Original article

Ganglion cell complex scan in the early prediction of glaucoma

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Abstract

Objective: To compare the macular ganglion cell complex (GCC) with peripapillary retinal fiber layer (RNFL) thickness map in glaucoma suspects and patients.

Subjects and methods: Forty participants (20 glaucoma suspects and 20 glaucoma patients) were enrolled. Macular GCC and RNFL thickness maps were performed in both eyes of each participant in the same visit. The sensitivity and specificity of a color code less than 5% (red or yellow) for glaucoma diagnosis were calculated. Standard Automated Perimetry was performed with the Octopus 3.1.1 Dynamic 24-2 program. *Statistics:* The statistical analysis was performed with the SPSS 10.1 (SPSS Inc. Chicago, IL, EUA). Results were expressed as mean ± standard deviation and a p value of 0.05 or less was considered significant.

Results: Provide absolute numbers of these findings with their units of measurement. There was a statistically significant difference in average RNFL thickness (p=0.004), superior RNFL thickness (p=0.006), inferior RNFL thickness (p=0.0005) and average GCC (p=0.03) between the suspects and glaucoma patients. There was no difference in optic disc area (p=0.35) and vertical cup/disc ratio (p=0.234) in both groups. While 38% eyes had an abnormal GCC and 13% had an abnormal RNFL thickness in the glaucoma suspect group, 98% had an abnormal GCC and 90% had an abnormal RNFL thickness in the glaucoma group.

Conclusion: The ability to diagnose glaucoma with macular GCC thickness is comparable to that with peripapillary RNFL thickness . Macular GCC thickness measurements may be a good alternative or a complementary measurement to RNFL thickness assessment in the clinical evaluation of glaucoma.

Key-words: FD- OCT, ganglion cell complex, retinal nerve fiber layer thickness

Introduction

Optical coherence tomography (OCT) has allowed in vivo quantitative analysis of the peripapillary retinal nerve fiber layer (RNFL), and measuring the RNFL has been useful for diagnosing glaucoma (Huang ML and Chen HY, 2005: Parikh RS et al 2007). However, the normal variation of the peripapillary RNFL and pathological peripapillary changes make the diagnosis of glaucoma difficult when interpreting OCT peripapillary RNFL measurements by comparing them with the normative database.

Retinal ganglion cells encompass three layers in the retina, 1) the retinal nerve fiber layer (RNFL) which is made up of the ganglion cell axons, 2) the ganglion

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cell layer (GCL) which is made up of the ganglion cell bodies, and 3) the inner-plexiform layer (IPL) which is made up of the ganglion cell dendrites. All three layers are collectively known as the ganglion cell complex (GCC) (Fig 1). Fourier Domain OCT can measure the thickness of the macular GCC, which extends from the internal limiting membrane to the inner nuclear layer including the ganglion cell layer and provides a unique analysis of the percent loss of these layers compared to an extensive normative database.

Glaucoma is characterized by the selective loss of retinal ganglion cells (RGC) (Garway-Heath DF et al 2000: Harwerth RS et al 1999: Zeimer R et al 1998). Because the macular region contains more than 50% of all the RGCs, assessing ganglion cell changes in the macular region may be more useful in diagnosing glaucoma than measuring peripapillary RNFL thickness (Ishikawa H et al 2005, Tan O et al 2008: Van Buren JM 1963). RTVue-100 (Optovue, Fremont, California) is a commercially available OCT device with Fourier-domain (FD) technology.

Although previous studies have shown the utility of peripapillary RNFL measurements in glaucoma patients, little is known about the comparison between RNFL thickness and macular GCC or the diagnostic ability of GCC using FD-OCT. In this study, we used FD-OCT to compare macular GCC and peripapillary RNFL thickness to aid in the early diagnosis of glaucoma.

