

Significance of macular thickness in glaucoma

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Keywords

*imaging methods,
macular thickness, optical
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Abstract

The revolution in diagnostic and investigative ophthalmology that was provoked with the invention of imaging diagnostic methods had brought to the light new evidence that have defined and resolved some dilemmas in a number of ocular diseases concerning retina and optic nerve.

Nowadays it is accepted as scientific fact that imaging technologies (Optical Coherence Tomography, Confocal Scanning Laser Ophthalmoscopy, and Scanning Laser Polarimetry) are providing quantitative information confirming that structural damage in glaucoma most often precede functional changes, identified through the condition of visual field.

Assessment of the peripapillary retinal nerve fiber layer thickness (RNFL) and parameters of optic nerve head (ONH) conducted through the imaging methods has proved its importance in the recognition and detection of early glaucoma.

Different studies have previously reported controversial results comparing diagnostic accuracy between RNFL and macular thickness in glaucoma.

The invention of Spectral domain Optical Coherence Tomography (SD-OCT) and the ability of evaluation of macular thickness and macular ganglion cell complex (mGCC) has improved the potential of early glaucoma diagnosis and monitoring of glaucoma progression.

It is common knowledge that retinal ganglion cell loss (RGCs) is basic pathophysiological phenomenon in glaucoma. Retinal nerve fiber layer (RNFL) and retinal ganglion cells (RGCs) together comprise about 35-40% of the macular thickness.

Early detection and recognition of structural damage is considered to be crucial for diagnosis and management of glaucoma.

But, on the other hand, glaucomatologists should always take into account the objective limitations of imaging methods that should not be used as substitution for the clinical evaluation and assessment of visual field in patients with glaucoma.

Proper diagnosing of glaucoma should be made only with complementary and comprehensive evaluation and interpretation of all available methods, in order to make the right diagnosis and start immediate treatment if necessary.

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Introduction

"A diagnosis of glaucoma requires not only spotting the condition's characteristics and signs, but also determining the rate of structural and functional progression" (Robert Murphy, 2012).

Nowadays, it is estimated that structural changes in glaucoma most often precede functional changes. According to some opinions, this process could appear up to 5 years before functional damage. Thus, making feasible early structural damage could be key strategy for future successful glaucoma management. Imaging diagnostic methods that provide quantitative information regarding structural parameters in glaucoma (ONH topography, retinal nerve fiber layer thickness and macular thickness) had become unavoidable and priceless tools in glaucoma diagnosing and progression assessment.

A number of glaucomatologists are reporting controversial results regarding diagnostic superiority and accuracy of different structural parameters, conducted with different imaging method (Optical Coherence Tomography, Confocal Scanning Laser Ophthalmoscopy or Scanning Laser Polarimetry).

Retinal ganglion cell (RGCs) loss has been clearly established as basic and crucial pathophysiological phenomenon in glaucoma development. Retinal nerve fiber layer (RNFL) and retinal ganglion cell together comprise about 40% of the retinal thickness, and about 50% of total RGCs are localized in the region of macula. In human and experimental primate models of glaucoma, RGCs loss was identified around the fovea at early disease stages. Loss of RGCs necessarily causes atrophy of the ganglion cell layer (GCL). Data emerging from some histological studies have reported that abnormalities in RGCs morphology and cell density precede clinically detectable VF loss. So, early detection of RGCs loss is considered essential for diagnosing glaucoma and monitoring glaucomatous progression. Retinal nerve fibers are the axons of the RGCs and emerge from the cells to form the optic nerve.

Therefore, circumpapillary retinal nerve fiber layer (cRNFL) thickness has been used to assess the extent of glaucomatous damage (1).

Number of total RGCs varies in range of 0.7-1.5 millions, in average about 1 million RGCs, with 50% localized within central 4-5 mm of the macular region and peak density of 15000 mm². It makes only about 7.3% of total retinal area, the part which is not properly covered with visual field assessment tests.

Macular ganglion cell loss is considered as early phenomenon in glaucoma. However, as glaucoma eventually involves the cell body of the RGCs, measurement of RGC thickness (if possible), rather than of the RNFL alone, would help estimate the glaucomatous damage accurately (1).

The main focus of this article is to emphasize the significance of macular thickness measurements in glaucoma. So, what are (if so) the advantages of macular thickness assessment over other structural parameters in glaucoma?

