LITERATURE REVIEW

Diagnostic Performance of Macular Ganglion Cell/Inner Plexiform Layer Thickness to Discriminate Normal Eye from Eye with Early Glaucoma Using Cirrus Spectral-Domain Optical Coherence Tomography

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ABSTRACT

Background: Glaucoma is a progressive optic neuropathy characterized by a progressive loss of retinal ganglion cells (RGC). In glaucomatous optic neuropathy, structural optic nerve changes may occur before detectable functional loss, which can be diagnosed early by detecting loss of RGC. This review was conducted to see the diagnostic performance of macular ganglion cell/inner plexiform layer (GC-IPL) thickness parameters to discriminate normal eye from early glaucoma eye using Cirrus Spectral-domain OCT compared to peri-papilarry Retinal Nerve Fiber Layer (RNFL) thickness parameters.

Methods: Literature search was conducted from MEDLINE database using Pubmed, Clinical Key, and ScienceDirect. No publication date was set, and only articles published in English were included. Reference list from the included studies were also checked for potentially relevant articles.

Results: Twenty articles were found related to search term. Seven articles met the inclusion criteria. Fourteen others were excluded. All studies revealed significant thinner GC-IPL and RNFL average thickness in glaucoma patients compared to normal patients. GC-IPL Average was inferior to GC-IPL Minimum and RNFL inferior in determining normal eye from early glaucomatous eyes. Studies evaluating the diagnostic performance of Ganglion Cells Complex (GCC) thickness also found low sensitivity values, ranging between 61.0% and 78.6% for average GCC.

Conclusion: Diagnostic performance of GC-IPL is comparable to RNFL parameters measurement in detecting early glaucoma eyes. Best performance in detecting early glaucoma were showed by GC-IPL minimum and RNFL inferior.

Keywords: Glaucoma, Retinal ganglion cells, Retinal nerve fiber layer

Glaucoma is a progressive optic neuropathy characterized by a progressive loss of retinal ganglion cells (RGC). This leads to clinically detectable structural and functional changes such as glaucomatous optic disc change and visual field defect.[1,2] Elevated intraocular pressure plays a major role in the development of glaucomatous optic neuropathy and is considered the most significant risk factor. Structural optic nerve changes in glaucomatous optic neuropathy may precede detectable functional visual loss. It has long

been suggested that glaucoma-induced structural changes start in the macula because of the dens population of retinal ganglion cells (RGC) in this region. Approximately 50% of these cells are concentrated within foveal center. Considerable loss of RGC can occur before visual field deficits are detected clinically.[1,3]

Assessment of clinical progression of glaucoma using the traditional ophthalmoscopy and optic disc photography can be quite subjective. New glaucoma diagnostic test is vital due to the fact that it is difficult to diagnose early glaucoma since the structural and functional changes in the eye are not yet obvious.[4,5] A tool for quantifying glaucomatous damage in the human posterior pole using retinal ganglion cell thickness measurement may represent a more sensitive method for early detection of structural glaucomatous damage. This is based on the relative lack of variability in the retinal ganglion cell population in the paramacular region among normal individual as demonstrated histologically.[6]

Optical coherence tomography (OCT) is a sophisticated image analysis system used to measure the optic disc and retinal nerve fiber layer in a noninvasive manner. OCT is developed to evaluate the structural damage caused by glaucoma. OCT has potential to yield total or local measurement of optic nerve head, nerve fiber layer thickness and any retinal layers.[7] Total macular thickness by Ganglion Cell Complex algorithm have been tested to detect pre-perimetric glaucoma in previous study, but its discriminating power has been shown to be lower than that of peri-papillary Retinal Nerve Fiber Layer (RNFL).[8]

Recent advances in OCT technology have enabled more detailed, selective and precise quantitative assessment of ganglion cells layer in glaucomaotus structural changes. Spectral-domain Optical coherence tomography (SD-OCT) is the latest generation of OCT, in which Cirrus SD-OCT is one of the most advanced OCT. The superiority of Cirrus SD-OCT is that it has ganglion cell analysis (GCA) algorithm that successfully detect and measure the thickness of the macular ganglion cell-inner plexiform layer (GC-IPL).[9]

