Longitudinal Assessment of Optic Nerve Head Progression in Glaucoma: A Population Based Study

Thesis

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By

Ramesh S Ve

Under the supervision of

Dr Ronnie George

Birla Institute of Technology and Science

Pilani (Rajasthan) India

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Dedicated to my family and teachers who were inspirational and continuously guiding in bringing about the change in my life

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ABSTRACT

Aim: To determine the structural changes using Scanning Laser Ophthalmoscope (Heidelberg Retinal Tomography: HRT III), Optical Coherence Tomography (Stratus OCT), Scanning Laser Tomography (GDx VCC) and functional damage estimated with Humphrey Visual Field (HVF (24-2) SITA Standard) and Frequency Doubling Perimetry (FDP) - on a population based cohort of subjects with primary glaucoma and ocular hypertension (OHT).

Methods: Detailed periodic clinical examination of subjects with primary glaucoma, OHT and an age matched control group was done over a 5 year follow up. Subjects underwent bi annual follow-up and controls had annual visit. Humphrey visual field examination (HVF 24-2, SITA Std), GDX, HRT and OCT was performed during every visits. Functional progression on HVF was determined using the point wise linear regression (Progressor) analysis. The clinical data obtained from the optic nerve head imaging tools (HRT, GDx and OCT) were considered, progression or change analysis was obtained from all instruments. Subjects were classified into two groups' progressed or non progressed based on functional loss on HVF and FDP.

Main outcome of this study is to investigate the efficacy of Stereo ONH photography, GDx, OCT and HRT in detecting progression of glaucoma and their relationship with functional loss as assessed by HVF & FDP in a subset of population based cohort with Glaucoma, at risk and controls.

Results: A total of 54 eyes of 30 subjects with primary glaucoma (open angle 16 (53.3%) and angle closure 14 (46.7%)), 54 eyes of 28 OHT subjects and 18 eyes of 10 age matched

control subjects were included for analysis. The mean follow-up period was 58.34 (SD: 3.76) months. 7 (13%, 95% CI: 6.4 – 24.4) primary glaucoma patients showed perimetric progression. There was no significant difference in the progression rates among the POAG and PACG groups in all the structural and functional technique. Older age, RNFL thickness on GDx and CSM in HRT were associated with the progression among primary glaucoma subjects over 5 years follow up period.

Planimetric values estimated with Cyoptique GL, small discs were taken as those with a disc area less than 2.21 mm^2, moderate disc as between 2.21 and 2.77 mm^2 and large discs when disc area was greater than 2.77 mm^2. 50% (95% CI: 41.4 to 58.6) of the study population had small disc followed by moderate disc (31.7%, 95% CI: 24.3 to 40.3) and Large discs (18.3%, 95% CI: 12.5 to 25.9).

The Generalized Linear Regression model (GLM) for significant change ($p<0.05$) for longitudinal follow up for clinical progression were observed for CA (R=0.276), RA (R=0.346), CSM (R =0.567), HVC (R=0.236), mean RNFL (R=0.335), FSM (R=0.346) and RB (R=0.296). These parameters of HRT III were used to assess progression. In both the primary glaucoma group and at risk population CSM showed statistically significant change and the RB discriminant function showed significant change in the at risk population (p=0.003) (-0.39 to -0.08). The long term variability was observed for CSM (p=0.001, 95% CI of difference: -0.56 to -0.03) and other HRT parameters did not show significant variability. CSM also showed significant change between the progressed (p=0.001, 95% CI of difference: -0.05 to -0.02) and non progressed (p=0.008, 95% CI of difference: -0.09 to -0.01) groups too.

In GDx VCC, GLM showed significance for NFI (R: 0.389, p<0.001) and Average RNFL thickness (R: 0.527, p<0.001). There was a significant difference in the change in the average RNFL among the primary glaucoma (0.001, 95% CI 3.27 to 6.43) and at risk group (0.001, 95% CI 1.23 to 4.47). There were significant differences between OHT and Glaucoma suspects (p<0.05). Change in NFI did not show statistically significant difference across the study groups. There was an increase in the change in RNFL thickness with increasing disc size, the distribution was statistically significant.

The GLM showed significant average RNFL thickness (R: 0.577, p<0.001) in OCT. There was a significant difference in the change in the average RNFL among the primary glaucoma (0.001, 95% CI 4.20 to 8.64) and at risk group (0.001, 95% CI: 4.85 to 8.42). Among 12 (80.0%, 95% CI: 54.8 to 92.9) of the 15 eyes of primary glaucoma who progressed, 77.8% (95% CI: 62.4 to 93.2) had small disc size. Rate of RNFL loss was significantly highest among the progressed group (p=0.001, 95% CI 5.82 to 8.22). The RNFL differences varied with increasing disc size, the distribution was statistically significant.

In HVF, there was significant difference (p<0.05) in the rates of progression estimated by each of the following techniques: Hodapp Anderson and Parrish (HAP) classification, Brusini GSS, including advanced strategies such as Progressor and Visual field Index (VFI) in Glaucoma Progression analysis.[24,26] 12 (9.5%, 95% CI: 5.5 to 15.9) showed progression in both Brusini, VFI and Progressor strategies. 8 (6.3%, 95% CI: 3.3 to 12) showed progression based on HAP classification. The distribution was significantly different (p<0.05) among the various study groups. There was a significant difference in the

rate of progression in the perimetric progressed group 1.79 (0.96, p=0.001 (95% CI: 1.18 to 2.40) dB/year. Progressor software determines the slope of the progressed point in a visual field as compared to the overall data. The mean slope of progressed points: -2.75 (SD: 1.8) and mean slope of overall field: 0.177 (SD: 0.97), the difference was statistically significant (p<0.001, (95% CI of diff. -3.46 to -2.38)). The mean VFI at baseline was 97.02 (2.18) and at final follow up was 94.67 (4.41), the difference was statistically significant (p=0.001, 95% CI: 1.52 to 3.18). The mean VFI at baseline for primary glaucoma, at risk and control group were 96.78 (2.27), 97.24 (2.18) and 97.11 (1.93) respectively. VFI did not show statistically significant difference in baseline (ANOVA p=0.540) and follow up visit (ANOVA p=0.954). Adjusting for age related normal variability there was a significant change in slope determined by HVF glaucoma progression analysis for the overall study population 2.35 (4.72) (p<0.001, 95% CI of diff 5.35 to 8.31) and for progressed group 6.83 (2.33) (p=0.001, 95 % CI of diff 5.35 to 8.31).

In the current study we report that long term change in MD, PSD and time in FDP did not vary significantly, though among the HVF progressed group the PSD showed a significant trend p=0.001 (95% CI of diff. 0.75 to 2.12). Point wise linear regression analysis was performed for each of the 19 FDP locations using threshold from each follow-up visit. The slopes of the PLR for individual point varied between the study groups and the variability was higher for peripheral points as compared to central points. Progression based on PLR model was determined if the individual slopes were significantly different from the age matched control data. The progression in cluster of points was observed in 23 (18.25%, 95 CI: 12.5 to 25.9) FDP reports using the PLR model. Among those who had progressed in advanced strategy 52% (95 % CI: 33 to 71) also progressed in FDP Brusini strategy and

35% (95% CI: 18 to 55) progressed in HVF advanced strategy. None showed progression in all the perimetric strategies and methods. Among the non progressed group, only 6.8% (95% CI: 3.3 to 13.4) showed progression in FDP Brusini classification system.

Conclusion: In this population based study, 13% (95% CI: 6.4 – 24.4) of the Primary Glaucoma showed perimetric progression. HRT showed higher progression (37%, 95% CI: 25.4 to 50.4) as compared to other imaging techniques. Older age, RNFL thickness on GDx and CSM in HRT were associated with the progression among primary glaucoma subjects over 5 years follow up period. Studies have also reported that poor control of IOP as a significant risk factor for progression. Though in the current study control of IOP did not emerge as a significant risk factor, this could be attributed to early stage of glaucoma and to the poor persistence and compliance rates noted in the study group. In this population based cohort, HVF progression was observed in only 9.3% (95% CI: 5.1 to 16.2%) and FDP point wise linear regression method (18.3, 95% CI: 12.5 to 25.9) showed higher progression rates.

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ABBREVIATIONS

AGIS	Advanced Glaucoma Intervention Study
ANOVA	Analysis of variance
CA	Cup Area
CCT	Central Corneal Thickness
CDR	Cup to Disc Ratio
CEDIS	Chennai Eye Disease Incidence Study
CGLONHIS	Chennai Glaucoma Longitudinal Optic Nerve Head Imaging Study
CGS	Chennai Glaucoma Study
CI	Confidence Interval
CIGTS	Collaborative Initial Glaucoma Treatment Study
CNTGS	Collaborative Normal-Tension Glaucoma Study
CSM	Cup Shape Measure
DA	Disc Area
EMGT	Early Manifest Glaucoma Trial
FDP	Frequency Doubling Perimetry
GDx VCC	Scanning Laser Polarimetry
GHT	Glaucoma Hemi Field Test
GLM	Generalized Linear Regression Model
GlPA	Glaucoma Progression Analysis in OCT
GPA	Guided Progression Analysis in GDx
GSS	Glaucoma Staging System
HAP	Hodapp Andersons Parish

HRT III	Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography
HVF	Humphrey Visual Field
IOP	Intraocular Pressure
ISGEO	International Society of Geographical and Epidemiological Ophthalmology
ISNT rule	Inferior Rim>Superior Rim>Nasal Rim>Temporal Rim
LOCS	Lens Opacity Classification System
MD	Mean Deviation
NFI	Nerve Fiber Indicator
OCT	Optical Coherence Tomograhy
OHT	Ocular Hypertension
OHTS	Ocular Hypertension Treatment Study
ONH	Optic Nerve Head
p	Probability
PACG	Primary Angle Closure Glaucoma
PLR	Pointwise Linear Regression
POAG	Primary Open Angle Glaucoma
PSD	Pattern Standard Deviation
R^2	Co-efficient of Determination
RNFL	Retinal Nerve Fiber Layer
SD	Standard Deviation
TCA	Topographic Change Analysis in HRT III
VES	Vellore Eye Study

CHAPTER 1

Introduction and Review of Literature

1.1 ASSESSING PROGRESSION IN GLAUCOMA

Glaucoma is the second leading cause of blindness worldwide. About 11.2 million persons are believed to be suffering from glaucoma, it is responsible for 13% of blindness in India and is acknowledged to be one of the major causes of visual loss in both developed and developing countries.[1] Early detection of glaucoma ensures better visual prognosis. Primary glaucoma is defined as an optic neuropathy (ONH) with typical disc and field changes for which intraocular pressure (IOP) is a causal risk factor.[2] Identifying the functional visual component as well as structural changes is essential in evaluating glaucoma progression. New techniques of testing and evaluating visual fields (Progressor, Visual Field Index), the optic-nerve head (Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany), and the retinal nerve fiber layer (Scanning laser polarimetry (GDx VCC; Carl Zeiss Meditec Inc., Dublin, CA, USA) and Optical coherence tomography (OCT; Stratus OCT, Carl Zeiss Meditec Inc) offer exciting opportunities to more accurately identify glaucoma progression.[3]

Progression is identified with either an 'event' analysis or with a 'trend' analysis in perimetry [4] and for imaging tools change may be identified at the level of the pixel or estimated parameter.[5] Figure 1.1 A, shows sample report of progression assessed using Glaucoma Progression analysis and Progressor software. Studies have shown that perimetric progression shows significant variability and also varies with the algorithm used.[6] Example of structural changes assessesed using Glaucoma Progression analysis in all the three imaging tools is shown in Figure 1.1 B. Studies have demonstrated that the newer quantitative techniques (GDx, OCT and HRT) were no better than ONH evaluation at

distinguishing normal eyes from those with early to moderate glaucoma.[7] However, a combination of the imaging methods significantly improved this capability.[8] Of the newer techniques, the ability to discriminate between normal and glaucomatous eyes and improved measurement repeatability makes HRT a good candidate for progression detection. [7-10] Vellore Eye Study (VES), [11] a population based study, report 5 year perimetric progressions rate among ocular hypertensives and glaucoma patients on a small cohort. But, there is little or no literature in assessing progression using all the three newer imaging tools in a population based study.

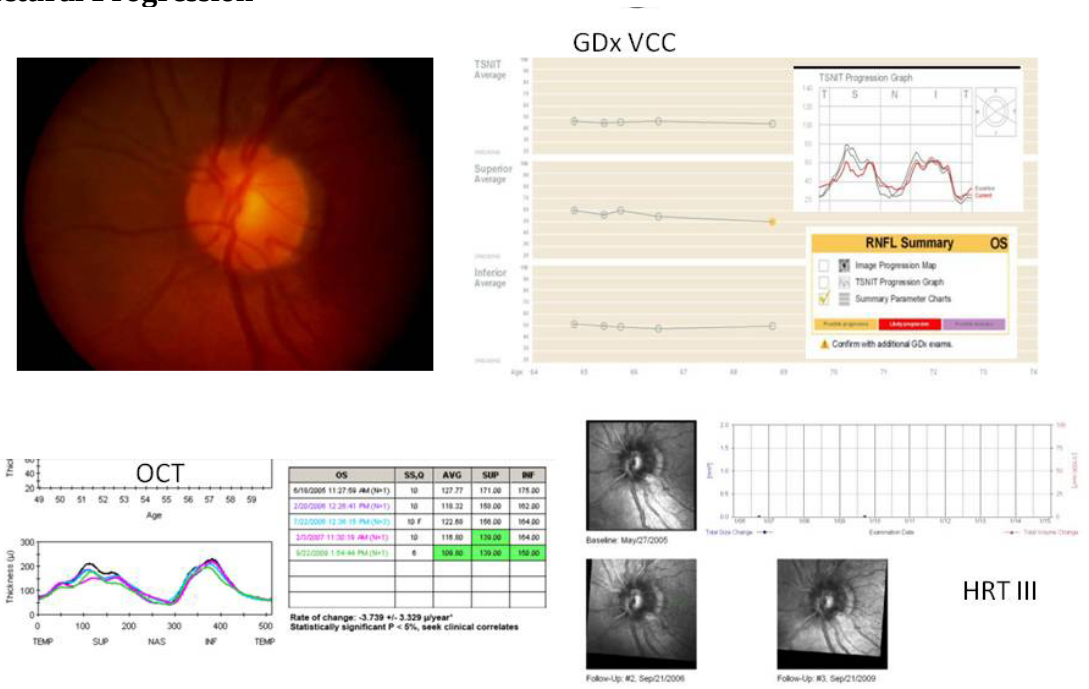
Structural and functional Progression

(A) Structural progression assessed using GDx VCC, OCT and HRT III.

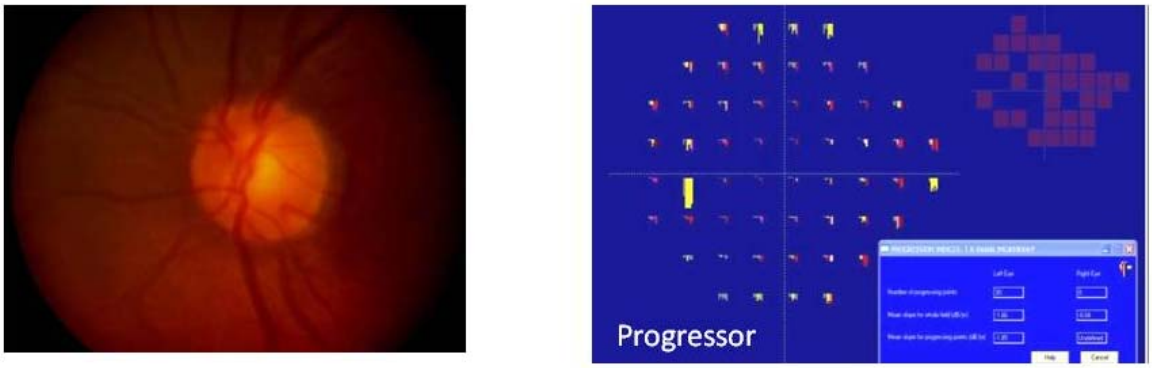
(B) Functional Progression assessed using Glaucoma progression analyzer and Progressor. Progression in this patient noted in perimetric techniques and only in GDx.

(Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT)), (Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Humphrey Visual field (HVF))

Structural Progression



Functional progression



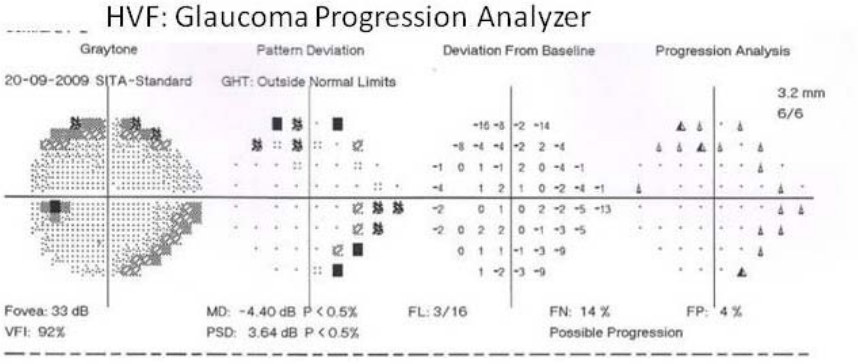


Figure 1.1: Structural and functional Progression

1.2 LITERATURE REVIEW

1.2.1: The Burden and Clinical Management of Glaucoma

The prevalence of primary glaucoma varies significantly between the rural and the urban Indian population. Chennai Glaucoma Study was a population based study in a south Indian population of over 40 yrs of age. We report that the prevalence of Primary open angle glaucoma (POAG) to be 3.51% and 1.62% in the urban and rural population respectively. [12] Though the prevalence of Primary Angle Closure Glaucoma (PACG) were similar (<1%), the rates of blindness are high among the urban subjects (5.9%) as compared to rural population (2.9%).[13] The rates of those at risk (Ocular Hypertension (OHT), Primary angle closure (PAC)) were high among urban population. Increasing age has been predominantly associated with prevalence of glaucoma. [13] The knowledge and awareness to glaucoma was 8.7% and 13% in a subset of this urban cohort. [14] Thus considering age related risk and poor awareness among the common people, timely detection and proper management could be achieved only through comprehensive ophthalmic evaluation including detailed history, slit lamp biomicroscopic evaluation, Intra ocular pressure (IOP) estimation, Gonioscopy, stereoscopic optic nerve head (ONH) evaluation. Perimetric techniques and advanced ONH imaging tools play an important role in early detection and in assessing progression of disease, so the treatment regime could be modified appropriately.

Glaucomatous ONH damage is monitored in a regular clinic by performing slit lamp biomicroscopy with +90/+78 D lens. In recent years, various objective methods have become available that provide digital images of the ONH and RNFL.[2] The various techniques available for optic disc evaluation include: Stereo Optic disc and RNFL photographs, planimetry, nerve fiber layer analyzer (GDx): GDx NFA and VCC, optical

Coherence Tomography (OCT), heidelberg retinal tomograph (HRT).[3] These techniques provide repeatable, reproducible measures and their ability to detect glaucoma has been described.[2,3]

1.2.2: ASSESSING PROGRESSION: FUNCTIONAL CHANGES & RISK FACTORS

Disease progression in glaucoma is common and despite treatment, most patients still progress. A retrospective community-based longitudinal study, from Olmsted County in the United States showed that at 20 year follow up, the Kaplan–Meier cumulative probability of glaucoma-related blindness in at least one eye was estimated to be 27%, and 9% in both eyes. Risk of progression of glaucoma leading to blindness was high even among those who had treatment. The study showed that rates of progressions were limited if IOP was controlled. [15]

Early Manifest Glaucoma Trial (EMGT) followed a cohort of 118 control patients for at least 6 years without treatment until the patient progressed. The mean overall progression rate was 1.08 dB per year (SD±2.07), the values for High tension Glaucoma (HTG), Normal Tension Glaucoma (NTG), and pseudo exfoliation glaucoma (PEXG) were 1.31 (SD±1.93), 0.36 (SD±0.94) and 3.13dB (SD±3.69) respectively. Progression was significantly faster in older patients (median rate, 1.48 dB per year) than in younger ones (median rate, 0.60 dB per year). The study estimated that the progression from normal visual field to blindness takes approximately 25 years, with PEXG patients progressing significantly faster than NTG and HTG patients. The study emphasizes the importance of identifying risk factors such as pseudo exfoliation and appropriate management of the disease.[16] Chauhan et al[17] describe the importance of number of follow-up required to truly

estimate progression in HVF and for a given number of exams, factors such as age at baseline examination and rate of progression should be considered for analysis. A progression of over 2 dB per year (a high progression rate) is reported to be high risk for visual disability among patients with early glaucoma. The study also suggest that 5-6 field tests, within the first three years would help in detecting this progression, recommended to repeat testing every 4 months during the first 2 years after diagnosis or to test twice per year for the first 3 years. They report that use of short-wavelength automated perimetry and frequency doubling technology, retinal nerve fibre layer, or optic disc examinations is not as suited to measure rates of HVF progression and the role of these tests replacing HVF is not clearly understood.[17] The importance of measuring HVF progression rates and its role in assessing progression are now well recognized. Data from important glaucoma clinical trials available to date such as EMGT,[18] Collaborative Initial Glaucoma Treatment Study (CIGTS),[19] Advanced Glaucoma Intervention Study *(*AGIS*),*[20] Ocular Hypertension Treatment Study *(*OHTS*)*[21] studied the role of various risk factor with HVF progression, results confirm that elevated IOP as a major risk factor, the reports differed in identifying additional risk factors such as VF damage, age, pseudo exfoliation, or presence of disc hemorrhages. All trials, except for Collaborative Normal-Tension Glaucoma Study (CNTGS),[22] show evidence for the importance of IOP reduction in management of OHT/POAG.

Glaucoma progression rates vary significantly among patients and risk factors do not identify this accurately. Therefore, target IOP needs to be individualized and in case of a significant progression a lower target should be sought. After a sufficient number of HVFs and when rate of progression is known, it should be the main factor to set or adjust the target

IOP. This approach should result in an earlier and a more aggressive treatment of at risk patients, but will also mean that patients with no direct risk for a faster progressive disease can be managed with less frequent visits and with higher target IOP. In case of a further significant progression, treatment should be adjusted and a lower target IOP to be set.[23] Lee et al,[6] compared the methods used to assess progression in clinical trials and reported limited comparability between the various strategies. The challenge of identifying early progression has contributed to the development of newer algorithm and methods to assess progression.

Viswanathan et al [24] described the efficacy of point wise linear regression (PLR) model to estimate progression in HVF. Progression criteria for PROGRESSOR were (1) inner points: slope < −1 dB/year, $p < 0.05$ and (2) edge points: slope < −2 dB/year, $p < 0.05$. [24] Strouthidis NG et al [25] followed 108 OHT and 21 control subjects with Progressor and report that the HVF progression detection was significantly higher with PLR method and confirmation of the defects further improved the results. Bengtsson and Heijl [26] developed a new visual field index (VFI), perimetric rate of progression with HVF are quantified, and has been implemented in the Humphrey Field Analyzer (Carl Zeiss Meditec Inc., Dublin, CA, USA). VFI replaces the mean deviation with a more comprehensible unit defined as percentage of a full field where 100% represents a normal VF and 0% represents a perimetrically blind field. The progression analysis also includes the short-term progression rates to predict long-term HVF outcomes. HVF progression rates were calculated from 100 patients with at least 10 HVF tests over an average period of about 8 years. Final VFI was predicted based on the first 5 HVF test results and also by using all viable test results from the observation period. Median VFI progression rate was found to be 1.1% per year using

both approaches. The study concluded that information from the first 5 HVF tests was a reliable predictor for future HVF loss in most patients.[27]

1.2.3: ASSESSING PROGRESSION: STRUCTURAL CHANGES & RISK FACTORS

Heidelberg Retinal Tomograph (HRT) has been in use for more than 20 years. It provides reproducible measurements of the surface height of the optic nerve head (ONH) and parapapillary retina.[28] Progression may be identified with an 'event' analysis or with a 'trend' analysis; change may be identified at the level of the pixel or parameter.[5, 7] Recent analysis in HRT evaluates topographic changes of the ONH to detect progression of glaucoma.[29, 30, 31] Although different stereometric parameters have been suggested as useful markers of progression, some studies have suggested that the neuroretinal rim area (RA) and Cup Shape Measure (CSM) are the most reliable and reproducible measure for detection of change.[32, 33, 34]

Topographic Change Analysis (TCA), was tested in a longitudinal data set of 77 patients with early glaucomatous visual-field loss and compared with progression determined from visual fields. [31] Progression was identified by visual fields alone in 4% of patients, by both visual field and HRT in 29%, and by HRT alone in 40%, suggesting that SLT may be more sensitive at detecting progression than visual-field analysis. In a clinical series, however, the true progression rate is unknown and it is possible that the visual field and imaging thresholds for change were not matched for specificity (false positive rates). Progression was better assessed using sectoral based analysis and the cupshape measure proved to be better predictors in a cohort of ocular hypertensives over a ten year follow up.[30, 31]

Heiko et al[34] reported that rate of change CSM showed significant linear association with progression in 108 OHT who converted to POAG over a ten year follow up period. Strouthidis et al[35] report that the rate of change of RA was higher compared to detection of progression by visual fields in patients with ocular hypertension. However, absolute values change were not reported, See et al[36] observing 94 glaucoma patients and 54 normal controls over 8.6±2.9 years, found a rate of change (RA loss/ year) of 0.0053 and 0.0012 mm^2/year, respectively.

The need to trace the outline of the optic disc, i.e. contour line is a shortcoming of the HRT. Alternative approaches for detecting progression in series of HRT images, such as the topographic change analysis,[31] the glaucoma probability score,[37] and statistic image mapping,[38, 39] have been developed to overcome this limitation. These methods have been reported to have moderate agreement among each other and have poor agreement with clinically assessed change in optic disc stereophotographs.[5, 39] Major advantage of the HRT compared to other imaging devices, is that latest commercially available versions of the instrument have shown relatively good compatibility with older ones, thus making it feasible to obtain long term analysis in detecting progressive glaucoma.

