Original article

Comparative analysis of macular and peripapillary retinal nerve fiber layer thickness in normal, glaucoma suspect and glaucomatous eyes by optical coherence tomography

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Abstract

Introduction: Peripapillary retinal nerve fiber layer (RNFL) thickness analysis is a subjective method of analysis of glaucomatous damage. As almost 50% of retinal ganglion cells are located in the macula, assessment of macular thickness can be an alternative method for diagnosis of glaucoma. **Objectives:** To evaluate the changes in macular and retinal nerve fiber layer thickness in controls, glaucoma suspects and glaucoma patients using time domain optical coherence tomography (TD-OCT). **Materials and methods:** Macular and peripapillary RNFL scans were performed in one eye of 70 controls, 35 glaucoma suspects and 70 glaucoma patients by TD-OCT. The discriminating power of each parameter between the groups was determined by area under the receiver operating characteristic (AROC) curve. The correlation of macular thickness and RNFL thickness parameters with global field indices were also performed. P-value of < 0.05 was considered statistically significant. **Results:** The differences in all the macular thickness parameters between the groups were statistically significant ($p< 0.05$) except foveal thickness (FT) and nasal inner (NI) quadrant thickness. The temporal outer (TO) macular quadrant produced largest AROC curve of 0.90 between controls and glaucoma patients. The differences in all the RNFL thickness parameters were highly significant between the groups ($p<0.001$). The AROC curve between control group and glaucoma patients for RNFL average thickness was 0.99. **Conclusion:** Macular thickness as detected by TD-OCT had high discriminating power between controls, glaucoma suspects and glaucoma patients comparable with peripapillary RNFL thickness parameters.

Keywords: Glaucoma, macula, retinal ganglion cell, retinal nerve fiber layer, time domain optical coherence tomography

Introduction

Glaucoma is an optic neuropathy characterized by the loss of retinal ganglion cells and their axons (Quigley et al, 1989). Historically, the measurement of peripapillary retinal nerve fiber layer (RNFL) thickness was found to be quantitatively associated with glaucomatous field damage (Sommer et al, 1991; Quigley et al, 1992; Harwerth et al, 1999). It has been estimated by Quigley et al (1982) that up to 40 to 50% of the RNFL could be lost before

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a glaucomatous visual field defect can be detected by conventional perimetry. However, retinal ganglion cells and axons constitute 30 to 35% of the retinal macular thickness (Zeimer et al, 1998). Almost 50% of retinal ganglion cells are located in the macula within 4 to 5 mm from the center of the fovea where these cells are 4 to 6 cell bodies thick (Wassle et al, 1989; Curcio et al, 1990). So, glaucomatous visual field damages are expected to be associated with a reduction of retinal macular thickness. Zeimer et al (1998) showed a significant correlation between glaucomatous visual field defects and retinal macular thickness by a retinal topographer based on slit lamp biomicroscopic principle.

Optical coherence tomography (OCT) is a noninvasive, noncontact imaging technology that allows in vivo visualization of retina and measurement of RNFL thickness with good reproducibility(Huang et al, 1991; Schuman et al, 1995; Budenz et al, 2005). Several studies have shown a reduction in retinal macular thickness in patients with glaucomatous field damages by using commercially available time domain OCT (TD-OCT). However, they have found that macular thickness measurements had less discriminating power of glaucomatous field defects than peripapillary RNFL thickness measurements (Greenfield et al, 2003; Medeiros et al, 2005; Leung et al, 2005; Tan et al, 2008). Nakatani et al (2011) had recently evaluated macular and peripapillary RNFL thickness by using spectral domain OCT (SD-OCT) which provides faster scan rate and higher resolution than TD-OCT. They had observed that macular parameters had high discriminating power and high reproducibility comparable with peripapillary RNFL parameters (Nakatani et al, 2011).

The objective of this study was to evaluate the correlation between macular and peripapillary RNFL thickness measured by TD-OCT in normal, glaucoma suspects and glaucomatous eyes.