By GCA algorithm, diagnostic power of the measurement of local macular thickness or inner retinal thickness is comparable to those of measurement of local RNFL thickness for diagnosing in patients with different stage of glaucoma.[9] Parameters such as GC-IPL Minimum and RNFL Inferior Thickness have been shown to have the best discriminating abilities differentiating normal eye from glaucoma eye thus making it an effective marker to detect early glaucoma.[10,11]

There has been no gold standard for identifying early glaucoma either structurally or functionally. Clinical examination for early glaucoma progression is often difficult and subjective, specifically the visual field methods have been used to assess early functional glaucoma only. The newer SD-OCT was designed to eliminate flaws such as subjectivity of the examiner and the limiting ability of Optic Nerve Head (ONH) and RNFL to evaluate the ganglion cell bodies.

This review was conducted to see the diagnostic performance of macular ganglion cell/ inner plexiform layer thickness parameters to discriminate normal eye from early glaucoma eye using Cirrus Spectral-domain OCT compared to peri-papilarry RNFL thickness paramaters.

MATERIAL AND METHOD

Literature search was conducted from MEDLINE database using Pubmed, Clinical Key, and ScienceDirect by entering keyword “Early Glaucoma”, “Cirrus Spec¬tral-domain Optical Coherence Tomo¬graphy”, ”Macular Retinal Ganglion Cell Thickness”, “Peripapillary Retinal Nerve Fiber Layer”. No publication date was set, and only articles published in English were included. Reference list from the included studies were also checked for potentially relevant articles.

Initial screening was performed by reviewing abstract based on keywords to choose articles that were related to the study. Inclusion and exclusion criteria were then applied to the studies. Inclusion criteria include cross sectional study that reported the evaluation of the performance of cirrus spectral domain optical

coherence tomo¬graphy – ganglion cell analysis algo-rithm in detection of early glaucoma patients compared to normal eyes. Study was excluded if the full text article was not available, the article was a review, or the article did not specify the outcomes for each assessment. All eligible studies were then rated based on level of evidence developed by Oxford Center, using the Evidence-based medicine 2011 Levels of Evidence.

The extracted information was proce¬ssed through a data sheet, which was then divided into basic characteristic, and outcomes.

The data included infor¬mation on the author, year of published, level of evidence, number of normal eye, number of early glaucoma eyes, mean subject's age, visual field mean deviation, and mean intraocular pressure.

Outcomes reviewed were GC-IPL average thickness measurement, RNFL ave-rage thickness measurement, GC-IPL mini-mum thickness measu-rement, RNFL inferior thickness measurement, Area Under the Receiver Operating Characteristic (AUC) between Normal vs Early Glaucoma Eyes, Accuracy Sensitivity and Specificity of Parameter Measurement between Normal vs Early Glaucoma Eyes. Articles are presented in table and figure form.

RESULT

Twenty articles were found related to search term. Seven articles met the inclusion criteria. Fourteen others were excluded. The articles that met the inclu¬sion criteria were listed in table 1 (one author might appear more than once in the table, depending on treatment).

The characteristic of each reviewed studies listed in Table 1. All reviewed articles were published from 2012 to 2014 and categorized in the level of evidence III. Six of the articles were prospective cross-sectional studies, one was retrospective observational study.

Total numbers of normal subject (eye) in each article varied from 43 to 119, with mean age distribution of 47.5 to 63.1 years old. The number of early glaucoma subject (eye) varied from 38 to 164, with mean age distribution of 50 to 66 years old. All visual field mean deviation of early glaucoma subjects in each articles are ≥ - 6 dB (- 3.54 to -2.33 dB). Visual field mean deviation of normal subject varied from – 0.55 to 0.08 dB. Two articles reported mean intraocular pressure of normal subject and early glaucomatous subject.

The GC-IPL average and RNFL average measurement in normal subject and subject with glaucoma are shown in Table 2. Patients with glaucoma had signi¬ficant¬ly thinner GC-IPL average and RNFL average thickness than normal subject in all studies.

