post Mean (SD)(1 ½ years) (n=37)	95% CI difference in means	Mean (SD) (2 years)(n=52)	95% CI difference in means
IOP mm Hg	15.77 (4.06)	14.85(3.65)	-0.64,1.42	14.52(3.15)	-0.21,2.21	15.17(3.39)	-0.44,1.72
Keratometry (D)	44.53(1.65)	44.54(1.65)	-0.03,0.25	44.45(1.62)	-0.02,0.26	45.24(1.96)	-0.06,0.30
Keratometry (D)	44.44(1.73)	44.69(1.97)	-0.14,0.24	44.46(1.81)	-0.25,0.18	44.91(1.88)	0.14,0.66
LD 90DS	0.40(0.14)	0.45(0.16)	-0.06,0.09	0.45(0.15)	-0.08,0.00	0.43(0.11)	-0.07,0.00
ACD(mm)	2.43 (0.37)	2.46(0.31)	-0.08,0.02	2.52(0.35)	-0.07,0.09	2.52 (0.33)	-0.11,0.03
LT(mm)	4.23 (0.74)	4.30(0.74)	**-0.16,-0.03**	4.24(0.78)	**-0.09,-0.02**	4.29(0.74)	**-0.27,0.03**
RLP	0.21(0.03)	0.21(0.03)	-0.002,0.004	0.20(0.03)	-0.007,0.006	0.22(0.03)	-0.01,0.007
AXL(mm)	22.10(1.01)	22.12(1.10)	-0.11,-0.01	22.14(1.14)	-0.13,0.03	22.11(1.18)	-0.10,0.02
UACD (mm)	2.10(0.29)	2.25(2.14)	-0.06,0.00	2.14(0.32)	-0.06,0.07	2.18(0.23)	-0.20,0.19
CCT (mm)	0.48(0.04)	0.48(0.04)	-0.01,0.02	0.49(0.40)	-0.02,0.02	0.48(0.04)	-0.05,0.07
AOD U (mm)	0.10(0.08)	0.11(0.09)	-0.06,0.03	0.09(0.08)	-0.04,0.05	0.13(0.06)	-0.10,0.03
AOD N(mm)	0.13(0.07)	0.15(0.10)	-0.05,0.03	0.13(0.10)	-0.03,0.09	0.13(0.31)	-0.03,0.03
AOD I(mm)	0.10(0.07)	0.11(0.09)	-0.04,0.05	0.12(0.95)	-0.07,0.05	0.11(0.08)	-0.08,0.13
AOD T(mm)	0.12(0.07)	0.12(0.10)	-0.04,0.05	0.13(0.10)	-0.05,0.08	0.13(0.06)	-0.11,0.10
AOD(mm)	0.11(0.06)	0.12(0.08)	-0.05,0.03	0.12(0.09)	-0.04,0.06	0.12(0.05)	-0.05,0.03
TCPD U(mm)	0.60 (0.25)	0.60(0.27)	-0.13,0.08	0.52(0.23)	-0.14,0.18	0.62(0.27)	-0.15,0.04
TCPD N(mm)	0.57(0.24)	0.55(0.23)	-0.08,0.10	0.57(0.16)	-0.07,0.20	0.60(0.19)	-0.10,0.07
TCPD I(mm)	0.63(0.23)	0.60(0.22)	-0.08,0.11	0.50(0.19)	-0.02,0.29	0.61(0.19)	-0.08,0.10
TCPD T(mm)	0.62(0.25)	0.62(0.18)	-0.06,0.11	0.54(0.16)	-0.07,0.22	0.62(0.18)	-0.12,0.09
TCPD (mm)	0.61(0.62)	0.59(0.16)	-0.03,0.12	0.53(0.16)	-0.09,0.21	0.61(0.14)	-0.09,0.07
ICPD T(mm)	0.14(0.14)	0.11(0.14)	**0.009,0.11**	0.05(0.07)	**0.008,0.15**	0.11(0.13)	-0.00,0.07
ICPD N(mm)	0.11(0.14)	0.08(0.09)	**0.006,0.09**	0.03(0.06)	-0.02,0.08	0.08(0.09)	-0.00,0.08
ICPD I(mm)	0.13(0.14)	0.08(0.09)	-0.00,0.09	0.07(0.15)	-0.07,0.13	0.10(0.12)	-0.03,0.08
ICPD T(mm)	0.14(0.15)	0.07(0.10)	**0.03,0.13**	0.06(0.10)	**0.02,0.19**	0.08(0.10)	**0.01,0.10**
ICPD(mm)	0.13(0.09)	0.08(0.08)	**0.02,0.01**	0.06(0.02)	**0.02,0.03**	0.10(0.07)	**0.03,0.00**
IT U(mm)	0.42(0.07)	0.40(0.08)	-0.12,0.04	0.40(0.07)	-0.02,0.07	0.40(0.09)	-0.02,0.04
IT N(mm)	0.42(0.07)	0.41(0.08)	-0.01,0.03	0.39(0.08)	-0.03,0.04	0.42(0.07)	-0.03,0.02
IT I (mm)	0.42(0.08)	0.40(0.08)	-0.02,0.04	0.37(0.07)	-0.00,0.09	0.39(0.08)	-0.02,0.04
IT T(mm)	0.41(0.07)	0.39(0.07)	-0.02,0.03	0.38(0.05)	-0.01,0.09	0.38(0.06)	-0.01,0.04
IT(mm)	0.42(0.05)	0.40(0.05)	-0.05,0.02	0.39(0.05)	-0.00,0.05	0.40(0.05)	-0.01,0.03
ACA U (degree)	5.13(6.76)	7.45(6.12)	-4.23,0.36	11.17(9.85)	**-9.92,-3.62**	8.00(6.10)	**-4.40,-0.43**
ACA N(degree)	5.68(6.84)	10.21(7.43)	**-6.71,-1.75**	11.07(9.68)	**-10.13,-1.16**	10.03(7.64)	**-5.59,-0.88**
ACA I (degree)	6.28(7.93)	8.50(6.86)	-4.89,1.04	7.67(9.23)	-5.06,2.34	9.21(7.50)	-5.40,0.74
ACA T(degree)	7.07(7.93)	9.29(7.39)	-4.79,0.05	12.28(9.40)	**-9.69,-1.12**	8.85(7.77)	-4.39,0.33
ACA (degree)	6.05(5.19)	9.09(4.93)	**-4.52,-0.84**	10.09(8.31)	**-7.00,-1.91**	9.08(5.11)	**-4.08,-3.44**
SCPA U(degree)	41.23(5.09)	40.47(4.98)	-3.08,4.62	40.07(5.24)	-3.46,5.49	38.78(5.74)	-4.19,10.94
SCPA N(degree)	40.38(5.42)	39.10(5.93)	-1.33,4.87	39.70(5.78)	**3.02,10.44**	36.30(3.76)	**1.12,11.93**
SCPA I(degree)	41.07(7.01)	44.63(9.05)	-5.77,8.18	40.65(3.16)	-4.52,17.06	31.50(12.56)	**-0.10,27.85**
SCPA T(degree)	43.52(6.98)	44.55(6.76)	-8.38,6.18	41.83(5.01)	-7.45,9.24	36.61(4.25)	-5.64,9.57

Peripheral anterior chamber depth evaluation using van Herick method showed significant difference ($p<0.001$; Wilcoxon signed Ranks test) between Pre LPI group and all the follow up groups. Using Kruskal Wallis non-parametric test, it was found that there was no significant variation in the amount of opening as subjectively observed by gonioscopy and UBM parameters (AOD and ACA).

Table 4.4: Gonioscopy and UBM in both angle quadrants before and after LPI (1 year and 2 year)

	Quadrant with LPI (Superior)			Quadrant opposite to LPI (Inferior)		
	Pre LPI	Post LPI	P value	Pre LPI	Post LPI	P value
Gonio scopy	0.99(0.75)	3.18(0.10) (1 year)	**<0.001***	0.99(0.78)	3.15(0.96) (1year)	**<0.001***
		3.00(1.13) (2 year)	**<0.001***		2.91(1.12) (2 year)	**<0.001***
AOD500	0.10(0.08)	0.11(0.09) (1 year)	NS	0.10(0.07)	0.11(0.09) (1year)	NS
		0.13(0.06) (2 year)	NS		0.11(0.08) (2 year)	NS
ACA	5.13(6.76)	7.45(6.12) (1 year)	NS	6.28(7.93)	8.50(6.86) (1 year)	NS
		8.00(6.10) (2 year)	**<0.001****		9.21(7.50) (2 year)	NS

*Wilcoxon signed rank test. ** Paired "t" test

In the quadrant with LPI and quadrant opposite to LPI, mean Modified Shaffer's grades increased significantly ($p<0.001$), from 0.99 to 3.18 at 1 year 0.99 to 3.00 at 2 year, and 0.99 to 3.15 at 1 year,0.99 to 2.91at 2 year respectively(Table 4.4). Similarly ,in the quadrant with LPI at the end of second year follow up after LPI, showed significant increase in mean ACA from 5.13 degree to 8.00 degree($p<0.001$). There was no such significant variation for AOD500 in both the quadrants at 1 year and 2 year follow up after LPI. However it was noted that there was tendency for increase in ACA at one year in LPI quadrant and in quadrant opposite to the LPI during follow up.

Cataract progression:

Table 4.5: Comparison of status of cataract before LPI and 1 year after LPI

Cataract region (LOCS- II)	Baseline (n=33) Number of subjects with cataract	**Mean (SD)**	Post LPI after 1 year (n=33) Number of subjects with cataract	**Mean (SD)**	p value
Posterior subcapsular	04	**2.00**	09	**2.11(0.33)**	
Nuclear Sclerosis	09	**3.00(0.83)**	14	**2.57(0.76)**	
Cortical cataract	01	**3.00**	03	**2.33(0.58)**	
Overall	14	**2.57(0.76)**	26	**2.38(2.00)**	**0.003**

33 patients (mean age, 51.1 $\pm$ 10.4 years; Male: Female: 09:27) were evaluated for cataract using LOCS –II system before LPI and at one year of follow-up (Table 4.5). With 12 months of follow-up, 12 of the 33 eyes (36.36%) showed significant (p=0.003) progression in any lens region. Progression in the nuclear, posterior subcapsular and cortical regions was documented in 5 (15.15%), 5 (15.15%) and 2 (6.06%) cases, respectively.

31 patients (mean age, 49.3±10.3 years; Male: Female: 08:23) were evaluated for cataract using LOCS –II system at the end of two year of follow-up .From 12 months to end of 24 months of follow-up, 4 of the 31 eyes (12.90%) showed significant progression (0=0.014) in any lens region. Progression in the nuclear, posterior subcapsular and cortical regions was documented in 4 (12.90%), 0 and 0 cases, respectively.

Logistic regression analysis did not find any risk association for cataract progression with the parameters analyzed both for one year and two-year follow ups.

PACS Progression to PAC:

15 eyes out of 52 eyes (28.85%) developed into PAC with synechial changes. 5 developed within 6 months, 4 developed between 6 months and 1 year, 5 developed between 1 and 11/2 years and 1 developed between 11/2 and 2 years.