Materials and methods

This is a prospective, non-randomized hospital based observational study during 1 year period from July 2012 through June 2013. The protocol was in accordance to the tenets of Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was signed by all the participants before enrolment. Participants were classified as control group of 70 healthy volunteers (controls), 35 glaucoma suspects and 70 primary open-angle glaucoma (POAG) patients. All the patients were examined and classified according to the eligibility criteria given below, independently by two glaucoma specialists (SB and DD) and only the cases agreed upon by them were included in the study. Furthermore, the patients with same glaucoma classification in both the eyes were included and only the right eye was selected for the study.

All the patients had full ophthalmologic checkup including best corrected visual acuity (BCVA), slit lamp examination, intraocular pressure (IOP) measurement by applanation tonometry, gonioscopy, dilated fundus examination with +78 D lens and standard automated perimetry (SAP) using Humphrey field analyzer (HFA, full threshold program 30-2, Carl Zeiss Meditech Inc., Dublin, California). The patients with BCVA less than 20/40, any ocular pathology other than POAG, history of previous ocular surgery, large refractive error (outside ± 4.00 D sphere or ± 2.00 D cylinder) and unreliable perimetry (false positive, false negative rates more than 33% and fixation losses more than 20%) were excluded from the investigation.

The control subjects were included from the persons attending refraction unit (refractive error inside ± 4.00 D sphere or ± 2.00 D cylinder) and had no ocular disease or any family history of glaucoma. They had IOP $\leq$ 21 mm of Hg, cup-disc ratio less than 0.6, vertical cup disc ratio asymmetry between two eyes less than 0.2 and normal optic disc (without hemorrhage, pallor, notches or localized RNFL

defect). In automated perimetry, mean deviation (MD) & pattern standard deviation (PSD) were within 95% confidence interval and glaucoma hemifield test were normal.

The glaucoma suspects had IOP ≥ 22 mm Hg but with cup-disc ratio less than 0.6, vertical cup disc ratio asymmetry between two eyes less than 0.2, normal optic disc (without hemorrhage, pallor, notches or localized RNFL defect) and normal automated perimetry results (i.e. MD & PSD within 95% confidence interval and normal glaucoma hemifield test).

The POAG patients had IOP ≥ 22 mm Hg before the administration of antiglaucoma medication but < 22 mm Hg following treatment, cup disc ratio ≥ 0.6, vertical cup disc ratio asymmetry between two eyes ≥ 0.2, peripapillary hemorrhage or notches and glaucomatous visual field defects.

Anderson's criteria (Anderson et al, 1999) was followed for detection of glaucomatous visual field defects in which any one of this was present: a cluster of 3 or more nonedge points with P < 5% and at least one point with P< 1% in pattern deviation probability plot; pattern standard deviation of less than 5%; or glaucoma hemifield test results outside normal limits.

OCT imaging

Optical coherence tomographic imaging was done by Stratus OCT 3(TD-OCT, version 4, Carl Zeiss, San Diego, CA, USA) in all the patients using near infrared (840 nm), low coherence illumination with an approximate tissue resolution of 10 µm. The pupil was dilated with 1% Tropicamide to a minimum diameter of 5 mm and image acquisitions were performed by an examiner (MS) masked to the clinical findings of each patient. For RNFL analysis, a fast RNFL protocol was used consisting of three 360^0 circular scans with a diameter of 3.4mm centered on the optic disc. Inbuilt RNFL thickness average analysis protocol was used to calculate mean RNFL thickness. Total retinal thickness was measured first by defining the inner and outer boundaries through location of the vitreoretinal interface and retinal pigmented epithelium respectively which were seen as sharp edges with high reflectivity. The posterior boundary of RNFL was detected after evaluation of each A-scan for a threshold 15 dB more than the filtered maximum reflectivity of the adjacent retina. To acquire macular thickness measurements fast macular thickness protocol was selected with 3 concentric circles having diameters of 1, 3, 6 mm & 2 diagonal lines dividing the macular regions into 9 sectorial zones comprising of fovea, temporal inner (TI), superior inner (SI), nasal inner (NI), inferior inner (II), temporal outer (TO), superior outer (SO), nasal outer (NO) and inferior outer (IO) areas.