Macular thickness does not change over time in healthy subjects and in the presence of reduced macular thickness it is most probably glaucoma. Besides, evidence is stating that, the ganglion cell population in the macula, unlike the total number of ganglion cells in the entire retina, is relatively stable among normals. On the other hand, the optic nerve varies individually in terms of size, shape, sloping, etc. Furthermore, because the ganglion cells represent a huge portion of the thickness of the retina, it is estimated easier to detect changes in macular thickness, compared with changes in a thin layer, as it is RNFL. Those features make macula ideal parameter for comparison to a normative database (2).

The significance of macular thickness in glaucoma starts with the introduction of Retinal Thickness Analyzer (RTA) by Zimmer and co-workers (1998), suggesting that reduced macular thickness could be useful in glaucoma detection. The measurements were recorded on macular thickness map (3). The studies based on RTA and introduction of time-domain Optical Coherence Tomography (TD-OCT) had offered evidence promoting macular thickness as "surrogate" parameter in assessment of glaucoma (1).

Studies evaluating data from TD-OCT suggested better reproducibility of macular scans over RNFL scans, due to the fact that macular scans require internal fixation and are less dependent on the operator skills, which increases scan reproducibility. On the other hand, RNFL scans require correct positioning of the scan circle by the operator performing the method (4).

The role of Optical Coherence Tomography

The advent of posterior segment Optical Coherence Tomography had brought new prospective in number of retinal diseases and optic nerve pathology. Optical coherence tomography (OCT) is a non-invasive, non-contact diagnostic tool that can provide in vivo cross-sectional images of the retina with high resolution, reproducibility and repeatability, as well as low variability. The new imaging diagnostic method has proved its superiority in the diagnosis and assessment of glaucoma and its progression. OCT enables measurements of structural parameters, identified through the optic nerve head features (ONH), evaluation of circumpapillary retinal nerve fiber layer thickness (RNFL) and assessment of central macular thickness and macular ganglion cell complex (GCC).

In general, advantages of Optical Coherence Tomography are due to the ability of providing quantitative

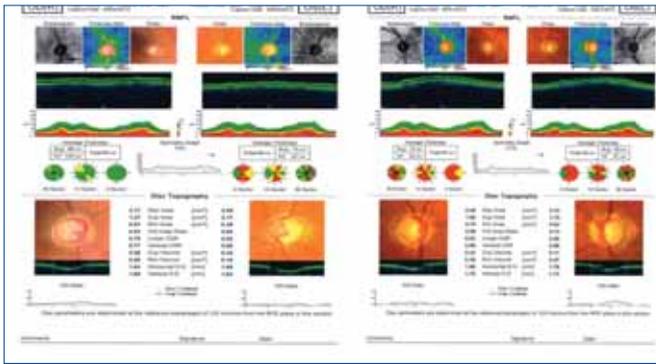


Fig. 1. RNFL thickness measurement (SD-OCT Topcon 3D 2000)

information with high resolution of the scans. The obtained measurements are objective, with high sensitivity, specificity and reproducibility.

The studies based on Time domain Optical Coherence Tomography (TD-OCT) are reporting controversial results comparing diagnostic accuracy of RNFL versus macular thickness measurements (Medeiros, 2005; Wollstein, 2005). Limitations of TD-OCT had been recognized as the ability of full retinal thickness assessment, without software of ganglion cell separation, and also, insufficient depth resolution for accurate evaluation and ganglion cell segmentation. A number of studies have demonstrated that automated macular GCC measurements obtained with SD-OCT have better diagnostic accuracy compared with macular thickness measurements provided by TD-OCT. However, the relationship between macular structural changes and topographic changes in the optic nerve head in glaucoma is still not completely clarified yet.⁵ The upgrade of OCT technology and introduction of Spectral domain (Fourier domain) Optical Coherence Tomography (SD-OCT) had enabled approach to more detailed and sophisticated information regarding macular thickness, compared with TD-OCT. Due to the high speed, large areas of the retina could be examined with great accuracy.

The most important and useful advantages of SD-OCT over TD-OCT were identified as:

- 2x better resolution depth (10 μm /5 μm)
- segmentation of ganglion cell layers
- improved scanning speed (50-70x)
- better reproducibility, sensitivity and specificity
- less artefacts due to eye movements
- software for evaluation of glaucoma progression (GPA- glaucoma progression analysis)

Those characteristics had made macular thickness valuable and reliable glaucoma marker (2).