None had acute angle closure attacks with symptoms or raised IOP within 2 years. No optic disc neuropathy was noticed till 2 years of follow up. Except for VH (0.32; 95% CI 0.011, 0.63; p=0.04) and TCPD (-0.12; 95% CI-0.23,-0.01; p=0.03) no other parameters showed significant difference between PAS group and Non PAS group in the study subjects. (Table 4.6)

Table 4.6: Comparison of ocular parameters in cases progressed to PAC and cases not progressed

Variable	Progressed cases (n= 15)	Non progressed cases (n=37)	95% CI mean difference	P value
Age yrs	50.53±8.81	51.67±11.22	-5.48,7.74	0.732
IOP (mm Hg)	14.60±3.91	16.62±3.59	-0.40,4.23	0.102
VH	1.47±0.52	1.79±0.48	0.01,0.63	**0.043**
Gonio	1.07±0.70	1.12±0.71	-0.39,0.50	0.805
Keratometry (D)	44.67±1.80	44.76±1.60	-0.96,1.12	0.877
Keratometry (D)	44.71±2.02	44.62±1.85	-1.28,1.10	0.879
LD 90 DS	0.41±0.15	0.42±0.15	-0.08,0.11	0.751
Anterior chamber Depth(mm)	2.50±0.35	2.44±0.41	-0.30,1.91	0.665
Lens Thickness(mm)	4.18±0.70	4.18±0.84	-0.51,0.50	0.992
RelativeLens Position	0.21±0.02	0.21±0.04	-0.02,0.02	0.911
Axial Length(mm)	22.07±0.99	21.10±1.23	-0.80,0.65	0.836
UACD(mm)	2.21±0.29	2.10±0.30	-0.30,0.09	0.268
CCT(mm)	0.49±0.03	0.49±0.03	-0.02,0.02	0.986
AOD(mm)	0.11±0.07	0.12±0.56	-0.03,0.05	0.741
TCPD(mm)	0.69±0.13	0.57±0.16	-0.23,-0.01	**0.029**
ICPD(mm)	0.13±0.13	0.19±0.37	-0.17,0.28	0.596
IT(mm)	0.42±0.05	0.41±0.05	-0.05,0.02	0.380
ACA(degree)	4.89±5.22	6.94±5.31	-1.47,5.61	0.245

Table 4.7: Univariate analysis for Predictive factors of Primary Angle Closure

Characteristic	Number of subjects	Risk Ratio (95% Confidence Interval)	p value
Age			
< 53.5 yrs	28	1	
≥ 53.5 yrs	20	1.36(0.61,3.1)	0.430
Gender			
Male	12	1	
Female	36	0.80(0.60,1.08)	0.208
IOP			
≤ 15.5mmHg	24	1	
>15.5mm Hg	24	1.73(0.80,3.74)	0.119
Gonioscopy			
> 1grade	15	1	
≤ 1 grade	33	0.91(0.62,1.34)	0.644
Lens Thickness			
<4.50mm	23	1	
≥4.50mm	25	1.44(0.73,2.86)	0.259
AOD			
>0.11	22	1	
≤ 0.11	21	0.77(0.42,1.43)	0.438
ACD			
≥2.00mm	23	1	
<2.00mm	25	2.73(0.36,20.71)	0.295
TCPD			
≥ 1	2	1	
< 1	41	1.18(0.94,1.49)	**0.028**
ICPD			
≤ 0.13	19	1	
> 0.13	21	1.37(0.65,2.9)	0.369
IT			
< 0.4	16	1	
>0.4	24	0.71(0.44,1.14)	0.205
ACA			
>4.65	22	1	
≤4.65	26	0.70(0.39,1.28)	0.273
VCDR			
≤ 0.4:1	17	1	
>0.4:1	31	1.11(0.69,1.79)	0.654

Univariate analysis (Table 4.7) showed that the Risk Ratio of PAC for TCPD was significant in the study subjects (Risk ratio, 1.18; 95% CI, 0.94 to1.49). No significant association was found for age, gender, and narrow angle, ACA, ACD, AOD, ICPD, IT and VCDR.

Figures 4.1 to 4.8 show the trend of all ocular parameters from baseline up to 2 years of follow-up after LPI. Using Friedman analysis, it was found that there was no specific trend noted among the parameters (AT (p=0.168), ACD (0.755), AXL (p=0.107), TCPD (p=0.410), ICPD (p=0.07), IT (p=0.947), ACA (p=0.102)) from before LPI up to 2 years follow up after LPI except for LT (p=0.04).

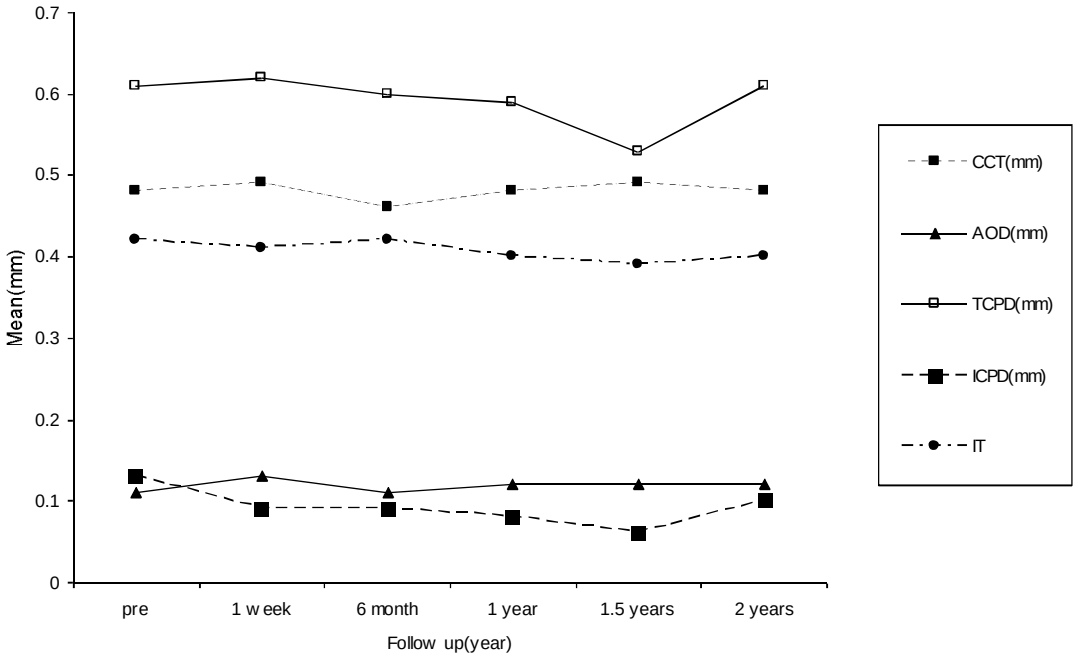

Figure 4.1: Mean value of Ultrasound biomicroscopy parameters before LPI and each follow-up upto 2 years.

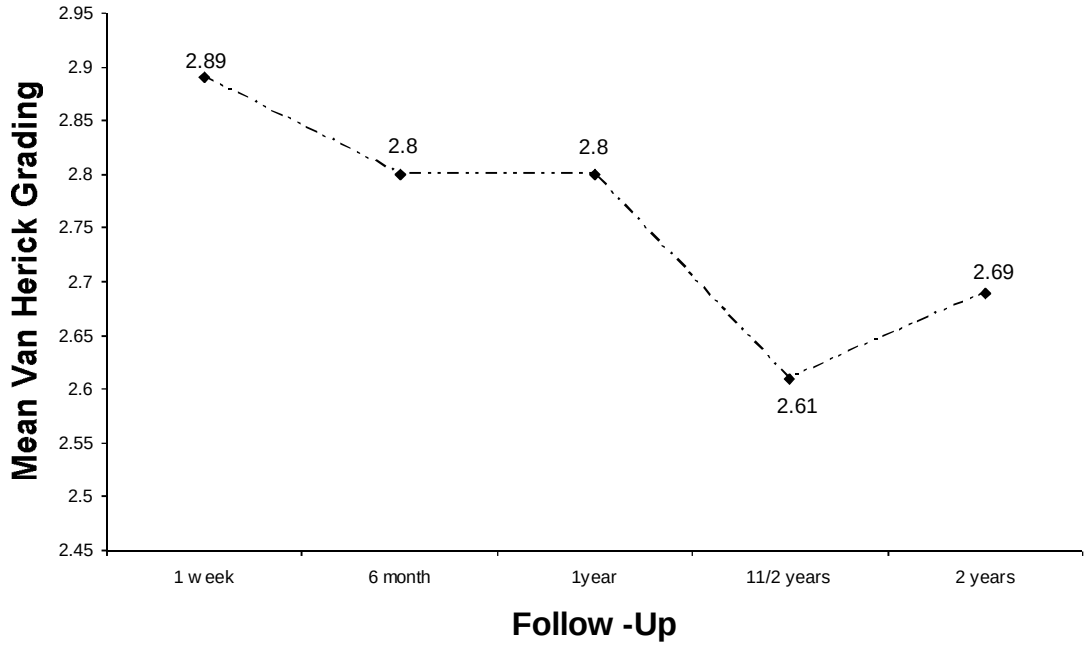

Figure 4.2: Mean value of van Herick Grading before LPI and each follow-up upto 2 years

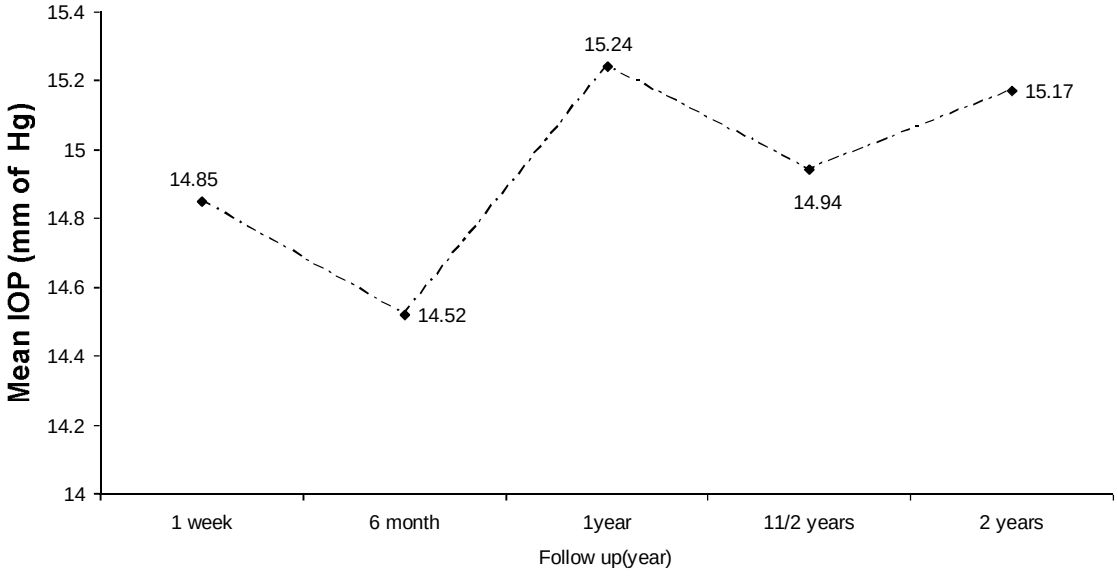

Figure 4.3: Mean value of Intraocular pressure (IOP) before LPI and each follow-up upto 2 years.