Statistical analysis was performed with SPSS software, version 14.0 (SPSS, Chicago, IL, USA). One way analysis of variance (ANOVA and subsequent post hoc analysis by Dunnett's T3 test) was performed to compare the different parameters among controls, glaucoma suspects and glaucomatous patients. The associations between MD, PSD, RNFL parameters and macular thickness were analyzed by Pearson correlation coefficient. The area under the receiver operating characteristic (AROC) curve was calculated by MedCalc version 10.4.0 to detect the ability of RNFL thickness and macular thickness parameters to differentiate normal, glaucoma suspect and glaucomatous eyes from one another. While an AROC of 1 represents perfect discrimination, an AROC of 0.5 denotes chance discrimination. P-value < 0.05 was considered statistically significant.

Results

Seventy eyes of 70 control subjects (C), 35 eyes of 35 glaucoma suspects (GS) and 70 eyes of 70 glaucoma patients (G) were included in the study. Their age ranged from 37 to 72 years in control subjects, 44 to 70 years in glaucoma

suspects and 54 to 78 years in glaucoma patients. Overall, 103 patients were male and 72 patients were female. On dilated fundus examination with +78 D lens there was no significant macular pathology detected in any of the three groups. The cup-disc ratio of the control, glaucoma suspect and glaucoma patients were 0.29±0.084, 0.30±0.074 and 0.72±0.106 respectively. The difference of cup-disc ratio between control and glaucoma patients were statistically significant ($p < 0.0001$) [Table 1]. The mean MD and PSD on Humphrey visual field analysis were -16.86± 6.92 and 7.34± 2.76 respectively in glaucomatous patients. The differences in MD and PSD between control and glaucoma suspects and between control and glaucoma patients were statistically significant [Table 1]. The macular thickness parameters in all the three groups were computed in Table 2. Average macular thickness in controls, glaucoma suspects and glaucoma patients were 232.37±8.92 µm, 229.54±8.9 µm and 217.01±7.58 µm respectively. The differences between the groups with respect to all the parameters were statistically significant (p-ANOVA) except foveal thickness (FT) and nasal inner (NI) quadrant. The AROC curve (70 controls vs 70 glaucoma patients) for macular average thickness was 0.88; the sensitivity and specificity was 81.43% and 70% respectively with a cutoff value of 225 µm. The temporal outer (TO) quadrant parameter produced largest AROC curve of 0.90 between controls and glaucoma patients, with a cutoff value of 205 µm the sensitivity was 78.6% and specificity was 90%.Whereas, the AROC curve between control and glaucoma suspects for superior inner (SI) macular quadrant was only 0.61 (the sensitivity and specificity was 60% and 71.4% respectively with a cutoff value of 265 µm). The temporal outer (TO) macular quadrant had the largest discriminating power between glaucoma and glaucoma suspects with an AROC curve of 0.87 and a cutoff of 205 µm gave 78.6% sensitivity and 85.7% specificity.

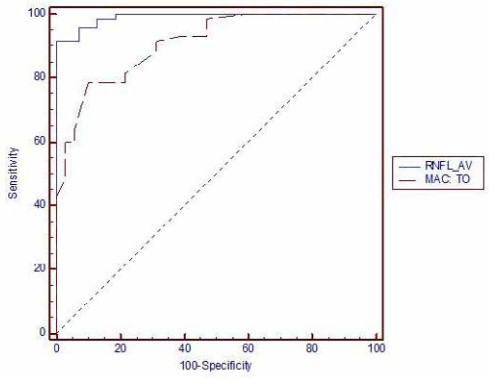

Figure 1: The AROC curves of the best macular (Superior Inner, SI: AROC, 0.61) and RNFL (Average: AROC, 0.86) parameters between control and glaucoma suspects

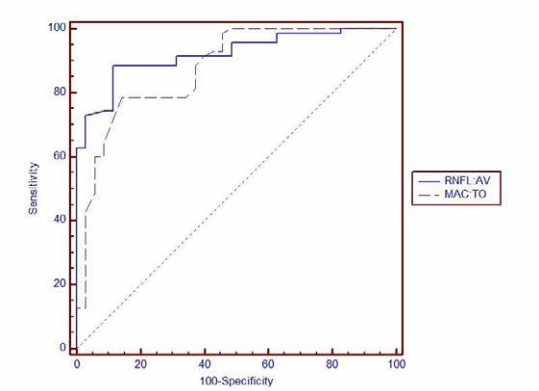

Figure 2: The AROC curves of the best macular (Temporal Outer, TO: AROC, 0.90) and RNFL (Average: AROC, 0.99) parameters between control and glaucoma patients