The GC-IPL average and RNFL average measurement in normal subject and subject with glaucoma are shown in Table 2. Patients with glaucoma had significant thinner GC-IPL average and NFL average thickness than normal subject in all studies. Thickness difference between normal and early glaucoma eyes on GC-IPL Average and RNFL Average thickness measurement are shown in Figure 1. RNF Average mea-surement showed bigger difference bet-ween normal and glaucoma eye, comparing with GC-IPL Average measurement in all studies.

Table 1. Characteristics of the Reviewed Articles

No	Literature	Year	LoE	Number of Eyes		Mean IOP		Mean Age		Visual Field Mean Deviation	
				Normal	EG	Normal	EG	Normal	EG	Normal	EG
1	Mwanza et al [4]	2012	III	99	58	n/a	n/a	62.30	64.40	0.08	-3.20
2	Takayama et al [3]	2012	III	47	38	n/a	n/a	55.5	58.5	-0.07	-2.33
3	Mahdavi et al [12]	2013	III	91	59	14.70	14.10	58.60	66.10	-0.1	-2.50
4	Jeoung et al [13]	2013	III	119	164	n/a	n/a	57.1	58.7	-0.22	-2.68
5	Shin et al [14]	2014	III	43	84	n/a	n/a	47.54	50.92	-0.17	-2.33
6	Mwanza et al [15]	2014	III	49	50	n/a	n/a	63.10	66.40	n/a	-2.96
7	Sung et al [16]	2014	III	72	70	13.92	16.01	50.68	53.97	-0.55	-3.54

Table 2. Ganglion Cell-Inner Plexiform Layer Average Thickness, Peripapillary Retinal Nerve Fiber Layer Average Thickness in Normal and Early Glaucomatous Subjects

No	Literature	Parameter	Normal	EG
1	Mwanza et al	GC-IPL	82.1	68.1
		RNFL	90.9	69.3
2	Takayama et al	GC-IPL	81.3	72.4
		RNFL	92.2	74.4
3	Mahdavi et al	GC-IPL	81.1	66.6
		RNFL	94.0	70.5
4	Jeoung et al	GC-IPL	80.4	72.0
		RNFL	93.5	76.7
5	Shin et al	GC-IPL	85.49	74.08
		RNFL	100.37	81.49
6	Mwanza et al	GC-IPL	78.2	69.4
		RNFL	89.7	70.5
7	Sung et al	GC-IPL	86.65	72.21
		RNFL	97.78	76.99

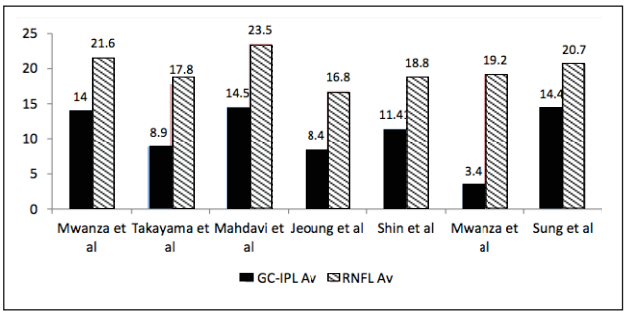

Fig 1. Thickness Difference (µm) between Normal and Early Glaucoma Eyes on GC-IPL Average and RNFL Average Thickness Measurement

Table 3. Ganglion Cell-Inner Plexiform Layer Minimum Thickness, Retinal Nerve Fiber Layer Inferior Thickness in Normal and Early Glaucomatous Subjects

No	Literature	Parameter	Normal	EG
1	Mwanza et al	GC-IPL	80.2	60.5
		RNFL	117.1	78.4
2	Takayama et al	GC-IPL	77	60.6
		RNFL	78.6	66.1
3	Mahdavi et al	GC-IPL	79.2	57.8
		RNFL	124.0	78.6
4	Jeoung et al	GC-IPL	77.2	61.2
		RNFL	119.5	86.7
5	Shin et al	GC-IPL	83.21	63.23
		RNFL	128.8	91.98
6	Mwanza et al	GC-IPL	75.9	61.3
		RNFL	116.2	80.7
7	Sung et al	GC-IPL	82.19	63.71
		RNFL	128.40	89.81

GC-IPL Minimum and RNFL Inferior thickness measurement in normal subjects and subjects with glaucoma are showed in Table 3. The result shows patients with glaucoma had significant thinner GC-IPL Minimum and RNFL Inferior thickness than normal subjects in all studies. Thickness differences between normal and early glaucoma eyes were bigger in GC-IPL Minimum measurement than in GC-IPL Average measurement (Figure 2).