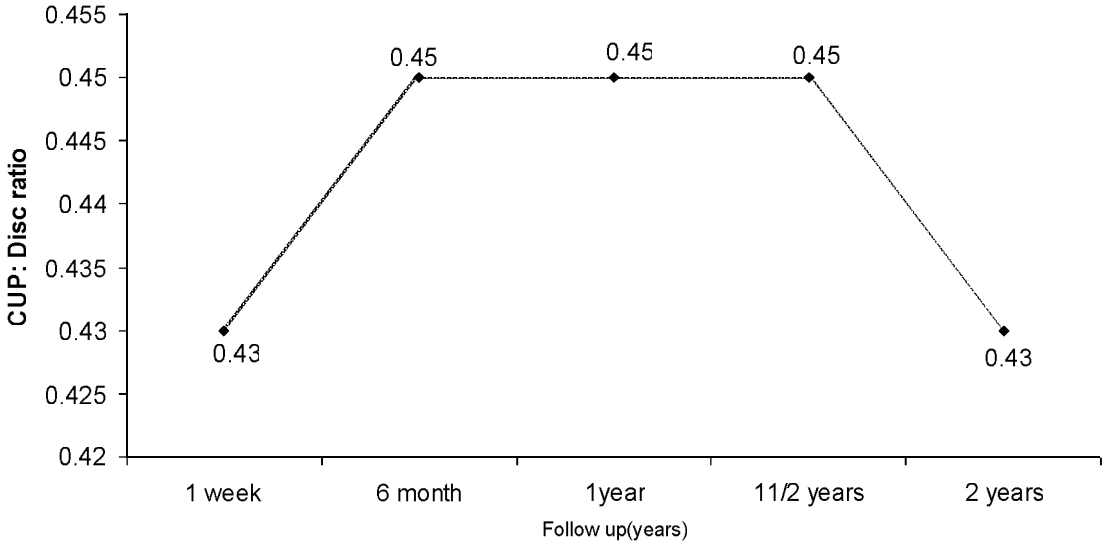

Figure 4.4: Mean value of Cup: Disc ratio before LPI and each follow-up upto 2 years

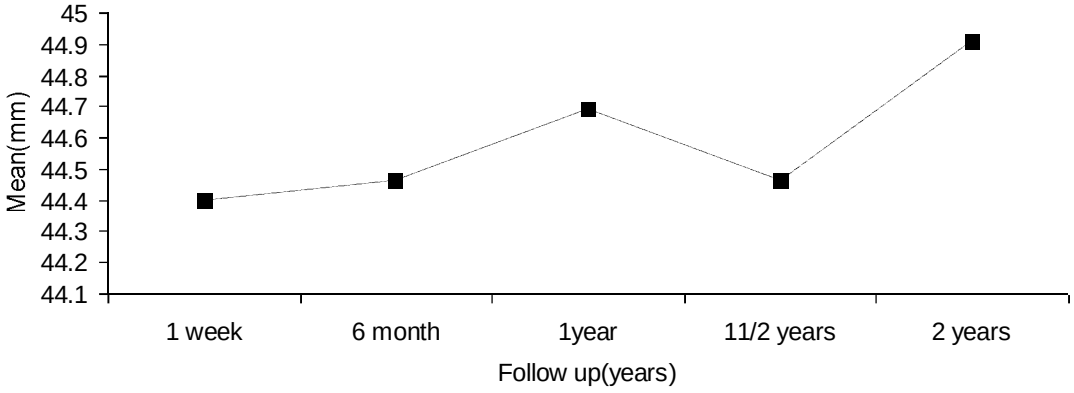

Figure 4.5: Mean value of Keratometry before LPI and each follow-up upto 2 years

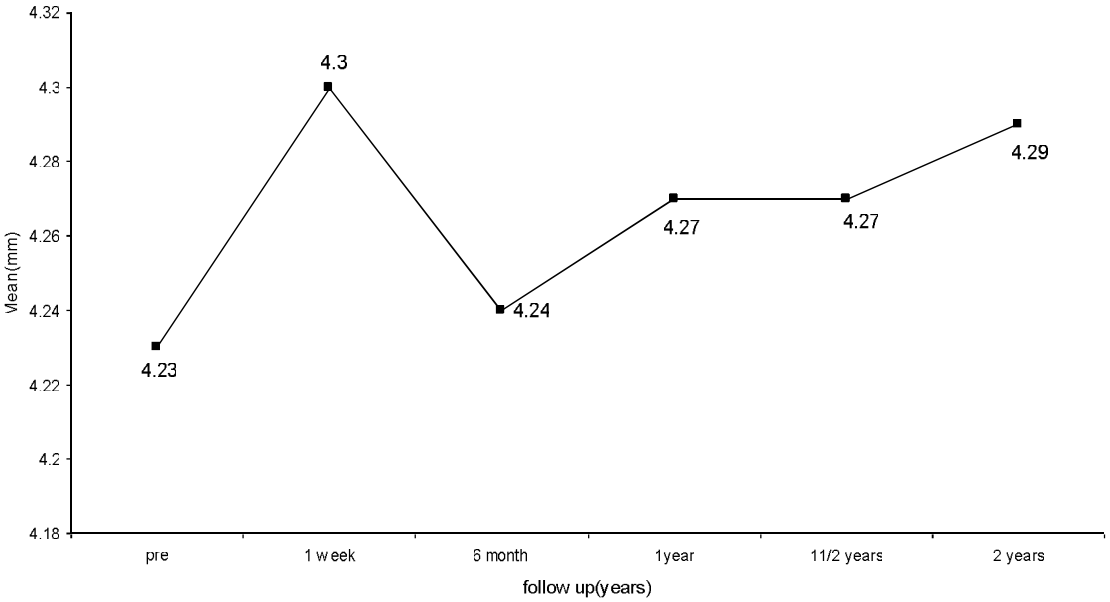

Figure 4.6: Mean value of Lens Thickness (LT) before LPI and each follow-up upto 2 years

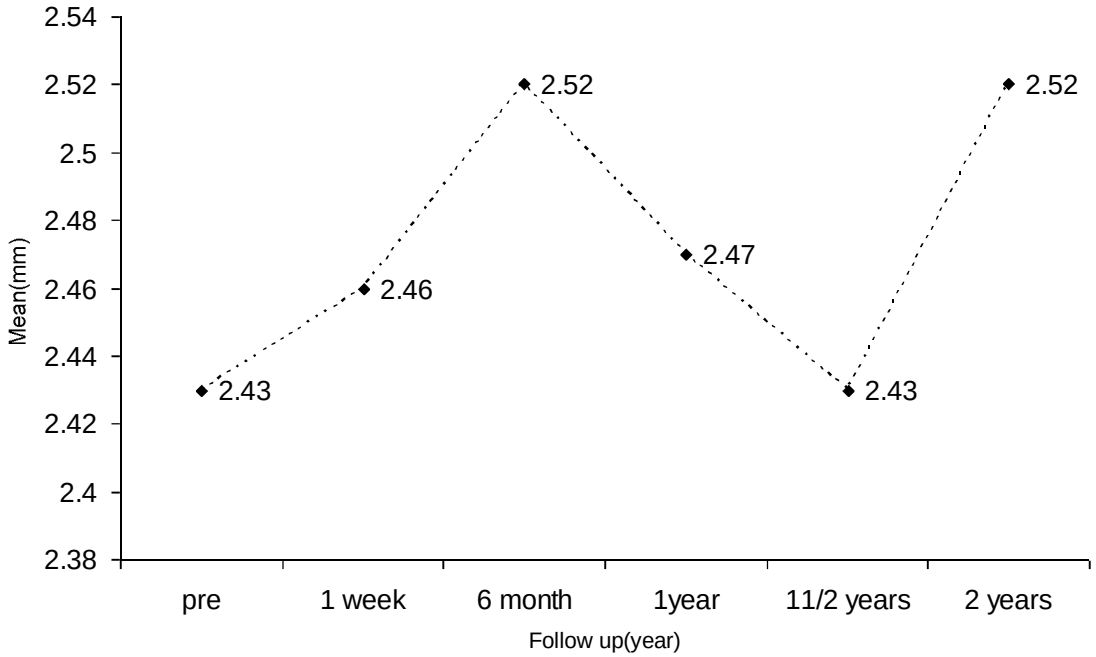

Figure 4.7: Mean value of Anterior Chamber Depth (ACD) before LPI and each follow-up upto 2 years

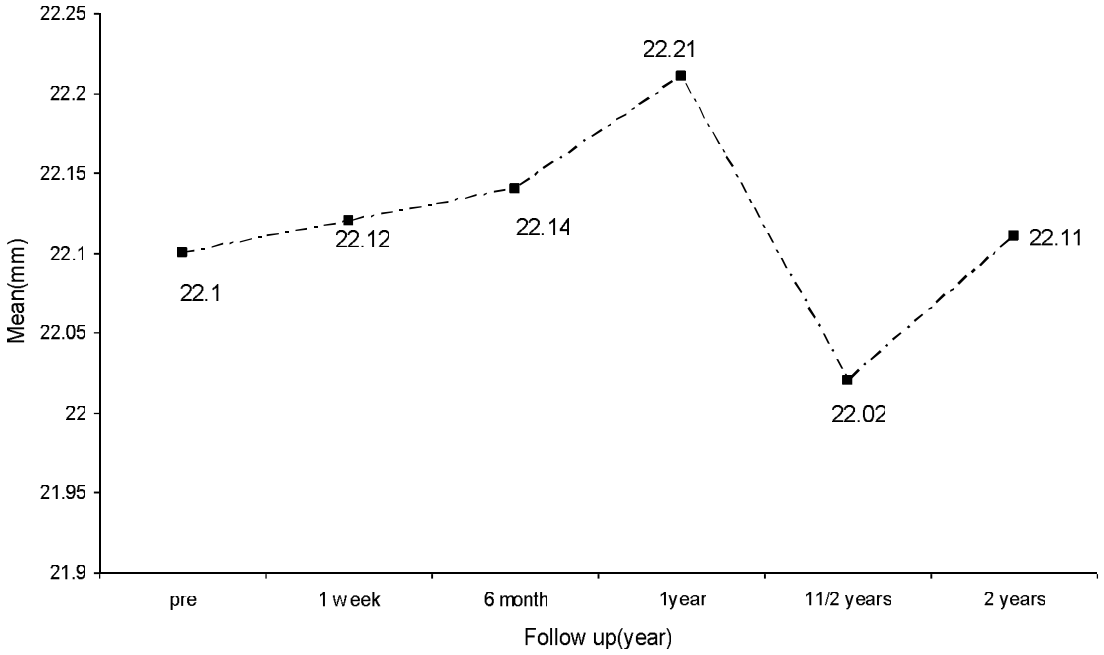

Figure 4.8: Mean value of Axial length (AXL) before LPI and each follow-up upto 2 years

Discussion:

This was the first longitudinal study done on PACS using the UBM. Among the other longitudinal studies in PACS, Ravi Thomas et al (14)., have shown that 11 out of 50 bilateral PACS subjects (22%, 95% CI 9.80 to 34.2) progressed to PAC after a five-year follow up. Ye et al. (19) in a six year follow up study of a Chinese population showed that 4.1% of PACS progressed to PAC, 14 cases had attack (Acute onset developed in 6 cases and 8 cases were in chronic stage) and 6 cases were found at early stage. Among Eskimos (17) 35% of PACS progressed to PAC over a ten year follow up period. The study also showed that ACD shallowed over a follow up period in 28% of the subjects. The present study showed that 15 out of 52 (28.85%) subjects who were followed up for

2 years after LPI had progressed to PAC. All 15 subjects developed PAS, without increased in IOP or optic disc changes. However, the site of PAS in four of the patients was adjacent to the PI site itself. If we do not consider those as true progression of the PACS, then 21.15% were found to have progressed in this study subjects. The difference between the present study and the previous studies was that this study did see the progression in subjects who underwent LPI whereas other studies followed up subjects who did not have any interventions. The other difference was that the present study was hospital based while the other two studies were population-based. Probably these might be the reasons for the difference of number of subjects who progressed to PAC between the studies. The reason for the high percentage of the PACS progression to PAC was not very clear. The criterion for PAS in our study was any pin point PAS confirmed by two examiners, which could have confounded the result.

