

# Comparison of macular parameters in primary open angle glaucoma patients using cirrus optical coherence tomography

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## Abstract

**Aim:** To compare macular parameters using Cirrus optical coherence tomography (OCT) in primary open angle glaucoma (POAG) patients with the normal subjects. **Materials and Methods:** This observational case control study included primary open angle glaucoma (POAG) patients (n = 184 eyes) and healthy subjects in the control group (n = 184 eyes). All subjects underwent detailed history, complete ocular examination. Complete ocular examination included best corrected visual acuity (BCVA), slit lamp examination, intraocular pressure (IOP), central corneal thickness, Gonioscopy, and dilated fundus biomicroscopy. Field analysis was done by white on white Humphrey Field Analyzer (Carl Zeiss). Optical coherence tomography imaging of macular area was performed using Cirrus HD- OCT. (Cirrus HD-OCT MODEL 4000, Carl Zeiss, Meditec Inc. Dublin CA, 94568). In both these groups, parameters analyzed were central macular thickness (CMT), inner inferior macular thicknesses (IIMT), inner superior macular thicknesses (ISMT), inner nasal macular thicknesses (INMT), inner temporal macular thicknesses (ITMT), and central macular volume (CMV). **Results:** The POAG group had significantly decreased values of CMT, IIMT, ISMT, INMT, ITMT and CMV compared to control group. Thus, macular thickness and volume parameters may be used for making the diagnosis of glaucoma especially in patients with abnormalities of disc. Statistical analysis done using student t-test. SPSS 13.0 software was used to calculate p value. There was statistically significant difference found in all macular parameters between cases and controls. (p=0.001). **Conclusion:** Macular parameters, such as total macular volume, inner macular thickness and outer macular thickness can be used in addition to RNFL thickness to aid in the diagnosis of early glaucoma using OCT, in certain conditions, where RNFL parameters may be distorted, such as disk abnormalities or peripapillary atrophy macular parameters may be relied upon. Macular thickness parameters showed thinning in diagnosed cases of glaucoma.

**Keywords:** Macular thickness, Glaucoma, Optical coherence tomography

## Introduction

Glaucoma is a progressive optic neuropathy with characteristic loss of retinal ganglion cells (RGC), which results in visual field impairment. Glaucoma is diagnosed by optic disc changes on 90 D examination and by measurement of visual fields defect in perimetry. Perimetry changes appear when up to 70% or more retinal nerve fiber layer (RNFL) is damaged, so to detect pre-perimetric glaucoma studies are focused now to evaluate RNFL and ganglion cells to make diagnosis of glaucoma early [1-3].

Quigley HA et al studied retinal ganglion cell atrophy correlated with automated perimetry in human eyes

with glaucoma. They measured the number and size of retinal ganglion cells from six human eyes with glaucoma. In each, the histologic findings were correlated with visual field results. Harwerth RS et study was based on retinal ganglion cell density and visual thresholds in patients with documented glaucoma. Data were analyzed with a model that predicted ganglion cell density from standard clinical perimetry, which was then compared with histologic cell counts. They concluded that Visual field defects based on standard clinical perimetry are proportional to neural losses caused by glaucoma [1,2].

Harwerth RS in 1999 also studied ganglion cell losses underlying visual field defects from experimental glaucoma. The investigate the relationship between

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ganglion cell losses and visual field defects caused by glaucoma. The relationship between the proportional losses of ganglion cells and visual sensitivity, measured with either white or colored stimuli, was nonlinear. The neural-sensitivity relationships were essentially identical for both white and monochromatic test stimuli, and it therefore seems unlikely that the higher sensitivity for detecting glaucoma with monochromatic stimuli is based on the size-dependent susceptibility of ganglion cells to injury from glaucoma [3].

The macula has over 50% of all retinal ganglion cells and is an ideal area for detection of early retinal ganglion cell loss and changes with time due to high cell density. In the macular region, ganglion cells are arranged in 4 to 6 layers making up 30 to 35% of retinal macular thickness. That is why the loss of macular ganglion cells results in significant retinal or retinal nerve fiber layer thinning. Several studies have already indicated that in glaucomatous eyes, decrease in macular thickness and volume are due to loss of RGCs and this finding correlate with RNFL thickness and visual field defects [4-8].