Sensitivities and specificities for the parameters evaluated in studies are listed in Table 4 and Table 5. GC-IPL Minimum is the most sensitive (mean = 78.2). RNFL Inferior parameter had the highest specificities among others (Mean = 95.1%).

Accuracies for the parameters are presented in Figure 3. All parameters showed comparable accuracies although RFNL Inferior slightly superior than other parameters.

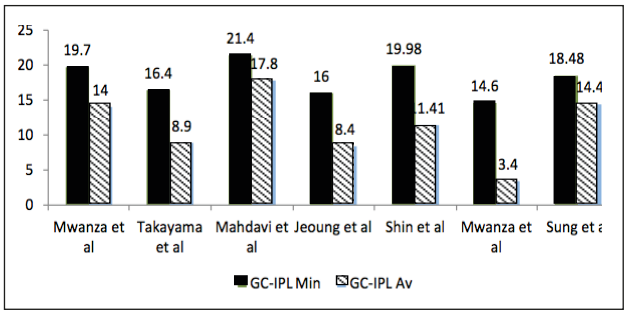

Fig 2. Thickness Difference (µm) between Normal and Early Glaucoma Eyes on GC-IPL Minimum and GC-IPL Average Thickness Measurement

Table 4. Specificity (%) of Parameter Measurement between Normal vs Early Glaucoma

No	Literature	Parameter			
		GCIPL av	RNFL av	GCIPL min	RNFL inf
1	Mwanza et al	86.8	92.9	87.9	98.9
2	Mahdavi et al	87.9	91.2	91.5	91.2
3	Jeoung et al	89.9	96.6	88.2	94.6
4	Mwanza et al	85.7	95.9	87.8	95.9
	Mean	**87.5**	**94.1**	**88.8**	**95.1**

Table 5. Sensitivity (%) of Parameter Measurement in Determine Normal Eyes from Eyes with Early Glaucoma

No	Literature	Parameter			
		GCIPL av	RNFL av	GCIPL min	RNFL inf
1	Mwanza et al	87.9	81	94.8	93.1
2	Takayama et al	23.4	34.0	46.8	17.0
3	Mahdavi et al	86.4	88.1	91.5	93.2
4	Jeoung et al	50.6	50.0	73.2	61.6
5	Mwanza et al	48	64	82.0	74.0
6	Sung et al	70	86	81	74
	Mean	**61.05**	**67.1**	**78.2**	**68.8**

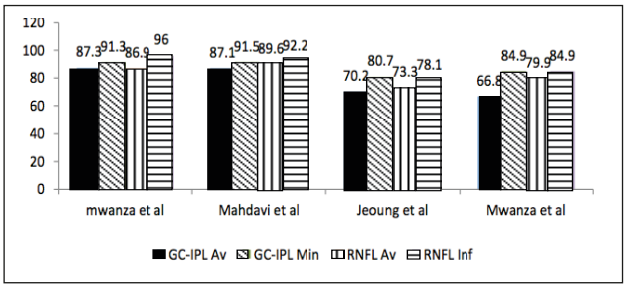

Fig 3. Accuracy (%) of Parameter for detect-ion of Early Glaucoma

Table 6. Area under the Receiver Operating Characteristic (AUC) (95% CI) between Normal vs. Early Glaucoma

No	Literature	Parameter			
		GCIPL av	RNFL av	GCIPL min	RNFL inf
1	Mwanza et al	0.935	0.936	0.959	0.939
2	Takayama et al	0.821	0.890	0.896	0.817
3	Mahdavi et al	0.937	0.946	0.976	0.962
4	Jeoung et al	0.817	0.897	0.902	0.890
5	Shin et al	0.962	0.972	0.973	0.944
6	Sung et al	0.893	0.928	0.939	0.907
	Mean	**0.894**	**0.928**	**0.940**	**0.909**

The AUC of GC-IPL and RNFL parameters from 6 studies for detecting early glaucoma are presented in Table 6. GC-IPL Minimum showed the best performance among parameters.