Interestingly none of the subjects who had progressed had any symptoms suggestive of acute attacks in the intervening period a conclusion similar to other report from India. (14)

On comparing all the ocular parameters between cases that have progressed to PAC and those who did not, it was seen, peripheral anterior chamber depth and TCPD showed significant difference between the groups. The other parameters did not show any significant difference. Similar to our results, a previous study (14) by Thomas et al. showed that there was no significant difference in ocular biometry measurements (AXL, ACD, LT) between those progressed and those who did not. Peripheral anterior chamber depth among those who progressed group was shallower compared to that of non-progressed group. However as expected, the TCPD in progressed group was not more

than that of the non-progressed group. **In the chapter Three**, we have documented the TCPD in PACS group and shown it to be lower as compared to normal group. Previous study (7) done in later stages of PACG have documented TCPD to be lower as compared to normal eyes. Studies have shown that TCPD in narrow angle eyes were less than 1mm. In the present study too, both progressed and non-progressed eyes had TCPD less than 1mm. The important finding in the present study was that the eyes with relatively high TCPD value (but less than 1 mm) were prone to progression from PACS to PAC compared to other eyes with a lower TCPD. The reason for the different behavior of TCPD among the present study subjects after LPI would need confirmation with different populations and with more prospective follow up studies among the same population. As expected, the TCPD being the one parameter within which the space between the iris and ciliary process, the iris, and angle opening distance are dependent, the possible progression of PACS to PAC could not be explained by increase in TCPD and anterior crowding of the angle.

In the present study, it was also noted that there was no significant increase in IOP within 2 years of follow up after LPI. A similar study result was noted by Wilensky et al., (17) among PACS without LPI. Previous studies (20-22) among Asian subjects in later stages of PACG (Acute angle closure glaucoma, Chronic angle closure glaucoma) showed that on follow up after LPI, there was increase of IOP even with patent peripheral iridotomy. Probably impact of LPI on IOP in the PACS (early stage of PACG) was significant unlike in the later stages of the PACG. However our study did show progression of PACS to PAC in some subjects despite there being no increase in IOP.

Evaluation of peripheral anterior chamber depth using van Herick method showed widening after LPI in all the follow-up groups up to two years. An earlier study (5) of acute angle closure glaucoma patients showed increase in peripheral anterior chamber depth after LPI. However this was the first report among PACS group after LPI. As in previous studies (4, 5), there was no significant variation in central anterior chamber depth. Other studies (14, 17) on subjects without LPI who had follow up for five to six years had shown similar findings among PACS.

Gonioscopy showed significant variation between Pre LPI group and the Post LPI groups in all the quadrants. A Study (16) on occludable angle had shown that in the mean follow up period of 51 months, 68% of the subjects had wide opened angle after LPI. An Indian study by Kaushik et al. (18) had shown that there was variation in the anterior chamber angle widening in the LPI quadrant compared to quadrant opposite to LPI. In the present study, no variation in the response of the widening of the anterior chamber angle in any quadrants was found. The difference was probably because of the variation in study subjects. The subjects here were PACS as against PACG of the other study. Early stages of the PACG (PACS) probably responded differently to LPI when compared to PACG. It was noted that other related parameters, namely, AOD and ACD were comparable with Gonioscopic angle widening. Gonioscopy method of angle study had subjective bias and could be avoided by objective documentation of the anterior chamber angle in future studies to confirm our results. In the present study we used the goniscopy technique as commonly practiced among eye care professionals.

Ocular biometry parameters, namely, axial length, central anterior chamber depth, and lens position did not show significant variation before LPI and after 2 year follow-up of

LPI group. However the Lens thickness showed increase after LPI. To our knowledge there was no study documenting the variation of lens thickness and /or no variation in axial length and lens position after LPI among PACS for a period of 2 years.

UBM parameters namely ICPD, and ACA showed significant difference between before LPI and after LPI groups. AOD500 distance showed variation only one week after LPI compared to before LPI. There was no significant variation between before LPI group and other after LPI groups. The difference in response of ACA and AOD500 indicated that though the apex of the anterior chamber angle widened up, it was not so significant at 500 microns from the scleral spur. This was the first time that such variation was documented in PACS group in the literature. Earlier study by Maraffa et al. (23) described that AOD500 showed significant variation before and after LPI in combined group of PACS and PAC. However they used lines drawn between the peripheral iris and cornea as the boundaries of the angle. The angle opening thus measured was prone to measurement errors because of anatomic variations in iris configuration. Caronia et al (4) demonstrated an increase in the AOD and the lens –iris contact following LPI with a flattening of the convex iris configuration. Gazzard et al (5) pointed to widening of the anterior chamber angle following LPI with no change in the anterior chamber depth. Yoon et al (24) compared the UBM change in angle morphology following LPI and trabeculoectomy and demonstrated existence of significant increases in AODs after both procedures. There were two Indian studies (7, 18) on UBM parameters after LPI among PACG subjects. In the first study (7), anterior segment features of PACG eyes imaged by the UBM included those eyes that had undergone LPI, but no baseline imaging had been carried out. The other study (18) did look at only one UBM parameter (AOD).

In the present study, Cataract progression was noted among the study subjects. The previous studies (25, 26) had documented the progression of cataract after LPI among Acute primary angle closure subjects. In the present study the progression at the end of first year was 36.36% of cases and from first year to second year 12.9% of cases. This progression was alarmingly high. Compared to previous studies the present study had shown significant progression of nuclear cataract rather than posterior subcapsular region cataract. Prior studies on the risk of cataract formation after iridectomy or LPI used visual acuity as a surrogate marker of cataract progression. Reviews by Quigley (27) and Robin and Pollack (28) on the long-term safety of laser iridotomy showed some visual loss presumably attributed to cataract when followed up to 1.8 and 5 years, respectively. A study by Hsiao et al (16) reported reduced visual acuity 6 months after LPI in 2.1% of cases, and this again, largely due to cataract formation. Our study being of the middle aged to elderly population, natural aging of the lens could have contributed to the progression in lens opacities. In the present study, Logistic regression analysis did not find any risk association for cataract progression with the parameters analyzed (age, anterior chamber angle, anterior chamber depth, lens thickness and peripheral anterior synechiae). Thus, this study was unable to uncover any factors that might otherwise have accounted for the cataract progression. Steroid use, Diabetes mellitus, and Hypertension, were also known (29, 30) as the risk factors for cataract progression. Absence of such factors among the present study subjects ruled out those possible contributors to the cataract progression. There were literatures that show photo disruptive property of Nd: YAG laser that cause craters in the superficial anterior lens capsule and superficial cortex (31) and 0% to 4% developing lens opacities. (32-36) However this was the first

prospective study showing the progression of cataract among PACS after LPI in Indian subjects. Previous prospective studies (25, 26) done in other Asian subjects among APAC group did show progression but more in posterior subcapsular region as against in this present study which showed more progression in nuclear region. There were studies that showed altered physiology of the eye after LPI demonstrating elevations in transforming growth factor- beta and other cytokines in the aqueous (37, 38) and this factor was documented to be the key aspect in the pathogenesis of PSC cataract in animal studies. (25) However there was no evidence in the literature as to the contribution of the factors that lead to the progression of nuclear sclerosis post LPI. Despite this limitation, it was still a concern with high rate of progression of cataract. The need for the LPI in PACS subjects with complication of increased rate of progression need to be studied further with larger sample size before advocating a modification in approach.

Using Univariate analysis, predictive factors for the progression of PACS to PAC were examined and the present study showed that Trabecular ciliary process distance (TCPD) could be an important parameter. This probably was the first study that documented TCPD as the risk factor for the progression of PACS to PAC among Indian hospital based subjects. Previous studies (7, 39, 40) showed decreased TCPD in severe forms of glaucoma and the presence of such a difference in the early stages such as PACS (Chapter 3) itself would give a clue to the pathogenesis of the disease in the absence of a thicker lens.

Interestingly, none of the study subjects developed increased IOP, acute attacks and symptoms related to angle closure. It is presumed that though LPI prevented acute attacks (41, 42) as documented before, it did not prevent the progression of the conditions in

some of the study subjects. Five-year follow –up study (14) done among PACS subjects (without LPI) had shown progression of both synechial and appositional form of PAC. Comparing the number of subjects progressed in the present study after LPI with other study of subjects without LPI, it was felt that though LPI prevented acute attacks, it might not prevent progression to chronic phase of the disease. A Study by Hsiao et al.(16) showed 17.6% (26 of 145) of eyes with occludable angles had peripheral anterior synechiae to a certain degree. Though not adequate support to justify, LPI itself would have triggered the progression of disease in some cases. This hypothesis should be confirmed by comparing the PACS subjects with and without LPI in a longitudinal study.

In the present study, we did not notice any specific trend among the parameters except for LT, from the time of enrolment before LPI and up to 2 years of follow-up after LPI .LT showed significant increase in thickness in the follow up. However this increase would not have contributed to the progression of PACS to PAC because LT did not vary significantly between progressed and non- progressed groups.

Limitations of the Study:

The limitations were drop-out of the subjects for follow up, no follow-up of controls (PACS without LPI), LOCS-II not done on all the subjects, photographs of lens and optic disc area not taken, appositional angle closure in the follow up not classified, and no documentation of orientation of ciliary body to look into the percentage of eyes with anterior rotation of ciliary process in each quadrant.

Conclusion:

In this hospital based study on the course of PACS subjects after LPI, as many as 28% progressed to PAC but none progressed to PACG. TCPD and Peripheral Anterior Chamber Depth showed significant variation between the eyes that progressed and those did not. TCPD was the predictive factor for the progression of PACS to PAC. ICPD, ACA and LT parameters varied significantly between the "Before LPI group" and "After LPI group". AOD before LPI was significantly different from AOD one week after LPI, but not with other follow-up groups. There was no variation of AOD and ACA between LPI quadrants and quadrant opposite to the LPI in this study subjects. It was found that nuclear sclerosis progressed more than the posterior sub capsular cataract. There was no increase in IOP, history or symptoms of acute attack of glaucoma among the study subjects after LPI.

Specific Contribution:

This was the first Indian based study on course of the PACS subjects after LPI with a follow up of 2 years. We are the first to report on the possible progression of PACS and cataract after LPI among the Indian subjects. In addition, it was for the first time that we documented the possible predictive factor (TCPD) for the progression of the disease process. It was also shown that Keratometry value, Cup-Disc Ratio, AXL, ACD, RLP, CCT, IT and TCPD did not vary significantly after LPI among PACS subjects; but, parameters, such as, LT, AOD, ACA and ICPD showed significant changes following LPI. This was the first study to show that peripheral anterior chamber depth and TCPD

were significantly different between PACS group that progressed to PAC and the PACS group that did not. This was also the only documentation that showed TCPD to be higher in the progressed group than in the non- progressed group.

Future scope of study:

By comparing two groups, namely, PACS with LPI and PACS without LPI, we can confirm the effect of LPI on the possible progression of the PACS and cataract. We may try to look into the possible biochemical triggering mechanism due to changes in the aqueous humor in the anterior chamber and the lens following LPI and its contribution to the progression of cataract. A prospective study can be done to look into TCPD as a predictive factor for the progression of PAC to PACG. Also a longer follow –up of up to five years can be planned to know the natural course of the PACS and its progression.

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Chapter 5:

A new software for analysing iris shape in Ultrasound biomicroscopy images

Abstract:

Aim: To analyze iris shapes of Ultrasound Biomicroscopy (UBM) images of normal and narrow angled subjects on the basis of a newly developed software using MATLAB 7.2.

Methods: Software in MATLAB 7.2 was developed to trace the anterior iris surface in UBM images. The software first flipped the images to the left side. It then enhanced and denoised them. The images were then resized to 500 x 500 pixels using nearest neighbour interpolation. They were rotated to a standard position. Then the image was binarised. In case of images of narrow angled eyes, the iris insertion was chosen before binarization. The software automatically traced the anterior surface of the iris to 2.5 mm horizontally. The area under the traced iris surface was calculated. This measurement was termed Iris Shape Factor (ISF). Lower ISF indicated flatter iris configuration and higher ISF indicated convex iris configuration. Interobserver and Intraobserver reliability of the measurement of ISF in normal angle eyes and narrow angle eyes were analysed. The coefficient of variation (CV) was measured. CV less than 10% was considered good reliability. The ISF was measured on UBM images of 11 normal eyes and 11 narrow angle eyes. A student - t-test was carried out on ISF measurements of normal angle eyes and narrow angle eyes. p value less than 0.05 was considered statistically significant.