Glaucoma Diagnostics (GDx) is a confocal scanning laser ophthalmoscope with an integrated polarimeter that measures the amount of retardation (phase shift) of a polarized near-infrared laser beam as it passes through the RNFL.[40] Changes in parapapilary RNFL have been suggested to be the earliest sign of glaucoma development and RNFL changes precede visual field loss.[41] Gunvant et al[42] derived limits of change from a test retest study in

27 normal eyes of 16 subjects. Of 17 eyes with a disc hemorrhage, followed for an average of 30.7 months, five (29%) exhibited change in GDX parameters greater than the limits for change. Groningen Longitudinal Glaucoma Study showed that the performances of FDT and GDx are approximately equivalent in terms of sensitivity, specificity and area under the ROC curve.[43] In glaucoma suspects, GDx in particular yielded a rather high percentage of positive test results. The majority of these positive test results could presumably be false-positive results rather than results indicating preperimetric glaucoma.[44]

The GDx software has been recently upgraded with the addition of a guided progression analysis (GPA). The GPA software compares GDX images acquired during follow-up and reports a summary analysis for progression in an individual eye after automated consideration of the expected test–retest variability. Studies show that GPA identifies a significant proportion of glaucoma progression with 50% sensitivity and 96% specificity compared with optic disc stereophotographs and visual fields.[45] Repeatability of GDx Variable Corneal Compensation (VCC) was demonstrated to be stable for all stages of disease severity with a repeatability coefficient within 4 mm.[46] Recently, several authors calculated rates of change for the GDx. Using GDx VCC, Medeiros et al[47] among suspected and established glaucoma, reported an average loss of RNFL thickness of 0.70 mm/year in glaucoma progressors as compared to 0.14 mm/year in non-progressors ($P<0.001$), very similar to rates of change reported elsewhere by the same group (0.65 and 0.11 mm/year, respectively).[48] To date, four longitudinal studies have evaluated GDx Enhanced Corneal Compensation (ECC) for detection of progression in glaucoma, with two of them comparing measurements obtained by GDxECC with GDxVCC. The studies report better disease

progression detection rates with ECC, as the newer software is less affected by atypical retardation patterns.[5, 48]

Optical Coherence Tomography (OCT) is a non-contact and non-invasive technique for examination of the human retina. The instrument uses a super luminescent diode light and works similar to a B-scan ultrasound, using light instead of sound. There is limited longitudinal data on newer spectral-domain OCT and Time domain OCT measure are prudent for estimating progression in Glaucoma.[49, 50] Longitudinal study in glaucomatous and glaucoma suspect subjects, Sixty-four eyes of 37 subjects were imaged over a median of 4.7 years. OCT progression was defined as RNFL thinning of at least 20 μm (twice the device reproducibility error) from baseline in two of three consecutive follow-up scans. Visual-field progression was defined as a reduction in mean deviation (MD) of 2 dB from baseline in two of three consecutive visits. Twenty-two percent of eyes progressed by OCT alone, 9% by visual field alone, and 3% by OCT and visual field.[51]

Wollstein et al[52] with an event-based approach concluded that the OCT was more sensitive than standard visual fields for the detection of progression. Medeiros et al[53] evaluated the ability of RNFL thickness, ONH, and macular thickness measurements to detect glaucomatous progression. In their study, progression was determined by HVF and longitudinal assessment of optic disc stereophotographs. Studies using the Glaucoma Progression analysis show that average RNFL thickness, a rate of change of 0.72 mm/year for the progressors compared with 0.14 mm/year in non-progressors was reported. The authors found a wide variation of rates of change, can be explained by individual characteristics, such as stage of disease and response to treatment, it is possible that non-centered scans and signal strength affected the ability to detect change.[54, 55, 56]

Micheal JG et al[57] in a clinic based study, demonstrated that the newer quantitative techniques (GDx, OCT and HRT) were no better than assessment of stereo optic disc photography by experienced observers at distinguishing normal eyes from those with early to moderate glaucoma. However, a combination of the imaging methods significantly improved this capability.[47, 58] The five year progression data from the population based study, Vellore Eye Study, reported perimetric progression of 29 OHT subjects to POAG to be 17.4% (3.5% per year). [11] They also report that 22% of the 50 PAC suspects progressed to PAC [59] and of the 28 PAC subjects 28.5% progressed to PACG [60] in this five year longitudinal study. There is little or no literature in assessing progression using all the three newer imaging tools. The growing evidence about the wide variability in disease progression and outcomes between patients means that it is essential to study the risk factors that influence this variability. More knowledge in this field will help the clinician to identify the patients who require more care and might need a more aggressive treatment to achieve a better outcome.

1.3 GAP IN EXSISTING RESEARCH

`Studies on hospital based population have shown that these newer imaging tools are good predictors of early ONH changes.[47, 51] There is little or no longitudinal data from population-based studies on ONH progression. There is also little information on the utility of these techniques in detecting disease progression in a population based setting. The aim of the study was to estimate the prevalence of glaucoma in rural and urban population of the southern Indian state of Tamil Nadu. The current study is a part of the Chennai glaucoma follow-up study.

The main outcome of this study is to investigate the efficacy of Stereo ONH photography, GDx, OCT and HRT in detecting progression of glaucoma and their relationship with functional loss as assessed by HVF & FDP in a subset of population based cohort with Glaucoma, at risk and controls.

1.4 STUDY OBJECTIVES

a. To determine the progression rates and structural changes in the optic nerve head (ONH) in population based cohort of subjects with primary glaucoma and ocular hypertension by using serial Stereo Photography, Scanning Laser Ophthalmoscope (Heidelberg Retinal Tomography), Optical Coherence Tomography (OCT), Scanning Laser Tomography (GDx) and functional damage by using Frequency Doubling Perimetry (FDP) and HVF (24-2) SITA Standard white on white perimetry.

b. To estimate the relationship between progressing visual field loss and change in ONH parameters assessed with each of these imaging systems

c. To assess the potential utility of each of these techniques for glaucoma detection and assessing progression, in a population based study.

CHAPTER 2

Methodology

2.1 OVERVIEW OF THE CHENNAI GLAUCOMA LONGITUDINAL ONH IMAGING STUDY (CGLONHIS)

The Chennai Glaucoma Study (CGS) is a population based cross sectional study designed to estimate the prevalence of glaucoma in a rural and an urban population aged 40 years and above in a southern Indian state of Tamil Nadu. The methods and design of the CGS are described in detail elsewhere.[61] A brief note, urban sampling was done using a multistage sampling procedure. The total population of Chennai was 3.8 million, 22% of the population was above the age of 40 years as per the 1991 Census of India report.[62] Based on this distribution, 4840 subjects aged 40 years or more were expected in our study area. 4800 persons were enumerated each in rural and urban areas. The city is divided into 10 corporation zones comprising 155 divisions as in the year 2001. One division was randomly selected from each of the 10 zones and 5 divisions were randomly picked from those 10 divisions. A simple random sample of 960 each from the 5 selected divisions was enumerated. Trained social workers performed the enumeration by door-to-door survey.

The Chennai Glaucoma Study (CGS) was started in June 2001 and the rural arm was completed in January 2003, the urban division of the study was examined between May 2002 and May 2004. Written informed consent was obtained from all subjects and the study was performed in accordance with the tenets of the Declaration of Helsinki.[63] CGS and its subsequent follow-up studies were approved by the institutional review board, Vision Research Foundation, Chennai. All subjects underwent a comprehensive ophthalmic evaluation. The baseline data for the current study was obtained from urban arm of CGS. (Figure 2.1)

Patients with primary glaucomas and ocular hypertension (OHT), as defined by the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification[64], from the urban arm of the population based Chennai Glaucoma study were included. ISGEO suggested a new classification for the diagnosis of glaucoma in population based prevalence surveys. In this classification, glaucoma is diagnosed on the basis of both structural and functional evidence of glaucomatous optic neuropathy. In the population based subset, the glaucomas and OHT would be classified based on the distribution of vertical cup to disc ratio (VCDR) and intraocular pressure (IOP) was analysed, from those healthy subjects with reliable and normal suprathreshold visual field tests using frequency doubling perimetry from the baseline study. Controls were periodically examined and the data was used to adjust for the inherent variability in psychophysical testing and age related nerve fiber layer loss.

The Chennai glaucoma follow-up study (Figure 2.1): Of 3851 (80.22 %) subjects who participated in the study from the five urban areas, persons with glaucoma and/or at risk of glaucoma (n=469) and a subset of age-matched controls (n=177) were eligible for the follow up study. This study commenced on February 2004, aimed to provide information regarding pattern and the progression of the glaucoma in our population. A total of 250 subjects from the follow-up study were enrolled for the proposed research work: The Chennai Glaucoma ONH Imaging Study: 40 primary angle closure glaucoma patients (PACG), 65 primary open angle glaucoma patients (POAG) and 65 OHT and 80 age matched controls from the Chennai Glaucoma follow-up Study were selected. The final visit for the Chennai Glaucoma Longitudinal Optic Nerve Head Imaging Study (CGLONHIS) was obtained during the Chennai Eye Disease Incidence Study (CEDIS): (Figure 2. 1.1) The

CEDIS participants from the CGS population were once again examined during the incidence study in 2008 to 2010. All subjects underwent comprehensive eye examination and the study cohort also underwent advanced imaging and perimetry tests. (Figure 2.1.2)

CGLONHIS was on the whole performed as a 5 year periodic follow up study: Bi annual follow-up for cases and once yearly for control subjects. Cases (Glaucoma Subjects) with at least 5 follow-up visits and control with at least 4 follow-up visits were included for analysis. Table 2.1.1, list the clinical and imaging based inclusion and exclusion criteria. Among both cases and controls, only subjects with good quality in imaging tests and ophthalmic photography were included for the analysis. Subjects who had undergone cataract or glaucoma surgery during the study period were excluded.

The clinical data obtained from the optic nerve head imaging tools (HRT, GDx (VCC) and OCT) were analyzed for image quality and eligible images are considered for further analysis. Contour line on the HRT was marked based on stereo optic disc photographs. Progression on all the three imaging tools were assessed using the progression algorithm available in each and significant change on pixel analysis were obtained for all instruments.[47, 51] Subjects were classified into two groups: progressed or non progressed based on functional loss on HVF. Reliable and repeatable visual field defects without any learning or artefactual defects were included. Subject with significant short term fluctuation were excluded. (Table 2. 1.1) Data from subjects who had 5 year follow up and all those who had met the listed inclusion criteria were eligible for the CGLONHIS analysis.

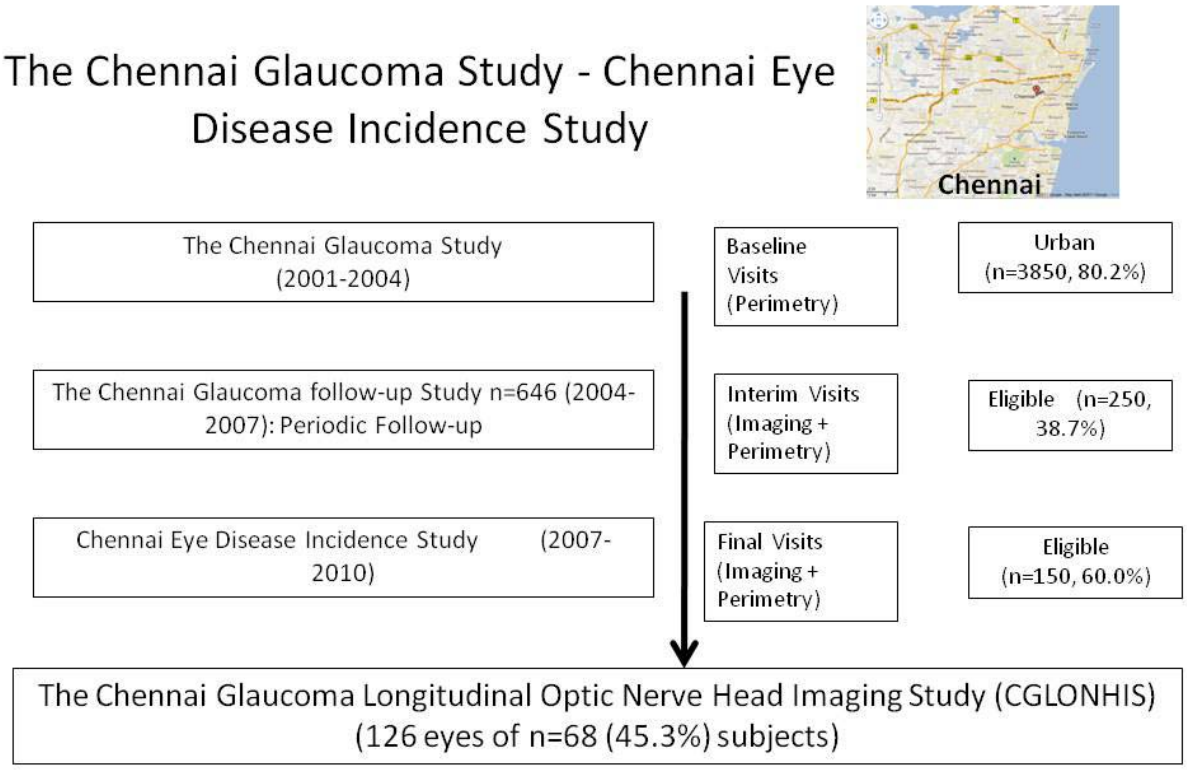


Figure 2.1.1: Population based cohort longitudinal follow-up: Study population and timeline

Study population recruited from the population based longitudinal study. Comprehensive examination was performed at each visit, Imaging: stereo optic nerve head photography, Heidelberg retinal tomography, Scanning laser polatimetry, Ocular coherence tomography, Perimetry: Humphrey Visual field and Frequency Doubling Perimetry

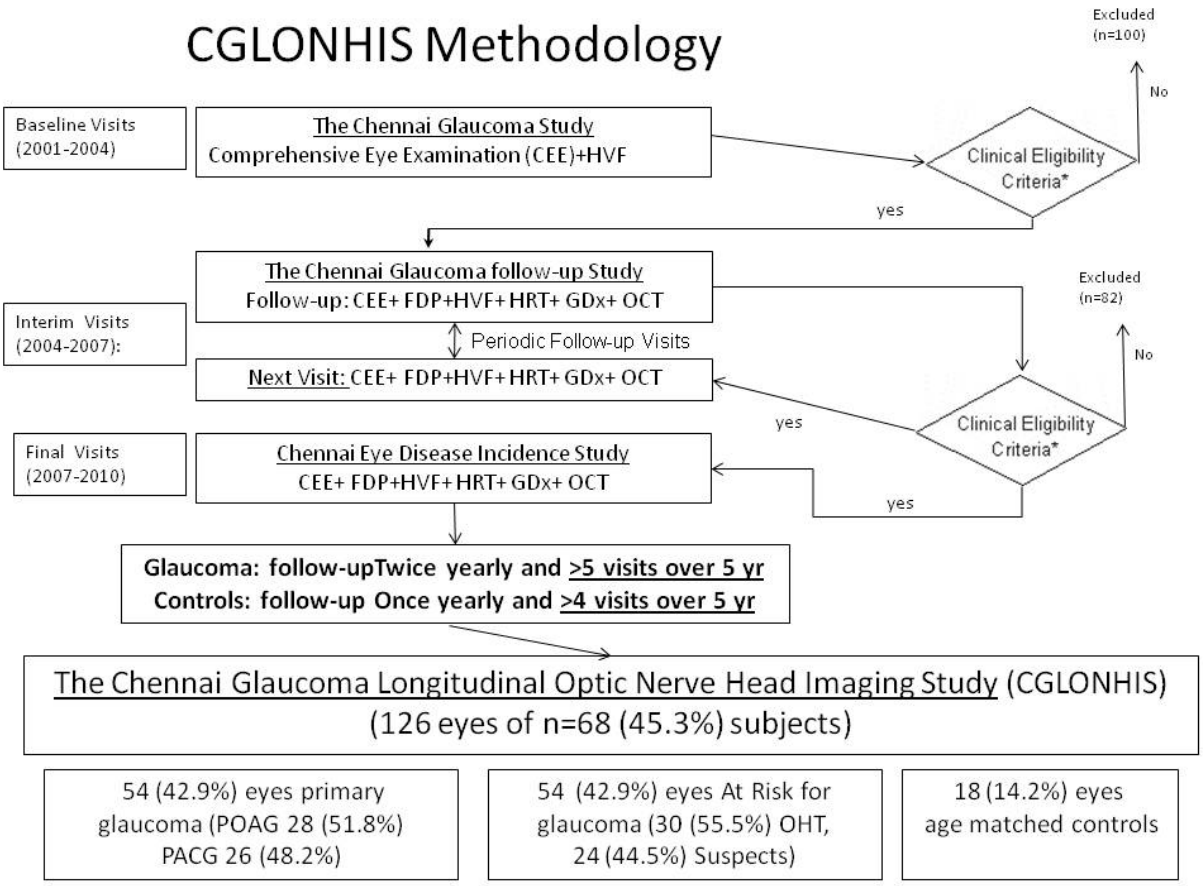


Figure 2.1.2: The Chennai Glaucoma Longitudinal Optic Nerve Head Imaging Study (CGLONHIS) methodology

(Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT)), (Scanning laser polatimetry (GDx VCC), Ocular coherence tomography (OCT), Frequency doubling perimetry (FDP), Humphrey Visual field (HVF))

Table 2.1.1: The Chennai Glaucoma Longitudinal Optic Nerve Head Imaging Study (CGLONHIS) Inclusion and Exclusion Criteria

Clinical Eligibility Criteria	Perimetry and Imaging Criteria
• Inclusion Criteria – No Ocular Diseases other than glaucoma – No h/o surgery or trauma (Prior or during the study) • Imaging – Good Quality – Reproducible • Perimetry – Reliable – Reproducible – Repeatable	Perimetry (HVF: Humphrey Visual Field: SITA std 24-2) • Reliable - Fixation loss<20% and False pos & neg rate<33% • Repeatable and reproducible defects • Progression: VFI and Progressor
• Exclusion Criteria – Cataract (LOCS II, > NII, PI, CI) – Congenital disc anomalies, corneal or retinal pathology – Loss to follow up (>3 visits) • Imaging – Poor centration – Artifactual • Perimetry – Artifactual – Fluctuation (long & short term)	Scanning Laser Ophthalmoscope (HRT III: Heidelberg Retinal Tomography) • Contour lines were marked by single observe - Based on colour stereo optic nerve head picture • Image quality: SD Less than 40 microns - Good Image alignment: Serial scans • Progression assessed - Change probability map: >20 super pixels - Stereo metric parameters Optical Coherence Tomography (Stratus OCT) • Periodic scans performed: Well centered & aligned images taken • Image quality: Signal strength > 7 • Progression assessed: Progression analysis - Significant change over time Scanning Laser Polarimetry (GDx VCC) • Disc margins were marked by single observer • Image Selection: Image quality score> 6 - Serial images with good centration • Progression assessed: Change probability map - Significant change over time

2.2 COMPREHENSIVE EYE EXAMINATION: TEST PERFORMED PERIODICALLY

The following procedures were performed during every follow-up visit

2.2.1 Refraction:

All the subjects underwent visual acuity checking with modified ETDRS (Early Treatment diabetic retinopathy study) chart (Light House Low Vision Products, New York, NY, USA) at 4 metres.[65] Objective refraction was performed using streak retinoscopy (Heine, Germany). Later subjective refraction was performed. Spherical equivalent was calculated as spherical error plus half of the cylindrical error.

2.2.2 Keratometry:

Keratometry was done using Bausch and Lomb keratometer. Corneal curvature was noted in the vertical and horizontal meridians.[66]

2.2.3 Pachymetry:

Central corneal thickness was measured using DGH 550 ultrasonic pachymeter (DGH Technology Inc., Exton, PA, USA). The cornea is anaesthetised using 0.5% proparacaine eye drops (Sunways, Mumbai India). The measurement was done in auto mode with subject in sitting position with fixation at a distant target. The probe was placed perpendicular to the corneal surface and readings were obtained.[66] Averages of ten readings were noted in microns.

2.2.4 Biometry:

Ocular biometry was performed using the Alcon ultrasonic biometer (Ocuscan, Alcon Laboratories Inc, Fort Worth, TX, USA). The cornea was anaesthetised using 0.5%

proparacaine eye drops (Sunways, Mumbai India). The corneal surface was then applanated with the probe and measurements were taken. The axial length, anterior chamber depth and the lens thickness were measured in millimetres.[66]

2.2.5 Slit lamp biomicroscopy:

The Zeiss SL 130 (Carl Zeiss, Jena, Germany) slit lamp was used.[66] Using a moderately wide beam, the eyelids, margins, lashes, canthi and puncta were systematically examined, followed by the palpebral and bulbar conjunctiva, sclera and cornea. Then, using a narrow parallelopiped beam, the cornea, anterior chamber and iris were examined for any abnormalities.

2.2.6 Applanation tonometry:

Intraocular pressure (IOP) recording with the Goldmann applanation tonometer (Zeiss AT 030 Applanation Tonometer, Carl Zeiss, Jena, Germany) was performed on all subjects. After applying 0.5% proparacaine eye drops for topical anaesthesia and staining the tear film with a 2 % flourescein strip, IOP was recorded in each eye.[67]

2.2.7 Gonioscopy:

A Sussmann-type 4 mirror hand held gonioscope (Volk Optical Inc, Mentor, Ohio, USA) was used. An angle was considered occludable if the pigmented trabecular meshwork was not visible in $> 180^0$ of the angle in dim illumination.[64, 68]

2.2.8 Grading of lens opacities:

The subject's pupils were dilated with 5% phenylephrine with 1% tropicamide eye drops (Unimed Technologies, Halol, Gujarat, India). Grading of lens opacities was performed using the Lens Opacities Classification System II (LOCS II).[69] With a minimum pupillary dilation of 6 mm, the lenticular opacities were graded by comparison with the standard set of photographs, which were retro illuminated by mounting on a light box. Nuclear colour, nuclear opalescence, and cortical and posterior sub capsular opacities were graded.

2.2.9 Dilated fundus examination:

The binocular indirect ophthalmoscope (Appasamy Associates, Chennai, India) was used to examine the entire ocular fundus, including the periphery. This was followed by examination of the disc and macula in detail using a +78 D lens (Volk Optical Inc, Mentor, Ohio, USA) at the slit lamp. As part of optic disc examination, vertical and horizontal cup disc ratios and presence of any notching or thinning of the neuroretinal rim, presence and extent of peripapillary atrophy in each eye were noted.[70]

2.2.10 Clinical decision making:

Subjects diagnosed to have primary open or closed angle glaucoma or at risk for glaucoma were managed as per the clinical presentation. Subjects with primary angle closure disease underwent prophylactic YAG peripheral iridotomy and were subsequently managed with anti glaucoma medication if warranted.[71] Maximum medical management to attain target pressure was performed during the follow-up period. The choice of the drug was determined by the treating ophthalmologist and decision for surgical intervention was

made as required.[72] Subjects who underwent any surgical intervention for their ocular condition were excluded from the study. Eyes of subjects without any retinopathy and clinically insignificant cataract, age related macular degeneration were included. (Table 2.1.1)

2.2.11 Optic disc photography:

All subjects with sufficient media clarity to permit good quality fundus photographs underwent fundus photography. The Zeiss FF450-plus fundus camera with VISUPAC digital image archiving system (Carl Zeiss, Jena, Germany) was used. Photography included one stereo-pair (non-simultaneous) of 20° optic disc photographs, 30° disc and macular stereo photographs for each eye, 30° red free stereo photographs in patients with glaucoma or glaucoma suspect.[73] The labeled optic disc photographs were exported from the VISUPAC system as DICOM format and saved in an external storage device for later analysis. Stereo optic disc photographs of subjects who have met the inclusion criteria were imported into the semi automated planimetry software.

2.3 STRUCTURAL IMAGING: BASIC TECHNIQUE AND PROGRESSION PROTOCOL

2.3.1 Planimetry - Cyoptique GL: Cyoptique-GL is a semi-automated planimetry software based on edge segmentation. In the software, stereo optic disc photographs were imported in a DICOM format. The stereo optic disc photographs were imported into the software and displayed side by side on a 19” LCD monitor. It has a Litmann[74] correction factor incorporated in it to correct for the ocular and camera magnification of optic disc photographs. Corneal curvature and refractive error of the patient were used for the

correction factor. It has a tool for marking the disc, cup both automatically and manually. Since automated marking needs additional refinements, planimetry was performed manually for marking the disc and cup margin.

The "Screenscope" (Berezin Stereo Photography products, Mission Viejo, CA, USA) is a stereo viewer that can be used on digital stereo photographs on a computer screen, and was used for this study. All the markings were performed by a single observer, on the right side image on the computer screen under direct stereo viewing conditions. First, the disc margin was marked inside the scleral ring of Elschnig manually. Then cup edge was marked by considering the contour and bending of blood vessels instead of pallor to differentiate the cup. The shortest distance between the disc and cup margin is detected automatically and shown by the software. Area between disc and cup was considered as rim.[75] The software divides the disc into 4 sectors, the planimetric measurements of the optic disc would be displayed both globally and sector wise. All the planimetric measures were made by single observer. The planimetric data obtained for each stereo image was exported into Microsoft excel 2003 at the end of marking. Figure 2.3.1 (A& B) shows the stereo optic disc photographs with optic disc and cup markings.