DISCUSSION

Diagnosis of early glaucoma is often challenging because there is no gold standard.[17] The latest spectral domain Optical Coherence Tomography (SD-OCT) has greatly enhanced scan resolution and reduced acquisition time, providing more reproducible images of the retinal nerve fiber imaging. OCT data have been incorporated into glaucoma assessment and many cross-sectional studies have confirmed that this approach can discriminate between

Key attributes of the Cirrus SD-OCT for monitoring RNFL changes are its ability to register and align follow-up images and to extract serial follow-up RNFL measurements at the same retinal location.[18,19] This method minimized variability in measurement associated with scan circle displacement.[20,21]

Macular layers measurement is now assessed for diagnosing and monitoring glaucoma, resulting in the development of powerful segmentation algorithm such as the Cirrus OCT ganglion cell analysis (GCA) that is included in the Cirrus SD-OCT. It detects and measures the thickness of macular GC-IPL within an elliptical annulus area centered on the fovea. The annulus has an inner vertical diameter of 1 mm, which was chosen to exclude the portions of the fovea where the layers are very thin and difficult to detect accurately. The GCA algorithm identifies the outer boundaries of the RNFL and IPL. The difference between the RNFL and the IPL outer boundaries segmentations yields the combined thickness of the retinal ganglion cell layer and IPL.[13]

Advantages of studying the macular GC-IPL for the diagnosis of glaucoma including (1) The normal macular GC-IPL is thick, which has the potential to increase the dynamic range in eyes with glaucoma, and (2) in glaucoma, the central visual field is usually spared until the last stage of the disease, which may make the macular GC-IPL a parameter that can be measured in severe and end-stage glaucoma when optic disc and peripapilarry RNFL parameter have already reached the based of the measurement. No consensus has been made to the best structural parameter for early glaucoma diagnosis, while the benefit using one parameter in favor to several parameters in the diagnosis of glaucoma is yet to be determined. One study showed it was not statistically significant by adding the parameters to the combination.[22,23,24,25]

This review found that the GC-IPL and RNFL thickness were thinner in subjects with early glaucoma than in normal subject. There was not any consensus about how much thickness difference between normal and early glaucomatous eyes, but Mwanza et al[12] used 20% thickness difference (± 15µm) to differ normal eye from early glaucomatous eyes in statistic analysis. Ishikawa et al[9] and Tan et al[26], by using custom intra-retinal segmentation algorithm on Time-domain OCT devices, found a statistically significant thinner GC-IPL in subjects with glaucoma compared with normal subjects. These findings were consistent with structural glaucomatous damage and support the hypothesis that loss of macular retinal ganglion

cells associated RNFL thinning because all axonal fiber emanating from retinal ganglion cells in the macula converge into the optic nerve head.

Our finding in this review showed GC-IPL Average was inferior to GC-IPL Minimum in determining normal eye from early glaucomatous eyes. The average thickness is not advantageous for detecting RGC loss limited to a local area since averaging (thickness divided by area) tend to underestimate the local RGCs loss as it takes into account the area with the normal or less affected RGC population.[27] Regional thickness has same averaging effect and regional may be presented within sectors. Developing a predefined sector that encloses the entire area with local RGC loss is difficult because areas of RGCs loss differ from patient to patient.[28]

GC-IPL Minimum was chosen as parameter in this review because theoretically this represents the location with local RGCs loss in early glaucoma. The GC-IPL Minimum measurement is based on anatomical characteristic of the GCL and IPL. Curcio et al[6] who studied the topography of RGC in six human retinas, obtained from eye bank donors, reported that the iso density contours of the RGC density in the macula form a horizontally oriented elliptical ring in all eyes. The GC-IPL thickness on all 360 spokes should be equivalent in healthy eyes. Consequently, the initial RGC loss limited to a small local area would be detectable as a decrease of the GC-IPL thickness on the spokes, leading to minimum GC-IPL thickness. Theoretically, this parameter should be sensitive in detecting initial RGC loss.[6] GC-IPL Minimum thicknesses should act as a compass to indicate the location with a local RGC loss in eyes with early glaucoma.[3] This theory is consistent with our finding that GC-IPL Minimum is superior to GC-IPL Average in thickness difference, in which it has the highest sensitivity among all parameters reviewed in determining normal eye from early glaucomatous eye.[16]