Recent studies have found that glaucoma diagnostic accuracy is improved if SD-OCT macular measurements are focused on inner retinal layers. It remains unclear whether the outer retinal layer (ORL), especially the photoreceptor layer, is involved in glaucoma.

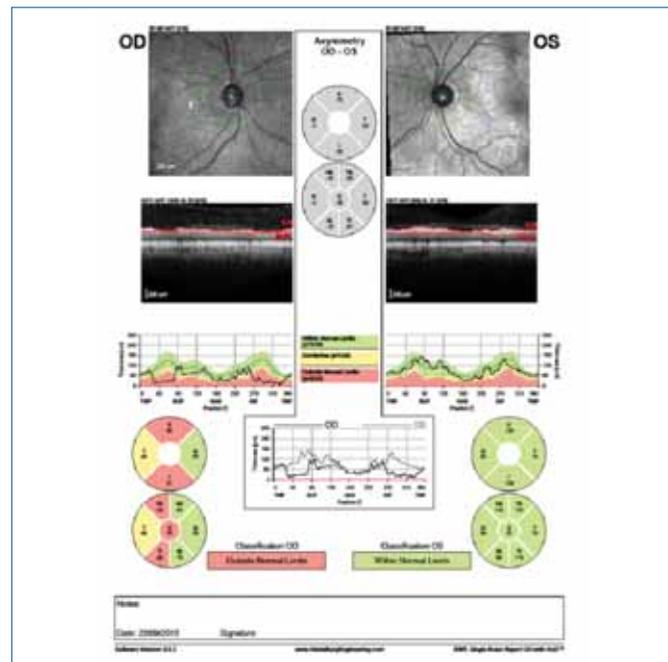


Fig. 2. RNFL thickness measurement (Heidelberg Spectralis) (Courtesy of d-r V.Poposki)

Some electrophysiological reports are suggesting that the outer retina is involved in glaucoma, and have appeared some studies noticing the involvement of the foveal photoreceptor layer in glaucoma (1).

It has been shown that circumpapillary retinal nerve fiber layer (cpRNFL) measurements with OCT have good ability to distinguish glaucomatous from healthy eyes. Although cpRNFL thinning is a useful marker of glaucomatous damage, there is growing evidence that measurement of the glaucomatous macula may also reveal changes in favour of diagnosing glaucoma. Measurements of macular retinal ganglion cell-related structure may therefore offer valuable adjunct or alternative to routine circumpapillary measurements for glaucoma diagnosis. As the macula is generally liberated from large vessels and has a readily identifiable center, assessment of the macula may also overcome some limitations of circumpapillary measurements, such as interference from retinal and optic nerve head vasculature, parapapillary atrophy, and variable placement of the measurement circle around the disc (6).

Future improvement in OCT technology embraces ability for evaluation of structures that have been inapproachable so far (lamina cribrosa and choroidal thickness measurements). The introduction of swept source (deep range OCT) obtains very high resolution scans and choroidal volume measurements.

Ultra-high resolution OCT (UHR-OCT), with an axial resolution of approximately 3 μm or less, has the ability to image retinal ultrastructure.

The repeatability and reproducibility of measurements are very important features that provide reliability of the obtained data, which would be compared with

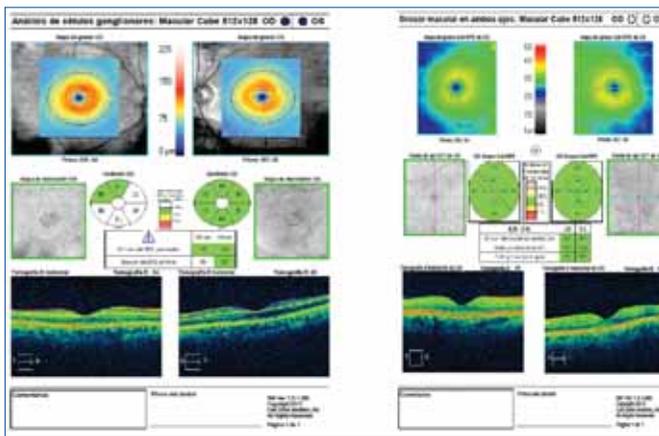


Fig. 3. Macular Ganglion Cell Complex (mGCC) (Courtesy of d-r V.Poposki)

the data form normative database. This information enables the clinician to evaluate if observed changes are due to fluctuations in the methods or if they are really valid changes in the structures. This is especially true for the measurements of the intra-retinal layers, which are important morphometric parameters in the diagnosis of retinal and neurological diseases and the monitoring of the progression of these disorders (7). The concordance between the patient's measurement and normative database is another very important and sensitive aspect of the interpretation of the results.