Recent studies show that thinning of RNFL is related to the thinning of macular ganglion cell complex (GCC), which is defined as three innermost retinal layers: (1) RNFL (made of ganglion cell axons), (2) ganglion cell layer (GCL) made of ganglion cell bodies and (3) the inner plexiform layer (IPL) made out of ganglion cell dendrites. All three layers of ganglion cell complex are significantly thinner in glaucoma patients, reflecting the proportion of dead ganglion cells. although Tan et al found that residual glial tissue maintains 50% thickness even when all ganglion cells are lost [9-12].

In this study, CMT, IIMT, ISMT, INMT, ITMT and CMV in primary open angle glaucoma (POAG) patients were evaluated and compared it with healthy subject, it is a case control observational method.

## Materials and Methods

**Study design/type of study** - This observational case control study was conducted at Eye Department, Bhopal memorial Hospital and Research Centre, Bhopal, M.P. Written Informed consent was obtained from all the participants before enrolment.

**Sample size & duration of study**- A total of 184 subjects were recruited for the study. Group A included 184 eyes of primary open angle glaucoma patients (POAG, n = 184 eyes) and group B included 184 eyes of normal subjects (Controls, n = 184 eyes).

**Inclusion & exclusion criteria**- One eye or both the eyes depending on the fulfilling of inclusion criterion was taken for study. Exclusion criteria included diabetic retinopathy, macular degeneration, macular edema, epiretinal membrane, retinal detachment, cataract, high myopia (greater than 4.00 D Sphere. or 2.00 D Cylinder), presence of non-glaucomatous optic nerve diseases and previous ocular surgery or trauma. Other exclusion criterion included all patients with secondary glaucoma, angle closure glaucoma or operated cases of POAG.

**Data collection procedure:** All subjects underwent detailed history, complete ocular examination. Complete ocular examination included best corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure (IOP) measurement using Goldmann Applanation Tonometry (corrected according to central Corneal thickness), central corneal thickness was done with ultrasound pachymetry (PAC Scan 300P digital biometric ruler, Sonomed), gonioscopy, dilated fundus bio microscopy using +90 diopter lens (diluted with tropicamide 0.5%). Field analysis was done by white on white Humphrey Field Analyzer (Carl Zeiss, USA). All patients were scanned with Cirrus OCT (Cirrus HD- OCT MODEL 4000, Carl Zeiss, Meditec Inc. Dublin CA, 94568). It was analyzed that the changes of inner macular thickness parameters and macular volume. *OCT analysis:* Macular thickness scan was obtained for all the subjects using OCT

**Procedures done:** The diagnosis of POAG was based on glaucomatous damage to the optic disk (optic nerve head cupping) and abnormal visual fields and IOP values. All eyes with glaucoma had visual field loss (mean deviation of glaucomatous eyes on visual field testing was -6.01 dB to -13.73 dB, according to Hodapp-Parrish-Anderson Grading scale of severity of visual field defect) in at least two consecutive examinations tested by automated perimetry.

**Central macular thickness:** The mean central macular thickness (CMT) was 213.23± 22.34 in the eyes of cases and 240.77± 19.10 in the eyes of control group. The mean difference among the two groups was 27.538, There is statistically significant difference (p < 0.05) in values of CMT among the two groups.

**Inner macular thickness:** The mean inner macular thickness (central 3 mm) of the superior, inferior, temporal and nasal quadrants among groups A and B are expressed in the Table 2. There is statistically significant difference (p < 0.05) in values among both the groups A and B.

All four parameters of inner macular thickness were lower among glaucoma patients (group A) than controls (group B) and the difference was significant ( $p < 0.05$ ).

**Inner inferior macular thickness:** The mean Inner inferior macular thickness (IIMT) among the cases was  $260.39 \pm 22.90$  and among the control group was  $292.71 \pm 25.38$ . the mean difference among the two groups was 32.315.

There is statistically significant difference ( $p < 0.05$ ) in values of IIMT among the two groups.

**Inner superior macular thickness:** The mean of Inner Superior macular thickness (ISMT) among the cases was  $257.68 \pm 26.53$ , whereas it was  $293.33 \pm 24.08$  among the control group.

The difference of mean among the two groups was 35.65.

There is statistically significant difference ( $p < 0.05$ ) in values of ISMT among the two groups.

**Inner nasal macular thickness inner nasal macular thickness (INMT)** among the cases was  $261.67 \pm 24.66$  and in control group it was  $292.45 \pm 25.35$ . the difference of mean is 30.78.

There is statistically significant difference ( $p < 0.05$ ) in values of INMT among the two groups.