Materials and methods

Forty participants [n=20 glaucoma suspects (GS; normal SAP, C/D ratio of more than 0.5 or asymmetry of more than 0.2 and/or ocular hypertension) and n=20 glaucoma patients (MD of less -12 dB, glaucomatous optic neuropathy)] were enrolled. The study was approved by our institutional review board (IRB) and complied with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

All eyes underwent applanation tonometry, dark room gonioscopy, stereoscopic optic disc photography, red-free RNFL photography and RTVue FD-OCT after pupillary dilation to a minimum diameter of 5 mm on the same day. Peripapillary RNFL and perifoveal GCC thickness measurements were obtained using RTVue-100 by the same operator in the same visit. Standard Automated Perimetry was performed with the Octopus 3.1.1 Dynamic 24-2 program.

OCT measurements

The average thickness of the GCC and RNFL was measured using RTVue-100 (software version: 4.0.5.39), which acquires 26,000 A scans per second and has a 5 ìm depth resolution in tissue. The RNFL thickness was determined by the nerve head map 4 mm diameter (NHM4) mode, which measures RNFL thickness by recalculating data along a 3.45 mm diameter circle around the optic disc using a map created from en face imaging utilizing six circular scans ranging from 2.5 to 4.0 mm in diameter (587 or 775 A scans each) and 12 linear data inputs (3.4 mm length, 452 A scans each). Disc area measurements were also obtained using the NHM4 mode.

GCC parameters were obtained by the MM7 protocols, centered 1 mm temporal to the fovea. This protocol uses one horizontal line with a 7 mm scan length (934 A scans) followed by 15 vertical lines with a 7 mm scan length and 0.5 mm interval (800 A scans)(Fig 2A). The GCC thickness was measured from the internal limiting membrane to the inner plexiform layer boundary. The focal loss volume (FLV) as the integral of deviation in areas of significant focal GCC loss and global loss volume (GLV) as the sum of negative fractional deviation in the entire area were also computed. Images with a Signal Strength Index less than 35 with overt misalignment of the surface detection algorithm or with overt decentration of the measurement circle location were excluded.

RNFL and GCC thicknesses in the normal range were represented by green backgrounds, those that were abnormal at the 5% level were represented by yellow backgrounds, and those that were

abnormal at the 1% level were represented by red backgrounds.

The statistical analysis was performed with the SPSS 10.1 (SPSS Inc. Chicago, IL, EUA). Results were expressed as mean ± standard deviation and a p value of 0.05 or less was considered significant.

Results

Patients were categorized into two groups: the glaucoma suspects (n=20) and glaucoma (n=20) groups. The mean age of the participants was 50.69±15.90 years (range 22–77 in the glaucoma suspect group; 22–78 in the glaucoma group). There was no difference in optic disc area (p=0.35) and vertical cup/disc ratio (p=0.234) comparing both groups (Table 1). However, there was a statistically significant difference in average RNFL thickness (p=0.004), superior RNFL thickness (p=0.006), inferior RNFL thickness (p=0.0005) and average GCC (p=0.03) between the suspects and glaucoma patients (Table 2). The GCC thickness showed strong correlations with RNFL thickness (correlation coefficient = 0.763, p<0.001). Fifteen of 40 (38%) eyes had an abnormal GCC and five of 40 eyes (13%) had an abnormal RNFL thickness in the glaucoma suspect group. Thirty-nine of 40 eyes (98%) had an abnormal GCC and 36 of 40 eyes (90%) had an abnormal RNFL thickness in the glaucoma group.