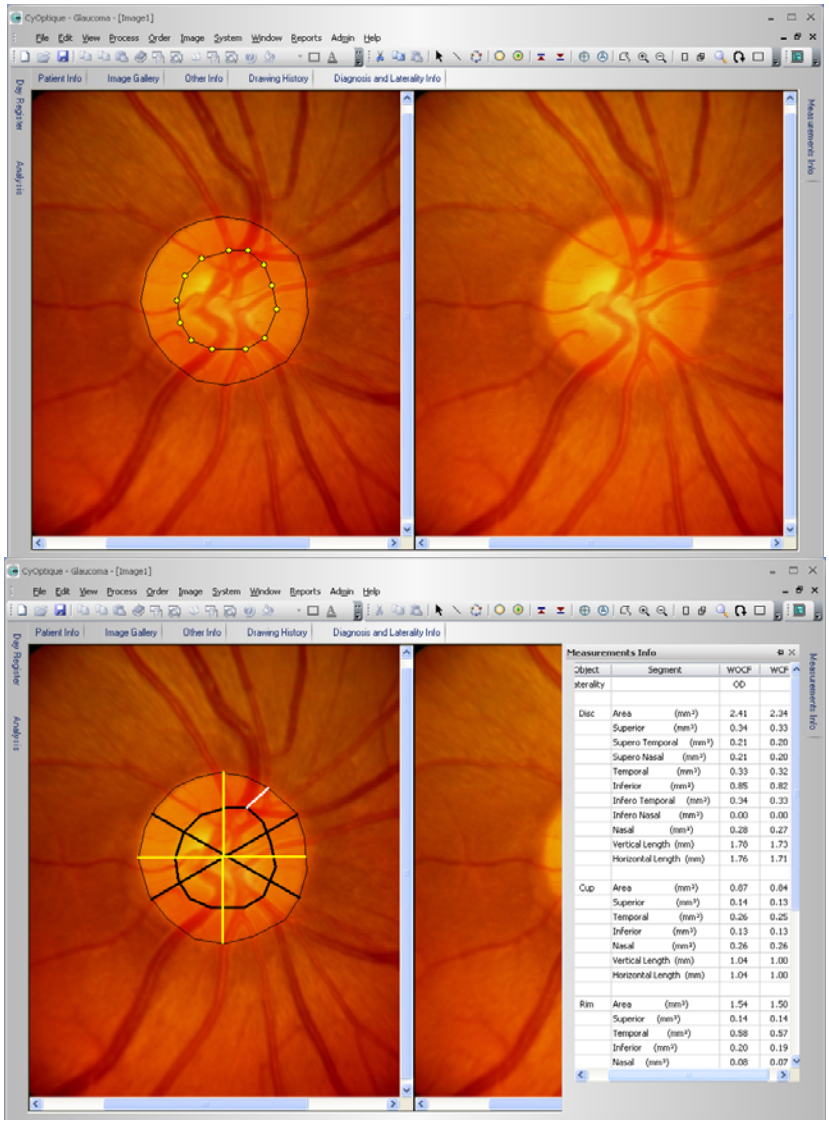


Figure 2.3.1: Optic disc photographs with planimetry markings in the cyoptique

Identifying progression: Serial measurements of relevant ONH parameters, such as rim area, measured by planimetry. Data from control subjects were used to establish true change from measurement imprecision and age-related changes.

2.3.1.1 Quantitative imaging

Studies reporting progression assessment from photographs usually assess the performance of expert observers. Expert observers, however, and the viewing conditions available to them, are not always available to the clinician. Quantitative imaging devices, such as confocal scanning laser tomography (HRT), scanning laser polarimetry (GDx), and optical coherence tomography (OCT), have a role in determining progression. Probability maps for change are applied to longitudinal series of images. Only images with adequate image quality and signal strength were included for analysis (Table 2.1.1). Two of initial good scans were considered as baseline and in case of significant alteration in the treatment, repeat scans were performed to re establish new baselines, data included of scans performed on or before January 2007.

2.3.2 Heidelberg Retinal Tomography (HRT III)

HRT derives a surface topography from a stack of confocal images of the ONH. Viewing a stereo ONH photograph, Contour line was marked around the ONH margin to generate conventional parameters, such as cup and rim. Progression may be identified with an 'event' analysis or with a 'trend' analysis; change may be identified at the level of the pixel or parameter. With event analysis, progression was identified when a measurement difference exceeds a predetermined threshold.

Chauhan et al[31] described an algorithm in which the change threshold was determined from an analysis of variance technique to quantify the height variability in groups of pixels in the three single topography images acquired at each imaging session. The Topographic Change Analysis (TCA) was used to determine progression among the study

population. The study database was upgraded from HRT II to HRT III software and alignment for all follow up visits was established.[76] TCA provides objective, trend based measurement of the rates of changes and the regression line provides both global as well as stereo metric parameters. Progression, defined as change greater than the 90% limit of variability in two of three consecutive images (Figure 2.3.2), i.e. greater than 20 connected super pixel points. Measurement variability in images acquired from the normal reference group was determined.

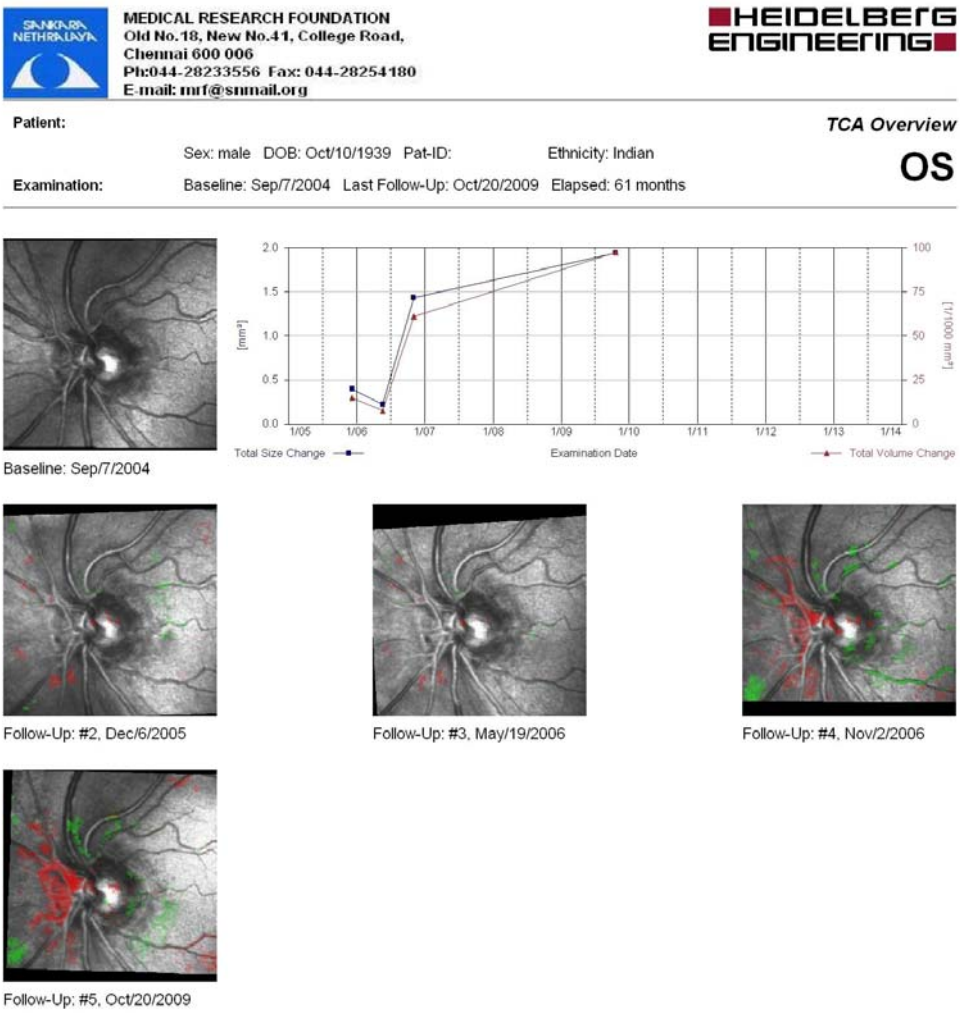


Figure 2.3.2: Topographic Change Analysis on HRT showing significant progression

2.3.3 Scanning Laser polarimetry (GDx)

In GDx VCC, a scanning laser ophthalmoscope is used to measure the change in polarization in light backscattered from the retinal nerve fiber layer. Once the polarizing properties of the anterior segment are neutralized, the change in polarization is proportional to the RNFL thickness. The hardware of the commercially available device has changed a number of times, so there are few reports with series sufficiently long to test the ability of the technique to identify glaucomatous progression. At the baseline examination, macular scan was performed and the anterior segment polarization parameters were estimated and corrected by the software. During follow up visit, macular scan was repeated if the refractive error changed (>3D), RNFL scan showed a score of <5 and if cataractous changes lead to poor image quality. GDx scans were performed in undilated pupil, RNFL scans with image quality score >5 were included for analysis. The Guided Progression Analysis (GPA) provides both event and trend based analysis of change in the RNFL thickness. (Figure 2.3.3) The analysis provides a colored map with a classification system: yellow: possible progression, red: likely progression and purple: possible increase in RNFL thickness. The graphical image of the regression analysis displays both global and sector wise RNFL thickness, assisting in determining progression over time. Progression was determined as likely or possible progression and significant change in RNFL thickness from baseline.

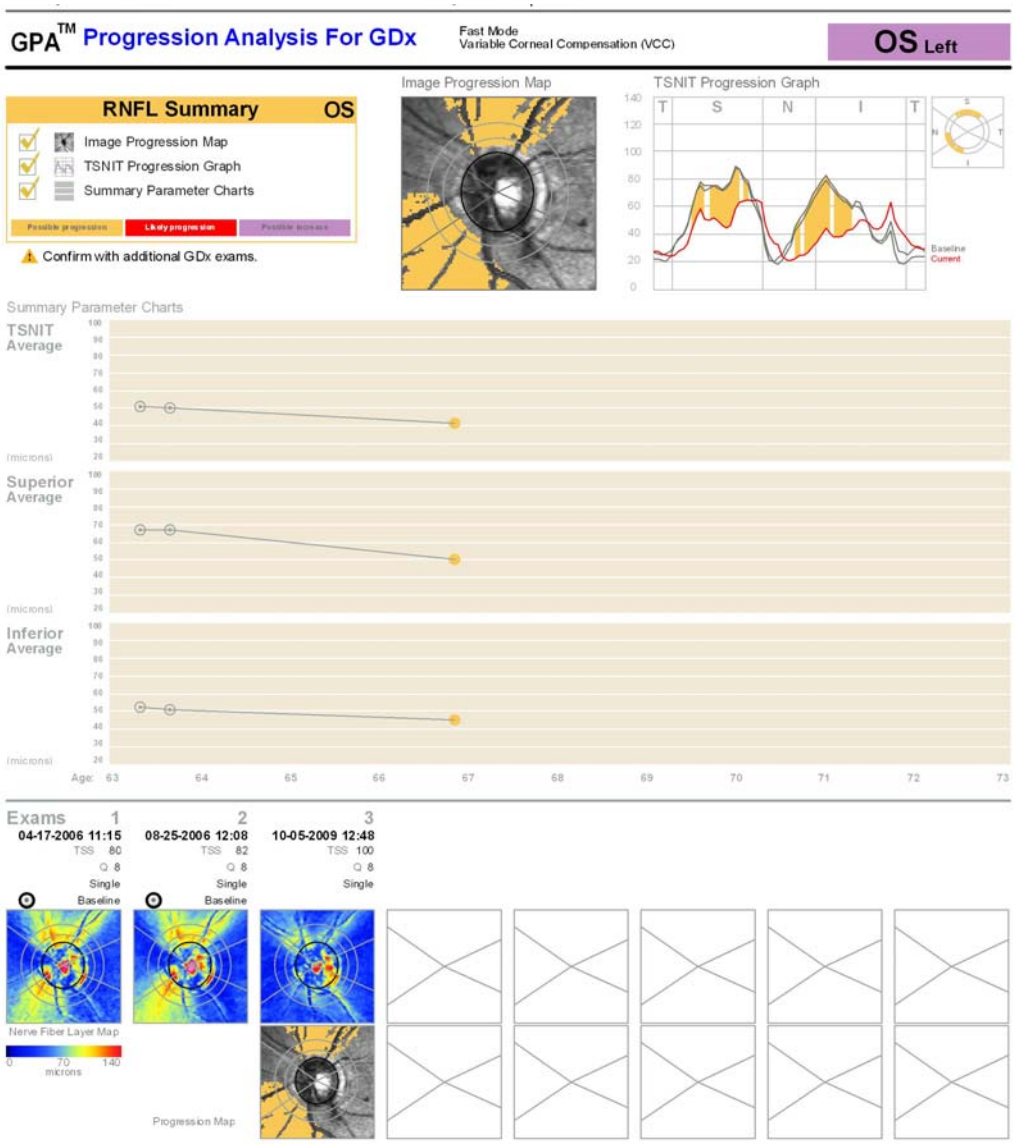


Figure 2.3.3: Guided Progression Analysis on GDx showing significant progression

2.3.4 Optical coherence tomography (OCT)

OCT is based on an imaging method called low coherence interferometry and acquires cross-sectional images through the retina with very high depth resolution (upto 10µm for commercially available devices). Thresholding algorithms identify layers in the retina, including the anterior and posterior borders of the RNFL. OCT was performed in a mydriatic pupil (>6 mm) after dilatation, on the same day or within 10 day period from the

date of follow up visit. The study included fast RNFL scans, optic disc scan and RNFL scan protocols. The parameters such as RNFL thickness globally, quadrant wise and other planimetric data was included for analysis. Though both hardware and software has changed significantly over the years, Time-Domain OCT has been reported to be able to assess structural progression. The Glaucoma Progression Analysis (GPA) advanced serial analysis determines the rates of RNFL thickness change (micron/year) and their significance level (p value). (Figure 2.3.4) Progression is determined if the rate of change is significant ($p<0.05$).

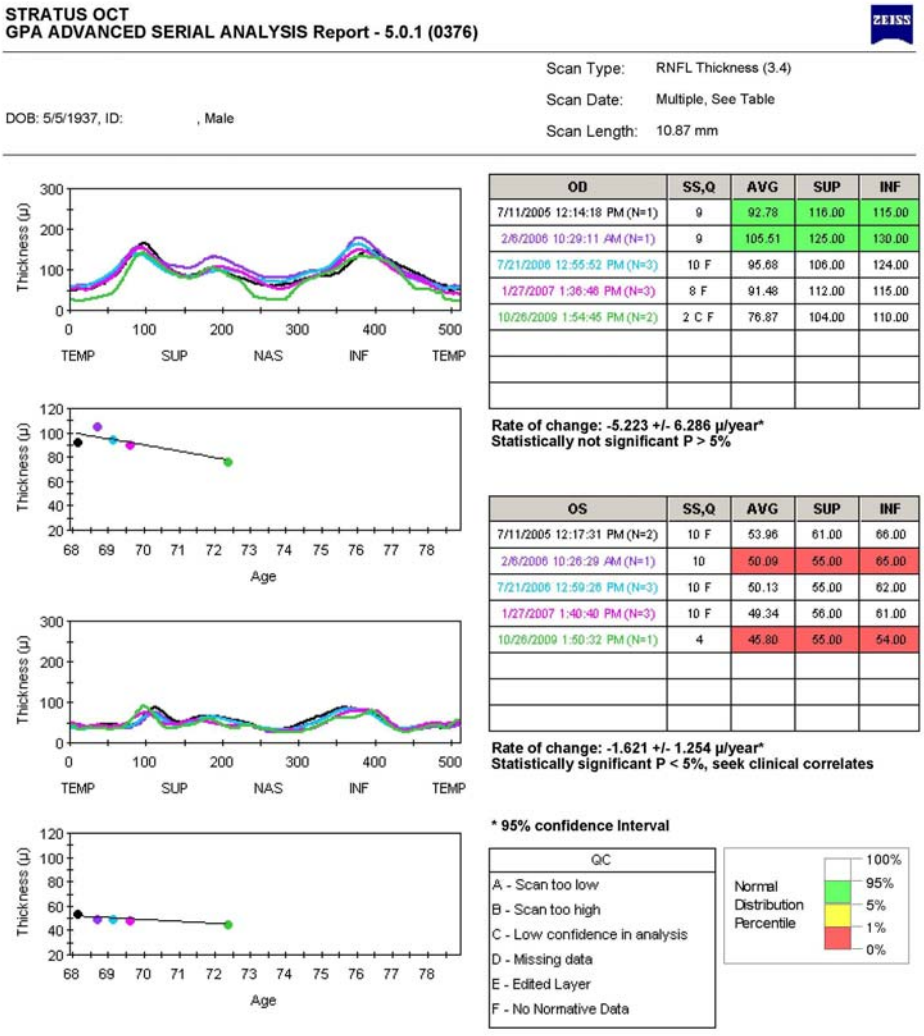


Figure 2.3.4: Glaucoma Progression Analysis on OCT showing significant progression

2.4 FUNCTIONAL PERIMETRY TECHNIQUES: BASIC TECHNIQUE AND PROGRESSION PROTOCOL

2.4.1 Visual field examination:

Visual field examination for all subjects was done using Frequency doubling perimetry (FDP: Carl Zeiss Meditec) and Humphrey automated perimetry (HVF model 750; Carl Zeiss Meditec), testing program used were full threshold N 30 and 24-2 SITA (Swedish interactive thresholding algorithm) standard respectively. Reliability criteria for both the perimetric techniques were defined as fixation losses, < 20%; false-positive and false-negative, < 33%. Reproducible defects were only considered, tests were repeated within a month period, as and when two or more new defect appears in either visual field tests. The results from the second repeat test were included for analysis. 2 initial reliable visual field reports were considered as baseline visual field for both HVF and FDP. Among glaucoma and controls a minimum of three and two follow up fields respectively over five year period were considered for the study. In case of significant alteration in the treatment, repeat fields were performed to re-establish new baselines, data included of new baseline fields performed on or before January 2007.

Each HVF reports were classified using the Hodapp Andersons Parish (HAP) Criteria[77] and Brusini Glaucoma Staging system (GSS) was used to classify the defect in both HVF[78] (Figure 2.4.1 A) and FDP[79] (Figure 2.4.1 B). The Brusini's classification system is a simple, quick and reliable in classifying visual field defects. It classifies visual field charts into disease stage and defect type by using a nomogram. The Cartesian co-ordinate diagram in the nomogram has mean deviation (MD) along the X-axis and pattern standard deviation (PSD) along the Y –axis. The disease is staged from stage 0 (normal) to stage 5

(severe loss) by plotting the intersection of MD and PSD global indices generated by the perimeters. Two regression lines divide all the stages except stage 0 into three types of defects, namely Generalized, Mixed and Localized. The system thus provides a comprehensive 16-stage classification (15 + stage 0) of visual field defect. Perimetric progression was estimated for both HVF and FDP. Change in the MD, PSD was estimated for both perimetric systems.

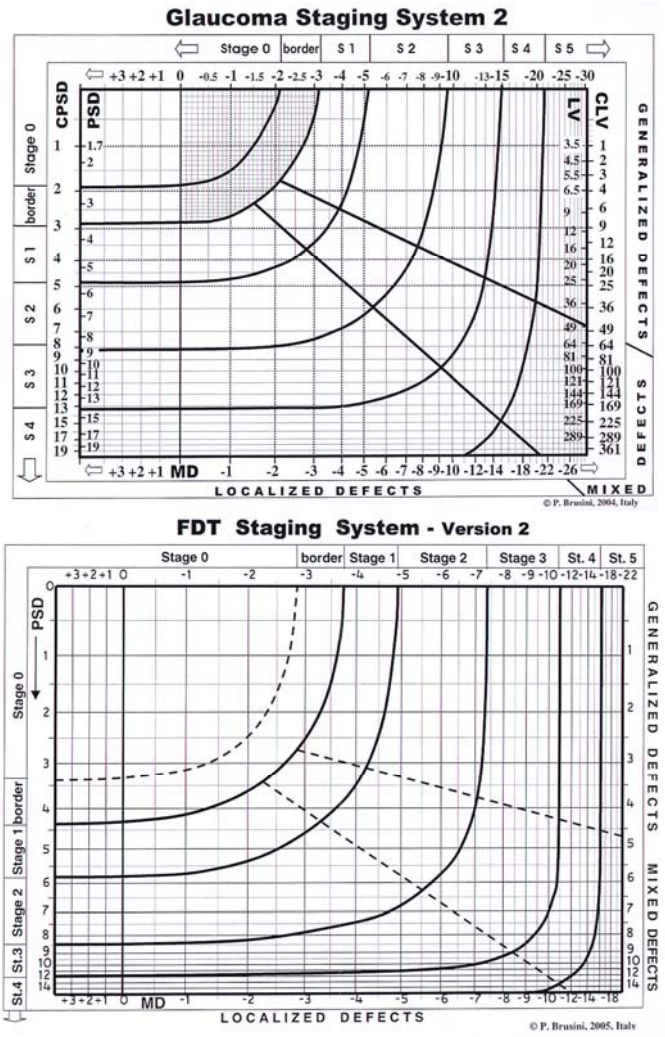


Figure 2.4.1: Brusini Glaucoma Staging system of classifying HVF and FDP perimetry reports.

Glaucoma Staging system 2 used for (A) Humphrey Visual Field and (B) FDT staging system version 2 used for frequency doubling perimetry

2.4.2 Humphrey visual field analyzer: Progression was assessed using Brusini GSS system and advanced perimetric progression algorithm (Progressor and Visual Field Index (VFI). Other progressions algorithms were not included due to limited follow up visits among control.

PROGRESSOR (Figure 2.4.2) includes a modification of point wise linear regression to adjust for the effect of developing cataract. Regression slopes of unadjusted visual sensitivity, total deviation and pattern deviation values, and trends in the pattern deviation are estimated to separate out the localized component of sensitivity loss from diffuse change; thereby adjusting for the influence of media opacities. A group of two or more points showing progressive defects (significant slope: $p<0.05$) corresponding to the clinical finding were considered as progression.

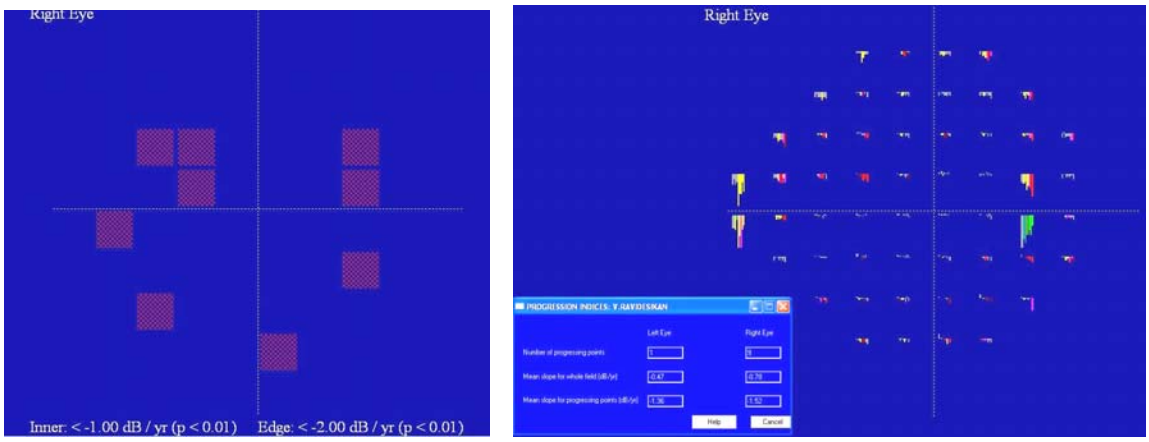


Figure 2.4.2: Progressor- Point wise linear regression

Progressor report (right eye) showing the (A) no of progressed points and (B) the point wise regression along with slope.

VISUAL FIELD INDEX (VFI): Glaucoma probability analysis with VFI (Figure 2.4.3) is a new global metric that represents the entire visual field as a single percentage of normal. VFI is age adjusted index that summarizes the global visual field status for each test in the follow up. A full visual field has a VFI of 100% while a perimetrically-blind visual field has a VFI of 0. It's based largely on the pattern deviation and weighs central points more than peripheral ones. The VFI provides both rate-based and event-based information. The rate of change of the VFI over time characterizes the rate of progression, while a statistical significant ($p<0.05$) difference indicating whether or not the rate of change is significantly different from zero.

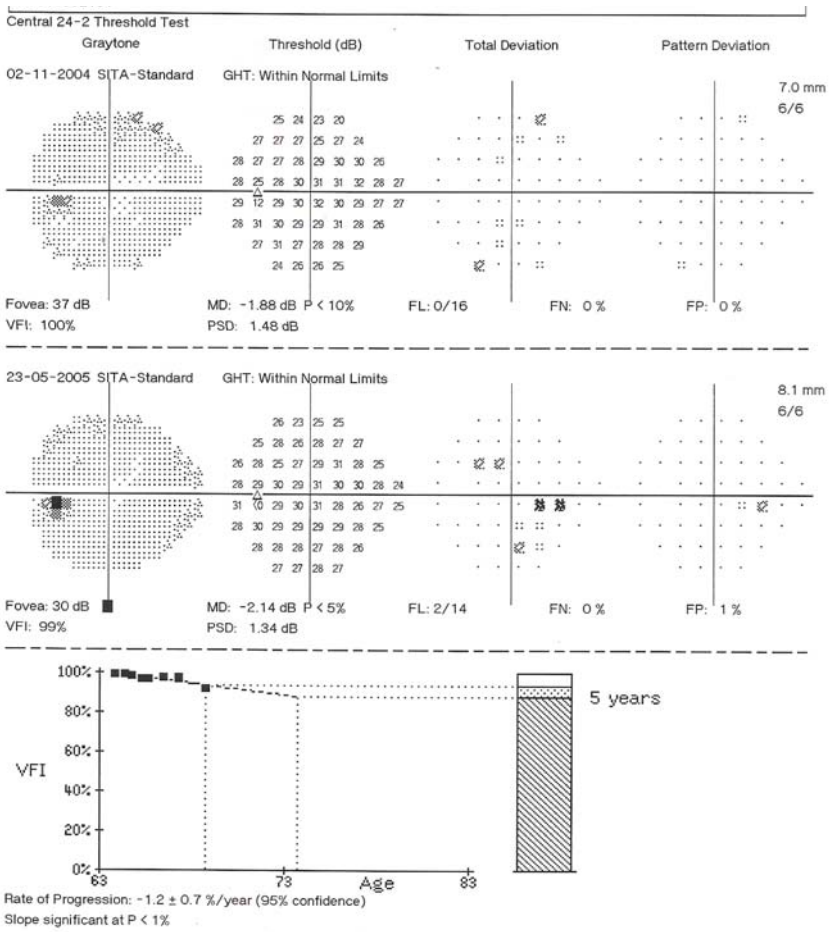


Figure 2.4.3: Humphrey Visual Field report assessing progression with visual field index (VFI)
VFI report (left eye) showing rate of progression in a patient with early glaucoma.