## Results

**Table-1: Demographic distribution of case (primary open angle glaucoma patients) and control (normal subjects) according to gender and age.**

Gender	Case N (%)	Control N (%)	Total N (%)	Chi Square Value	Significance 'p' Value
Male	118 (32.1%)	92 (25.0%)	210 (57.1%)	7.498	0.006(S)
Female	66 (17.9%)	92 (25.0%)	158 (42.9%)		
Total	184 (50.0%)	184 (50.0%)	368 (100.0%)		
<b>Age Groups</b>					
20-40 years	17 (4.6%)	93 (25.3%)	110 (29.9%)	77.320	0.001(HS)
41-60 years	87 (23.6%)	57 (15.5%)	144 (39.1%)		
>60 years	80 (21.7%)	34 (9.2%)	114 (31.0%)		
Mean Age (Year)	$57.58 \pm 11.74$	$49.36 \pm 11.21$			

**Inner temporal macular thickness:** The mean value of Inner temporal macular thickness (ITMT) was  $243.38 \pm 29.29$  among the cases and among the control group it was  $278.35 \pm 26.82$ . the difference of mean among the two groups was 34.98.

There is statistically significant difference ( $p < 0.05$ ) in values of ITMT among the two groups.

**Central macular volume:** The mean total macular volume in POAG group was  $7.92 \pm 1.15 \text{ mm}^3$  as compared to  $9.25 \pm 1.05 \text{ mm}^3$  among the control eyes.

The difference of was 1.33 in between the two groups which was statistically significant ( $p < 0.05$ ).

The control group included the subjects with no history of glaucoma or retinal pathology IOP of  $< 21 \text{ mm Hg}$ , normal optic nerve head appearance and normal visual field testing results (mean defect  $-2.0$  to  $+2.0 \text{ dB}$ ) normal eyes served as control group.

**Data Analysis:** The various statistical techniques i.e. the mean, standard deviation and test of significance (t-test and chi-square-test) were used for drawing valid conclusions.

Statistical analysis done using student t-test. SPSS 13.0 software was used to calculate p value.

**Ethical approval: Taken**

**Table-2: Comparative evaluation of Macular parameters in Primary Open Angle Glaucoma Patients and normal subjects.**

Macular parameters	CASE	CONTROL	Mean Diff.	Student 't' Test Value	Significance 'p' Value
	Mean± SD	Mean± SD			
CMT- Central macular thickness	213.23±22.34	240.77±19.10	27.538	12.707	0.001
IIMT- Inner inferior macular thickness	260.39±22.90	292.71±25.38	32.315	12.820	0.001
ISMT- Inner superior macular thickness	257.68±26.53	293.33±24.08	35.647	13.494	0.001
INMT- Inner nasal macular thickness	261.67±24.66	292.45±25.35	30.783	11.803	0.001
ITMT- Inner temporal macular thickness	243.38±29.29	278.35±26.82	34.978	11.946	0.001
CV- Central macular volume	7.92±1.15	9.25±1.05	1.3312	11.567	0.001

The number of subjected investigated were 184. Group A included 96 patients of primary open angle glaucoma (POAG, n = 184 eyes) and group B included 93 normal subjects (controls, n = 184 eyes). Total 184 cases of primary open angle glaucoma and 184 controls were selected for the study. Out of 368 eyes, 210 eyes (57.1%) were from male patients and 158(42.9%) eyes were from female patients. Out of 368 eyes, 110 (29.9%) eyes were from 20-40-year-old age group, 144(39.1%) eyes were from 41-60-year-old age group and 114 (31.0%) eyes were from more than 60 years old. Mean age of all cases was 57.58±11.74 year and of controls was 49.36±11.21. There was statistically highly significant difference found in demographic distribution of case (Primary Open Angle Glaucoma Patients) and control (Normal subjects) according to gender and age.

Table reveals comparative evaluation of Macular parameters in Primary Open Angle Glaucoma Patients and normal subjects. All the macular parameters were found significantly less among cases as compare to controls. Central macular thickness was 213.23±22.34 among cases and 240.77±19.10 among controls. Central macular volume was 7.92±1.15 among cases and 9.25±1.05 among controls.

**Statistical analysis:** The data thus obtained was analyzed using student 't' test for statistical significance. A p-value less than 0.05 considered statistically significant. The various statistical techniques i.e. the mean, standard deviation and test of significance (t-test and chi-square-test) were used for drawing valid conclusions. Statistical analysis done using student t-test. SPSS 13.0 software was used to calculate p value. There was statistically significant difference found in all macular parameters between cases and controls. (p=0.001)

## Discussion

Curcio CA et al studied topography of ganglion cells in human retina. They quantified the spatial distribution of presumed ganglion cells and displaced amacrine cells in unstained whole mounts of six young normal human retinas whose photoreceptor distributions had previously been characterized.