Results: Interobserver reliability and Intraobserver reliability of measurement of ISF for normal angle UBM images and narrow angle eyes was good (CV < 10%). The average area in the normal eyes was found to be $0.46 \pm 0.16 mm^2$ and in narrow angles to be 1.12

± 0.33mm^2. Significant difference was found between the area of normals and narrow angles ($p<0.000$) using student's t-test.

Conclusion: The measurement of ISF using MATLAB 7.2 was found to have ensured good inter and intra observer reliability. ISF could differentiate normal angle eyes from narrow angle eyes. ISF in normal angle eyes was less than eyes with narrow angle.

***Review of Literature*:**

Glaucoma is recognized as a major cause of ocular morbidity worldwide. It has been estimated that by the year 2020 India will have 23.9% and 18.9% of world angle closure glaucoma (ACG) and Open Angle glaucoma (OAG) population respectively. (1)

Iris apposition to the trabecular meshwork is the most common pathway of angle closure glaucoma, which represents a group of disorders. In ACG, the iris is abnormally positioned and physically impedes the aqueous humor outflow through trabecular meshwork. ACG derives its name from the narrow anterior chamber angle defined by anterior iris surface and posterior surface of corneoscleral shell. This condition can be caused by one or more abnormalities in sizes or positions of anterior segment structures or by abnormal forces in posterior segment that alter the anatomy of anterior segment. Forces generated to cause angle closure in four anatomic sites include, the iris (pupillary block), the ciliary body (plateau iris), lens (phacomorphic glaucoma), a combination of various forces behind iris (malignant glaucoma). (2) Lee,Brubaker and Illstrup used biometric photography to analyse iris configuration before and after surgical iridectomy. (3)

With the advent of high frequency Ultrasound Biomicroscopy (UBM), attention was centred on crowded anterior segment with high-resolution scanned images in vivo. The main advantage of UBM is its high reproducibility and its accuracy (4). It enables us to measure linear and angular parameters capable of defining the characteristics of normal and glaucomatous eyes. (5) UBM has in-built software, which helps us with various measurements on UBM images. UBM pro2000 (6) a separate software similarly helps us to measure a few more parameters of the anterior chamber. Both these software are

helpful to measure parameters like anterior chamber angle, anterior chamber depth, Trabecular Ciliary process distance and Iris ciliary process distance. Both could not measure directly or indirectly the iris configuration. There were studies, which showed subjective variation of iris configuration in normal and narrow angle eyes (7). A new method (8) of measuring the iris contour was devised with a personal computer. The model of a parabolic curve, an approximate mimic iris contour curve, was traced to define the profile contour of the iris from a photograph. A radius measured from the apex of the curvature of the parabola, named iris radius (IR), was calculated by a computer to describe the degree of the curvature of the iris contour. This study (8) showed mean Iris radius to be significantly different between glaucoma and normal eyes. The other study (9) attempted to measure similarly the iris radius but it concentrated only on inter and intraobserver reliability of the measurement technique. This study aimed to develop software to measure the area under the anterior iris surface, which indirectly represented the iris configuration, and apply it on normal and narrow angle UBM images to see its viability to differentiate the two groups.

Patients and Methods:

There are three distinct parts in this study:

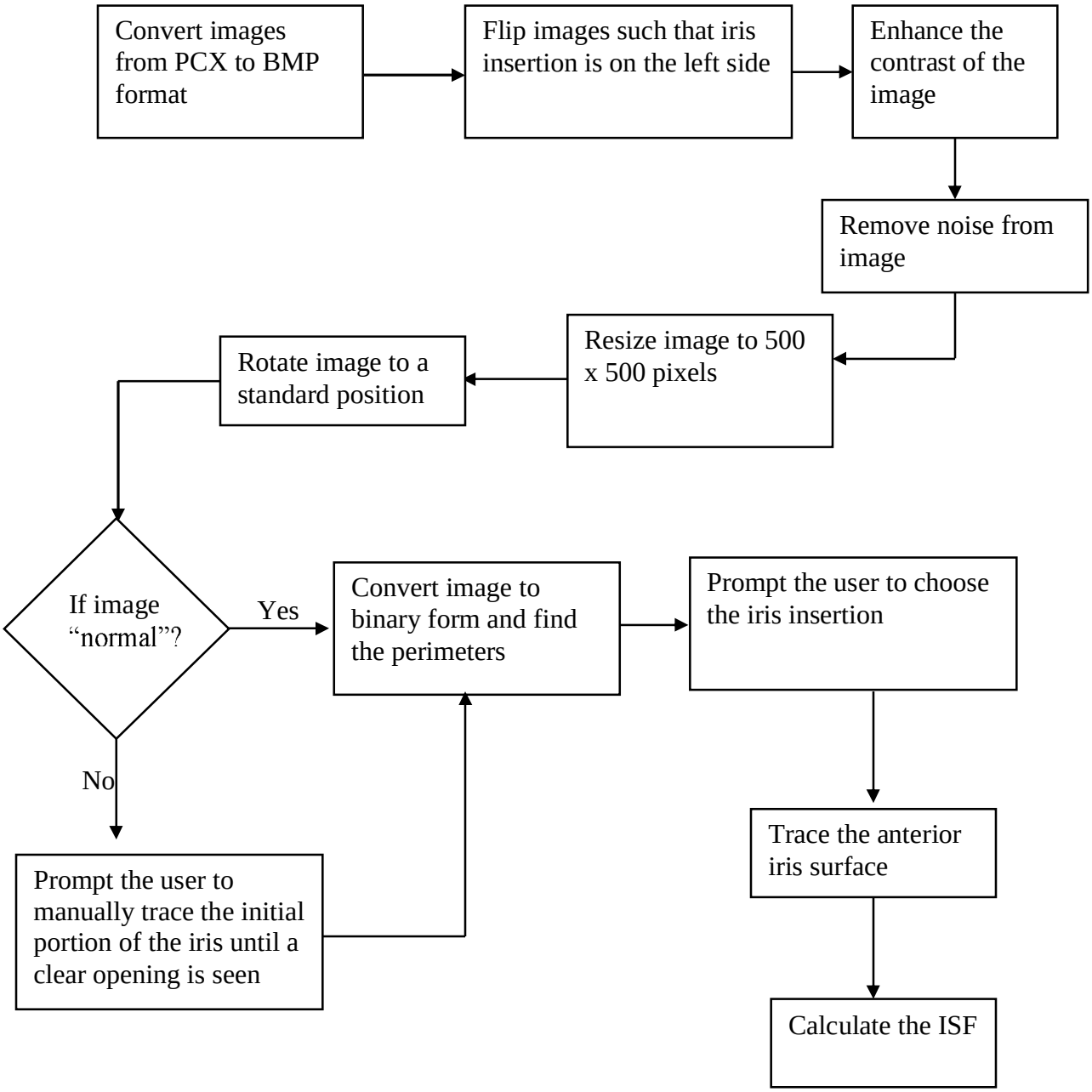
Part I: Development of new software for quantifying iris configuration by tracing the anterior surface of the iris in UBM images and calculating the area under the traced curve.

Part II: Measurement of inter and intra-observer reliability of the new software.

Part III: Comparison of the iris configuration as defined by the calculated area between normals patients and those with narrow angles.

The source for the UBM images (normal angles and narrow angles) was the department of Glaucoma of a tertiary care centre.

Flow Chart 1 - Illustrating steps in the development of software:



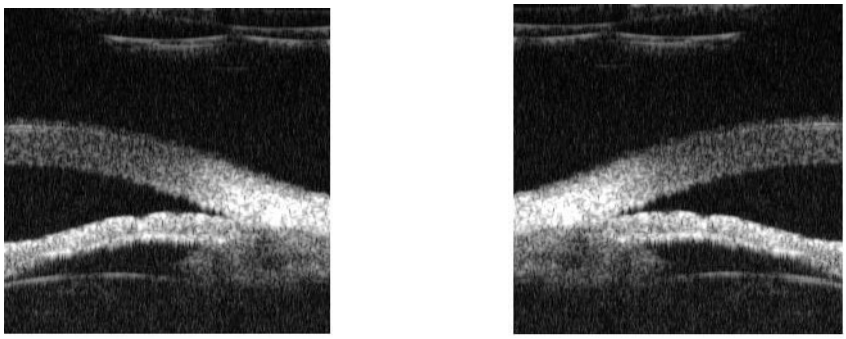
Part I

Software using MATLAB 7.2 was developed to quantify iris configuration by measuring the area beneath the iris (Appendix 1). The flow chart above shows the steps involved in the development of the new software.

The aim of this part of the study was to develop software for quantifying the iris configuration.

UBM images (normal angles and narrow angles) were originally in the PCX formats. All images were pre-processed, binarised and then the iris was traced.

Pre-processing consisted of converting the PCX formatted images into bitmap files. These bitmap images were then flipped in such a way that the iris insertion was on the left side of the image (figure 5. 1a and 5. 1b). The next step was image enhancement. Image contrast was enhanced such that 1% of the data was saturated at the highest and lowest intensity values. A flood fill operation was performed on the background of the contrast-enhanced image. This helped to remove the noise in the background.The images were then resized to 500 x 500 pixels using the nearest neighbour interpolation. This standardization of the size eased the process of comparing images obtained from various patients.



(a) (b)

Fig 5.1: (a) Original Image; (b) Flipped image. The iris insertion in the first image is in the right half of the image while in the flipped image it is in the left half.

Standardization of the images was done by rotating the image to a standard angle theta. Theta is the angle formed by a triangle whose sides are defined by, (i) a line drawn from iris insertion O to a point A that is at a distance of 2.5mm horizontally (The horizontal visible diameter of the iris is about 12mm (10) of which about the central 4mm makes the aperture (pupil). The distance between the pupillary border and the iris root is about 4mm. It will vary from person to person. Therefore, for all images, we traced 2.5 mm of the anterior surface of the iris from the iris root using our software.), a perpendicular from A to anterior corneal surface B and a line joining OB (see figure 5.2) were drawn. If the calculated theta for the image was less than the standard, the image was rotated anti clockwise; if it was more, the image was rotated clockwise.

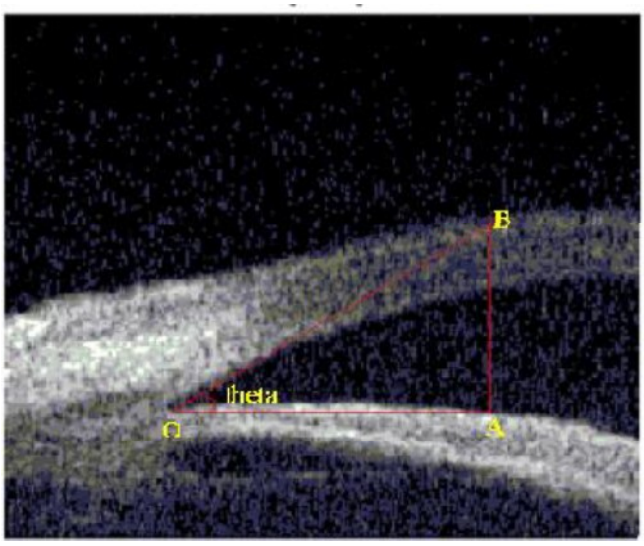


Fig 5.2: Standardization of the UBM images by measuring angle theta

This angle theta was calculated for all the straight images using UBM pro software. The average angle (theta) was found to be 43.37 degrees for normal angle images and 33.92 degrees in narrow angle images. The angle of each image was calculated and compared to that of average angle calculated. All images were rotated in such a way that they had the angle equivalent to that of the calculated average angle.

Following standardization, image binarisation was done so that the binary image had only two pixel values, namely zero and one. Zero indicated black and one indicated white. Then the perimeter of the binary image was traced (fig 5.3).