2.4.3 Frequency Doubling Perimetry: Progression was assessed using Brusini FDT classification system on the full threshold N 30 reports (Figure 2.4.1). Change in two grades was considered as progression and the results were correlated clinically.

The N 30 full threshold test comprises of 19 (10 X 10 degree target) (Figure 2.4.4) and threshold estimates for each of the target is provided. Taking the initial two reliable FDP test as baseline, average threshold for each location was estimated. Point wise linear regression slopes were estimated for all the subsequent FDP data for both disease and control group. Progression was determined as statistically significant change for cluster of three or more points compared to the control slope.

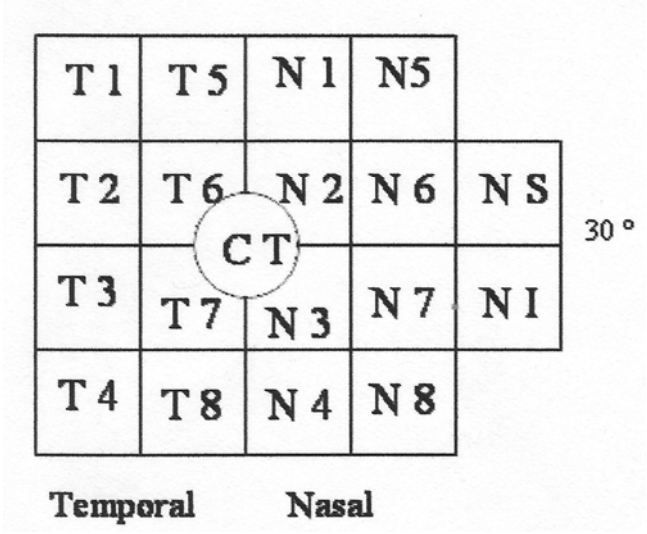


Figure 2.4.4: Pattern of points on Full threshold N 30 test on Frequency Doubling perimetry (FDP)

The 19 test locations on the FDP full-threshold test are denoted with different notation based on location of the target to the CT. CT: central threshold.

2.5 STATISTICAL ANALYSIS

Parametric data such as age, intraocular pressure, disc area were tested using one way ANOVA, significance was considered including Bonferroni correction for multiple comparisons. Categorical and nominal parameters were compared with chi square or z test as appropriate. Of the 126 eyes data included, 54 (42.9%) were grouped as "At Risk", these included 30 (56%) ocular hypertensive subjects and 24 (44%) glaucoma suspects. Progression rates were estimated for each group of subjects, for all imaging systems and with perimetric procedures and compared using chi square statistic. The difference or overlap of the rates of progression across imaging and perimetry techniques was expressed as ven diagrams. Generalized linear regression model was used to assess the significance ($p<0.05$) of change in parameters between baseline and final visit. Further analysis was performed for those parameters that showed significant difference over the 5 year follow up period. The following parameters and gradations were used in determining the risk factors associated with progression, using a multivariate regression model:

Clinical: presenting age, age group (0<60 years, 1≥60 years), gender, baseline intraocular pressure (0<22 mmHg, 1≥22 mm HG), baseline central corneal thickness (0<520 microns, 1≥520 microns), IOP control. IOP control was determined based on target IOP, compliance and persistence to medication used by the patients. Target pressure was determined for individual eyes based on presenting IOP, age, life expectancy, level of glaucoma damage. The following parameters showed significant change over 5 year period.
Imaging parameters: Planimetric parameters such as Disc area (DA) and thinnest rim width of Cyoptique GL were included. DA between tools was compared using Pearson coefficient of correlation. The disc area were graded as small < 2.21mm^2, moderate 2.22 and 2.77 mm^2

and large>2.78 mm^2 disc. Stereo metric parameters such as Cup Area (CA), Rim Area (RA) and Cup Shape Measure (CSM) from HRT were included. RNFL thickness (average/global) from OCT and GDx along with nerve fiber indicator (NFI) were included for regression analysis. Planimetry Parameter: The global indices such as mean deviation (MD) and pattern standard deviation (PSD) from both HVF and FDP were analyzed. Comparison of Brusini GSS classification systems, HAP and GHT was done and compared using chi square statistic.

CHAPTER 3

Results and Discussion

3.1: GENERAL AND DEMOGRAPHIC INFORMATION

A total of 54 eyes of 30 subjects with primary glaucoma (open angle 28 (51.8%) and angle closure 26 (48.2%)), 54 eyes at risk for glaucoma (30 (55.5%) ocular hypertensives (OHT) and 24 (44.5%) glaucoma suspects) and 18 eyes of 10 age matched control subjects were included for analysis. (Figure 2.2) The mean follow-up period was 58.34 (SD: 3.76, min: 50 - max: 67) months and the mean age of the study cohort was 54.65 (5.7) years, the glaucoma group were significantly older than the other groups ($p<0.001$).

3.1.1: Non Participants Vs Participants

Of the 100 subjects excluded after the baseline visit, (Figure 2.2) 28 (28%) had significant cataract, 16 (16%) had underwent surgery, 13 (13%) had diabetic retinal changes, 9 (9%) had corneal changes, 15 (15%) had artifacts on perimetry or unreliable perimetry performance, 18 (18%) did not meet eligibility for imaging and 1 (1%) had a history of trauma. Those excluded during follow-up visit (n=82) (Figure 2.2) were because, imaging criteria were not satisfied, not meeting perimetric criteria, incidence of cataract, incidence of corneal and retinal diseases and missing periodic visits were 24 (29.3%), 20 (24.4%), 16 (19.5%), 13 (15.9%) and 9 (10.9%) respectively. There was a significant differences ($p<0.001$) in the proportions of subjects excluded between primary glaucomas, at risk and control groups over the study period. The MD in HVF (mean diff: -1.32, SE: 0.67) was higher among those excluded from analysis and this difference was statistically significant ($p<0.001$). None of the other clinical, perimetric and imaging parameters showed statistically significant differences between the two groups.

3.2 STRUCTURAL IMAGING AND PROGRESSION

3.2.1: Planimetry

The mean disc area (DA) at baseline was found to be 2.33 ± 0.48 mm^2 (95 % CI: 2.19 to 2.58). Similarly disc area was found to be larger in glaucoma subjects (2.75 ± 0.54 mm^2) compared to normals, p = 0.043, 95 % CI for difference: -0.13 to -0.06. Thirty third and sixty seventh percentiles were calculated to divide disc area into small, moderate and large discs. Small discs were taken as those with a disc area less than 2.21 mm^2, moderate disc as between 2.21 and 2.77mm^2 and large discs when disc area was greater than 2.77mm^2. 50% (95% CI: 41.4 to 58.6) of the study population had small disc followed by moderate disc (31.7%, 95% CI: 24.3 to 40.3) and Large discs (18.3%, 95% CI: 12.5 to 25.9). A similar (p=0.502) trend was observed in both the study groups (Table 3.2.1) and disc area showed a correlation with increasing age (r = 0.20, p <0.0001).

The mean cup area (CA) at baseline was found to be 0.58 ± 0.33 mm^2 (95 % CI: 0.48 to 0.71) in normal subjects which was significantly less than cup area in the glaucoma population (1.36 ± 0.43 mm^2), p < 0.0001. The mean rim area at baseline in the study population was 1.98 ± 0.28 mm^2 (95 % CI: 1.86 to 2.18). Rim area (RA) was significantly thinner in glaucoma (1.19 ± 0.29 mm^2) than normals, p <0.0001. Though the rim area was dependent on the disc area, there was a positive correlation with increasing disc area, r=0.33, p<0.001). The smallest rim width was significantly shorter among the glaucoma group as compared to normals, p<0.001. The change in planimetric parameters was not statistically significant over the follow-up period. Of the glaucoma, two (3.7%, 95% CI: 1.0 to 12.5) eyes showed changes in the ISNT pattern, but there was no statistical significance for the mean RA (p=0.194), CA (p=0.172) and shortest rim width (p=0.244).

Table 3.2.1: Distribution across various study groups: Coded disc area derived from disc area (mm^2) of ONH photos

Coded Disc Area / Study Group	Small Disc: <2.21mm^2 (n=63) n (%, 95% CI)	Moderate Disc: 2.21 to 2.77 mm^2 (n=40) n (%, 95% CI)	Large Disc: >2.77 mm^2 (n=23) n (%, 95% CI)
Primary Glaucoma (n=54)	25 (46.3%, 33.7 to 59.4)	19 (35.2%, 23.8 to 48.5)	10 (18.5%, 10.4 to 30.8)
At Risk (n=54)	13 (24.1%, 14.6 to 36.9)	30 (55.6%, 42.4 to 68.0)	11 (20.4%, 11.8 to 32.9)
Controls (n=18)	8 (44.4%, 24.6 to 66.3)	8 (20.0%, 24.6 to 66.3)	2 (11.1%, 3.1 to 32.8)

CI: Confidence interval, ONH: Stereo Optic Nerve head

3.2.2 Heidelberg Retinal Tomography (HRT III)

Topographic parameters included with HRT III software are disc area(DA), cup area (CA), rim area (RA), cup/disc area ratio, rim/disc area ratio, cup volume, rim volume, mean cup depth, maximum cup depth, height variation contour (HVC), cup shape measure (CSM), mean RNFL thickness, RNFL cross-sectional area, horizontal cup/disc ratio, vertical cup/disc ratio, and 2 linear discriminant functions, from Mikelberg et al (FSM) and Bathija et al (RB). The proportion of subjects showing progression on HRT, significantly varied ($p<0.001$) among between primary glaucoma, at risk and control population.(Table 3.4.1) The GLM regression model for significant change ($p<0.05$) for longitudinal follow up for clinical progression were observed for CA (R=0.276), RA (R=0.346), CSM (R =0.567), HVC (R=0.236), mean RNFL (R=0.335), FSM (R=0.346) and RB (R=0.296). These parameters were used to assess progression.

Optic nerve head planimetry measure compared to the HRT III showed significant correlation ($r=0.576$, $p<0.05$) for DA only. Other planimetric measures CA, RA and sectoral values between the two techniques showed correlation, but they were not statistically significant.

Table 3.2.2 shows comparison of structural imaging parameters between various study groups. In both the primary glaucoma group and at risk population CSM showed statistically significant change and the RB discriminant function showed significant change in the at risk population ($p=0.003$) (-0.39 to -0.08). Among the at-risk population the CSM ($p=0.045$, -0.01 to 0.00) showed limited significant difference and there was no significant difference for change in CSM between OHT and glaucoma suspect ($p=0.076$). Figure 3.2.1, shows that the 83.8% (95% CI: 79.0 to 94.3) of the progressed HRTs in the primary glaucoma had small disc and only 3.2% (95% CI: 1.2 to 24.3) with large disc showed progression in the glaucoma group, the distribution showed statistically significant difference ($p<0.05$). Among the at-risk groups, 53.7% (95% CI: 39.4 to 69.4) with moderate sized discs and 42.6% (95% CI: 31.4 to 59.7) with large disc size showed significant progression, the trend correlates with the distribution among the OHT and glaucoma suspect population in the at risk group.

The long term variability was observed for CSM ($p=0.001$, 95% CI of difference: -.56 to -0.03) and other HRT parameters did not show significant variability. CSM also showed significant change between the progressed ($p=0.001$, 95% CI of difference: -0.05 to -0.02) and non progressed ($p=0.008$, 95% CI of difference: -0.09 to -0.01) groups too. (Table 3.2.3) The CSM measure is dependent on the disc size, assessing the effect of disc

size showed that with increasing disc size there was insignificant variation in CSM parameter. (Table 3.2.4) There was insignificant or limited variability of HRT III parameters adjusted for increasing disc size, between progressed and non progressed groups. Though the variability among the progressed group was more in small disc size for HVC, CA (Figure 3.2.2) and CSM (Figure 3.2.3) the difference was not statistically ($p>0.05$) significant.

Among those with progression in HRT, 35.5% (95% CI: 21.1 to 53.1) show progression in GDx and 7 (22.6%, 95% CI: 11.4 to 39.8) each showed progression also in FDP and OCT. Among those non progressed in HRT, 16.8% (95% CI: 10.6 to 25.6) showed progression in FDP followed by 13.7% (95% CI: 8.2 to 22.0) in GDx, the differences were statistically significant ($p<0.001$). OCT progression was observed only in a limited no of subjects. (Figure 3.2.4)

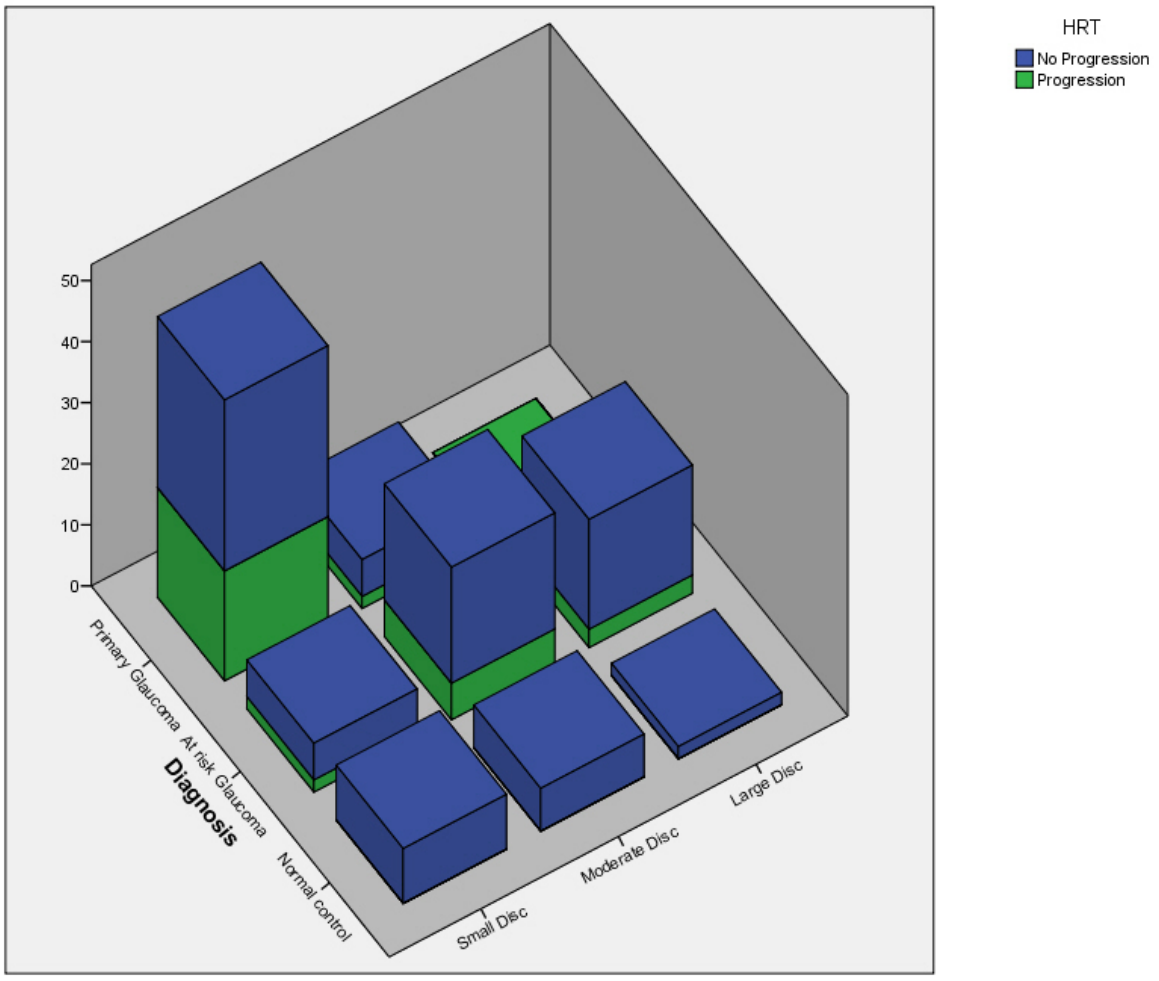


Figure 3.2.1: Distribution of progression in Heidelberg retinal tomography (HRTIII) among the study population, increasing disc size and progressed

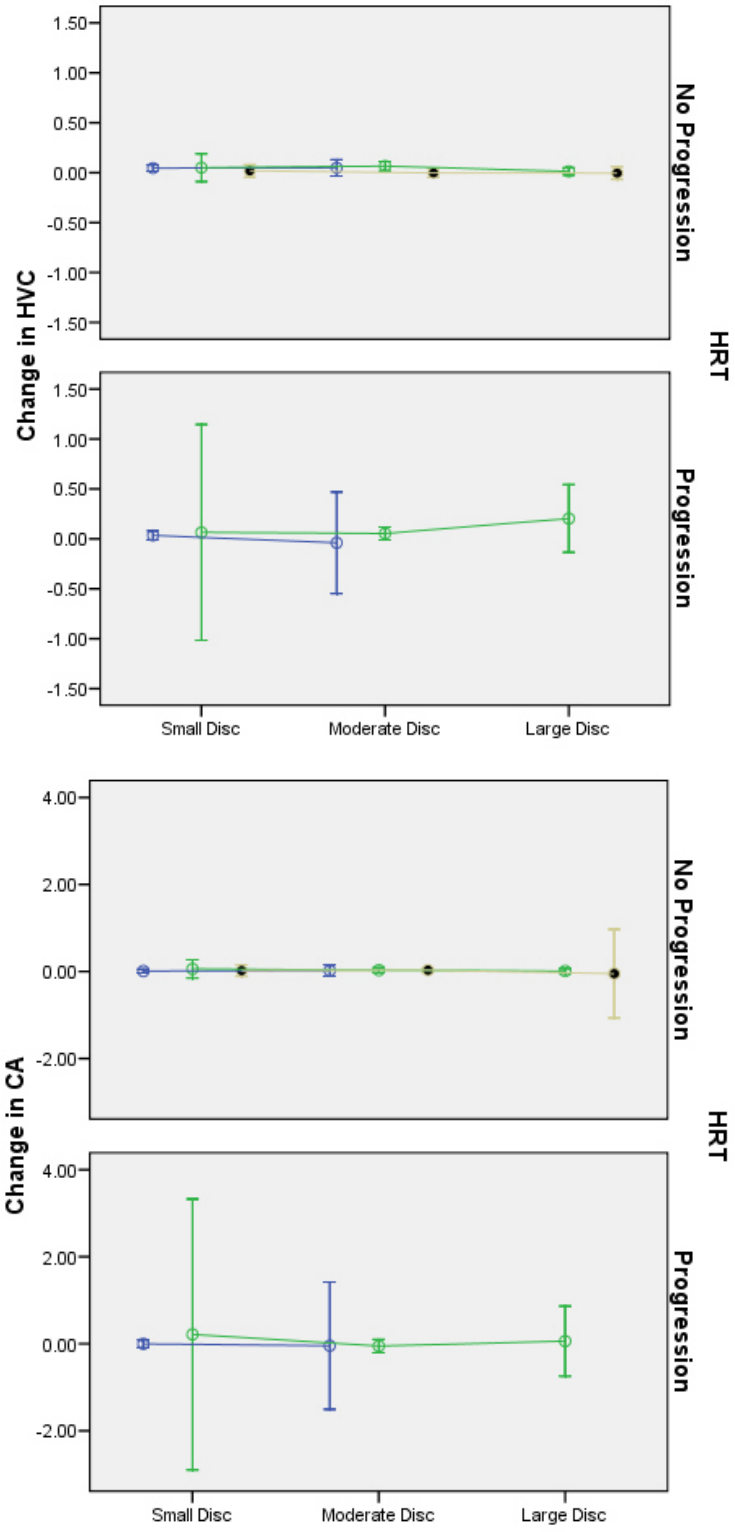


Figure 3.2.2: Comparison of HRT parameters HVC and CA between progressed and non progressed groups with increasing disc size

Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT), HVC: Height variation contour, CA: Cup Area. Graphical representations: Primary Glaucoma: Blue, At risk: Green and Control: Golden yellow (black spots)

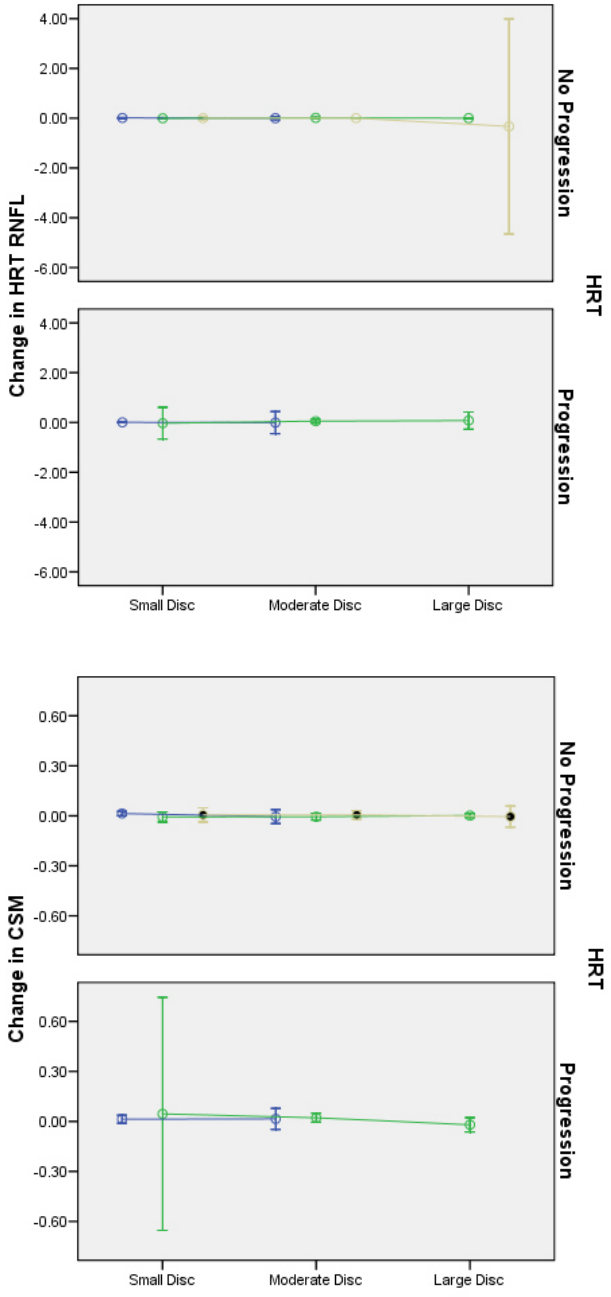


Figure 3.2.3: Comparison of HRT parameters CSM and RNFL between progressed and non progressed groups with increasing disc size

Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT), CSM: Cup shape measure, RNFL: Retinal nerve fiber layer thickness Graphical representations: Primary Glaucoma: Blue, At risk: Green and Control: Golden yellow (black spots)

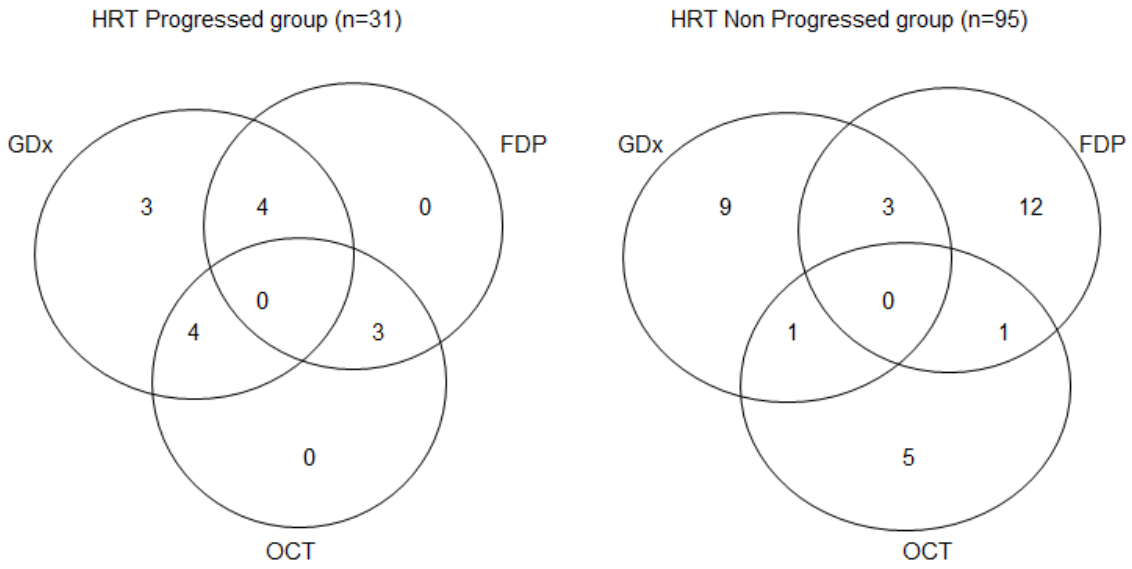


Figure 3.2.4: Progression HRT compared to GDX,OCT,FDP progression rates

Venn Diagram shows the numbers of subjects progressed on GDx, OCT and FDP techniques among the progressors and non progressors on HRT. Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT), Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Frequency Doubling Perimetry (FDP).

3.2.3: Scanning Laser polarimetry (GDx VCC)

GDx VCC parameters such as Nerve Fiber Indicator (NFI), Average RNFL, Sectoral RNFL, Superior and inferior maximum, sectoral difference parameter were included for analysis. Figure 3.2.5, shows distribution of progression estimated using Scanning Laser Polarimetry (GDx VCC) among the study population, the 3D graph also shows relation with increasing disc size among progressed and non progressed groups, the spread showed

statistical ($p<0.05$) significant differences. 64.8% (95% CI: 51.3 to 77.9) of those who progressed in primary glaucoma group had small optic discs. Among, the at risk group those which, progressed were evenly distributed between moderate (48.4%, 95% CI: 37.8 to 61.3) and large disc (51.9%, 95% CI: 44.3 to 63.7), this was comparable to the progression among OHT and Glaucoma suspect in the at risk group.