Comparison of ganglion cell topography with the visual field representation in V1 reveals similarities consistent with the idea that cortical magnification is proportional to ganglion cell density throughout the visual field. In a similar study, Wassel H et al studied cortical magnification factor and the ganglion cell density of the primate retina. By reconstructing the fovea from serial sections, the authors were able to compare the densities

of cones, cone pedicles and ganglion cells; in this way they found that there are more than three ganglion cells per foveal cone. Between the central and the peripheral retina, the ganglion cell density changes by a factor of 1,000–2,000, which is within the range of estimates of the cortical magnification factor. There is therefore no need to postulate a selective magnification of the fovea in the geniculate and/or the visual cortex [4, 5].

Garway-Heath DF et al worked on the physiological relationship between light sensitivity and ganglion cell numbers. Differential light sensitivity (DLS) in white-on-white perimetry is used as a measure of ganglion cell function to estimate the amount of neuronal damage in glaucoma. They concluded that the number of

underlying ganglion cells, adjusted for local spatial summation, is better reflected by the DLS scale of  $1/L$  than by dB. If spatial summation is unchanged in glaucoma, this scale more accurately reflects the amount of neuronal damage. Zeimer R et al did a pilot study for quantitative detection of glaucomatous damage at the posterior pole by retinal thickness mapping.

The posterior pole ganglion cell bodies form a substantial fraction of the retinal thickness, prompting the authors to study the feasibility of detecting, by scanning retinal thickness analysis, retinal changes at the posterior pole due to glaucomatous damage. Mapping of the retinal thickness may provide a sensitive method for the detection and monitoring of early glaucomatous tissue loss in the posterior pole [6, 7].

Greenfield DS et al also studied macular thickness changes in glaucomatous optic neuropathy using optical coherence tomography. Changes are well correlated with changes in visual function and RNFL structure in glaucoma and may be a surrogate indicator of retinal ganglion cell loss. Guedes V et al did optical coherence tomography measurement of macular and nerve fiber layer thickness in normal and glaucomatous human eyes.

They concluded that both macular and NFL thickness as measured by OCT showed statistically significant correlations with glaucoma, although NFL thickness showed a stronger association than macular thickness. There was good correspondence between findings using both the prototype and commercial OCT units. Macular and NFL thickness measurements made with OCT may have usefulness in the clinical assessment of glaucoma. [8, 9].

Wollstein G did Optical coherence tomography (OCT) macular and peripapillary retinal nerve fiber layer measurements and studied the correlation between macular retinal and peripapillary NFL. Macular retinal thickness, as measured by OCT, was capable of detecting glaucomatous damage and corresponded with peripapillary NFL thickness; however, peripapillary NFL thickness had higher sensitivity and specificity for the detection of VF abnormalities. Rao HL et al did comparison of different spectral domain optical coherence tomography scanning areas for glaucoma diagnosis. The RTVue RNFL and inner retinal macular thickness measurements had good ability to detect eyes with glaucomatous visual field loss and performed significantly better than ONH parameters [10, 11].

A study similar to our was done by Tan O et al in which they did detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Repeatability was assessed by intraclass correlation, pooled standard deviation, and coefficient of variation. Macular imaging with FD-OCT is a useful method for glaucoma diagnosis and has potential for tracking glaucoma progression. Kanadani FN et al did structural and functional assessment of the macular region in patients with glaucoma. 54 of the 55 eyes showed an abnormal 10-2 HVF and 50 had central mfVEP defects.

The two OCT criteria resulted in sensitivities of 85% and 91%. When both functional tests showed a defect (in 49 eyes), the OCT was abnormal in 45. For the OCT the outer and inner inferior regions were the most likely to be abnormal, and both functional techniques were most abnormal in the superior hemifield. It was concluded that a good agreement exists between macular thickness and functional defects in patients with glaucoma. Study of the macular region may provide a quantitative measure for disease staging and monitoring [12, 13]

Sung MS studied diagnostic validity of macular ganglion cell-inner plexiform layer thickness deviation map algorithm using cirrus HD-OCT in preperimetric and early glaucoma. mGCIPL thickness deviation map showed good diagnostic ability in detecting preperimetric and early glaucoma, and it was comparable with pRNFL thickness deviation map. Our findings suggest that it can be an important parameter in detecting subtle glaucomatous structural change. Delbarre M et al worked on the diagnostic use of macular layer analysis by SD-OCT in primary open angle glaucoma. The minimum macular GCIPL is a new index obtained with the GCA algorithm of the Cirrus HD-OCT. It appears to have an excellent ability to detect glaucoma at every stage and demonstrates performance comparable to that of the cpRNFL parameter, in combination with which it may provide important complementary information for clinical practice [14, 15].