Table 1
Shows the optic disc area and the vertical C/D ratio between two groups

Group	Optic disc Area	Vertical C/D ratio
Glaucoma suspects	2.52±0.72	0.78±0.10
Glaucoma patients	2.33±0.46	0.83±0.09

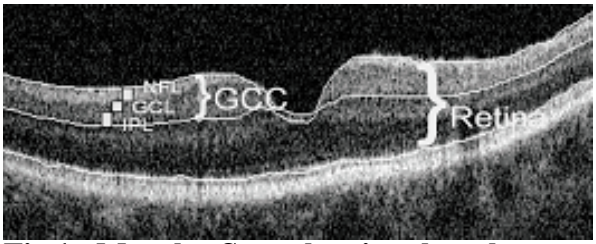

Fig 1: Macular Scan showing three layers of GCC(FD-OCT)

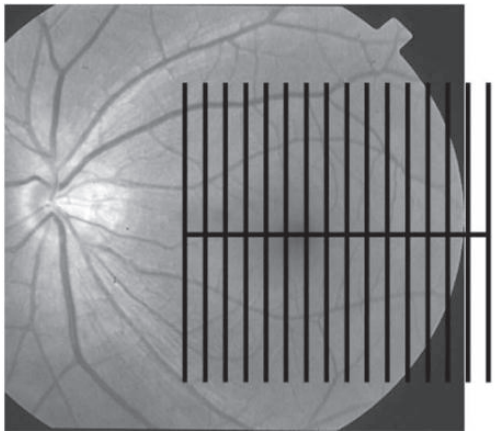

Fig 2A-GCC Complex scan pattern

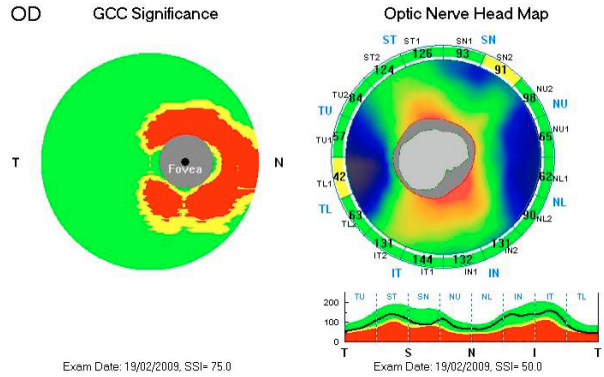

Fig 2B - Abnormal GCC in spite of normal RNFL Thickness

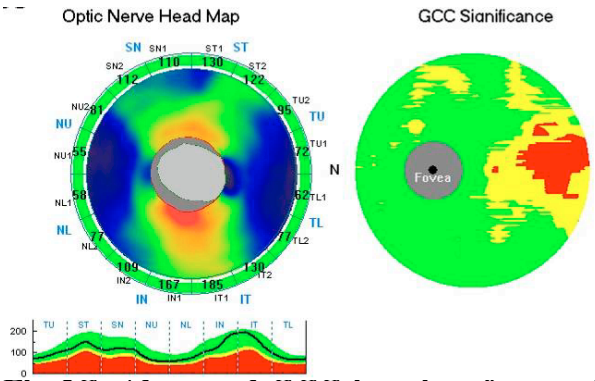

Fig 2C- Abnormal GCC in spite of normal RNFL Thickness

Table 2

GCC vs RNFL thickness

Group	RNFL thickness	Superior	Inferior	GCC thickness
Glaucoma suspects	112.41 ± 10.92	110.42 ± 9.91	114.38 ± 13.61	95.40 ± 8.11
Glaucoma patients	98.57 ± 13.68	100.45 ± 16.35	98.49 ± 15.79	86.06 ± 12.43

Discussion

Although glaucoma is clinically defined as optic disc cupping with corresponding visual field defects, the underlying disease process in glaucoma is the loss of RGC (Quigley HA et al1989: Quigley HA et al1980: Sommer A et al 1977). Approximately one-third of the RGC population resides within the posterior pole. In the macula, the RGC layer is more than one cell layer thick with the RGC body diameter being 10 to 20 times larger when compared to their axons. In addition, the central retina has less variability in cell density when compared to the peripheral retina (Glovinsky Y et al 1993). Thus, in some cases detecting RGC loss in the macula may allow for earlier detection of glaucoma.