GLM showed significance for NFI (R: 0.389, $p<0.001$) and Average RNFL thickness (R: 0.527, $p<0.001$). There was a significant difference in the change in the average RNFL among the primary glaucoma (0.001, 95% CI 3.27 to 6.43) and at risk group (0.001, 95% CI 1.23 to 4.47). There were significant differences between OHT and Glaucoma suspects ($p<0.05$). Change in NFI did not show statistically significant difference across the study groups. (Table 3.2.2) Rate of RNFL loss was significantly highest among the progressed group ($p=0.001$, 95% CI 4.82 to 11.35). (Table 3.2.3) There was an increase in the RNFL differences with increasing disc size, the distribution was statistically significant. (Table 3.2.4) Among the control groups there 16.7% (95% CI: 5.8 to 39.2) showed progression in GDx, the variability in NFI and RNFL measures were significantly ($p<0.05$) higher. (Figure 3.2.6).

Among those with progression in GDx, 45.8% (95% CI: 27.9 to 64.9) show progression in HRT. 29.2% (95% CI: 14.9 to 49.2) and 20.8% (95% CI: 9.2 to 40.5) showed progression in FDP and OCT respectively. Around 15.7% (95% CI: 9.9 to 23.9) and 12.8% (95% CI: 7.6 to 20.6) showed progression in FDP and HRT respectively, among the GDx non progressed group, the differences were statistically significant ($p<0.001$). (Figure 3.2.7)

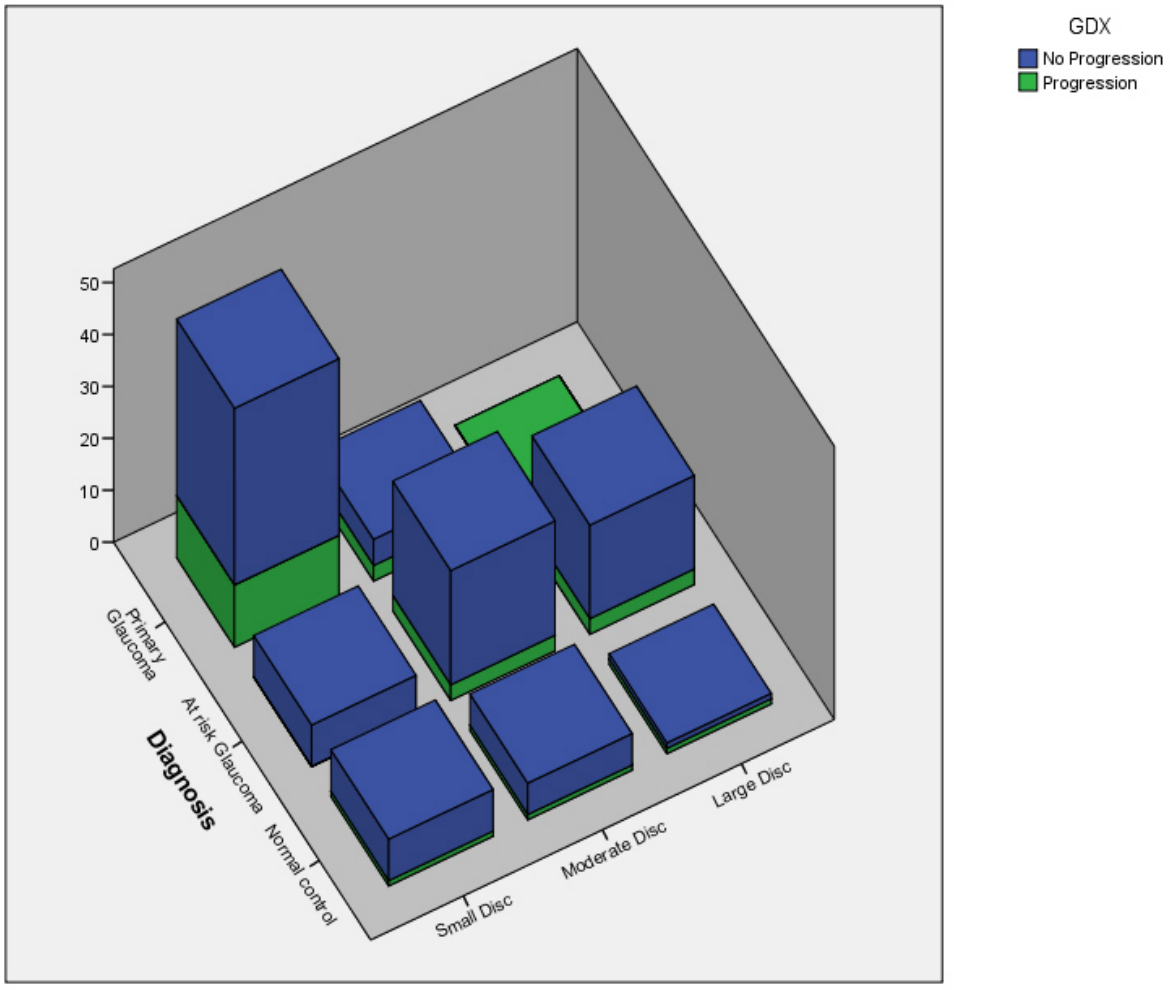
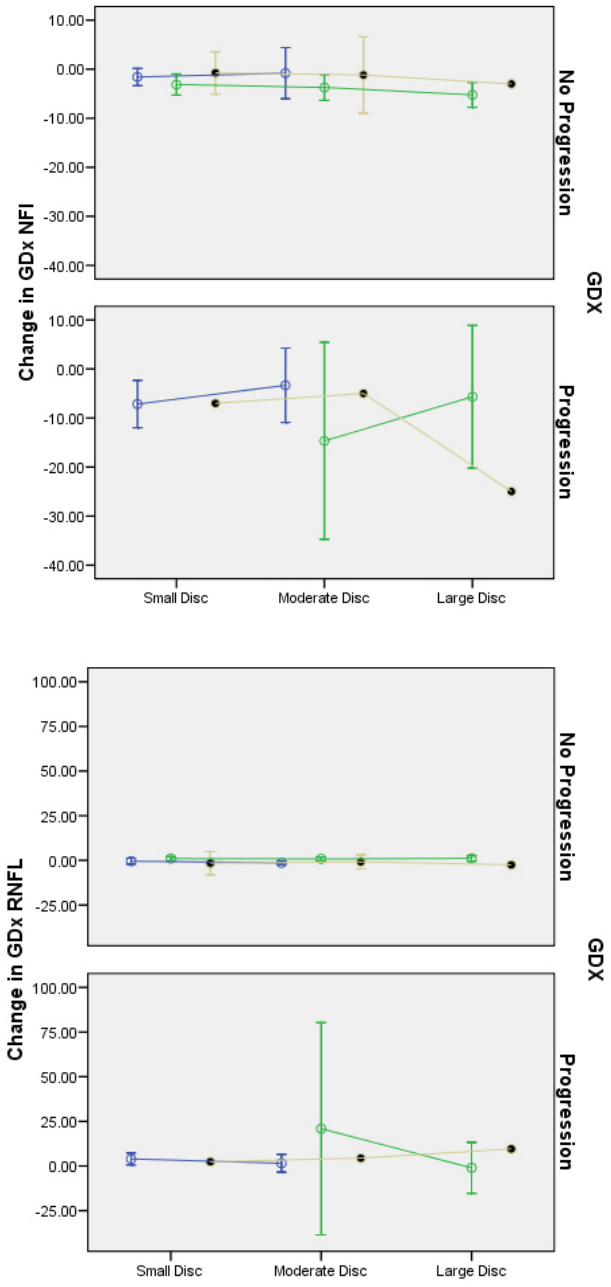


Figure 3.2.5: Distribution of progression in Scanning Laser Polarimetry (GDx VCC) among the study population, increasing disc size and progressed



3.2.6: Comparison of GDx parameters: NFI and RNFL between progressed and non progressed groups with increasing disc size

Scanning laser polarimetry (GDx VCC), NFI: Nerve fiber indicator, RNFL: Retinal nerve fiber layer thickness. Graphical representations: Primary Glaucoma: Blue, At risk: Green and Control: Golden yellow (black spots)

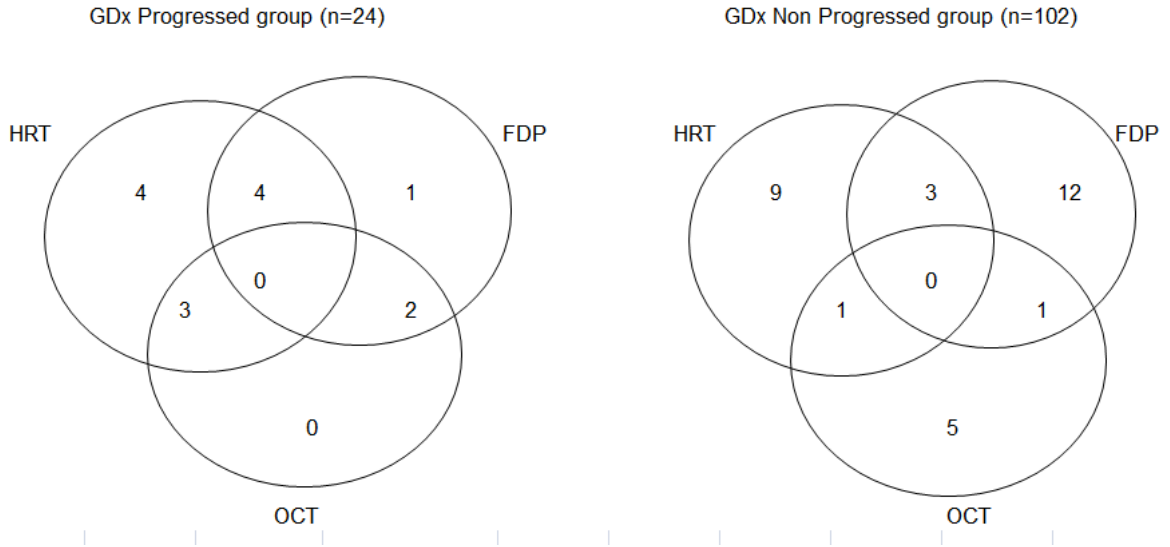


Figure 3.2.7: Progression GDx compared to HRT, OCT, FDP progression rates

Venn diagram shows the numbers of subjects progressed on GDx, OCT and FDP techniques among the progressors and non progressors on GDx. Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT), Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Frequency Doubling Perimetry (FDP)

3.2.4: Optical Coherence tomography (OCT)

RNFL and Optic scans from Time domain OCT report were used to obtain Average RNFL thickness, CD ratio, Cup depth, sectoral thickness and planimetry measures. The GLM showed significant average RNFL thickness (R: 0.577, $p<0.001$). There was a significant difference in the change in the average RNFL among the primary glaucoma (0.001, 95% CI 4.20 to 8.64) and at risk group (0.001, 95% CI: 4.85 to 8.42). There was no significant difference between OHT and Glaucoma suspects ($p>0.05$). (Table 3.2.2) A similar trend but lower values were observed for the RNFL thickness on GDx, the difference was not significant among primary glaucoma group (mean diff: -1.79, p=0.117 (95% CI: -

0.46 to 4.04)) but shows significant different in the at risk group (mean diff: -3.57, p=0.010 (95% CI: -6.28 to -0.86)).

Among 12 (80.0%, 95% CI: 54.8 to 92.9) of the 15 eyes of primary glaucoma who progressed, 77.8% (95% CI: 62.4 to 93.2) had small disc size. (Figure 3.2.8) Rate of RNFL loss was significantly higher among the progressed group (p=0.001, 95% CI 5.82 to 8.22). (Table 3.2.3) The RNFL differences varied with increasing disc size, the distribution was statistically significant. (Table 3.2.4) The distribution was different to that compared to GDx (p<0.001). Variability in RNFL was higher among the progressed group as compared to non progressed group. (Figure 3.2.9) Among those with progression in OCT, 50.0% (95% CI: 26.8 to 73.2) show progression in HRT. 28.6% (95% CI: 11.7 to 54.7) and 35.7% (95% CI: 16.3 to 61.2) showed progression in FDP and GDx respectively. Around 16.9% (95% CI: 11.1 to 24.9), 16.1% (95% CI: 10.4 to 23.9) and 21.4% (95% CI: 14.8 to 29.9) showed progression in GDx, FDP and HRT respectively, among the OCT non progressed group, the differences were statistically significant (p<0.001). (Figure 3.2.10)

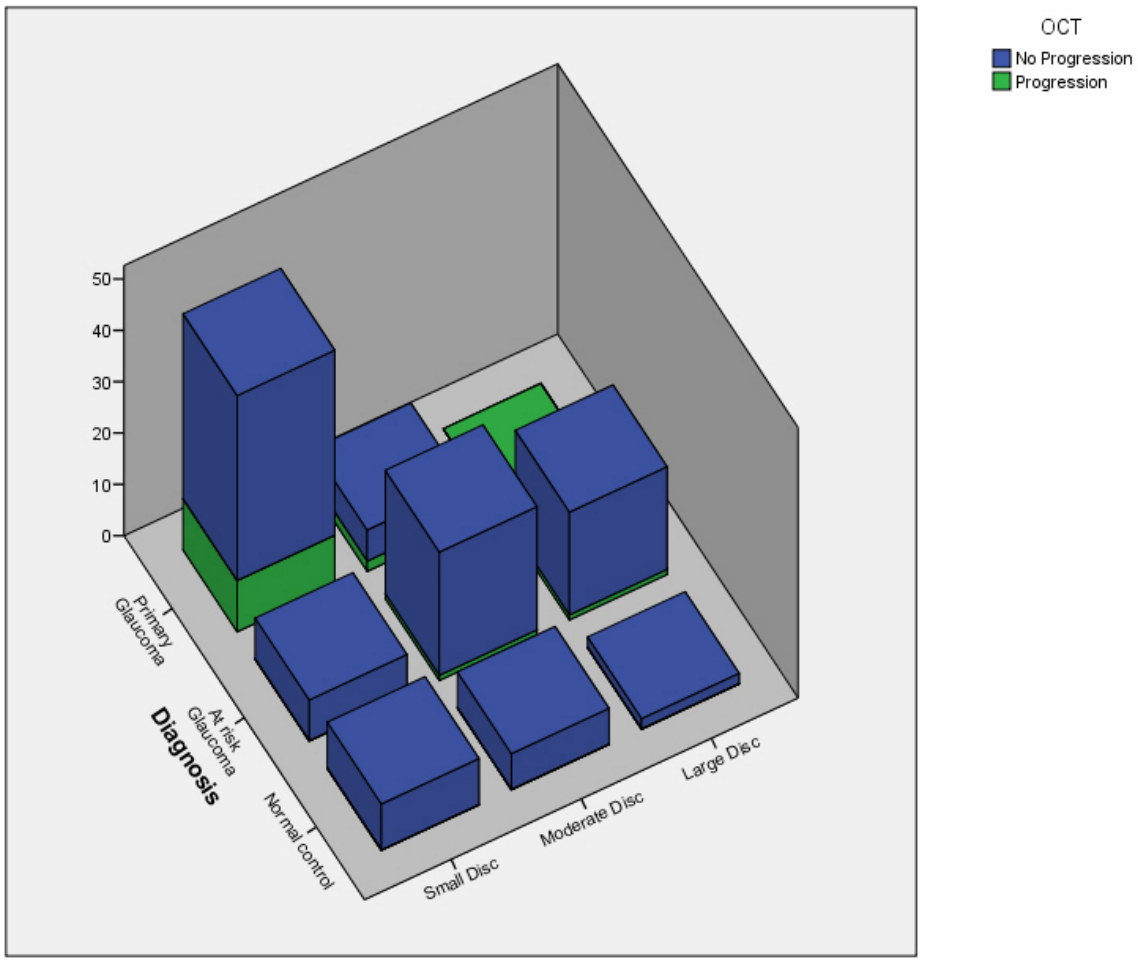


Figure 3.2.8: Distribution of progression in Optical Coherence Tomography (OCT) among the study population, increasing disc size and progressed

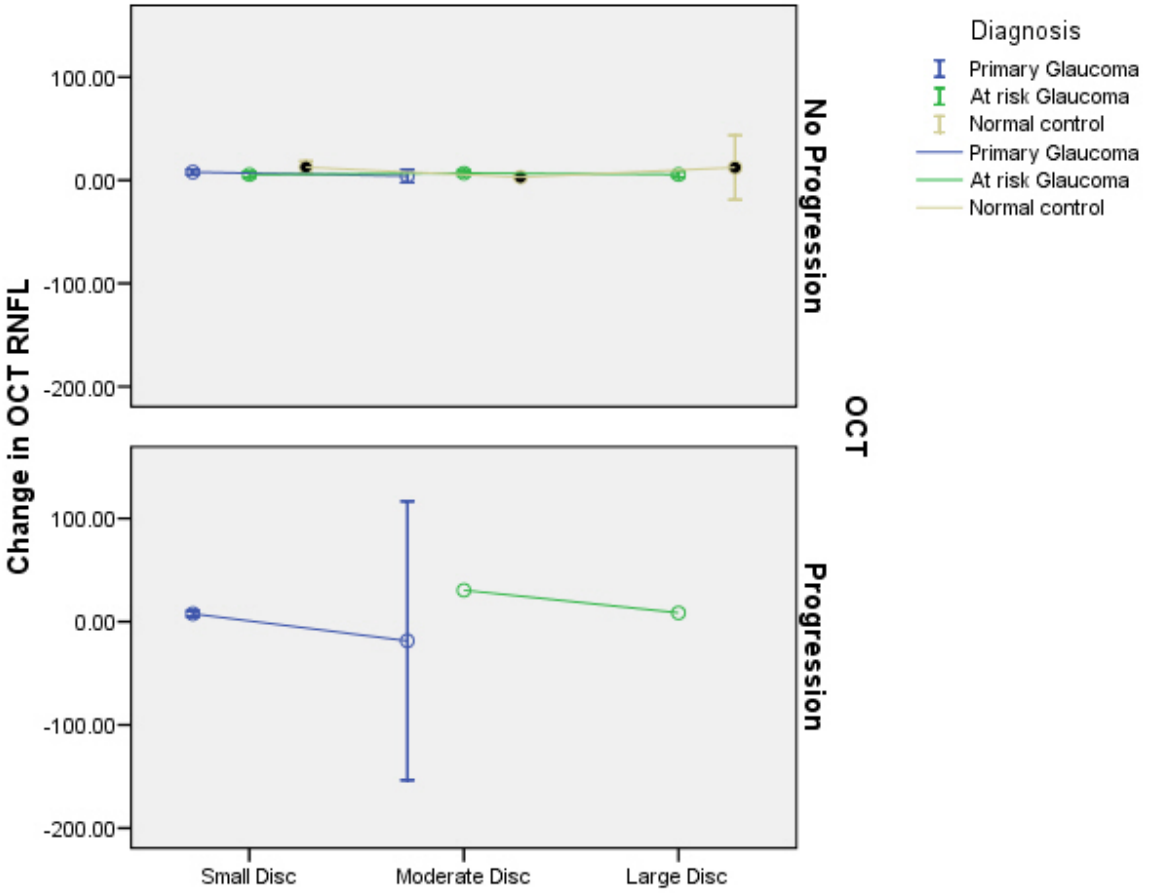


Figure 3.2.9: Comparison of OCT RNFL parameter between progressed and non progressed groups with increasing disc size

Optical coherence tomography (OCT), RNFL: Retinal nerve fiber layer thickness. Graphical representations: Primary Glaucoma: Blue, At risk: Green and Control: Golden yellow (black spots)

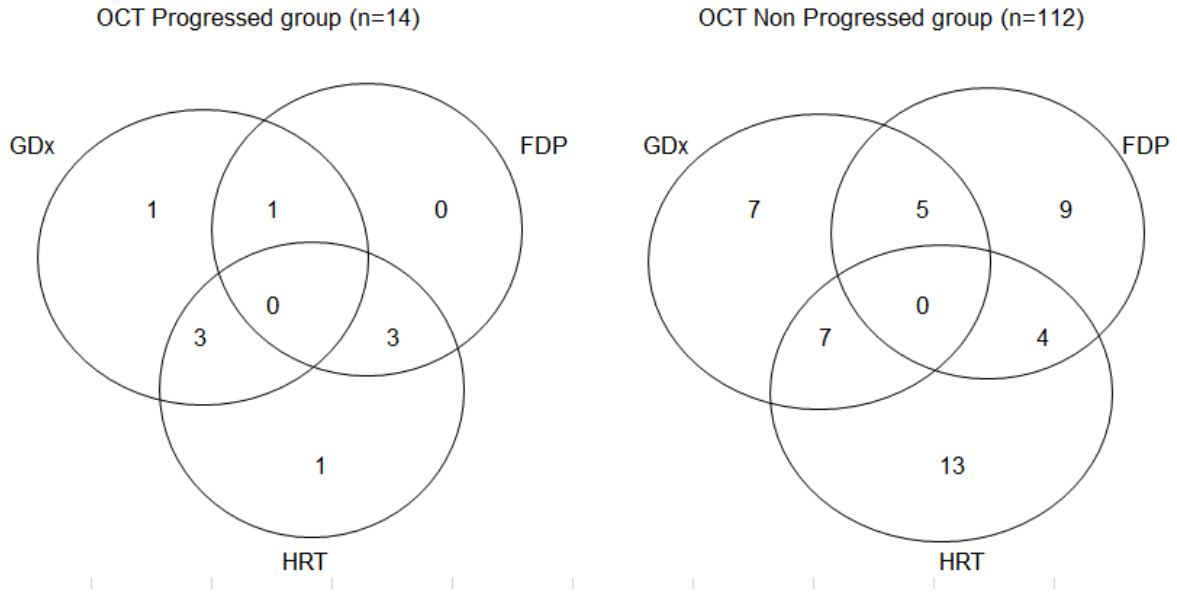


Figure 3.2.10: Progression OCT compared to HRT, GDx, FDP progression rates

Venn diagram shows the numbers of subjects progressed on GDx, OCT and FDP techniques among the progressors and non progressors on OCT. Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT), Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Frequency Doubling Perimetry (FDP)

Table 3.2.2 Comparison of structural imaging parameters between study populations

Parameter	Primary Glaucoma: n=54 #	Primary Glaucoma: n=54 *	At Risk Glaucoma: n=54 #	At Risk Glaucoma: n=54 *	Control: n=18 #	Control: n=18 *
HRT III						
Cup Area (in sq mm)	0.00 (0.13)	0.792 (-0.41 to 0.03)	-0.02 (0.15)	0.208 (-0.07 to 0.01)	-0.02 (0.13)	0.587 (-0.08 to 0.04)
Rim Area (in sq mm)	0.00 (0.13)	0.761 (-0.03 to 0.04)	0.02 (0.15)	0.207 (-0.01 to 0.07)	0.01 (0.13)	0.625 (-0.05 to 0.08)
HVC	-0.03 (0.03)	0.01 (-0.02 to 0.00)	0.00 (0.04)	0.939 (-0.01 to 0.00)	-0.01 (0.07)	0.529 (-0.04 to 0.02)
CSM	**-0.05 (0.09)**	**0.001 (-0.08 to -0.02)**	**-0.01 (0.05)**	**0.045 (-0.01 to 0.00)**	0 (0.04)	0.775 (-0.02 to 0.01)
RNFL (in microns)	0.00 (0.04)	0.262 (-0.01 to 0.01)	-0.14 (0.05)	0.90 (-0.03 to 0.00)	0.04 (0.16)	0.366 (-0.05 to 0.12)
FSM	0.10 (1.02)	0.466 (-0.17 to 0.38)	0.08 (1.06)	0.595 (-0.21 to 0.37)	-0.13 (1.38)	0.705 (-0.82 to 0.56)
RB	-0.08 (0.60)	0.304 (-0.25 to 0.08)	**-0.24 (0.56)**	**0.003 (-0.39 to -0.08)**	0.17 (0.83)	0.400 (-0.24 to 0.58)
GDx VCC						
NFI	0.54 (4.87)	0.413 (-0.78 to 1.87)	1.95 (7.06)	0.047 (-0.02 to 3.88)	-2.94 (7.79)	0.126 (-6.81 to 0.92)
RNFL (in microns)	**4.85 (5.79)**	**0.001 (3.27 to 6.43)**	**2.85 (5.92)**	**0.001 (1.23 to 4.47)**	0.19 (6.13)	0.898 (-3.23 to 2.85)
OCT						
RNFL in microns	**6.64 (6.52)**	**0.001 (4.85 to 8.42)**	**6.42 (8.13)**	**0.001 (4.20 to 8.64)**	4.05 (9.47)	0.163 (-0.32 to 8.47)

Change in parameters # mean difference (SD) * p value (95% CI of difference), statistical significance p<0.05. Height variation contour (HVC), cup shape measure (CSM) , Retinal nerve fiber layer (RNFL), linear discriminant functions, from Mikelberg et al (FSM) and Bathija et al (RB)

Table 3.2.3 Comparison of structural imaging parameters between progressed and non progressed groups

Parameter	Total: n=126 #	Total *	Progressed #	Progressed *	Not Progressed #	Not Progressed *
HRT III (Progressed: 31(24.60%)						
Cup Area (in sq mm)	-0.02 (0.14)	0.209 (-0.04 to 0.01)	0.01 (0.19)	0.876 (-0.08 to 0.07)	-0.02 (0.12)	0.122 (-0.04 to 0.01)
Rim Area (in sq mm)	0.02 (0.14)	0.207 (-0.01 to 0.04)	0.01 (0.19)	0.832 (-0.06 to 0.08)	0.02 (0.12)	0.132 (-0.01 to 0.04)
HVC	0.00 (0.04)	0.125 (-0.12 to 0.01)	-0.01 (0.04)	0.107 (-0.03 to 0.01)	0.00 (0.03)	0.469 (-0.01 to 0.01)
CSM	**-0.04 (0.09)**	**0.001 (-0.56 to -0.03)**	**-0.03 (0.09)**	**0.001 (-0.05 to -0.02)**	**-0.05 (0.101)**	**0.008 (-0.09 to -0.01)**
RNFL (in microns)	0.00 (0.08)	0.592 (-0.02 to 0.01)	-0.02 (0.06)	0.128 (-0.04 to 0.01)	0.00 (0.08)	0.922 (-0.16 to 0.01)
FSM	0.06 (1.09)	0.544 (-0.13 to 0.25)	0.18 (1.22)	0.416 (0.27 to 0.63)	0.02 (1.05)	0.855 (-0.19 to 0.23)
RB	-0.15 (0.63)	0.044 (-0.23 to 0.00)	-0.16 (0.67)	0.192 (-0.40 to 0.08)	-0.09 (0.62)	0.122 (-0.22 to 0.03)
GDx VCC (Progressed: 24 (19.04%)						
NFI	1.04 (6.08)	0.056 (-0.02 to 2.11)	**5.32 (10.35)**	**0.019 (0.95 to 9.69)**	0.04 (4.00)	0.923 (-0.75 to 0.82)
RNFL (in microns)	**5.12 (6.18)**	**0.001 (4.05 to 6.19)**	**8.08 (7.72)**	**0.001 (4.82 to 11.35)**	**2.69 (5.31)**	**0.001 (1.65 to 3.74)**
OCT (Progressed: 14 (11.11%)						
RNFL (in microns)	**6.86 (7.37)**	**0.001 (5.56 to 8.16)**	**7.02 (6.41)**	**0.001 (5.82 to 8.22)**	5.60 (13.02)	0.132 (-1.92 to 13.10)