Also important to the issue of "normative" data is stratification by age, ethnicity and even gender of the subjects who make up the "normal," since measurements in healthy individuals may vary according to these factors. It is clear that large amounts of in vivo information can be acquired without invasive intervention, effectively allowing a "virtual biopsy" of the retina. In practice, clinicians and operators should stick to the rule for quantitatively and qualitatively reviewing scans before comparing them to the macula or RNFL normative databases (8).

The macular Ganglion Cell Complex (GCC) significance

Glaucoma preferentially thins the ganglion cell complex (GCC) in macula, which includes the axons, cell bodies and dendrites of retinal ganglion cells. Human and experimental studies have confirmed RGCs loss around fovea occurring in early glaucoma. Moreover, the GCC has been identified as highly sensitive and specific for diagnosing glaucoma and monitoring its progression (Rao et al, Ophthalmology 2010). Therefore, studies based on imaging methods had revealed the possibility of using macular thickness as a marker for glaucoma detection and progression assessment. Recent studies have found that glaucoma diagnostic accuracy is improved if SD-OCT macular measurements are focused on inner retinal layers (1).

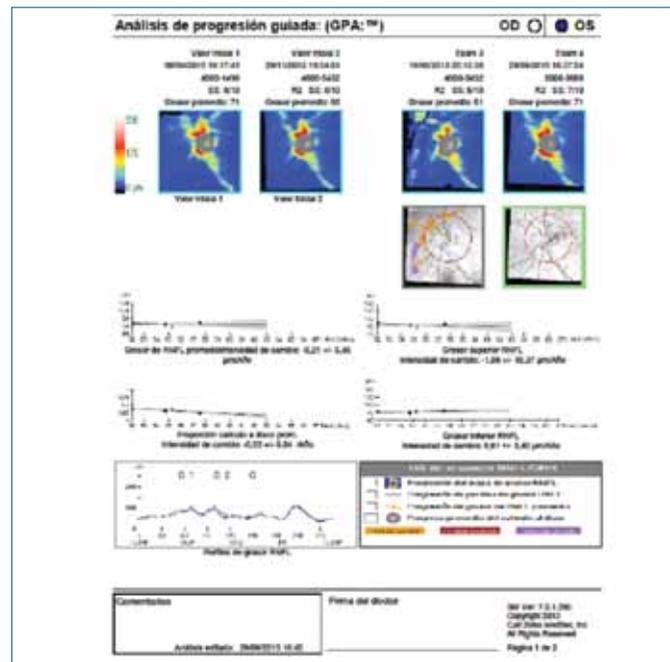


Fig. 4. Glaucoma progression analysis (Courtesy of d-r V.Poposki)

The macular GCC thickness measurement incorporates several retinal layers, including ganglion cell layer, inner plexiform layer and overlying retinal nerve fiber layer. According to data emerging from some studies, it is possible that finer segmentation of the ganglion cell-containing retinal layers alone might facilitate better detection of glaucomatous damage, particularly as it is loss of retinal ganglion cells that is the defining histological feature of glaucoma. Recent developments in SD-OCT provide the ability for segmentation of the ganglion cell containing macular ganglion cell inner plexiform layer (mGCIPL) (6).

There are few commercially available OCT technologies that have software algorithm capable of ganglion cell complex assessment. It is affordable with Optovue (RTVue), Carl Zeiss Meditec (Cirrus) and Heidelberg (Spectralis) OCT algorithm.

Several imaging technologies have included progression analysis software algorithms tending to assist the clinician in monitoring glaucoma progression. In order for progression analysis to be useful in clinical practice, three criteria must be met: the measurements must be reproducible and have minimal noise, follow-up images must be accurately registered to each other, and a statistical test must distinguish between true biological change and instrument measurement variability (9).

Relationship between diagnostic accuracy of different structural parameter measurements

It was mentioned previously that structural damage of the optic nerve head (ONH) precedes functional loss identified through visual field impairment.

Number of studies conducted with imaging devices, especially SD-OCT, that are assessing such relationship are reporting good correlation between GCC thinning and visual field changes (VF) (5, 10, 11).