GC-IPL Average as a parameter was less reliable compared to the GC-IPL Minimum and RNFL Inferior. Studies evaluating the diagnostic performance of Ganglion Cells Complex (GCC) thickness also found low sensitivity values, ranging between 61.0% and 78.6% for average GCC.[22] Early glaucoma mostly affect the superior and inferior macular poles first, while the average remains within normal limit, making the GC-IPL Average being less sensitive and less specific for detecting early glaucoma. Macular GC-IPL thickness are only based on sampling of approximately 50% of retinal ganglion cell population, whereas RNFL thickness measurements result from the total number of retinal ganglion cells axons and not affected by conditions that can change the thickness of the macula, for example macular degenerations and diabetic retinopathy. Macular thickness is derived from scanning only a portion of the para-foveal region, leaving out others areas of macula. The clinical implication of this is that glaucomatous damage outside this scanned macular region will likely not be detected using GCIPL measurement, but may still be detected on RNFL scan analysis because all the retinal ganglion cell axons from and outside the macular converge onto the optic nerve head. [29,30]

It was revealed that GC-IPL Minimum and RNFL Inferior were the best parameters compared to others. GC-IPL Minimum and RNFL Inferior showed comparable sensitivities and specificities. Anatomically, good performance of RNFL inferior is due to the fact that Retinal ganglion cells located in the superior or inferior macula sends their axons in an arcuate manner to the superior and inferior portions of the optic nerve, respectively. Glaucomatous optic disc rim loss usually occurs in the inferior and superior areas, making these locations abnormal in early cases before other areas.[31]

There was no significant difference between overall AUC of GC-IPL Minimum and RNFL Inferior as the best parameters. It means GC-IPL Minimum has the same diagnostic power as RNFL Inferior for diagnosing early glaucoma. However, it was found that GC-IPL Minimum to be the most sensitive parameter in detecting early glaucoma. This finding suggests that in the macular region, early damage can be and often is localized, similar to the RNFL region. Mahdavi et al[12] found GC-IPL Minimum as the most sensitive parameter were located in the inferior hemifield. This fact is consistent with the finding that the inferior rim is the most common site of early disc

and RNFL glaucomatous damage. Mahdavi et al[12] also found that early retinal ganglion cell thickness loss typically gives rise to isolated paracentral loss of visual field on early glaucoma eyes. As we know, paracentral visual field loss is a type of early glaucoma functional damage detected by visual field. From this result, macular GC-IPL parameters have a theoretic advantage over RNFL parameter. Moreover, macular GC-IPL topography is less variable among normal individual than other diagnostically important structure, such as the optic disc and RNFL, which may result in a superior diagnostic accuracy of macular GC-IPL parameters in the early stage of glaucoma. However, direct comparison between OCT GC-IPL and RNFL parameters may be limited because the OCT RNFL map does not include any "minimum" parameter corresponding to the minimum GC-IPL.[6]

No significant difference was found in accuracy between GC-IPL parameters and RNFL parameters. Both parameters have comparable probability of test resulting true if the subject have or do not have early glaucoma. However, these parameters would have different characteristic. The GC-IPL parameter would be advantageous to sensitively detect local RGC loss in the macula because the macular elliptical annulus used for the GCA method is designed to cover the highest density and the thickest of RGC. GC-IPL parameters can also detect damage to both RGC axons and cell bodies. A limitation of this GCA method (GC-IPL parameters) is RGC loss limited to the area outside the elliptical annulus, which is smaller than the macula area, may be missed.[32] By contrast; RNFL encompasses all RGC axons that assemble to the optic disc. A limitation of the RNFL is that RNFL can detect only RGC axons, but not cell bodies. For the practical detection of glaucoma, the macular parameters should be used together with the parameter.[3]

CONCLUSION

In conclusion, diagnostic performance of macular GC-IPL parameters measurement is comparable to that of the RNFL parameters measurement for detection of early glaucoma eyes. GC-IPL Minimum and RNFL Inferior showed the best performance in detection early glaucoma.

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