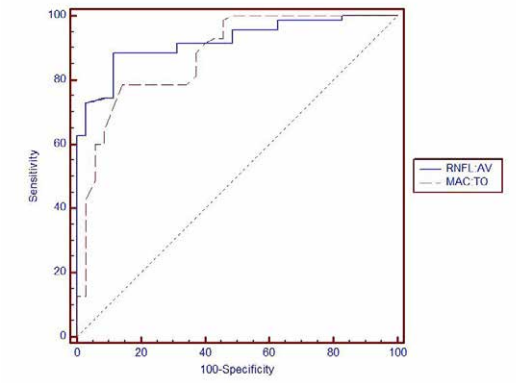

Figure 3: The AROC curves of the best macular (Temporal Outer, TO : AROC, 0.87) and RNFL (Average: AROC,0.92) parameters between glaucoma suspects and glaucoma patients

Table 1: Clinical Characteristics of Study Population

	Control (C)	Glaucoma suspect (GS)	Glaucoma (G)	p value	p value
	n=70	n=35	n=70	(C-GS)	(C-G)
Age, Mean±SD (range)	59.34±9.04 (37-72)	57.8±7.79 (44-70)	65.92±6.32 (54-78)	0.39	0.0001
Sex (male/female)	39/31	21/14	43/27	0.834	0.6064
CD Ratio, Mean±SD	0.29±0.084	0.30±0.074	0.72±0.106	0.1473	<0.0001
MD, Mean±SD(range) dB	-1.008±1.2848 (-2.45 to 1.32)	-1.9586±1.4816 (-4.46 to 1.13)	-16.8679±6.9272 (-31.35 to -4.43)	0.001	< 0.001
PSD, Mean±SD (range) dB	1.8824± .4717 (1.12 to 2.73)	3.4049± 1.1252 (1.17 to 5.59)	7.3444± 2.7618 (2.57 to 13.47)	< 0.001	< 0.001

Table 2: Results of macular thickness (µm) parameters by TD-OCT

	Control (C)	Glaucoma suspect (GS)	Glaucoma (G)	Significance p (ANOVA)	AROC(SE) (C vs GS)	AROC(SE) (C vs G)	AROC(SE) (G vs GS)
	Mean±SD	Mean±SD	Mean±SD				
	n=70	n=35	n=70				
Foveal Thickness (FT) (µm)	201.21±18.17	201.23±15.18	202.5±12.61	0.565	0.53(0.05)	0.51(0.05)	0.58(0.06)
SO (µm)	237.04±11.91	234.71±12.19	225.56±11.01	<0.001	0.54(0.05)	0.72(0.04)	0.65(0.05)
IO (µm)	225.34±10.49	221.06±10.03	207.71±1071	<0.001	0.54(0.06)	0.85(0.03)	0.79(0.04)
NO (µm)	249.56±11.45	251.0±11.99	236.31±12.41	<0.001	0.50(0.06)	0.76(0.03)	0.76(0.05)
TO (µm)	215.14±7.91	216.4±10.48	196.93±18.48	<0.001	0.52(0.06)	0.90(0.02)	0.87(0.03)
SI (µm)	273.94±10.03	267.11±12.78	262.41±15.63	<0.001	0.61(0.06)	0.71(0.04)	0.63(0.05)
II (µm)	268.94±11.76	254.6±11.47	257.31±11.98	<0.001	0.59(0.05)	0.74(0.04)	0.67(0.05)
NI (µm)	264.13±13.35	264.63±11.84	259.53±26.84	0.396	0.55(0.06)	0.53(0.05)	0.55(0.06)
TI (µm)	253.63±13.92	263.6±14.99	247.76±13.86	0.027	0.52(0.05)	0.60(0.04)	0.56(0.05)
Macular Average (µm)	232.37±8.92	229.54±8.9	217.01±7.58	<0.001	0.60(0.05)	0.88(0.02)	0.83(0.03)