Change in parameters # mean difference (SD) * p value (95% CI of difference), statistical significance p<0.05. Height variation contour (HVC), cup shape measure (CSM) , Retinal nerve fiber layer (RNFL), linear discriminant functions, from Mikelberg et al (FSM) and Bathija et al (RB)

Table 3.2.4 Comparison of structural imaging parameters across disc size groups

Parameter	Small Disc: n=63 #	Small Disc: n=63 *	Moderate Disc: n=40 #	Moderate Disc: n=40 *	Large Disc: n=23 #	Large Disc: n=23 *
HRT III						
Cup Area (in sq mm)	-0.02 (0.16)	0.330 (-0.06 to 0.02)	-0.01 (0.12)	0.491 (-0.05 to 0.03)	-0.01 (0.14)	0.697 (-0.07 to 0.03)
Rim Area (in sq mm)	-0.02 (0.15)	0.313 (-0.02 to 0.06)	0.01 (0.12)	0.501 (-0.03 to 0.05)	0.01 (0.14)	0.718 (-0.05 to 0.07)
HVC	-0.01 (0.04)	0.500 (-0.02 to 0.00)	0.00 (0.04)	0.860 (-0.01 to 0.01)	0.00 (0.03)	0.693 (-0.01 to 0.01)
CSM	**-0.04 (0.09)**	**0.001 (-0.06 to -0.02)**	**-0.04 (0.08)**	**0.002 (-0.07 to -0.01)**	-0.04 (0.10)	0.084 (-0.08 to 0.01)
RNFL (in microns)	0.00 (0.05)	0.415 (-0.02 to 0.01)	-0.01 (0.05)	0.083 (-0.03 to 0.01)	0.02 (0.16)	0.578 (-0.05 to 0.09)
FSM	0.15 (1.22)	0.347 (-0.16 to 0.45)	0.01 (0.57)	0.983 (-0.32 to 0.32)	-0.07 (0.85)	0.698 (-0.44 to 0.29)
RB	-0.09 (0.59)	0.188 (-0.25 to 0.05)	-0.17 (0.57)	0.059 (-0.36 to 0.01)	-0.05 (0.83)	0.771 (-0.41 to 0.31)
GDx VCC						
NFI	0.48 (5.23)	0.473 (-0.84 to 1.79)	1.95 (8.11)	0.137 (-0.65 to 4.54)	1.03 (3.76)	0.202 (-0.59 to 2.66)
RNFL (in microns)	**2.83 (5.73)**	**0.001 (1.38 to 4.27)**	**3.80 (6.54)**	**0.001 (1.71 to 5.89)**	**6.25 (5.90)**	**0.001 (3.27 to 8.81)**
OCT						
RNFL (in microns)	**8.22 (6.44)**	**0.001 (6.59 to 9.84)**	**5.08 (9.06)**	**0.001 (2.18 to 7.98)**	**6.25 (5.91)**	**0.001 (3.70 to 8.81)**

Change in parameters # mean difference (SD)* p value (95% CI of difference), statistical significance $p<0.05$. Height variation contour (HVC), cup shape measure (CSM) , Retinal nerve fiber layer (RNFL), linear discriminant functions, from Mikelberg et al (FSM) and Bathija et al (RB)

3.2.5 Discussion on Structural Imaging and Progression

The CSM in HRT and RNFL thickness on OCT and GDx were associated with the progression among primary glaucoma subjects over 5 years follow up period. Studies have also reported that RNFL thickness estimated in OCT and GDx were associated with progression. In HRT, the rate of RA and CSM measures loss was higher in glaucoma subjects who showed significant progression.[5]

There was no significant change in the planimetric measures among those progressed on HVF. ISNT pattern showed difference in only 4% of the study population. Studies from hospital based glaucoma groups report that change in ISNT to be associated with faster progression ratio. [80] In the current study 50% (95% CI 41.4 to 58.6) of the study population had small disc size and only 18.3% (95 %CI 12.5 to 25.9) had large disc. Recent studies also show that there is an increasing risk for progression with increasing disc size.[33,81] Lower progression rates in this population based cohort due to low severity scales at baseline could be attributed to insignificant change in planimetric measures.

Among the HRT parameters change in CSM showed significant association with progression. Significant change in CSM was observed among the primary glaucoma ($p=0.001$, 95% CI of diff. -0.08 to -0.02) and among the at risk population there was limited change in this study. (Table 3.2.2) Clinical studies report that the true progression rate is

unknown and it is possible that the visual field and imaging thresholds for change were not matched for specificity (false positive rates). Progression was better assessed using sectoral based analysis and the cup shape measure proved to be better predictors among primary glaucoma [30,31] and in cohort of ocular hypertensives over a ten year follow up.[34] Similar results were also reported in longitudinal studies, they also show that RA to be significant risk factor.[37,39] Cross-sectional studies have shown that the diagnostic ability of HRT to be influenced by increasing disc size.[81] Increasing disc size did not show significant change among the disc size independent HRT parameter, CSM showed significant change among small (p=0.001, 95% CI diff. -0.06 to -0.02) and moderate disc size (p=0.002, 95% CI diff. -0.07 to -0.01) group, after adjusting there was insignificant variability noted (Figure 3.2.3).

The rate of change of RNFL in GDx was associated with progression, the rate of change was significantly ($p<0.05$) higher among the primary glaucoma (4.85 (5.79)) and at risk population (2.85 (5.92)). Similar reports of change in GDx RNFL parameters have been reported by studies on glaucoma and at risk group. [40,42,48] The Groningen Longitudinal Glaucoma Study showed that the RNFL change is to be associated with losses in functional progression.[43-45]Increasing disc size was associated with higher variability in rate of change of RNFL.[81] (Table 3.2.4).

The rate of change of RNFL in OCT was associated with progression, the rate of change was significantly ($p<0.05$) higher among the primary glaucoma (6.64 (6.52)) and at risk population (6.42 (8.13)). OCT progression as defined by RNFL thinning was significantly different from baseline in two of three consecutive follow-up scans. Limited longitudinal OCT study in glaucomatous and glaucoma suspect subjects has been published. [52,53,56] RNFL thickness measured with these imaging techniques are not comparable, this has

been due to variability in the region of the retina examined by these techniques.[55,56] The change in RNFL thickness was higher for OCT as compared to GDx, this could be due to limitation in image centration, while capturing in time domain OCT technology. Increasing disc size was associated with higher variability in rate of change of RNFL thickness. (Table 3.2.4) In this population based cohort, the rate of change in RNFL thickness on OCT, GDX and CSM in HRT were associated with the progression over 5 years follow up period. Since most glaucoma subjects in this study population had less severe disease could have attributed to lower progression rates, estimated both qualitatively and progression in parameters among the structural imaging techniques.

3.3 FUNCTIONAL PERIMETRY AND PROGRESSION

3.3.1 Humphrey visual field Analyzer (HVF):

Progression in HVF was determined by using Hodapp Anderson and Parrish (HAP) classification,[76] Brusini GSS,[77] including advanced strategies such as Progressor and Visual field Index (VFI) in Glaucoma Progression analysis.[24,26] There was significant difference ($p<0.05$) in the rates of progression by each of the following techniques, 12 (9.5%, 95% CI: 5.5 to 15.9) showed progression in both Brusini, VFI and Progressor strategies. 8 (6.3%, 95% CI: 3.3 to 12) showed progression based on HAP classification. The distribution was significantly different ($p<0.05$) among the various study groups. One (5.6%, 95% CI 0.9 - 25.8) of the control subject showed progression in all the three techniques, the reports were verified and progression was confirmed by blinded observer. (Table 3.3.1) This subject showed significant change in GDx and not on HRT and OCT. The subject did not have any other ocular disease except that his cataract progressed significantly.

Over 63.8% (95% CI: 51.2 to 76.3) of the study population showed one stage worsening from baseline. In the early stages 0 to1 change was noted in 73% (95% CI: 65.1 to 87.4), 53% (95% CI: 40.3 to 69.1) and 52% (95% CI: 39.8 to 67.8) in control, at risk and primary glaucoma group respectively. Significant change was observed in 12 (9.5%, 95% CI: 5.5 to 15.9) of the study group, 8 (67%, 95% CI: 39.1 to 86.2) at risk group progressed and there was no difference in the OHT and glaucoma suspect subjects. 3 (5.6%, 95% CI: 1.9 to 15.1) primary glaucoma subjects showed shift to stage 3 in the final visit. The distribution was statistically significant ($p<0.05$). (Figure 3.3.1)

Among those who had progressed in HVF: 41.7% (95% CI: 19.3 to 68.1), 33.3% (95% CI: 13.8 to 60.9) and 25.0% (95% CI: 8.9 to 53.2) showed progression in FDP advanced, HVF Brusini and HVF HAP strategies respectively. One subject showed progression in all the three methods. Among the non progressed group progression was noted in FDP advanced (15.8%, 95% CI: 10.2 to 23.6) followed by 7.0% (95% CI: 3.6 to 13.2) in HVF Brusini method. In both the groups HVF HAP progression was the minimal compared to other strategies. (Figure 3.3.2)

There was a significant difference in the rate of progression in the perimetric progressed group 1.79 (0.96, $p=0.001$ (95% CI: 1.18 to 2.40) dB/year. Progressor software determines the slope of the progressed point in a visual field as compared to the overall data. The mean slope of progressed points: -2.75 (SD: 1.8) and mean slope of overall field: 0.177 (SD: 0.97), the difference was statistically significant ($p<0.001$, (95% CI of diff. -3.46 to -2.38)). (Table 3.3.2) VFI did not show statistically significant difference in baseline (ANOVA $p=0.540$) and follow up visit (ANOVA $p=0.954$). Adjusting for age related

normal variability the slope showed significant change in slope determined by HVF glaucoma progression analysis for the overall study population 2.35 (4.72) ($p<0.001$, 95% CI of diff 5.35 to 8.31) and for progressed group 6.83 (2.33) ($p=0.001$, 95 % CI of diff 5.35 to 8.31). The change in MD, PSD and time taken to perform test did not show statistical significant difference. (Table 3.3.2)

The mean VFI at baseline 97.02 (2.18) and at final follow up were 94.67 (4.41), the difference was statistically significant ($p=0.001$, 95 % CI: 1.52 to 3.18). The mean VFI at baseline for primary glaucoma, at risk and control group were 96.78 (2.27), 97.24 (2.18) and 97.11 (1.93) respectively. The mean VFI score at the final follow-up visit for primary glaucoma, at risk and control were 94.63 (4.70), 94.79 (4.25) and 94.44 (4.24) respectively and difference was statistically significant $p=0.002$ (95% CI of diff 0.85 to 3.44), $p=0.001$ (95% CI of diff 1.18 to 3.70) and $p=0.043$ (95% CI of diff 0.09 to 5.23). Comparing the change in other perimetric parameters among the various study population, the MD showed significant difference ($p=0.001$, 95 % CI of diff -2.56 to -0.82). (Table 3.3.3)

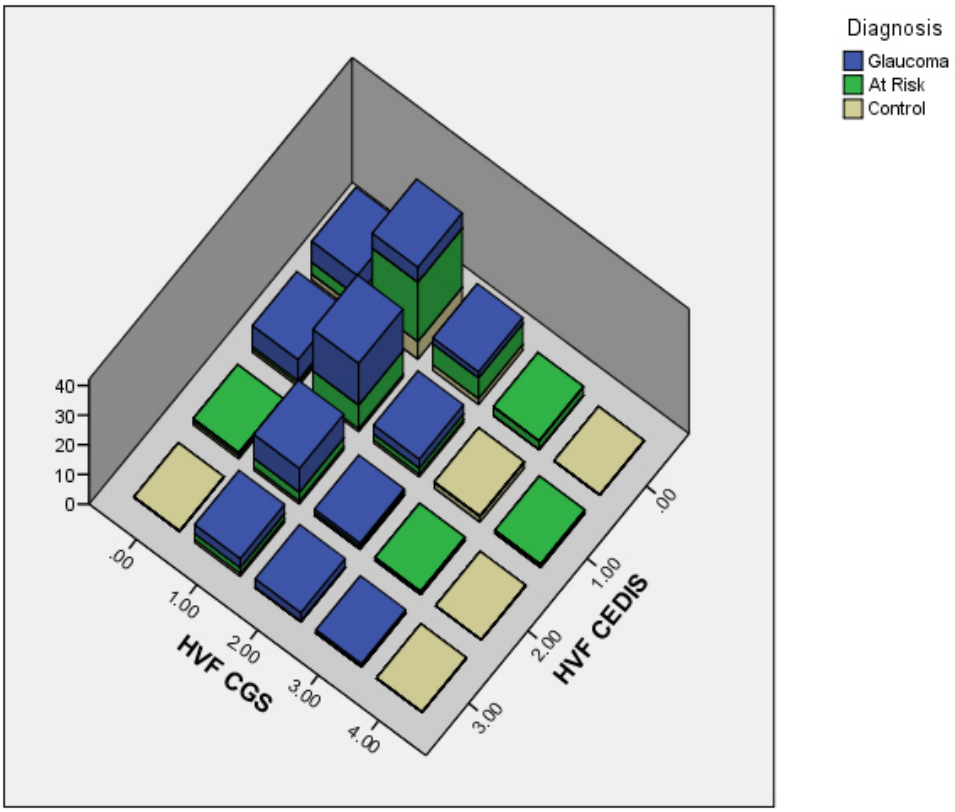


Figure 3.3.1: Distribution of HVF Brusini GSS from baseline to final visit across study groups

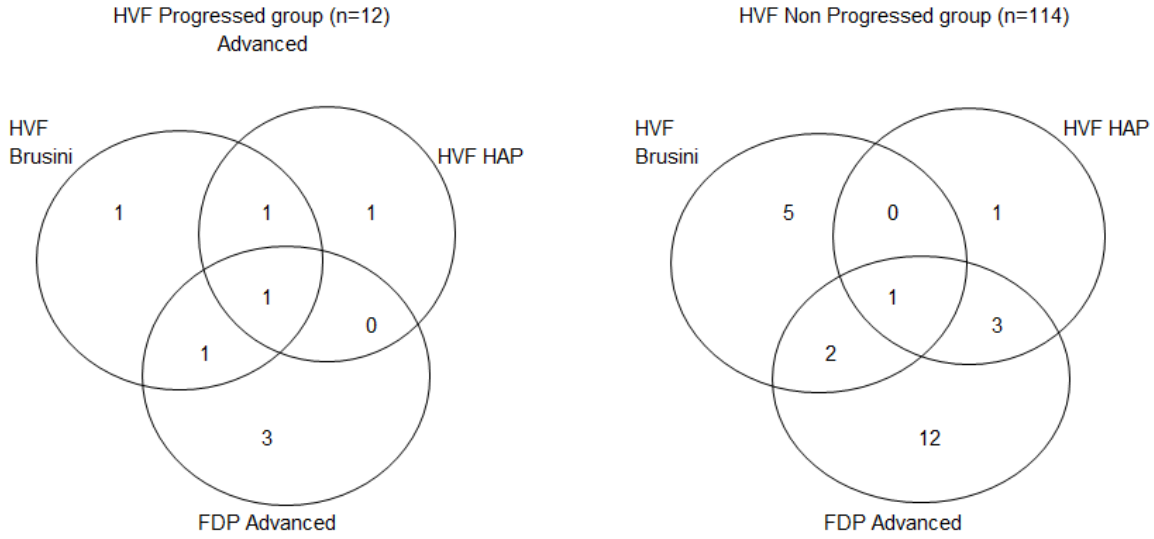


Figure 3.3.2: Progression by HVF advanced compared to HVF HAP, HVF Brusini GSS and FDP advanced strategies

Venn diagram shows the numbers of subjects progressed on HVF Brusini GSS2, HVF HAP and FDP advanced techniques among the progressors and non progressors on HVF advanced algorithm. Humphrey Visual Fields (HVF), Hodapp Anderson and Parrish (HAP), Frequency Doubling Perimetry (FDP)

3.3.2 Frequency doubling perimetry (FDP)

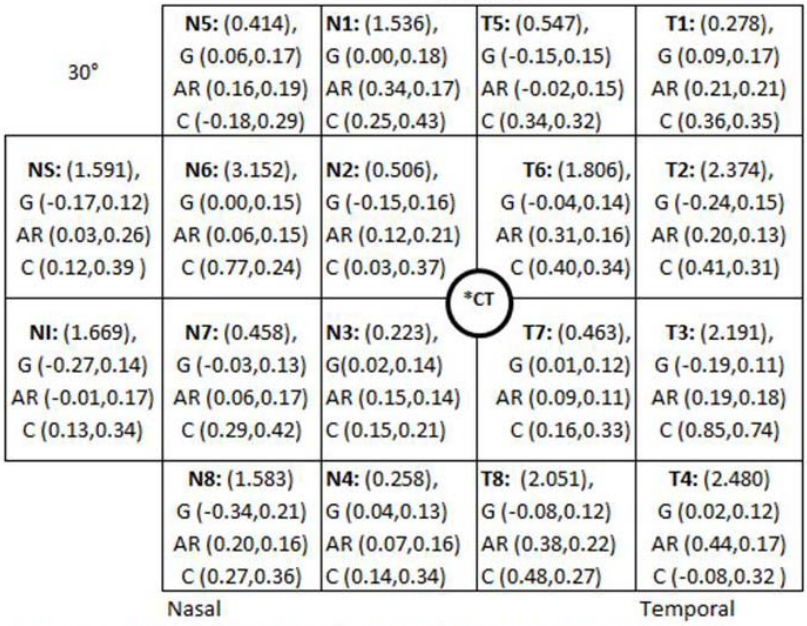
In the baseline study we analyzed the population norms for FDP and we reported the normal age related reduction in thresholds among healthy normals. The cross sectional study on 1299 subjects who participated in the CGS showed that the normal effect of aging on MD, PSD, CT, MS and Peripheral sensitivity on FDP were assessed on emmetropic controls. A weak negative, but significant correlation was observed for increasing age and CT (r -0.159, p=0.0001), and MS (r -0.258, p=0.0001), and peripheral average (r -0.234, p=0.0001). The MD (r- 0.033, p=0.404) and PSD (r –0.003, p=0.931) did not vary with increasing age among normal.[82] In the current study we report that long term change in MD, PSD and time in FDP did not vary significantly, though among the HVF progressed group the PSD showed a significant trend p=0.001 (95% CI of diff. 0.75 to 2.12). (Table 3.3.2)

Point wise linear regression analysis was performed for each of the 19 FDP locations using threshold from each follow-up visit. The mean slope (SE) in PLR for glaucoma, at-risk and control for either eye and for every threshold point is given in Figure 3.4.3. The slopes of the PLR for individual point varied between the study groups and the variability was higher for peripheral points as compared to central points. Progression based on PLR model was determined if the individual slopes were significantly different from the age matched control data. The progression in cluster of points was observed in 23 (18.25%, 95

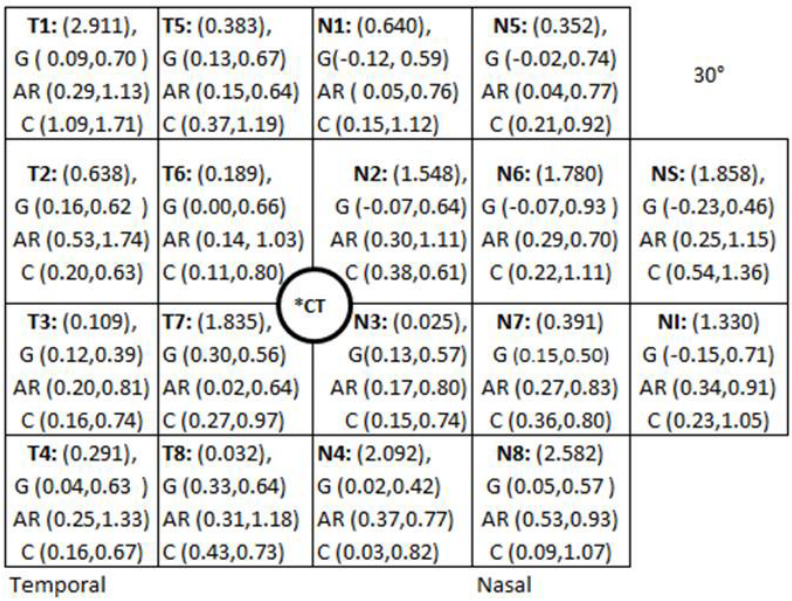
CI: 12.5 to 25.9) FDP reports using the PLR model. The change in other global indices of FDP did not show any significant trend between the study groups. (Table 3.3.3)

Among those with progression (n=23) and no progression (n=103) in FDP, structural progression was observed in any of the three imaging tools in 11 (47.8%, 95% CI: 29.2 to 67.0%) and 34 (33.0%, 95% CI: 24.7 to 42.6) respectively. Predominantly progression was noted in HRT and only 1 subject showed progression in GDx, OCT and HRT. (Figure 3.3.4)

Among those who had progressed in advanced strategy 52% (95 % CI: 33 to 71) also progressed in FDP Brusini strategy[79] and 35% (95% CI: 18 to 55) progressed in HVF advanced strategy. None showed progression in all the perimetric strategies and methods. Among the non progressed group, only 6.8% (95% CI: 3.3 to 13.4) showed progression in FDP Brusini classification system. (Figure 3.3.5)



* CT: Central Threshold- 0.702, G (0.05, 0.13), AR (0.10,0.18), C (0.26,0.26)
G: Primary Glaucoma, AR: at risk for glaucoma, C: Control
(T Stat), Disease(mean slope, standard error)



* CT: Central Threshold- 0.549, G (0.01, 0.44), AR (0.12,0.61), C (0.21,0.63)
G: Primary Glaucoma, AR: at risk for glaucoma, C: Control
(T Stat), Disease(mean slope, standard error)

Figure 3.3.3: Point wise linear regression (PLR) data for Frequency doubling perimetry

The PLR slopes measures between the study groups are shown for each location in Right and Left eye. The 19 test locations on the FDP full-threshold test are denoted with different notation based on location of the target to the CT. CT: central threshold.

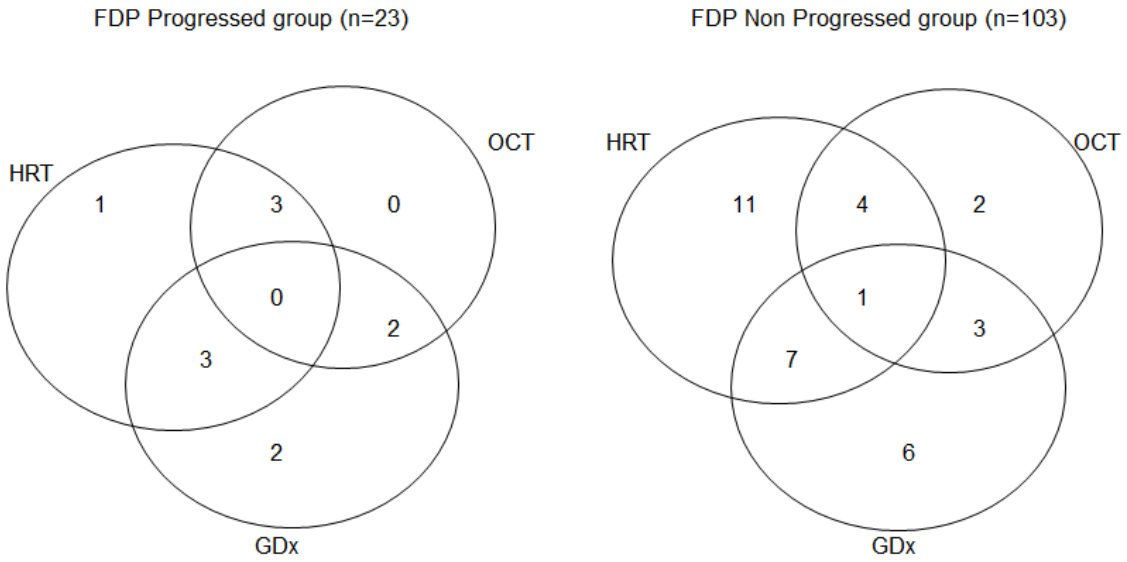


Figure 3.3.4: Progression by FDP advanced compared to HRT, OCT and GDx

Venn diagram shows the numbers of subjects progressed on GDx, OCT and HRT techniques among the progressors and non progressors on FDP. Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT), Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Frequency Doubling Perimetry (FDP)

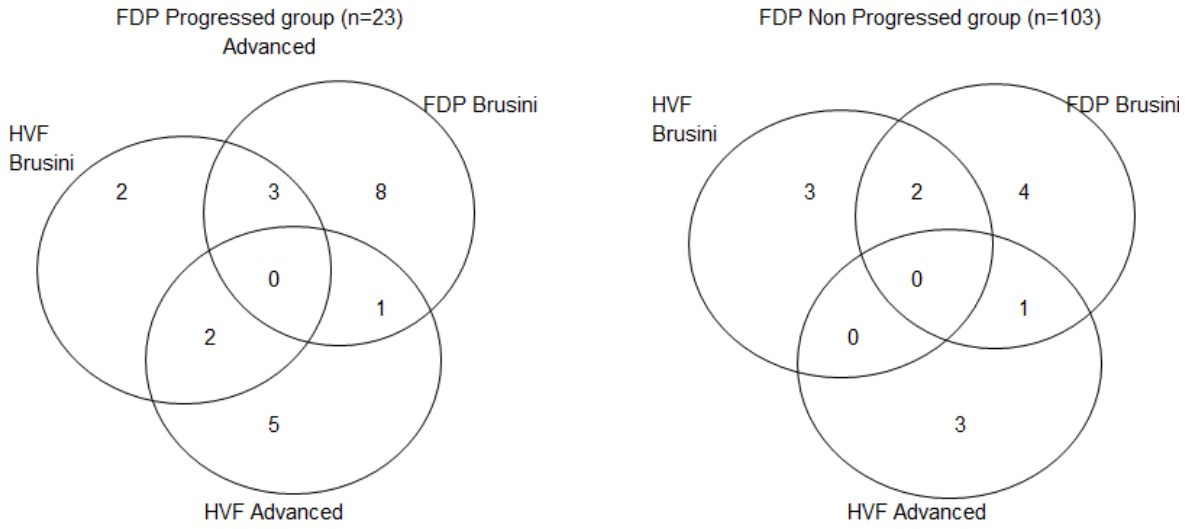


Figure 3.3.5: Progression by FDP advanced compared to FDP Brusini, HVF Brusini GSS and HVF advanced strategies

Humphrey Visual Fields (HVF), Frequency Doubling Perimetry (FDP)

Table 3.3.1: Comparison of perimetric progression rates estimated using various classification system.