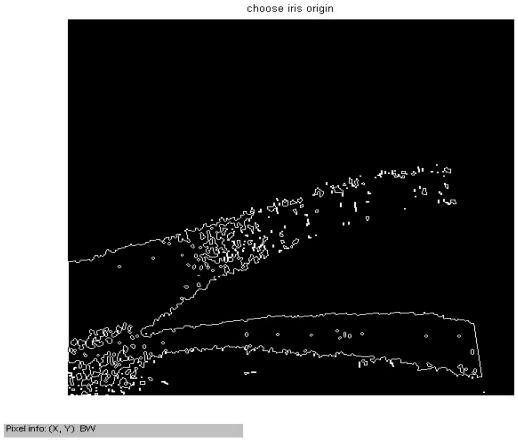


Fig 5.3: Binary image

Following binarization, the iris origin was selected manually by clicking the mouse on the white part of the image at iris insertion site. Then the program automatically traced the iris from the selected point to 2.5mm horizontally. The program connected all the white regions from selected point to 2.5mm horizontally.

In case of apposition of iris (Fig 5.4a), the binary image provided false iris insertion point of origin (Fig 5.4b). Hence, the apposition part of iris surface was traced manually before converting it into a binary image (Fig 5.4c). If the input image was that of a narrow angle eye, the user was prompted to manually trace the initial portion of the iris from the iris insertion and the software automatically traced the reminder up to 2.5mm.

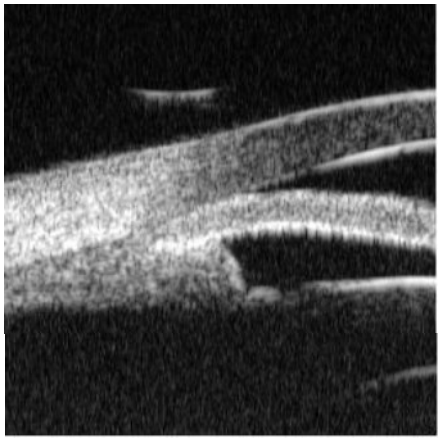


Fig 5.4a

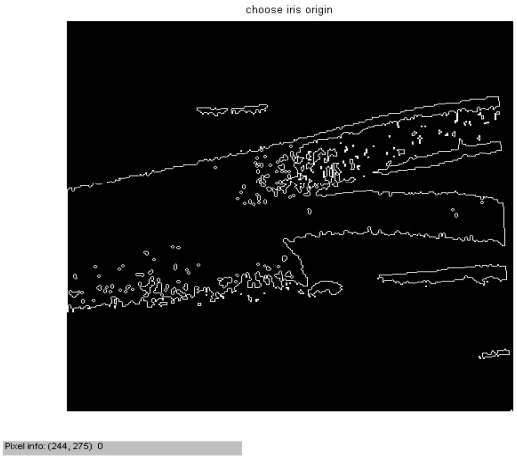


Fig 5.4b

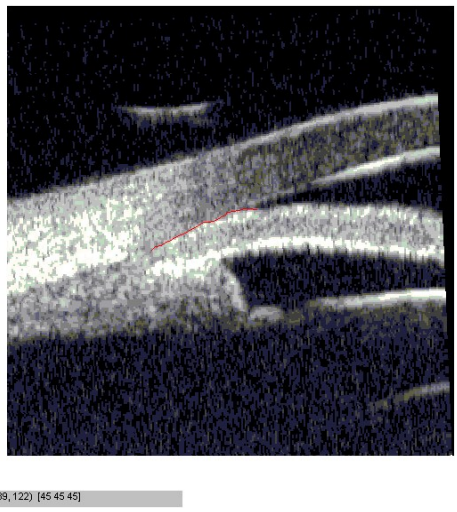


Fig 5.4 c

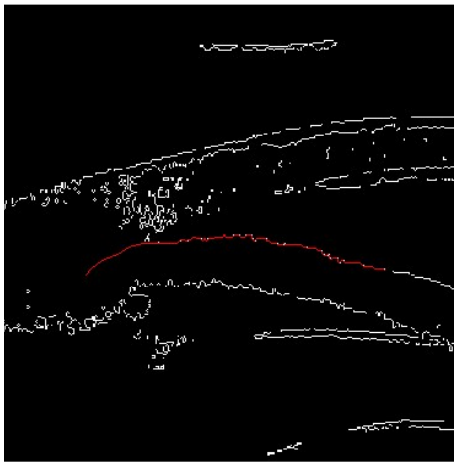


Fig 5.4 d

Fig 5.4: a) UBM image of Angle closure eye b) Binary image showing false tracing of Iris c) Manual Iris tracing done in angle closure eye before binarisation d) Binary image of fig in (a) with iris traced upto 2.5mm horizontally.

Then the traced iris was plotted in a graph (see figure 5).

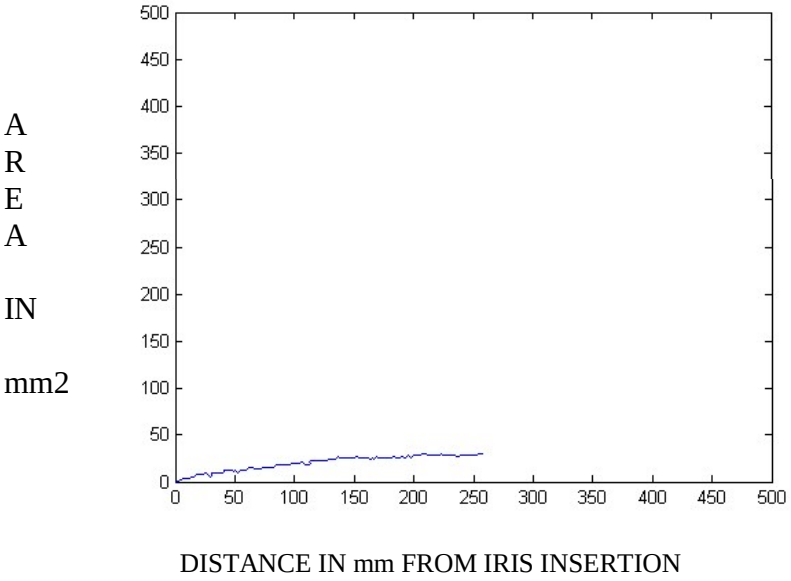


Fig 5.5: Graph representing the traced iris for an UBM image of an individual eye.

By integrating the area under the plotted curve, the iris shape was calculated. The calculated area gave the Iris Shape Factor (ISF). The larger the ISF, the more convex would be the iris configuration. For example, the eye with ISF of 0.4645mm^2 compared to eye with ISF 1.1241mm^2 was to have a flatter iris configuration.

Part II

The goal of this part was to evaluate inter and intra observer reliability of measurement of ISF.

UBM images from all the quadrants were obtained from 57 Primary Angle closure suspects (PACS) patients seen by one of the authors between March 2003 and July 2003 at the glaucoma clinic of a tertiary eye care center. For each patient, one good UBM image was selected. The criteria for good UBM images were clear anterior corneal

surface, iris insertion and iris length of 2.5mm horizontally. For obtaining the interobserver reliability, three experienced examiners, masked to each other, measured ISF parameter of 11 randomly selected images using the new software. For intraobserver reliability measurement, same 11 images were used to measure ISF twice by all three examiners. The time interval between the first and the second measurements by a single examiner was a week. Based on the data obtained, inter- and intraobserver reliability coefficient of variation (CV) was measured. CV less than 10% was considered indicative of good reliability (11)

Part III

The goal of this part was to compare iris configuration by measuring ISF between normals and narrow angles. Eleven images of PACS subjects were used for the study. We selected age matched normal angle subjects (defined as Shaffer grade 3 or more) from previously collected normative data for UBM. A trained ophthalmologist performed the UBM and gonioscopy for all the normal subjects using the same protocol. (12) The demographics and ocular biometry data were taken from the medical records except for UBM measurements. Eleven images out of 57 normal UBM images were selected randomly. One of the authors calculated the ISF for 11 normal and 11 narrow angle images. Student's "t" test was done to compare the ISF for normal and narrow angle eyes. $p < 0.05$ was assumed to be statistically significant.

Results:

The individual ISF measurements as measured by three observers are given in Tables 5.1 and 5.2. Inter and intra observer reliability for calculating ISF using CV was found to be good (Table 5.3).

Table 5.1: ISF (mm^2) Measurements as measured by three observers on 11 UBM images each of Normal and Narrow angle eyes

	Normal Eyes			Narrow angle Eyes		
Patient	Observer 1	Observer 2	Observer 3	Observer 1	Observer 2	Observer 3
1	0.14	0.30	0.32	1.32	1.46	1.51
2	0.51	0.62	0.62	1.18	1.26	1.19
3	0.53	0.58	0.65	1.33	1.57	1.06
4	0.41	0.49	0.48	0.9	1.61	1.62
5	0.21	0.26	0.25	1.24	0.96	0.95
6	0.53	0.66	0.68	0.98	0.72	0.61
7	0.68	0.70	0.73	0.87	1.39	1.08
8	0.30	0.38	0.38	0.96	0.87	0.8
9	0.32	0.27	0.38	0.82	0.86	0.92
10	0.73	0.68	0.71	1.91	1.82	1.77
11	0.34	0.36	0.38	0.77	0.83	0.79

Table 5.2: ISF (mm2) measurements as measured twice by three observers on 11 UBM images each of Normal eyes and Narrow angle eyes.

	Normal eyes			Narrow angle eyes		
Patient	Observer 1	Observer 2	Observer 3	Observer 1	Observer 2	Observer 3
1	0.14 (0.32)	0.3(0.13)	0.32(0.2)	1.32(1.01)	1.46(1.3)	1.51(1.41)
2	0.51(0.64)	0.62(0.52)	0.62(0.43)	1.18(1.12)	1.26(1.3)	1.19(1.21)
3	0.53(0.5)	0.58(0.56)	0.65(0.41)	1.33(1.13)	1.57(1.01)	1.06(1.1)
4	0.41(0.57)	0.49(0.49)	0.48(0.52)	0.9(1.36)	1.61(1.46)	1.62(1.48)
5	0.21(0.21)	0.26(0.32)	0.25(0.33)	1.24(0.71)	0.96(1)	0.95(0.98)
6	0.53 (0.6)	0.66(0.58)	0.68(0.65)	0.98(0.66)	0.72(0.64)	0.61(0.57)
7	0.68 (0.49)	0.7(0.63)	0.73(0.71)	0.87(1.08)	1.39(1.16)	1.08(1.25)
8	0.3 (0.48)	0.38(0.41)	0.38(0.47)	0.96(0.96)	0.87(0.89)	0.8(0.85)
9	0.32 (0.27)	0.27(0.38)	0.38(0.27)	0.82(1.29)	0.86(0.87)	0.92(0.9)
10	0.73 (0.69)	0.68(0.95)	0.71(0.88)	1.91(0.78)	1.82(1.84)	1.77(1.87)
11	0.34 (0.32)	0.36(0.43)	0.38(0.26)	0.77(1.65)	0.83(0.76)	0.79(0.84)

Values given within the bracket indicate the second measurement

Table 5.3: Inter and Intra observer reliability of ISF measurement in Normal and Narrow angle eyes

	Intraobserver Reliability			
	Observer 1	Observer 2	Observer 3	**Interobserver Reliability**
Normal	4.17	4.82	5.21	8.65
Narrow angle	2.29	2.29	0.45	4.84

Coefficients of variation (%) are given for parameters measured by observers.