The higher resolution RTVue system allows for more specific segmentation by allowing only the retinal layers associated with the ganglion cells to be analyzed. This method of segmenting out the ganglion cell complex targets the layers directly associated with the ganglion cells, whereas the stratus method can only analyze the entire retinal thickness.

In the past, most investigators have focused on comparing the measurements of the macula and the optic disc. At the time, most commercial imaging instruments yielded measurements of only one or the other. Now, many techniques are available for obtaining both measurements in one session. The perifoveal region yields information on the ganglion cells and their axons located at the centre of the macula, which are represented in perimetry by only a few points at the centre of the visual field, whereas the peripapillary region reflects the entire retina. The time course of the disease and treatment decisions may differ between eyes with a well-preserved central macula and damaged peripheral retina, and one with damage to both areas. By including both regions, it may be possible to gain new knowledge on the process of glaucomatous damage through an additional role for measuring GCC in glaucoma assessment.

Ishikawa H et al (2000) developed a software algorithm to perform automatic retinal layer segmentation in the macula for the commercially available Stratus TD-OCT and reported that macular inner retinal layer thickness measurements could indeed be used to discriminate normal from glaucomatous eyes. They found that the outer retinal layers were not affected in glaucoma. However, one of the limitations of the study was variable scan quality. Over one-third of the scans on glaucomatous eyes had to be excluded from segmentation analysis due to poor quality scans related to speckle noise and uneven tissue reflectivity. The authors suggested that higher resolution and improved signal quality (higher signal-to-noise ratio), as provided by FD-OCT, may be needed for better quality image acquisition to allow accurate retinal layer segmentation.

Greenfield et al (2003) reported that OCT-derived macular thickness was well correlated with changes in visual function and RNFL structure in moderately advanced glaucoma. They reported a strong correlation between mean macular thickness and visual field mean deviation (R^2=0.47, p<0.001), and suggested that reduced macular thickness could be a surrogate for loss of RGCs in glaucoma.

Tan O et al (2009) showed that the GCC average measured by the RTVue FD-OCT were significantly better at diagnosing glaucoma in the perimetric group, compared to the macular retinal thickness(MR) average measured by either FD-OCT or TD-OCT. Thus, isolating GCC from the

outer retina improved the diagnostic power of the macular measurement. This could be explained by the fact that the outer retina, which is not much affected by glaucoma, takes up 65% to 70% of total retinal thickness and, therefore, could contribute variation in thickness that decreases discriminant power. The diagnostic power of GCC average was also higher than that of MR in the discrimination between pre-perimetric group (PPG) and normal eyes, but the advantage was not statistically significant.

Macular GCC measurement by OCT may detect pre-perimetric glaucoma earlier in those cases where the ganglion cell loss is more predominantly macular rather than peripheral (Tan O et al 2009). The addition of GCC data to NFL increased glaucoma detection rate from 78% to 87% in the perimetric group and from 45% to 56% in the pre-perimetric group (Tan O et al 2009).

Tan O et al (2009) in their study showed GCC detected an additional 9% of perimetric glaucoma cases and 11% of pre-perimetric glaucoma cases that were not detected by NFL. These results are consistent with our results, 38% eyes had an abnormal GCC and 13% had an abnormal RNFL thickness in the glaucoma suspect group, 98% had an abnormal GCC and 90% had an abnormal RNFL thickness in the glaucoma group. The reliability of the GCC increases in the glaucoma grooup than in the suspects or pre-perimetric group.Even though our results show that GCC imaging can detect glaucoma cases in spite of normal RNFL thickness (Fig 2B&2C),further prospective studies are needed before such a definitive conclusion is made due to a small sample size and also we did not compare the two groups (Glaucoma and Glaucoma suspects) with the normal group.

Conclusion

The ability to diagnose glaucoma with macular GCC thickness is comparable to peripapillary RNFL thickness. Macular GCC thickness measurements may be a good alternative or a complementary measurement to RNFL thickness and visual field test in the clinical evaluation and management of glaucoma.

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