Progression	**Overall (n=126): no (%, 95% CI)**	**Primary Glaucoma (n=54): no (%, 95% CI)**	**At risk for glaucoma (n=54): no (%, 95% CI)**	**Control (n=18): no (%, 95% CI)**
Humphrey Visual Fields (HVF)				
Brusini GSS[77]	12 (9.5, 5.5 to 15.9)	3 (5.6, 1.9 to 15.1)	8 (14.8, 7.7 to 26.6)	1 (5.6, 0.9 to 25.8)
HAP classification[76]	8 (6.3, 3.3 to 12.0)	2 (3.7, 1.0 to 12.5)	5 (9.3, 4.0 to 19.9)	1 (5.6, 0.9 to 25.8)
Advanced (Progressor[24] and VFI[26])	12 (9.5, 5.5 to 15.9)	7 (13.0, 6.4 to 24.4)	4 (7.4, 2.9 to 17.6)	1 (5.6, 0.9 to 25.8)
Frequency Doubling Perimetry (FDP)				
Brusini GSS[78]	19 (5.1, 9.9 to 22.4)	6 (11.1, 5.2 to 32.9)	12 (22.2, 13.2 to 34.9)	1 (5.6, 0.9 to 25.8)
Advanced (PLR)	23 (18.3, 12.5 to 25.9)	11 (20.4, 11.7 to 32.9)	11 (20.4, 11.7 to 32.9)	1 (5.6, 0.9 to 25.8)

Brusini GSS; Brusini Glaucoma Staging system, HAP; Hodapp Anderson Parrish Classification, PLR: Pointwise linear regression

Table 3.3.2: Comparison of perimetric parameters among progressed and non progressed group.

Parameter	Total Mean diff (SD), n=126	Total p* value (95% CI of difference)	Progressed Mean diff (SD)	Progressed p* value (95% CI of difference)	Not Progressed Mean diff (SD)	Not Progressed p* value (95% CI of difference)
Humphrey Visual Field (Progressed: 12(9.50%)						
Time (in seconds)	5.82 (71.82)	0.365 (-6.85 to 18.4)	-8.92 (81.57)	0.712 (-60.75 to 42.91)	7.37 (70.93)	0.270 (-5.79 to 20.53)
MD (in dB)	-0.22 (3.28)	0.450 (-0.80 to 0.35)	-0.30 (5.98)	0.863 (-4.10 to 3.49)	-0.21 (2.91)	0.435 (-0.75 to 0.33)
PSD (in dB)	0.04 (1.96)	0.837 (1.52 to 3.19)	0.14 (2.49)	0.850 (-1.44 to 1.72)	-0.24 (1.84)	0.890 (-0.32 to 0.37)
VFI	**2.35 (4.72)**	**0.001 (1.52 to 3.19)**	**6.83 (2.33)**	**0.001 (5.35 to 8.31)**	0.87 (5.76)	0.534 (-0.19 to 0.50)
Slope (dB/year)	**0.32 (1.49)**	**0.017 (0.06 to 0.58)**	**0.79 (0.96)**	**0.001 (0.48 to 2.40)**	017 (1.45)	0.224 (-0.10 to 0.44)
Frequency Doubling Perimetry (Progressed: 23(18.30%)						
Time (in seconds)	4.74 (30.05)	0.079 (-0.55 to 10.04)	7.87 (22.85)	0.113 (-2.01 to 17.75)	4.05 (31.48)	0.195 (-2.10 to 10.20)
MD (in dB)	0.22 (1.63)	0.412 (-0.31 to 0.76)	-0.87 (3.66)	0.267 (-2.44 to 0.76)	0.07 (2.89)	0.781 (-0.49 to 0.65)
PSD (in dB)	0.37 (1.62)	0.011 (0.09 to 0.66)	**1.44 (1.58)**	**0.001 (0.75 to 2.12)**	-0.14 (1.55)	0.369 (-0.44 to 0.16)

Change in parameters # mean difference (SD) * p value (95% CI of difference), statistical significance $p<0.05$. MD: Mean Deviation, PSD: Pattern standard deviation, VFI: Visual field index, dB; Decibel.

Table 3.3.3: Comparison of change in perimetric parameters between study groups

Parameter	**Primary Glaucoma: Mean diff (SD) n=54**	**Primary Glaucoma: p* value (95% CI of difference)**	**At Risk Glaucoma: Mean diff (SD) n=54**	**At Risk Glaucoma: p* value (95% CI of difference) n=54**	**Control: Mean diff (SD), n=18**	**Control: p* value (95% CI of difference) n=18**
Humphrey Visual Field						
Time (in seconds)	34.64 (61.95)	0.001 (17.70 to 51.52)	-7.20 (66.94)	0.433 (-25.47 to 11.07)	-41.50 (80.29)	0.043 (-81.42 to -1.57)
MD (in dB)	**-1.69 (3.20)**	**0.001 (-2.56 to -0.82)**	-0.64 (2.74)	0.093 (-1.38 to 0.11)	1.61 (3.35)	0.058 (-0.06 to 3.27)
PSD (in dB)	-0.45 (1.74)	0.060 (-0.93 to 0.02)	-0.34 (1.95)	0.212 (-0.87 to 0.19)	-0.11 (2.07)	0.814 (-1.14 to 0.92)
VFI	**2.44 (4.62)**	**0.001 (1.18 to 3.71)**	2.15 (4.75)	0.002 (0.85 to 3.45)	2.66 (5.16)	0.043 (0.09 to 5.23)
Slope (dB/year)	0.44 (1.62)	0.050 (0.00 to 0.88)	0.13 (1.48)	0.508 (-0.27 to 0.54)	0.05 (0.12)	0.647 (-0.01 to 0.03)
Frequency Doubling Perimetry						
Time (in seconds)	7.91 (33.06)	0.085 (-1.12 to 16.93)	4.37 (28.42)	0.264 (-3.39 to 12.13)	-3.61 (24.62)	0.542 (-15.85 to 8.62)
MD (in dB)	-0.29 (2.43)	0.374 (-0.96 to 0.37)	-0.06 (3.72)	0.900 (-1.07 to 0.95)	-0.36 (1.32)	0.156 (-0.37 to 2.09)
PSD (in dB)	-0.26 (1.52)	0.273 (-0.16 to 0.67)	-0.49 (1.83)	0.050 (-0.99 to 0.00)	-0.36 (1.32)	0.264 (-1.02 to 0.29)

Change in parameters # mean difference (SD) * p value (95% CI of difference), statistical significance $p<0.05$. MD: Mean Deviation, PSD: Pattern standard deviation, VFI: Visual field index, dB; Decibel.

3.3.3 Discussion on functional tests and progression

Clinically significant progression in HVF was observed in only 9.3% (95% CI: 5.1 to 16.2%) of the study cohort. The rate of progression was higher among the glaucoma (13%, 95% CI: 6.4 to 24.4) followed by OHT (7.4%, 95% CI: 2.9 to 17.5) and only 1 (5.6%, 95% CI: 0.9 to 25.8) of the control group showed progression. The Vellore Eye Study reported the progression after 5 year of OHT to POAG to be 17.4%. The rate of progression is low as compared to population based study published reports from the Indian population. [11] The possible differences could be due to the difference in study methodology and smaller cohort in these studies. The rate of progression in this cohort was 0.32 (1.49) db/year as defined by the glaucoma progression analysis. There was no significant difference ($p>0.05$) in the change in global indices. Rate of change of VFI index was significantly different among those who progressed ($p=0.001$, (95 % CI diff: 5.35 to 8.31) and the change was more among the primary glaucoma population ($p=0.001$, 95% CI diff. 1.18 to 3.71). Among the primary glaucoma group, MD ($p=0.001$, 95% CI diff -2.56 to -0.82) showed significant change, the variability could be due to the age related change in the cataract.

Clinical trials report the progression rates of visual field among glaucoma subjects. Heijl et al [83] compared the results published by these clinical trials. The Collaborative Normal Tension Glaucoma study report a rate of progression as 0.43 dB/year,[22] early manifest Glaucoma trial reported that the rate of progression as 0.36/dB and advanced glaucoma intervention study report a projected 0.3 db/year among the glaucoma subjects.[16,18] The studies also report association of higher or poor control of IOP to be significantly associated with progression.[16-21] Other major clinical studies show limited data on rate of progression and these variation in the published reports could be attributed to the

differences in study method and populations.[4,6,23,83] Perimetric severity is associated with risk for progression and most of the glaucoma subject in this study had early glaucomatous changes and risk factors.[83] This probably could be attributed to the poor association between control of IOP and rates of progression in this study.

The higher VFI at baseline among the study group relates to earlier or less advanced disease and thus the lower progression rates reported among this population based cohort.[26,83] Lower progression rates could also be due to stringent inclusion criteria for both imaging and perimetric data, thus limiting the number of eligible sample for this longitudinal study.

To the best of our knowledge, the current study is the first to report point wise linear regression data for assessing progression with FDP. Higher progression rate was reported for FDP 23 (95% CI: 18.3, 12.5 to 25.9) PLR method and 30.4 % (95 % CI: 15.6 to 50.9) showed progression in HRT. The change in other global indices of FDP did not show any significant trend between the study groups. FDP PLR shows higher progression among the study population, but only 34.8% (95% CI: 18.8 to 55.1) show progression in HVF advanced algorithm. The earlier progression should be assessed with caution, recent report show that the loss of FDP sensitivity is more a cortical phenomenon than retinal ganglion cell loss.[84] The true progression among this population based study would be obtained on extended longitudinal follow up of this cohort of subjects. There is poor comparison between various classification systems in assessing progression in perimetric techniques; studies comparing the efficacy on perimetric progression algorithm, also report higher variability in HVF. [6,17] In this population based cohort, HVF progression was observed in

only 9.3% (95% CI: 5.1 to 16.2%) and FDP PLR method (18.3, 95% CI: 12.5 to 25.9) showed higher progression rates.

3.4 RESULTS OF THE CGLONHIS: STRUCTURAL AND FUNCTIONAL PROGRESSION

Table 3.4.1 shows the structural and functional progression rates among the study groups, chi square for trend showed significant difference ($p<0.001$). 12 (9.5%, 95% CI: 5.5 – 15.9%) subjects of the overall study showed progression on visual field. There was no significant difference in the progression rates among the POAG and PACG groups in all the structural and functional techniques. Among the controls, progression on the GDx as defined was noted in 3 (16.7%, 95% CI: 5.8 – 39.2) and 1 (5.5%, 95% CI: 0.9 – 25.7%) showed perimetric progression. The LOCS II grades of these subjects were higher as compared to others, though this was not statistically significant ($p>0.05$). A statistically significant change was observed for mean retinal nerve fiber layer thickness (RNFL) on GDx (($p=0.002$), mean difference: -0.99 (SE: 0.25) microns) between the progressers and non progressed group. Generalized logistic linear regression analysis showed, the cup shape measure (CSM) in HRT (RR: 1.36, 95% CI: 1.23 to 2.13), and RNFL in GDx (RR: 1.45, 95% CI: 1.22 to 1.89) were significantly associated with the progression of glaucoma. Increasing Nerve Fiber Indicator on GDx VCC was not significantly associated (RR: 1.34, 95% CI: 0.97 to 2.32). Other parameters were not significantly associated with the progression. There was no difference in perimetric progression between the right and left eye in all the study groups.

3.4.1 Structural Progression:

A. Heidelberg retinal tomography- HRT III:

Among those with progression on HRT, 35.5% (95% CI: 21.1 to 53.0) showed progression in GDx and only 1 subject showed progression in GDx, OCT and HVF. 13.7% (95% CI: 8.2 to 22.0) showed progression on GDx among the HRT non progressed group, the differences were statistically significant ($p<0.001$). Perimetric progression was observed only in a limited number of subjects. (Figure 3.4.1)

B. Scanning laser polarimetry- GDx VCC:

Among those with progression on GDx, 45.8% (95% CI: 27.9 to 64.9) show progression in HRT. 20.8% (95% CI: 9.2 to 40.5) and 8.3% (95% CI: 2.3 to 25.9) showed progression in OCT and HVF respectively. Only 16.7% (95% CI: 10.7 to 25.1) showed progression on HRT among the GDx non progressed group, the differences were statistically significant ($p<0.001$). (Figure 3.4.2) GDx also showed progression among 3 (16.7, 95% CI: 5.8 to 39.2) controls. (Table 3.4.1)

C. Optical Coherence Tomography (Stratus OCT)

Among those with progression in OCT, 50.0% (95% CI: 26.8 to 73.2) show progression in HRT. 35.7% (95% CI: 16.3 to 61.2) and 14.3% (95% CI: 4.0 to 39.9) showed progression on GDx and HVF respectively. Only 21.4% (95% CI: 14.8 to 29.9) showed progression on HRT among the OCT non progressed group, the differences were statistically significant ($p<0.001$). Among the OCT non progressed group, 2 (1.8%, 95% CI: 0.5 to 6.3) subjects showed progression in GDx, HRT and HVF. (Figure 3.4.3)

3.4.2 Functional Progression:

A. Humphrey Visual Field (Progressor- HVF):

Among those with progression (n=12) and no progression (n=114) in HVF, structural progression was observed in any of the three imaging tools in 8 (66.7%, 95% CI: 39.1 to 86.2%) and 36 (31.5%, 95% CI: 23.7 to 40.6) respectively. Predominantly progression was noted in HRT and only 1 subject showed progression in GDx, OCT and HRT. (Figure 3.4.4)

3.4.3: Risk Factors Associated With Progression

The following risk factors were evaluated for its association with perimetric progression (Table 34.2). 63.8% (95% CI: 56.7 to 70.3) of the glaucoma group(s) were periodically using medication over two year period and 46.6% (95% CI: 38.7 to 54.1) were using medication for the complete follow-up period of the study. The compliance and persistence rates at the last follow-up visit was 43.3% (95% CI: 33.8 to 51.4) and 32.9% (95% CI: 25.3 to 42.2) respectively.

Table 3.4.1: Structural and Functional Progression among the study population

Techniques/study group	Glaucoma (n=54) Progression n (%, 95% CI)	At risk (n=54) Progression n (%, 95% CI)	Control (n=18) Progression n (%, 95% CI)
HRT	20 (37.0, 25.4 – 50.4)	11 (20.4, 17.6 – 40.9)	0
GDx VCC	15 (27.8, 17.6 – 40.9)	6 (11.1, 5.2 – 22.2)	3 (16.7, 5.8 – 39.2)
OCT	12 (22.2, 13.2 – 34.9)	2 (3.7, 1.0 – 12.5)	0
HVF	7 (13.0, 6.4 – 24.4)	4 (7.4, 2.9 – 17.5)	1 (5.6, 0.9 – 25.8)

(Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT)) , (Scanning laser polarimetry (GDx VCC) , Optical coherence tomography (OCT), Humphrey Visual field (HVF))

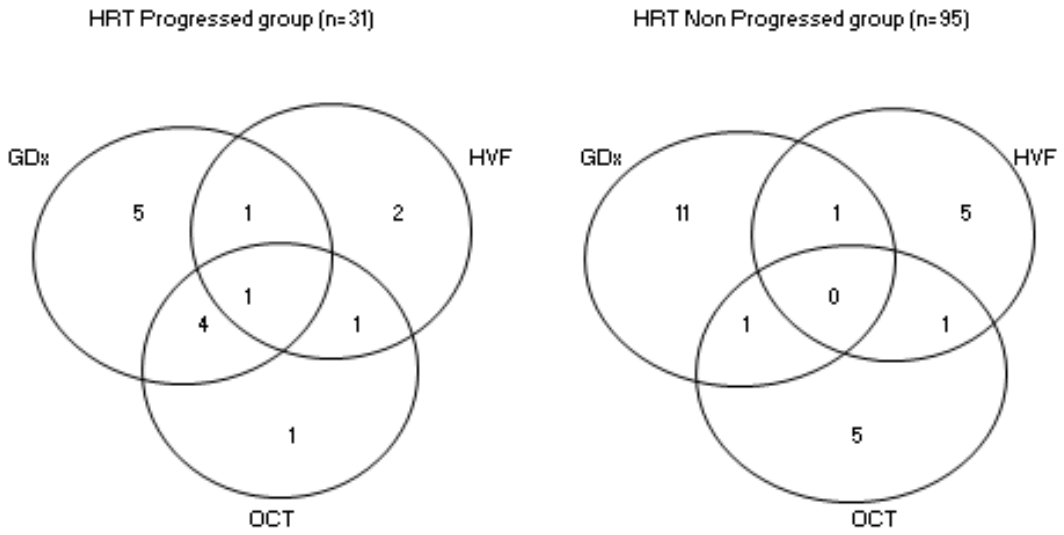


Figure 3.4.1: Progression HRT compared to GDX,OCT,HVF progression rates

Venn diagram shows the numbers of subjects progressed on GDx, OCT and HVF techniques among the progressors and non progressors on HRT. (Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT)), (Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Humphrey Visual field (HVF))

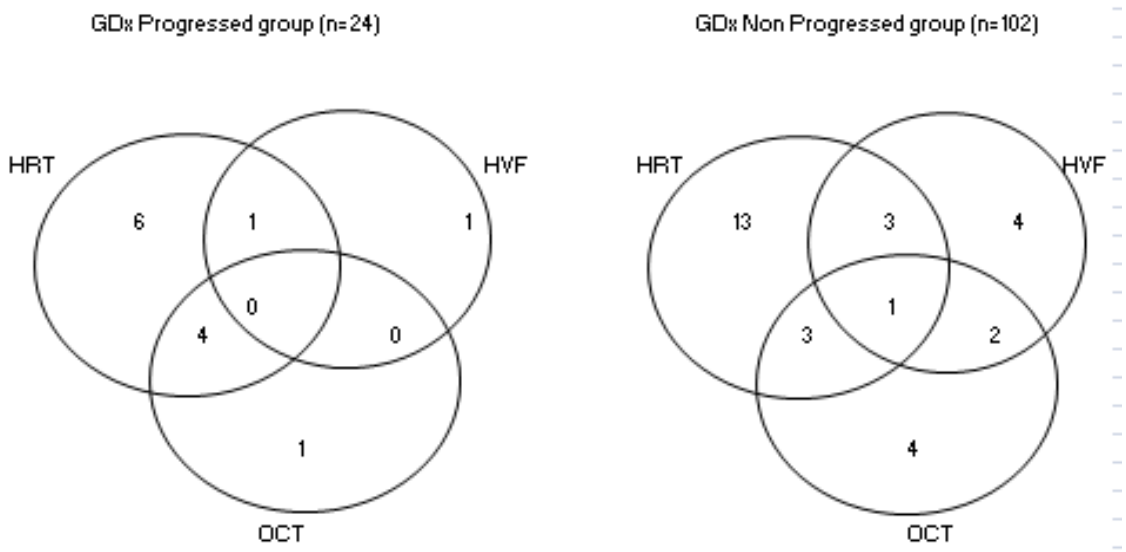


Figure 3.4.2: Progression among GDx group compared to HRT,OCT,HVF

Venn diagram shows the numbers of subjects progressed on HRT, OCT and HVF techniques among the progressors and non progressors on GDx. (Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT)) , (Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Humphrey Visual field (HVF))

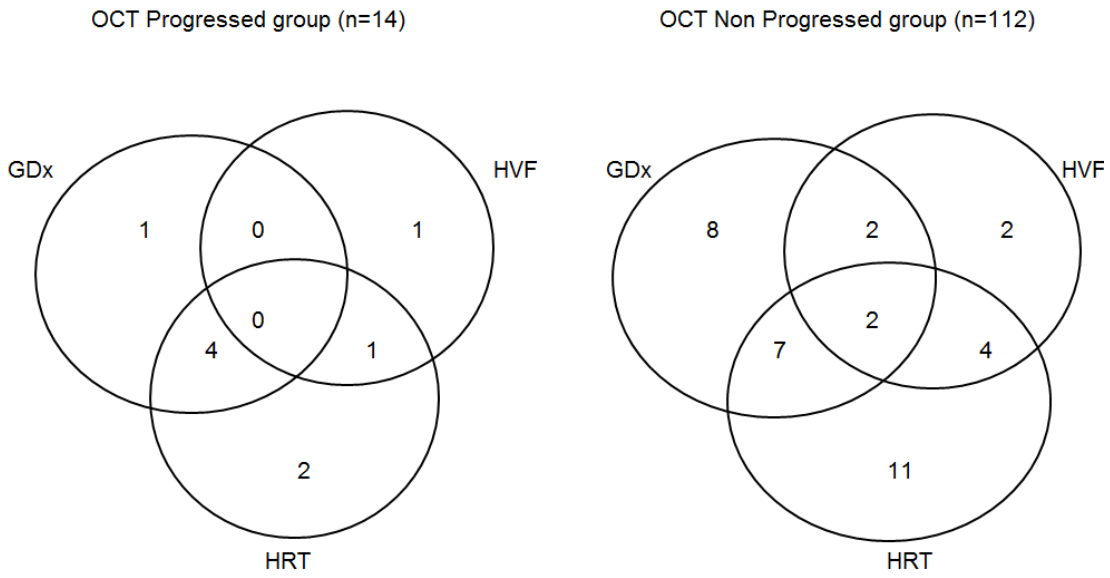


Figure 3.4.3: Progression among OCT group compared to HRT,GDx,HVF

Venn diagram shows the numbers of subjects progressed on GDx, HRT and HVF techniques among the progressors and non progressors on OCT. (Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT)) , (Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Humphrey Visual field (HVF))

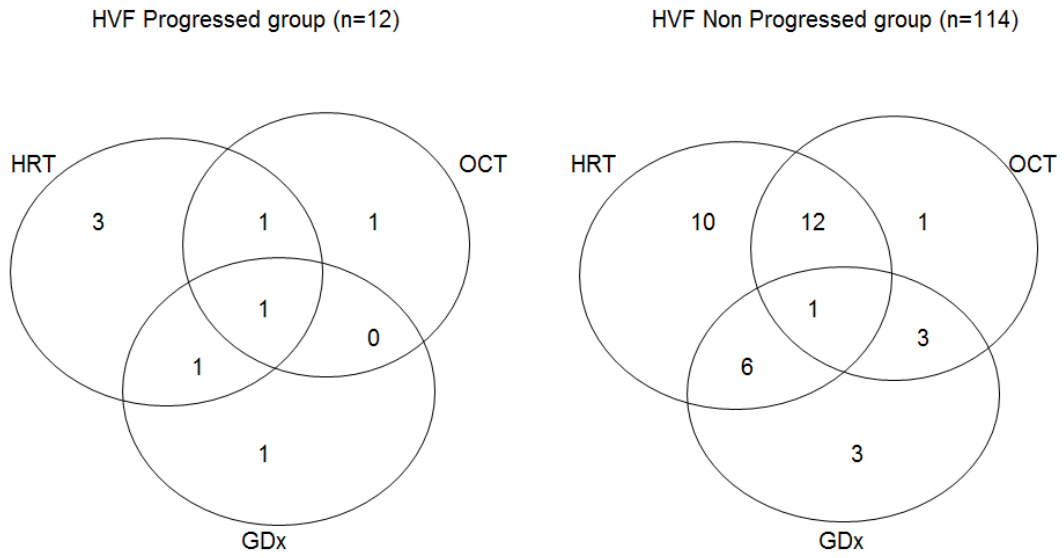


Figure 3.4.4: Progression among HVF group compared to HRT,GDx,OCT

Venn diagram shows the numbers of subjects progressed on GDx, OCT and HRT techniques among the progressors and non progressors on HVF. (Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT)), (Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Humphrey Visual field (HVF))

Table: 3.4.2 Risk Factors associated with Progression

Clinical		
Parameter	**Relative Risk**	**95% CI**
Age (>60 yrs)	**2.59**	**1.92 to 4.34**
Gender (Female)	0.78	0.56 to 1.67
Baseline IOP >22 mm Hg	1.33	0.95 to 1.87
Baseline CCT < 520 microns	1.10	0.98 to 1.54
IOP control	1.32	0.90 to 1.78
Disc Size (Moderate)	1.43	0.96 to 1.96
Disc Size (Large)	1.72	0.63 to 2.78
Perimetric (HVF)		
Mean deviation	1.35	0.88 to 1.76
Pattern Standard Deviation	1.26	0.92 to 1.98
	Perimetric (FDP)	
Mean deviation	1.23	0.76 to 1.65
Pattern Standard Deviation	1.06	0.72 to 1.88
Imaging Techniques		
HRT III		
Rim Area (in sq mm)	1.21	0.76 to 1.89
Cup Shape Measure	**1.36**	**1.23 to 2.13**
OCT		
Avg RNFL thickness (in microns)	1.11	0.89 to 2.10
GDx		
Avg RNFL thickness (in microns)	**1.45**	**1.22 to 1.89**
Nerve Fiber Indicator	1.34	0.97 to 2.32

The relative risk measures of Sig nificant risk factors are highlighted. IOP: Intraocular pressure, CCT: Central corneal thickness, RNFL: retinal nerve fiber layer, Confocal Scanning laser Ophthalmoscope: Heidelberg retinal tomography- III (HRT), (Scanning laser polarimetry (GDx VCC), Optical coherence tomography (OCT), Humphrey Visual field (HVF)).