Table 3: Results of peripapillary RNFL thickness (µm) parameters by TD-OCT

	Control (C)	Glaucoma suspect (GS)	Glaucoma (G)	Significance p (ANOVA)	AROC(SE) (C vs GS)	AROC(SE) (C vs G)	AROC(SE) (G vs GS)
	Mean±SD	Mean±SD	Mean±SD				
	n=70	n=35	n=70				
Inferior (µm)	118.83±10.43	97.11±20.65	68.12±26.70	<0.001	0.74(0.05)	0.98(0.007)	0.85(0.03)
Superior (µm)	116.59±13.21	110.43±17.57	75.19±25.85	<0.001	0.55(0.06)	0.94(0.02)	0.86(0.03)
Nasal(µm)	70.76±8.57	65.2±13.62	56.38±22.72	<0.001	0.59(0.06)	0.65(0.05)	0.58(0.05)
Temporal (µm)	60.7±5.80	52.97±9.42	44.32±12.97	<0.001	0.75(0.05)	0.84(0.03)	0.67(0.05)
Average (µm)	94.54±7.45	94.77±7.32	59.44±19.66	<0.001	0.86(0.04)	0.99(0.004)	0.92(0.02)

Table 4: Pearson correlation coefficient (r) and level of statistical significance (p) for RNFL thickness with MD and PSD on Humphrey visual field analysis

RNFL thickness	MD		PSD	
	R	p	r	p
Average	0.6958	<0.0001	-0.68	<0.0001
Inferior	0.6157	<0.0001	-0.6243	<0.0001
Superior	0.6798	<0.0001	-0.64	<0.0001
Nasal	0.2484	0.0009	-0.2526	0.0007
Temporal	0.5131	<0.0001	-0.4809	<0.0001

Table 5: Pearson correlation coefficient (r) and level of statistical significance (*p*) for Macular thickness with MD and PSD on Humphrey visual field analysis

Macular thickness	MD		PSD	
	r	p	r	p
Average	0.4889	<0.0001	-0.4502	<0.0001
Foveal thickness(FT)	-0.0491	0.5183	-0.0031	0.9669
Inferior Outer (IO)	0.4939	<0.0001	-0.4123	<0.0001
Superior Outer (SO)	0.3442	<0.0001	0.2929	0.0001
Nasal Outer (NO)	0.3921	<0.0001	-0.3269	<0.0001
Temporal Outer (TO)	0.3553	<0.0001	-0.2955	0.0001
Inferior Inner (II)	0.2624	0.0005	-0.2399	0.0014
Superior Inner (SI)	0.2522	0.0008	-0.2681	0.0003
Nasal Inner (NI)	0.1064	0.1612	-0.1113	0.1427
Temporal Inner (TI)	0.2456	0.0011	-0.2750	0.0002

The RNFL thickness parameters in the three groups were shown in Table 3. The average RNFL thickness were 94.54±7.45 µm, 94.77±7.32 µm and 59.44±19.66 µm in controls, glaucoma suspects and glaucomatous patients respectively which was statistically significant ($p< 0.001$). All the other RNFL thickness parameters were also significant between groups (p ANOVA). The AROC curve between control group and glaucoma patients for RNFL average thickness was 0.99, with a cutoff value of 80.22 µm the sensitivity and specificity was 91.4% and 100% respectively. The inferior, superior and temporal RNFL thickness also produced large AROC curves of 0.98, 0.94 and 0.84 respectively between these two groups. When compared between controls and glaucoma suspects the RNFL average thickness had the largest discriminating power with an AROC curve of 0.86, a cutoff value of 89 µm gave the sensitivity and specificity of 91.4% and 80% respectively. Similarly, the RNFL average thickness produced an AROC curve of 0.92 while discriminating between glaucoma patients and glaucoma suspects. The superior and inferior RNFL thickness also produced large AROC curves of 0.85 and 0.86 respectively between these two groups. Figure 1 shows the comparison of AROC curves of the best macular (Superior Inner, SI: AROC, 0.61) and RNFL (Average: AROC, 0.86) parameters between control and glaucoma suspects. The AROC curves between control and glaucoma patients with respect to the best macular (Temporal Outer, TO : AROC, 0.90) and RNFL (Average: AROC,0.99) parameters are shown in figure 2. Similarly figure 3 shows the AROC curves of the best macular (Temporal Outer, TO : AROC, 0.87) and RNFL (Average: AROC,0.92) parameters between glaucoma suspects and glaucoma patients.