Macular retinal and nerve fiber layer thickness in early glaucoma was studied by Arvanitaki V et al. The finding that RT was significantly lower in early manifest glaucoma patients and glaucoma suspects indicates that the transposition of the OCT fast RNFL thickness (3.4) protocol from the peri-papillary area to the peri-macular area can be used for early glaucoma diagnosis. Intraretinal changes in early glaucoma, likely precede nerve fiber changes [16].

Muscat S et al and Koozekanani D et al assessed the accuracy, precision, repeatability and reproducibility of OCT and found it as a useful tool in glaucoma. OCT macular and RNFL parameters may be useful in patients who may not be cooperative for visual field studies. Muscat S studied repeatability and reproducibility of macular thickness measurements with the Humphrey OCT system. Measurements made from OCT scans were found to be accurate and precise.

Both concluded that OCT measurements of macular thickness made with the Humphrey 2000 OCT system are repeatable over different sessions with an expected variation of less than 11  $\mu\text{m}$  (99% confidence interval).

Similarly, the present study showed statically significant lower mean inner macular thickness among glaucoma patients as compared to normal subjects. Thus, it was seen that macular thickness was decreased in glaucomatous patients as compared to normal subjects. These findings are in correlation with studies discussed above and published literature [17, 18]

There are few studies which were specifically done to show correlation between macular volume and glaucoma status. Giovannini A et al showed in their study that the OCT macular volumes correlate significantly with glaucoma status. Lederer et al evaluated macular volume in normal, glaucoma suspects and glaucomatous subjects using a time domain OCT.

Their results demonstrated a significant correlation between the macular volume and glaucoma status with decreased macular volume in patients with advanced disease as well as significant difference of macular volume between normal and glaucomatous eyes. In the present study mean total macular volume in glaucoma group was  $7.92 \pm 1.15\text{mm}^3$  as compared to  $9.25 \pm 1.05\text{mm}^3$  among the control eyes [19, 20].

Park SB et al did a comparison of glaucoma diagnostic capabilities of Cirrus HD and Stratus optical coherence tomography. Overall, both OCT instruments showed similar glaucoma discrimination capability in average retinal nerve fiber layer thickness. Cirrus OCT displayed significantly higher AUCs in the average, inferior, temporal, and superior quadrants. To conclude, cirrus OCT showed better glaucoma discrimination capability than Stratus OCT in early stages of glaucoma.

Their findings suggest that spectral-domain technology of OCT may offer an improved capability of early-stage glaucoma detection [21].

The third-generation Stratus OCT (Carl Zeiss Meditec, Inc, Dublin, California) has shown good glaucoma diagnosis capabilities in many studies. Glaucomatous structural damage may precede functional loss associated with glaucoma progression. Thus, quantitative and objective assessment of structural damage by optical coherence tomography (OCT) might enable detection of anatomical changes before occurrence of irreversible functional impairment.

**Limitation of the present study:** The limitation of the present study are that sample was Future studies with large sample size may be required to validate our findings. Also, correlation of structural OCT changes with functional parameters such as perimetry or multifocal visual evoked potential (mfVEP) may add to the strength of the study.

## Conclusion

Thus, this study conclude that macular parameters, such as total macular volume, inner macular thickness and outer macular thickness can be used in addition to RNFL thickness to aid in the diagnosis of early glaucoma using OCT, in certain conditions, where RNFL parameters may be distorted, such as disk abnormalities or peripapillary atrophy macular parameters may be relied upon. However, these findings would require prospective long-term studies to see the progression of visual field defects or increase in glaucoma damage.

## What this study adds to existing knowledge?

It can be stated that macular thickness and volume shows a significant correlation with the glaucomatous damage. It may be useful method of documenting early glaucoma and monitoring progression. Mapping of the retinal thickness may provide a sensitive method for the detection and monitoring of early glaucomatous tissue loss in the posterior pole, which is unique due to the combination of (1) the direct measurement of neuroretinal loss in the central field of vision; (2) the mapping capability; and (3) the rapid image acquisition.

## Author's contribution

**Dr. Anjali Sharma:** Concept and design of the study.

**Dr. Hemlata Yadav:** Data collection and references

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