CV<10% was considered good reliability

The ISF of normal eye was found to be significantly ($p<0.000$) low when compared to that of narrow angles (Graph 5.1). The mean ISF in the normal eyes was $0.46 \pm 0.16 mm^2$ and $1.12 \pm 0.33 mm^2$ in narrow angles

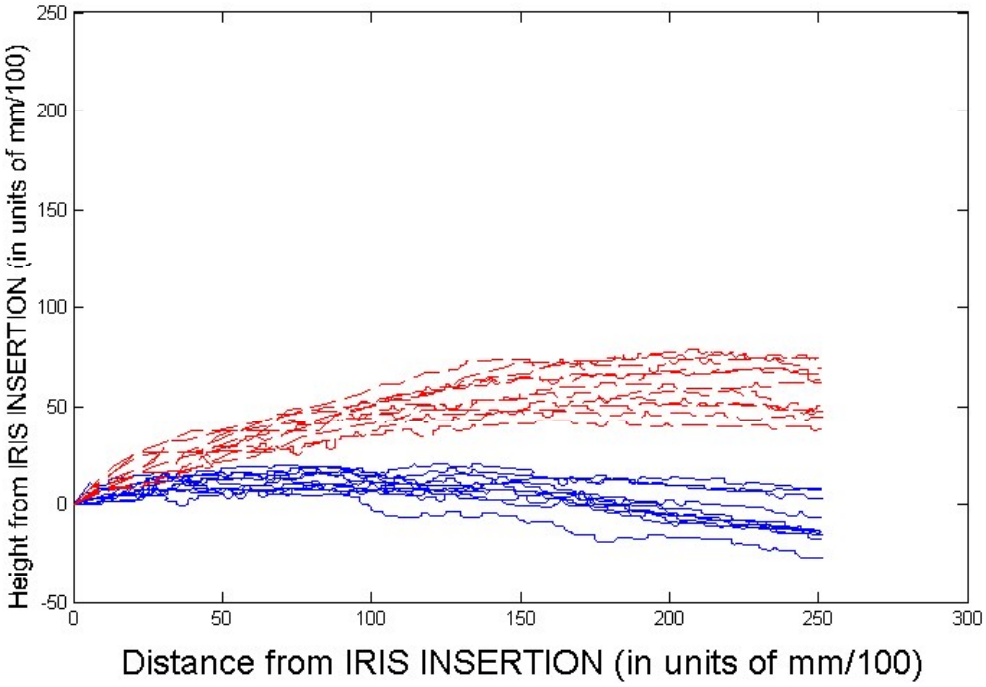


Fig 5.6: Graph comparing Iris Shape Factor (ISF) in Normal and Narrow angle eyes

Discussion:

This was the first study that led to development of software to measure the area beneath the anterior contour of the iris thus quantifying iris configuration. There were studies (7, 13, 14, 15) on understanding the iris configuration. The study done by Spaeth (13, 7) evaluated subjectively and classified it into "q" type when there was posterior iris concavity, "r" type when there was flat iris or a mild regular curvature without sudden change in the curve and "s" type when there was a plateau appearance with a sudden anterior convexity, bending sharply to a flat iris centrally. The Inter and Intra observer

agreement was high for the subjective measurement. The limitation of this study was that it was a subjective evaluation.

Potash et al. (14) tried to quantify iris configuration in UBM images with an inbuilt calliper of the instrument. Iris concavity was determined by creating a line from the most peripheral to the most central points of iris pigment epithelium. A perpendicular line was extended from this line to the iris pigment epithelium at the point of greatest concavity or convexity. A concave or convex surface was determined to exist when there was a measurable difference between the plane of the iris pigment epithelium and the initial reference line. Negative values were assigned to concave irides, positive values indicated convex irides and Zero value represented planar irides. Though it could solve the problem related to quantification using a calliper in the instrument itself, the subjective assessment of the greatest concavity or convexity was a limitation. There was then no report on the reproducibility of the technique.

Jin et al. (15) attempted to understand the iris contour after iridotomy and were able to demonstrate the iris convexity before iridotomy and no perceptible change after iridotomy. They used photographs using the scheimpflug principle. Computer corrected image was used for quantifying the depth of the anterior chamber. The iris configuration changes were subjectively documented without quantification.

The software now developed here using MATLAB 7.2 took into account the limitations of the previous studies and tried to solve the major issue of subjectivity in measuring iris configuration. Except for identification of the reference point at the iris insertion area, the other steps in calculating the ISF were automated. The only limitation of the software was that manual iris tracing in the cases of angle closure (synechial or appositional angle

ABSTRACT

The chief objective of the study was to understand the natural history of the Primary Angle Closure Suspects (PACS) among hospital based Indian subjects after Laser Peripheral Iridotomy (LPI). The study also explored the possibility of predictive factors for the progression of the disease process in study subjects. Inter and Intra observer reliability of the measurement of ultrasound biomicroscopy (UBM) images in PACS was examined. In addition, a new approach to differentiate normal eyes and the PACS eyes was attempted by developing a new algorithm using MATLAB 7.2.

The study subjects were recruited from the glaucoma clinic of a tertiary eye care center. The selected subjects based on inclusion and exclusion criteria, underwent detailed clinical evaluation, gonioscopy, A-scan biometry and ultrasound biomicroscopy before undergoing LPI and 1 week, 6 months, 1 year, 1½ years and 2 years after intervention. Reliability of the measurement of parameters of UBM images of PACS subjects was measured. Interobserver reliability was good for Angle Opening Distance (AOD500), Trabecular Meshwork Ciliary Process Distance (TCPD), and Iris Thickness (IT) (CV < 10%). Intraobserver reliability of all the parameters was good. Anterior Chamber Depth (ACD), Axial Length (AXL), Central Corneal Thickness (CCT), TCPD, Anterior Chamber Angle (ACA) and AOD500 were significantly low in PACS group than in normals. In the female population, the lens was thicker in PACS than in normals. Lens was more anterior-placed in PACS group than in normals among males.

Analysis of follow up data of the PACS subjects after LPI revealed that 15 (28.85%) cases out 52 progressed from PACS to Primary Angle Closure (PAC) by developing peripheral anterior synechiae. Trabecular Ciliary Process Distance (TCPD) and

Peripheral Anterior Chamber Depth (using van Herick method) were significantly different between PACS group that progressed to PAC and the group that did not progress. Univariate analysis showed that Risk Ratio (RR) for PAC for TCPD was significant. TCPD might be the predicting parameter for the progression of PACS to PAC. None of the other parameters namely, age, gender, anterior chamber angle, intraocular pressure, anterior chamber depth, lens thickness, lens position, iris ciliary process distance, iris thickness, and angle opening distance at 500 microns from scleral spur pointed to significant risk ratio. Out of 33 patients who underwent Lens Opacification Classification System II (LOCS II) at 12 months of follow-up, 13 (39.39%) showed significant (p=0.003) progression of cataract in any lens region. At 24 months of follow-up, 4 of 31 eyes (12.90%) showed significant progression (p=0.014) in any lens region. There was significant progression of cataract in the nuclear region as compared to that in posterior sub capsular region. Logistic regression analysis did not indicate risk association for cataract progression with the parameters age, gender, intraocular pressure, peripheral anterior synechiae, lens thickness, and axial length.

A new software algorithm for identifying Iris Shape Factor (ISF) in UBM images using MATLAB 7.2 was developed. The ISF appeared to be significantly different between normal and narrow angle eyes.

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APPENDIX - 1

PROGRAM

```
function [output] = finalpro(imagetype);
% The format of this function is
%    [output] = irisshape(imagetype);
% imagetype = 0 (default) for normals; 1 for narrow angles

currdir = pwd;

getinput = input ('enter one if the iris has narrow angle else enter zero. Enter your choice = ');
imagetype = getinput;

[filename, pathname, fileindex] = uigetfile({'*.bmp', 'Bitmap (*.bmp)';...
   '*.jpg', 'JPEG (*.jpg)';...
   '*.fig', 'Matlab figure (*.fig)'},...
   'Open a UBM image');

% Check to see if 'Cancel' was done
if isequal(filename,0)
   error('');
end;

% If a file is selected read the image and do some image prepocessing
fullfilename = fullfile(pathname, filename);
a = imread(fullfilename);
```

```
a = imresize(a, [500,500], 'nearest');
nncol = a(:,498,:);
nnrow = a(498,:,:);
for i = 1:3,
   a(:,499,i) = nncol(:,1,i);
   a(:,500,i) = nncol(:,1,i);
   a(499,:,i) = nnrow(1,:,i);
   a(500,:,i) = nnrow(1,:,i);
end;

% get iris origin
imshow(a);title('original image')
impixelinfo
% msgbox('select iris origin')
[x,y] = getpts;
hold on;

% tracing 250 points from the intial point.
np = [x+250 y];
dummyx=x;
dummyy=y;
d=[];
c=[];
for i=1:250;
   d=dummyx+1;
   c=dummyy;
   plot(d,c,'r');
   hold on;
   dummyx=d;
```

```
end;

hold on;

% tracing vertically upto the corneal anterior surface.
dd=[];
cc=[];
[x1,y1]=getpts;
dummy=y1;
for counter=y1:np(1,2);
   dd=np(1,1);
   cc=y1+1;
   plot(dd,cc,'r');
   hold on;
   y1=cc;
end;
 % distace between corneal anterior suface and the anteriror iris surface.
distance=y1-dummy
 % degree
tetha = atan (distance/250);
getangle = input('enter the standardised angle =')
hold on;

% vertical padding
ybelow= 500-y;
toadd = y-ybelow-1;
padbelow= zeros(toadd,500,3);
a1 = [a;padbelow];
```

```
impixelinfo;

% horizondal padding
xright = 500-x;
xleft = xright - x;
[r c] = size(a1);
padleft=zeros(r,xleft,3);
a2=[padleft,a1];
impixelinfo
hold on;

 %% Rotation of image
 difference = getangle-tetha;

a4 = a2;

if tetha~= getangle
    a2=imrotate(a4,difference,'nearest','loose');
else
    return;
end

 % removing extra rows and colums;
[rr,cc, np] = size(a2);
a3 = a2;
a3(501:end, :, :) = [];
a3(:,1:cc-500,:) = [];
ubmimage = a3;
figure, imshow(ubmimage),title('Rotated image')
```

```
impixelinfo

% intialize the x and y vectors
x = [];
y = [];

% Make the image of the size 500 x 500.
ubmimage = imresize(ubmimage, [502, 502], 'nearest');

% Enhance the contrast in the image
ubmimage = imadjust(ubmimage,stretchlim(ubmimage),[]);

% Remove noise by doing floodfill on the background
ubmimage = imfill(ubmimage,'holes');



% if not normal, ask user to trace the initial portion of the iris
if ~isequal(imagetype,0),
    figure; imshow(ubmimage);title('Trace the hidden iris');
    truesize;
    impixelinfo;
    [x,y] = getpts;
    hold on;
    plot(x,y,'r');
end;

% Convert to greyscale image
ubmimage = im2bw(ubmimage,graythresh(ubmimage));
```

```
% Find the perimeters
ubmimage = bwperim(ubmimage);

% Do morphological changes to remove noise and spurious pixels and
% clean the image
ubmimage = bwmorph(ubmimage,'fill',inf);
ubmimage = bwmorph(ubmimage,'spur',inf);
ubmimage = bwmorph(ubmimage,'clean',inf);
h_bwfig = figure; imshow(ubmimage);title(' binary image');
truesize(h_bwfig);
impixelinfo;

% Trace the front surface of the iris
% Correctness of origin selection indicator is initially set to zero
selection = 0;
msgbox('Please click on a point on the iris and then press enter',...
    'Click: Choose the Origin','none',[],[],'modal');

% Keep trying until the user selects a plausibly correct origin
while selection == 0,
    pause
    % Get the origin from user input
    origin = get(gca,'CurrentPoint');
    ynew = round(origin(1,2));
    xnew = round(origin(1,1));

    % In case of non-normal UBM images
    if ~isempty(x),
        % Check to see if the newly selected origin is to the left of the
```

```
        % selection already made. If yes, force them to reselect
        if x(end) > xnew,
            msgbox('Please choose a point to the right',...
                'Left: Choose the Origin','none',[],[],'modal');

            % If the newly selected point is to the right of the selection
            % already made, check if the new point is on the background
        elseif ubmimage(ynew, xnew) == 0,
            msgbox('The chosen origin is not on the iris. Make another
Choice',...
                'Black: Choose the Origin','none',[],[],'modal');
            % If the selection is on the iris to the right of the already
            % selected points, set correctness to 1
        else
            selection = 1;
        end;

        % In case of normal UBM images
        % Check if the new point is on the background
    elseif ubmimage(ynew, xnew) == 0,
        msgbox('The chosen origin is not on the iris. Make another
Choice',...
            'Empty: Choose the Origin','none',[],[],'modal');
        % If the selection is on the iris, set the correctness to 1
    else
        selection = 1;
    end;
end;
```

```
% Append the selected origin to the x and y coordinates
x = [x(:); xnew];
y = [y(:); ynew];
xy = [x y];

% Find the size of the x and y vectors
lenx = length(x);

% Check to see if any two rows of [x y] are equal and if yes, remove
one
xy = pegsort(xy,1,1,'ascend');
i = 1;
while i < lenx,
   i = i + 1;
   if xy(i,:) == xy(i-1,:),
      xy(i,:) = [];
      lenx = lenx - 1;
      i = i-1;
   end;
end;
clear i;

% Find the new size of the x and y vectors
[lenx dummyvar] = size(xy);
hold on;

% Starting from the last element of xy, collect all the contiguous
points
% that are white.
```

```
while (lenx < 250) & (xy(end,1) < 500)
    % The last point so far traced
    xlast = xy(end,1); ylast = xy(end,2);

    % The set of points that need to be checked in order of descending
    % priority
    pttochk = [ylast-1, xlast; ...
        ylast+1, xlast; ...
        ylast, xlast+1; ...
        ylast+1, xlast+1; ...
        ylast-1, xlast+1; ...
        ylast, xlast-1; ...
        ylast+1, xlast-1; ...
        ylast-1, xlast-1];

    % Check those point to find which ones have a white value. Use a
dummy
    % variable, int, to break the search when a white point is found and
    % move to the next point. Use a dummy variable, quitvar, to quit
    % tracing on reaching a dead end. i is the variable used to count
the
    % number of adjacent points.
    int = 0;
    quitvar = 0;
    i = 1;
    while int == 0,
        if ubmimage(pttochk(i,1), pttochk(i,2)) == 0,
            i = i + 1;
            if i > 8,
```

```
            msgbox('Seems like I have reached a deadend.
Quitting.',...
                'Quitting','none',[],[],'modal');
            int = 1;
            quitvar = 1;
            lenx = 251;
        end;
    else
        int = 1;
        xy = [xy; pttochk(i,2), pttochk(i,1)];
        ubmimage(pttochk(i,1), pttochk(i,2)) = 0;
    end;
end;
clear i;
plot(xy(:,1), xy(:,2), 'r');

% If not quitting,
if quitvar == 0,
    xysorted = pegsort(xy,1,1,'ascend');
    i = 1;
    lenxysorted = length(xysorted(:,1));
    while i < lenxysorted,
        i = i + 1;
        if xysorted(i,1) == xysorted(i-1,1),
            xysorted(i,:) = [];
            lenxysorted = lenxysorted - 1;
            i = i-1;
        end;
    end;
```

```
        clear i;
        [lenx dummyvar] = size(xysorted);
    end;
end;

% ploting the graph at origin(0,0)
% the curve value is subtracted from the intial value so that the curve
is
% brought to origin(0,0)
xy(:,1) = xy(:,1) - xy(1,1);
xy(:,2) = xy(:,2) - xy(1,2);
z = find(sign(xy(:,2))>0);
xy(:,2) = sign(xy(:,2)).*xy(:,2);
temp = xy(:,2);
temp(z) = -1*temp(z);
xy(:,2) = temp;

output = xy;
%ploting the curve in a graph
figure,plot(output(:,1),output(:,2)),%title(filename),
axis([0 500 -100 400]);

% area of the curve
area = sum(output(:,2))

cd(currdir);
```