The Pearson correlation coefficients were computed between RNFL thickness parameters and MD & PSD on Humphrey visual field analysis [Table 4]. The MD was significantly positively correlated with average, inferior, superior, temporal RNFL thickness ($p< 0.0001$ in all cases) and nasal RNFL thickness ($p< 0.001$). There was significant negative correlation of PSD with average, inferior, superior, temporal RNFL thickness ($p< 0.0001$ in all cases) and nasal RNFL thickness ($p< 0.001$).

The correlation coefficients between macular thickness parameters and MD& PSD are shown in Table no. 5. All the macular thickness parameters except foveal thickness and nasal

inner quadrant were significantly positively correlated with MD ($p< 0.01$). Similarly, the same parameters were significantly negatively correlated with PSD ($p< 0.01$ in all cases except foveal thickness and nasal inner quadrant).

Discussion

In our study, all the RNFL thickness parameters in TD-OCT have shown discriminating power between the controls, glaucoma suspects and glaucoma patients. However, most macular parameters except foveal thickness and nasal inner quadrant showed similar discriminating power among the groups. The average RNFL thickness (AROC: 0.99) and temporal outer macular thickness (AROC: 0.90) have produced the best results. Inferior and superior RNFL thickness & inferior outer macular thickness also showed high power of discrimination (AROC: 0.98, 0.94 and 0.85 respectively). These findings are in agreement with other studies in TD-OCT showing greater susceptibility of the inferior region of the optic disc along with temporal & inferior macular regions to glaucomatous damage (Medeiros et al, 2005; Bowd et al, 2001; Wollstein et al, 2004; Ojima et al, 2007). The foveal thickness was not correlated with visual field changes in our study which was expected as foveola is devoid of ganglion cells. The study by Nakatani et al (2011) with SD-OCT found comparable performance of macular thickness parameters to RNFL thickness parameters for diagnosis of early glaucoma patients, indicating improved diagnostic ability of SD-OCT regarding macular parameters. However, Buchser NM et al (2012) observed high level of imprecision in peripapillary RNFL measurements by three different make SD-OCT devices (RTVue-100, Cirrus HD-OCT and 3D OCT-1000). They opined that three dimensional cube scanning with post-hoc data sampling may reduce this imprecision.

In our study, the most macular thickness parameters (except foveal thickness and nasal inner quadrant) and all the RNFL thickness parameters in controls, glaucoma suspects and glaucomatous patients is strongly correlated with visual field global indices (MD & PSD). Nakatani et al (2011) had also detected significant correlation between MD & inferior inner macular volume and between MD & peripapillary RNFL thickness average in early glaucoma patients. Sihota et al (2006) observed similar correlations between MD & PSD with average peripapillary RNFL thickness in patients with early, moderate, severe and blind glaucoma.

Arvanitaki et al (2012) has measured total macular thickness and macular RNFL thickness (using the same protocol for RNFL analysis around optic nerve head) by TD-OCT and compared them. They observed both early manifest glaucoma patients and glaucoma suspects had significantly lower macular retinal thickness than controls in all quadrants.

There is one limitation in the study that macular co morbidity in the form of scarring or edema can restrict the use of macular thickness parameters for monitoring progress of glaucoma. Future studies with differentiation of the patients in early, moderate, severe and blind glaucoma groups can show more specific results.

Conclusion

Macular thickness parameters had high discriminating power between controls, glaucoma suspects and glaucoma patients comparable with peripapillary RNFL thickness parameters as detected by TD-OCT. Further studies of macular thickness using SD-OCT with higher resolution power can be a new method for detection and monitoring progress of glaucomatous damage.

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