3.4.4 Discussion

Clinically significant progression on HVF was observed in only 9.3% (95% CI: 5.1 to 16.2%) of the study cohort. The rate of progression was higher among the glaucoma (13%, 95% CI: 6.4 to 24.4) followed by OHT (7.4%, 95% CI: 2.9 to 17.5) and only 1 (5.6%, 95% CI: 0.9 to 25.8) of the control group showed any progression. The rate of progression is low as compared to published reports from the Indian population.[11, 60] The possible differences could be due to difference in study methodology and smaller cohort in this study. The study included stringent criteria for both imaging and perimetric data, thus limiting the number of eligible sample for this longitudinal study. Structural progression was noted in 29.6% (95% CI: 21.8 to 38.8%) on any imaging technique. We also report that HRT showed higher progression 50% of those progressed in HVF showed progression in HRT also. (Figure 3.4.4)

Studies report that severity of the disease to be an important variable in assessing progression in glaucoma, higher risk for progression was strongly associated with the higher severity of glaucoma at presentation.[85,86] We compared clinical parameters of glaucoma subjects between this population based study and to an age matched hospital based patients and reported that that the clinical parameters such as IOP, CD ratio, PSD were significantly

lower among the population based study population. [85] The lower progression rates in this study could be related to the lesser severity of the disease among the primary glaucoma and at risk population.

The current study showed that among the three imaging tools HRT (24.6%, 95% CI: 14.84 to 29.9) showed higher progression rates followed by GDx (19%, 95% CI: 13.2 to 26.8) and then by OCT (11.1%, 95% CI: 6.7 to 17.8). HRT showed higher rates of progression for Glaucoma groups followed by OHT group and none of the controls showed progression (Table 1). Among those with progression in HRT, 35.5% (95% CI: 21.1 to 53.1) show progression in GDx and only 1 subject showed progression in GDx, OCT and HVF. (Figure 3.4.1) The CSM in HRT were associated with the progression among primary glaucoma subjects over 5 years follow up period. Chauhan et al. showed similar results with HRT, Topographic Change Analysis (TCA), was tested in a longitudinal data set of 77 patients with early glaucomatous visual-field loss and compared with progression determined from visual fields. [31] Progression was identified by visual fields alone in 4% of patients, by both visual field and HRT in 29%, and by HRT alone in 40%, suggesting that HRT may be more sensitive at detecting progression than visual-field analysis. Progression was better assessed using sectoral based analysis and the cup shape measure proved to be better predictors in a cohort of ocular hypertensive's over a ten year follow up.[34]

Progression in GDx was observed in 37.0% (95% CI: 28.5 to 46.4) of the glaucoma cohort and 16.7% (95% CI: 5.8 to 39.2) of the controls also showed significant progression. (Table 3.4.1) Among those with progression in GDx, 45% (95% CI: 27.9 to 64.9) show progression in HRT. 21% (95% CI: 9.2 to 40.5) and 8.3% (95% CI: 2.3 to 25.9) showed progression in OCT and HVF respectively. (Figure 3.4.2) RNFL in GDx (RR: 1.45, 95% CI:

1.22 to 1.89) were significantly associated with the progression of glaucoma. Statistically significant change was observed for mean retinal nerve fiber layer thickness (RNFL) on GDx ((p=0.002), mean difference: -0.99 (SE: 0.25) microns) between the progressed and non progressed group. Gunvant et al.[42]derived limits of change from a test retest study in 27 normal eyes of 16 subjects. Of 17 eyes with a disc hemorrhage, followed for an average of 30.7 months, five (29%) exhibited change in GDx parameters greater than the limits for change. In this study 3 (16.7%, 95% CI: 5.8 to 39.2) control subjects showed progression in GDx, this could possibly be due to effect of cataract on polarizing light ray and the effective retardation measured. [46] In glaucoma suspects, GDx in particular yielded a rather high percentage of positive test results. The majority of these positive test results are presumably false-positive results rather than results indicating preperimetric glaucoma.[44-48]

Lower rates of progression were observed with the OCT among the study cohorts. (Table 3.4.1) This could be due to the large test retest variability which is due the centration differences while imaging in stratus OCT. Among those with progression on OCT, 50% (95% CI: 26.8 to 73.2) show progression in HRT. 36% (95% CI: 16.3 to 61.2) and 14% (95% CI: 4.0 to 39.9) showed progression in GDx and HVF respectively. (Figure 3.2.3) Sixty-four eyes of 37 subjects were imaged over a median of 4.7 years. OCT progression was defined as RNFL thinning of at least 20 μm (twice the device reproducibility error) from baseline in two of three consecutive follow-up scans.[52] Visual-field progression was defined as a reduction in mean deviation (MD) of 2 dB from baseline in two of three consecutive visits. Perimetric progression with HVF was seen in 13.0% (95% CI: 6.4 to 24.4) of the glaucoma cohort. HRT showed more significant progression rates followed by GDx and OCT in this population.

Older age, RNFL thickness on GDx and CSM in HRT were associated with the progression among primary glaucoma subjects over 5 years follow up period. Studies have also reported that low control of IOP was a significant risk factor for progression.[4, 6, 17, 23] Though in the current study control of IOP did not emerge as a significant risk factor, this could be attributed to early stage of glaucoma and to the poor persistence and compliance rates noted in the study group.

CHAPTER 4

Summary and Conclusion

4.1: SUMMARY OF RESULTS

A total of 54 eyes of 30 subjects with primary glaucoma (open angle 28 (51.8%) and angle closure 26 (48.2%)), 54 eyes at risk for glaucoma (30 (55.5%) ocular hypertensives (OHT) and 24 (44.5%) glaucoma suspects) and 18 eyes of 10 age matched control subjects were included for analysis. The mean follow-up period was 58.34 (SD: 3.76, min: 50 - max: 67) months and the mean age of the study cohort was 54.65 (5.7) years, the glaucoma group were significantly older than the other groups ($p<0.001$). There was a significant differences ($p<0.001$) in the proportions of subjects excluded between primary glaucomas, at risk and control groups. The MD in HVF (mean diff: -1.32, SE: 0.67) was higher among those excluded from analysis and this difference was statistically significant ($p<0.001$). None of the other clinical, perimetric and imaging parameters showed statistically significant differences between the two groups. Longitudinal studies on population based[11] and clinic based[79, 80] cohort report a similar trend in dropout and lower sample sizes.

Seven (13%, 95% CI: 6.4 - 24.4) of the primary glaucoma group showed perimetric progression. HRT showed higher progression (37%, 95% CI: 25.4 to 50.4) as compared to other imaging techniques. There was no significant difference in the progression rates among the POAG and PACG groups in all the structural and functional techniques. Among the controls, progression on the GDx as defined was noted in 3 (16.7%, 95% CI: 5.8 - 39.2) and 1 (5.5%, 95% CI: 0.9 - 25.7%) showed perimetric progression. A statistically significant change was observed for mean retinal nerve fiber layer thickness (RNFL) on GDx (($p=0.002$), mean difference: -0.99 (SE: 0.25) microns) between the progressers and non progressed group. Generalized logistic linear regression analysis showed, the cup shape measure (CSM) in HRT (RR: 1.36, 95% CI: 1.23 to 2.13), and RNFL in GDx (RR: 1.45,

95% CI: 1.22 to 1.89) were significantly associated with the progression of glaucoma. Lower rates of progression were observed with the OCT among the study cohorts. Older age, RNFL thickness on GDx and CSM in HRT were associated with the progression among primary glaucoma subjects over 5 years follow up period. HRT showed more significant progression rates followed by GDx and OCT in this population. Similar results have been shown by studies comparing all imaging techniques with perimetric progression.[47,49,89]

The rate of progression is low as compared to published reports from the Indian population.[11, 60] 17% of the OHTs converted to POAG over a five year period in small cohort from the VES, [11] as compared to 7.4 % (95% CI: 2.9 – 17.5) in this study. The possible differences could be due to difference in study methodology and smaller cohort in this study. The study included stringent criteria for both imaging and perimetric data, thus limiting the number of eligible sample for this longitudinal study. Studies report that severity of the disease to be an important variable in assessing progression in glaucoma, higher risk for progression was strongly associated with the higher severity of glaucoma at presentation.[79,80] The lower progression rates in this study could be related to the lesser severity of the disease among the primary glaucoma and at risk population.

Studies show that HRT may be more sensitive at detecting progression than visual-field analysis. [31] Progression was better assessed using sectoral based analysis and the cup shape measure proved to be better predictors in a cohort of ocular hypertensive's over a ten year follow up.[34] Studies have also reported that control of IOP was a significant risk factor for progression.[4,6,17,23] We found that Older age, RNFL thickness on GDx and CSM in HRT

were associated with the progression among primary glaucoma subjects over 5 years follow up period.

Planimetric values estimated with Cyoptique GL, Small discs were taken as those with a disc area less than 2.21 mm^2, moderate disc as between 2.21 and 2.77 mm^2 and large discs when disc area was greater than 2.77 mm^2. 50% (95% CI: 41.4 to 58.6) of the study population had small disc followed by moderate disc (31.7%,95% CI: 24.3 to 40.3) and Large discs (18.3%, 95% CI: 12.5 to 25.9). Planimetric measure on ONH photographs did not show significant change over time, this could be explained due to the more number of smaller disc and less severe disease status in the entire group studied. There was no significant change in the planimetric measures among those progressed on HVF. ISNT pattern showed difference in only 4% of the study population. Studies from hospital based glaucoma groups report that change in ISNT to be associated with faster progression ratio. [80] Recent studies also show that there is an increasing risk for progression with increasing disc size.[33,83] In the current study 50% (95% CI 41.4 to 58.6) of the study population had small disc size and only 18.3% (95 %CI 12.5 to 25.9) had large disc.

The GLM regression model for significant change ($p<0.05$) for longitudinal follow up for clinical progression were observed for CA (R=0.276), RA (R=0.346), CSM (R =0.567), HVC (R=0.236), mean RNFL (R=0.335), FSM (R=0.346) and RB (R=0.296). These parameters from HRT III were used to assess progression. In both the primary glaucoma group and at risk population, CSM showed statistically significant change and the RB discriminant function showed significant change in the at risk population (p=0.003, 95% CI of diff. -0.39 to -0.08). The long term variability was observed for CSM (p=0.001, 95%

CI of difference: -0.56 to -0.03) and other HRT parameters did not show significant variability. CSM also showed significant change between the progressed (p=0.001, 95% CI of difference: -0.05 to -0.02) and non progressed (p=0.008, 95% CI of difference: -0.09 to -0.01) groups too.

Clinical studies report that progression was better assessed using sectoral based analysis and the cup shape measure proved to be better predictors among primary glaucoma [30,31] and in cohort of ocular hypertensives over a ten year follow up.[34] Similar results were also reported in longitudinal studies, they also show that RA and CSM to be significant risk factor.[37,39] Cross-sectional studies have shown that the diagnostic ability of HRT to be influenced by increasing disc size.[82] Increasing disc size did not show significant change among the disc size independent HRT parameter, CSM showed significant change among small (p=0.001, 95% CI diff. -0.06 to -0.02) and moderate disc size (p=0.002, 95% CI diff. -0.07 to -0.01) group, after adjusting there was insignificant variability noted.

In GDx VCC, GLM showed significance for NFI (R: 0.389, p<0.001) and Average RNFL thickness (R: 0.527, p<0.001). There was a significant difference in the change in the average RNFL among the primary glaucoma (0.001, 95% CI 3.27 to 6.43) and at risk group (0.001, 95% CI 1.23 to 4.47). There were significant differences between OHT and Glaucoma suspects (p<0.05). Change in NFI did not show statistically significant difference across the study groups. There was an increase in the RNFL differences with increasing disc size, the distribution was statistically significant.

The rate of change of RNFL in GDx was associated with progression, the rate of change was significantly (p<0.05) higher among the primary glaucoma (4.85 (5.79)) and at

risk population (2.85 (5.92)). Similar reports of change in GDx RNFL parameters have been reported by studies on glaucoma and at risk group. [40,42,48] The Groningen Longitudinal Glaucoma Study showed that the RNFL change to be associated with losses in functional progression.[43-45]Increasing disc size was associated with higher variability in rate of change of RNFL.[82] (Table 3.3.4)

The GLM showed significance Average RNFL thickness (R: 0.577, $p<0.001$) in OCT. There was a significant difference in the change in the average RNFL among the primary glaucoma (0.001, 95% CI 4.20 to 8.64) and at risk group (0.001, 95% CI: 4.85 to 8.42). Among 12 (80.0%, 95% CI: 54.8 to 92.9) of the 15 eyes of primary glaucoma who progressed, 77.8% (95% CI: 62.4 to 93.2) had small disc size. Rate of RNFL loss was significantly highest among the progressed group ($p=0.001$, 95% CI 5.82 to 8.22). The RNFL differences varied with increasing disc size, the distribution was statistically significant

The rate of change of RNFL in OCT was associated with progression, the rate of change was significantly ($p<0.05$) higher among the primary glaucoma (6.64 (6.52)) and at risk population (6.42 (8.13)). OCT progression as defined by RNFL thinning significantly different from baseline in two of three consecutive follow-up scans. Limited longitudinal OCT study in glaucomatous and glaucoma suspect subjects has been published. [52,53,56] RNFL thickness measured with these imaging techniques are not comparable, this has been due to variability in the region of the retina examined by these techniques.[55,56] The change in RNFL thickness was higher for OCT as compared to GDx, this could be due to limitation in image centration, while capturing in time domain OCT technology. Increasing disc size was

associated with higher variability in rate of change of RNFL. In this population based cohort, the rate of change in RNFL thickness on OCT, GDX and CSM in HRT were associated with the progression over 5 years follow up period. Since most glaucoma subjects in this study population had less severe disease could have attributed to lower progression rates, estimated both qualitatively and progression in parameters among the structural imaging techniques.

In HVF, there was significant difference ($p<0.05$) in the rates of progression by each of the following techniques: Hodapp Anderson and Parrish (HAP) classification,[76] Brusini GSS,[77] including advanced strategies such as Progressor and Visual field Index (VFI) in Glaucoma Progression analysis.[24,26] 12 (9.5%, 95% CI: 5.5 to 15.9) showed progression in both Brusini, VFI and Progressor strategies. 8 (6.3%, 95% CI: 3.3 to 12) showed progression based on HAP classification. The distribution was significantly different ($p<0.05$) among the various study groups. There was a significant difference in the rate of progression in the perimetric progressed group 1.79 (0.96, $p=0.001$ (95% CI: 1.18 to 2.40) dB/year. Progressor software determines the slope of the progressed point in a visual field as compared to the overall data. The mean slope of progressed points: -2.75 (SD: 1.8) and mean slope of overall field: 0.177 (SD: 0.97), the difference was statistically significant ($p<0.001$, (95% CI of diff. -3.46 to -2.38)). The mean VFI at baseline 97.02 (2.18) and at final follow up were 94.67 (4.41), the difference was statistically significant ($p=0.001$, 95 % CI: 1.52 to 3.18). The mean VFI at baseline for primary glaucoma, at risk and control group were 96.78 (2.27), 97.24 (2.18) and 97.11 (1.93) respectively. VFI did not show statistically significant difference in baseline (ANOVA $p=0.540$) and follow up visit (ANOVA $p=0.954$). Adjusting for age related normal variability the slope showed significant change in slope determined

by HVF glaucoma progression analysis for the overall study population 2.35 (4.72) ($p<0.001$, 95% CI of diff 5.35 to 8.31) and for progressed group 6.83 (2.33) ($p=0.001$, 95 % CI of diff 5.35 to 8.31).

The Vellore Eye Study reported the progression after 5 year of OHT to POAG to be 17.4%. The rate of progression is low as compared to population based study published reports from the Indian population. [11] The possible differences could be due to difference in study methodology and smaller cohort in these studies. Clinical trials report the progression rates of visual field among glaucoma subjects. Heijl et al [85] compared the results published by these clinical trials. The Collaborative Normal Tension Glaucoma study report a rate of progression as 0.43 dB/year,[22] early manifest Glaucoma trial reported that the rate of progression as 0.36/dB and advanced glaucoma intervention study report a projected 0.3 db/year among the glaucoma subjects.[16,18] The studies also report association of higher or poor control of IOP to be significantly associated with progression.[16-21] Other major clinical studies show limited data on rate of progression and these variation in the published reports could be attributed to the differences in study method and populations.[4,6,23,84] Perimetric severity is associated with risk for progression and most of the glaucoma subject in this study had early glaucomatous changes and risk factors.[84] This probably could be attributed to the poor association between control of IOP and rates of progression in this study. The higher VFI at baseline among the study group relates to earlier or less advanced disease and thus the lower progression rates reported among this population based cohort.[26,84] Lower progression rates could also be due to stringent inclusion criteria for both imaging and perimetric data, thus limiting the number of eligible sample for this longitudinal study.

In the current study we report that long term change in MD, PSD and time in FDP did not vary significantly, though among the HVF progressed group the PSD showed a significant trend p=0.001 (95% CI of diff. 0.75 to 2.12). Point wise linear regression analysis was performed for each of the 19 FDP locations using threshold from each follow-up visit. The slopes of the PLR for individual point varied between the study groups and the variability was higher for peripheral points as compared to central points. Progression based on PLR model was determined if the individual slopes were significantly different from the age matched control data. The progression in cluster of points was observed in 23 (18.25%, 95 CI: 12.5 to 25.9) FDP reports using the PLR model. Among those who had progressed in advanced strategy 52% (95 % CI: 33 to 71) also progressed in FDP Brusini strategy[78] and 35% (95% CI: 18 to 55) progressed in HVF advanced strategy. None showed progression in all the perimetric strategies and methods. Among the non progressed group, only 6.8% (95% CI: 3.3 to 13.4) showed progression in FDP Brusini classification system.

To the best of our knowledge, the current study is the first to report point wise linear regression data for assessing progression with FDP. Higher progression rate was reported for FDP 23 (95% CI: 18.3, 12.5 to 25.9) PLR method and 30.4 % (95 % CI: 15.6 to 50.9) showed progression in HRT. The change in other global indices of FDP did not show any significant trend between the study groups. FDP PLR shows higher progression among the study population, but only 34.8% (95% CI: 18.8 to 55.1) show progression in HVF advanced algorithm. The earlier progression should be assessed with caution, recent report show that the loss of FDP sensitivity is more a cortical phenomenon than retinal ganglion cell loss.[85] The true progression among this population based study would be obtained on extended longitudinal follow up of this cohort of subjects. There is poor comparison

between various classification systems in assessing progression in perimetric techniques; studies comparing the efficacy on perimetric progression algorithm, also report higher variability in HVF. [6,17] In this population based cohort, HVF progression was observed in only 9.3% (95% CI: 5.1 to 16.2%) and FDP PLR method (18.3, 95% CI: 12.5 to 25.9) showed higher progression rates.

4.2: ADVANTAGES AND LIMITATION

The current study assessed clinical progression of glaucoma in both structural and perimetric in a population based cohort. The Chennai glaucoma study reported the prevalence and causes of blindness using standard definitions postulated by International Society for Geographical and Epidemiological Ophthalmology (ISGEO). Emphasizing more on the structural and functional damage and the limits were defined from the control population from the south Indian population. The Chennai Glaucoma Longitudinal Optic Nerve Head Imaging Study, studied progression in subjects with glaucoma, ocular hypertension and compared to healthy controls both structurally, using advanced ONH imaging techniques like HRT, GDx, OCT and perimetric progression assessed with HVF and FDP. The study also reported the point wise linear regression measure for FDP. The rates and risk factors associated with progression in glaucoma and at risk population were compared with both imaging and perimetric techniques.

The inclusion criteria imaging and perimetric performance were stringent enough to avoid undue confounding effect in the study. This lead to exclusion of glaucoma and control subjects during the course of the study, thereby limiting the no of subjects in each groups. The lower progression rates and smaller sample in each cohort lead to lower power to

perform survival and cluster analysis which would have provided appropriate hazard ratios and also estimated fluctuation during follow up. Inter test variability could not be estimated due to the above mentioned reasons and non uniformity in the follow up visit in each of the study cohort. The above mentioned limitations are pitfalls observed in studies of similar methodology. Population based study, such as Vellore eye Study[11] had progression reported in 20 OHT patients and even hospital based studies report lesser sample size in long term follow ups.[79] Age related disorders lead to increase in morbidity and mortality rates among study groups in longitudinal glaucoma studies.

4.3: CONCLUSION

Primary Glaucoma subjects in this population based study showed perimetric progression in 13% (95% CI: 6.4 – 24.4). HRT showed higher progression (37%, 95% CI: 25.4 to 50.4) as compared to other imaging techniques. Older age, RNFL thickness on GDx and CSM in HRT were associated with the progression among primary glaucoma subjects over 5 years follow up period. In the current study poor control of IOP did not emerge as a significant risk factor, this could be attributed to early stage of glaucoma and to the poor persistence and compliance rates noted in the study group. In this population based cohort, HVF progression was observed in only 9.3% (95% CI: 5.1 to 16.2%) and FDP point wise linear regression method (18.3, 95% CI: 12.5 to 25.9) showed higher progression rates.

4.4: SPECIFIC CONTRIBUTION

Longitudinal ONH imaging study on a Population based cohort studied for over 5 years. To the best of our knowledge this is the first study to report the progression of glaucoma using three advanced imaging and two perimetric modalities in a population based

study. We report a lower progression in HVF, but structural progression assessed with HRT shows more promising results in assessing progression. Perimetric progression with FDP point wise linear regression method also shows earlier progression, there is need for refinement by development of point wise linear regression software for FDP. The current study also incorporated new software Cyoptique GL for ONH planimetric measurements. This fast and easy semi automated software was developed in collaboration with Cynaptix Technologies PVT ltd. This cost effective software provides 2 dimensional linear and area measurements from optic nerve head photograph.

4.5: FUTURE SCOPE OF THE STUDY

Functional and structural methods to determine progression among glaucoma subjects should be studied in clinical trials and there is scope for development of newer efficient algorithm or software assessing the true progression. Such computerized algorithm should estimate true progression with all these techniques (such as HRT, OCT, GDx, HVF and FDP), adjusting for short and long term variability. Efficient algorithm would help clinicians to determine early structural and functional changes in glaucoma, so that treatment paradigms can be appropriately modified to prevent visual disability. The results from the current study would be useful in assessing early changes among glaucoma and at risk groups. The current study also provides the frame work of point wise linear regression for FDP. This could be used to develop pictorial assessment of PLR for FDP and incorporate methods to relate structural and functional change. The efficacy of such software programs integrating the subjective and functional progression should be tested for their performance and consistency with the reported risk factor in hospital based glaucoma patients.

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Publications and Presentations

PUBLICATIONS AND PRESENTATIONS

Publications from thesis:

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1. Comparison of severity of glaucoma between a tertiary care referral center and population based glaucoma study. December 2006, South East Asian Glaucoma Interest Group (SEAGIG) Conference, Chennai, India
2. Chennai Glaucoma Optic Nerve Head Imaging study (Three year follow): Population based Longitudinal Assessment of optic nerve Head progression in primary open angle Glaucoma and primary Angle Closure Glaucoma**.** January 2009**,** ASIA ARVO 2009, Hyderabad, India (Received travel grant fellows and was also awarded the best scientific paper award)
3. Role of HRT III in reclassifying perimetrically normal "disc suspect" and the influence of planimetric characteristics on reclassification**.** January 2011: 35th All India Optometry Congress, Goa, India
4. The Chennai Glaucoma Optic Nerve Head Imaging Study (Five year follow)**:** Structural and Functional Progression of glaucoma: Estimated using advanced imaging techniques (like GDx, OCT and HRT) and functional changes in HVF estimated using Progressor**.** August 2011: Ruby Banik Award, Chennai, India

Other Publications

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BRIEF BIOGRAPHY OF THE CANDIDATE

Ramesh.S.Ve graduated from Elite school of Optometry, Chennai in 2001. He did his M Phil in optometry in 2004 from BITS Pilani. He has published around 39 research articles in peer reviewed indexed journals and has presented in around 30 national and international conferences. He received the Amjad Rahi Prize for best paper in Clinical Research, presented at the XIV annual Indian Eye Research Group (IERG: 2005). He also received the best scientific research paper award at the ASIA ARVO, Hyderabad- January, 2009. He is a senior optometrist cum research scholar practicing at the Glaucoma department, Medical and Vision Research Foundation since 2001.His areas of interest include Telemedicine, clinical epidemiology, glaucoma, optic nerve head analyzers and visual field. He is the executive committee member (education institute representative: 2011-2013) of the Indian Optometric Association. He holds the post of secretary Association of Schools and Colleges of Optometry- India (2012-2015). He is also member of the Optometric Glaucoma Society.

He has currently enrolled in PhD program on "*Longitudinal Assessment of Optic Nerve Head Progression in Glaucoma: A Population Based Study*" with Birla Institute of Technology and Science, Pilani.

BRIEF BIOGRAPHY OF THE SUPERVISOR

Dr Ronnie George is the Director of Research, Medical and Vision Research foundation, Sankara Nethralaya, Chennai. After completing his MBBS from St John's Medical College, Bangalore in 1993, he commenced Ophthalmology training at Christian Medical College, Vellore, first doing Diploma in Ophthalmology in 1998 and then MS Ophthalmology in 2001. He received his Diplomate of National Board of Education in the year 2001and was part of the Vellore Eye Study. He has sub-specialized in Glaucoma and joined Sankara Nethralaya in the year 2001.

A distinguished academic, he has published over 68 indexed publications in several national and international journals and 4 chapters in textbooks. He has presented papers in various national and international conferences and has delivered lectures as an invited guest speaker. He is the Associate investigator in the Chennai Glaucoma Study and Chennai Eye Disease Incidence Study, a major Epidemiological project on glaucoma in the South Indian Population. He is the principal investigator in various clinical trials. He is a reviewer for several national and international journals in ophthalmology. Not only is he an excellent clinician and surgeon, he is also a dedicated teacher, and has been instrumental in training several ophthalmology trainees over the years. He is an Associate Professor at Elite School of Optometry, providing guidance to Doctoral candidates and teaching at Bachelors & Masters Program in Optometry.