PEGSORT

```
function output = pegsort(input, dim, num, type);
% The format of this function is
%    output = pegsort(input, dim, num, type);
% output is a sorted version of input. Sorting is of the type ('ascend'
or
% 'descend') about the dimension dim. The difference with the regular
sort
% function is that only the num-th row or col is sorted and all other
% elements in the same row or col are moved along with the sorted
row or
% col.
% Defaults:
% type: 'ascend'
% num: 1
% dim: 1 (sort by row)
% Example:
% A = [ 1 4 5; 2 7 9; 3 -1 -6]
% B = pegsort(A,1,2,'ascend')
% B = [3 -1 -6; 1 4 5; 2 7 9]

error(nargchk(1,4,nargin));
[mrows ncols] = size(input);

if nargin < 4,
   type = 'ascend'
end;
if nargin < 3,
```

```
    num = 1
else,
    if (num > mrows) | (num > ncols)
        error('"num" is greater than the size of the "input"')
    end;
end;
if nargin < 2,
    dim = 1
elseif dim > 2,
    error('This function works only with 2-dim matrices.')
end;

output = sort(input,dim,type);

i = 1;
if dim == 1,
    while i <= mrows,
        x = output(i,num);
        xind = find(input(:,num) == x);
        for j = 1:length(xind),
            output(i+j-1,:) = input(xind(j),:);
        end;
        i = i+j;
    end;
elseif dim == 2,
    while i <= ncols,
        y = output(num,i);
        yind = find(input(num,:) == y);
        for j = 1:length(yind),
```

```
            output(:,i+j-1) = input(:,yind(j));
        end;
        i = i+j;
    end;
end;
```

Publications and Presentations from Thesis:

International Publications

Krishna Kumar R, Baskaran M, Ronnie G, Roy J, Vijaya L. Gender Variation in Ocular Biometry and Ultrasound biomicroscopy of Primary Angle Closure Suspects and Normal eyes. *J Glaucoma 2007; 16:122-128.*

Krishna Kumar R, Baskaran M, Ronnie G, Roy J, Vijaya L. Inter and Intraobserver reliability of Measurement of Ultrasound Biomicroscopy Images in Primary Angle closure Suspects (PACS). *Asian J Ophthalmol.2007; 9:13-6.*

Presentations

Krishna Kumar R, Baskaran M, Ronnie G, Roy J, Vijaya L. Ocular parameters in Normal and Primary angle closure suspects among hospital based Indian subjects. All India optometry conference, Khajrahao, India, December 2005.

Krishna Kumar R, Aditya NG, Baskaran M, Ronnie G, Roy J, Vijaya L. Ocular Biometry parameters before and after Iridotomy among PACS subjects. Tamilnadu Ophthalmology Conference, Pondicherry, India, August 2006.

Krishna Kumar R, Baskaran M, Ronnie G, Raja C, Vijaya L. Cataract progression after Iridotomy among Primary angle closure suspects among Indian subjects. Asian Association for Research in Vision and Ophthalmology Conference, Singapore, March 2007.

Krishna Kumar R, Sekar U, Shonraj BG, Vijaya A, Shweta M, Sathish S, Srinivasa Varadharajan, Vijaya L. New software for quantifying Iris shapes using MATLAB 7.2. Asian Association for Research in Vision and Ophthalmology Conference, Singapore, March 2007

Brief biography of the candidate

Ramani Krishna Kumar obtained his degree in Optometry in 1992 from Elite School of Optometry, Chennai, India. He joined Sankara Nethralaya, Chennai, as an optometrist in October 1992. Since then he has been working in the organization without any interruption. He did his M.Phil in Optometry between 1996 and 1998 from the Birla institute of Technology and Science, Pilani. In 1997, he became head of the department of Optometry in Sankara Nethralaya and was holding the post until 2004.From 2004, he is the Principal, Elite School of Optometry. He is also in the faculty for training optometry students in Optometry clinical skill, teaching courses on Clinical examination of visual system; Recent advances in optometry and Visual optics. He was also teaching Geriatric Optometry and Binocular vision until last year to optometry students. He is also a visiting lecturer for certificate course in occupational health conducted by Sri Ramachandra Medical College and Research Centre, Chennai for the past 3 years. His research interests are psychophysical diagnostic aspects of open angle glaucoma, characteristics of primary angle closure suspects after laser iridotomy, quality of life among villagers after cataract surgery, and occupational visual standards. He has five publications in International journals. He has also contributed to national and In-house scientific journals. He has to his credit presentations in international and national conferences.

Brief biography of the supervisor

Dr. L Vijaya is the Director of Department of Glaucoma, Medical Research Foundation, Sankara Nethralaya, Chennai. She did MBBS (1980) from S V Medical College, Tirupati, DO - Ophthalmology (1984), and M S – Ophthalmology (1985) from Kurnool Medical College, Kurnool. She had specialized training in Vitreoretinal surgery (1986) at Sankara Nethralaya, unit of Medical Research Foundation. Since 1987, she was working as consultant in Sankara Nethralaya. . Many postgraduates have been trained by her. She has published more than 50 papers and 2 chapters in textbooks. She has presented papers in various national and international conferences and has delivered lectures as an invitee guest speaker. She is the principal investigator in a major epidemiological project on glaucoma called Chennai Glaucoma Study. She is in the editorial board of Asian journal of Ophthalmology and Tamilnadu Ophthalmology Association Journal. She is a reviewer for the following journals: Indian Journal of Ophthalmology (IJO), British Journal of Ophthalmology (BJO), Investigative Ophthalmology and visual Science (IOVS), Journal of Glaucoma (JOG), Journal of Postgraduates & Medicine (JPGM), British Medical Journal (BMJ), Clinical Ophthalmology and Ophthalmic Epidemiology BioMed Central Ophthalmology (BMC). She is a member of the Glaucoma Society of India, All India Ophthalmological Society, Association of Research in Vision and Ophthalmology (ARVO), SEAGIG (South East Asian Glaucoma Investigative Group), TamilNadu Ophthalmology Association (TNOA), and the AIGS-Angle Closure Glaucoma Consensus Group.

UBM images) had to be done before calculating the ISF. Inter and Intra observer reliability of the parameter among normal angle eyes and narrow angle eyes showed appreciable reliability like other UBM parameters documented herein earlier (Chapter II). On analysing the ability of the ISF to differentiate normal angle eyes from narrow angle eyes, it was found that the parameter indeed could differentiate. UBM parameters as given by Pavlin et al. (16) were measured manually, whereas the ISF measurement was a more objective method.

Conclusion:

The measurement of ISF using MATLAB 7.2 was found to have shown good inter and intra observer reliability. ISF could differentiate between normal angle eyes and narrow angle eyes. ISF in normal angle eyes was lower than that in eyes with narrow angle.

Limitations of the study:

The need for manual iris tracing in closed angle eyes was one of the limitations in the present software. Also the patient's clinical data, namely intraocular pressure, anterior chamber angle, anterior chamber depth, axial length, lens thickness, cup to disc ratio, and severity of the disease, were not taken into consideration. In addition, sample size for the third part of the study was small.

Specific contribution:

Development of new software to measure the area beneath the anterior iris curvature thereby quantifying the iris shape. A semi-automated measuring technique with good reproducibility. Possibly an additional parameter to Pavlin's UBM parameters, especially among narrow angle eyes.

***Future scope of study*:**

Future studies using this software and comparing other parameters measured using conventional techniques with ISF may help us decide on the usage of ISF in clinical practice. A study with a larger sample size on different types (open angle, angle closure, pigmentary) and stages of glaucoma can help us evaluate the efficacy of the software in distinguishing one condition from the other. The effect of iridotomy on iris configuration before and after iridotomy among narrow angles and pigmentary glaucoma can be studied using this software.

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