Recent studies have registered that eyes with SAP progression have significantly greater rates of macular thickness loss consistent with glaucomatous atrophy of RGCs, compared with non-progressing eyes (12).

Combined Structure-Functional Indices (CSFI) are recently recognized as more objective and relevant indicator of glaucomatous damage assessment, compared with structural and functional parameters alone¹³ Combined structure and functional index described by Medeiros and co-workers serves the purpose of merging the results of structural and functional tests into a single index that could be used for diagnosing, staging and detection of progression in glaucoma. Limited agreement between structural and functional tests shows necessity of combined approach for detecting and monitoring the disease.

Also, it was found that macular thickness assessed on OCT is directly related to the best corrected visual acuity and contrast sensitivity, which is predictable to expect (14).

But, speaking of diagnostic accuracy of different structural parameters, the key question is, could be one structural parameter (retinal nerve fiber layer thickness or macular thickness obtained through GCC) recognized as most relevant and superior, with best diagnostic accuracy for early glaucoma detection?

And, the other issue, which one of the imaging methods (OCT, CSLO, SLP) has better diagnostic accuracy over the others? But, this is highlight for some other occasion as a challenging topic.

One of the most important features of SD-OCT is high reproducibility and low variability of the measurements.

Speaking of diagnostic accuracy of different parameters and measurements, the relevance of the performed studies should be based on STARD Guideline - Standards for Reporting of Diagnostic Accuracy. It is internationally accepted method of assessing a study conducted on diagnostic equipment. The STARD Guideline contents 25 points that should be fulfilled for good diagnostic accuracy of the study.

The majority of studies investigating correlation between different structural measurements are reporting good inter-measurements agreement (5, 6, 7, 15–19). The reports are emphasizing that advanced imaging devices with their sophisticated technology are capable of identifying glaucomatous damage at the early stage. On the other hand, clinicians have always to have in mind the objective limitations of imaging methods that provide quantitative information with high resolution, reproducibility and repeatability. Aside from the real "revolution" that imaging methods brought to diagnostics in ophthalmology, those meth-

ods should not be interpreted without thorough clinical examination of the patients, complementary with the functional tests data.

Another challenging issue related to the diagnostic superiority of imaging methods, is the assessment and monitoring of glaucoma progression. High resolution and low variability of measurements conducted with imaging devices are essential for detecting glaucoma progression.

Some of the sophisticated and upgraded OCT technologies had developed commercially available software algorithm for detection and assessment of glaucoma progression.

The Cirrus High definition OCT (HD-OCT), as well as RTVue 100 optical coherence tomography, have in-built ganglion cell analysis algorithm (GCA), which allows successful segmentation of inner macular layers, with reproducible measurements of the layers thickness. Studies performed with this algorithm are suggesting that macular parameters, such as total macular thickness and ganglion cell analysis, obtained by OCT, could be found useful in detecting glaucoma progression (1, 7, 9).

Finally, "an optimal method for detecting glaucoma progression should not only give an indication of whether or not the eye is changing over time, but also should estimate the rate of deterioration (20).

Comment and recommendation

Imaging technologies that evaluate the structure of the optic nerve head, peripapillary retinal nerve fiber layer and macular thickness provide important and useful quantitative information that could be adjunct and complement, but not substitute for thorough and comprehensive clinical examination and functional investigation data.

Advanced ocular imaging technologies are facilitating objective and reproducible quantification of change in glaucoma, but, at the same time, they put substantial challenge in front of the clinicians in order to determine true structural change due to glaucoma. But, on the other hand, clinicians should be fully aware of the objective limitations of imaging methods that in some case could even mislead inexperienced ophthalmologist and provoke false glaucoma diagnosis. The advent and upgrading of Spectral domain Optical Coherence Tomography technology has enabled advanced macular protocols to play significant role in the diagnosis and monitoring of glaucoma. OCT is useful tool for detection of glaucomatous structural progression and quantification of the velocity of progressive macular loss.

OCT measurements of macular structures such as macular ganglion cell complex (GCC) has been shown to be very useful adjunct for differentiating healthy and glaucomatous eyes. Additionally, thick-

ness measurements of the intra-retinal layers have good repeatability and reproducibility. There are still controversial opinions regarding superiority and overestimation of diagnostic accuracy of single imaging device over the others. No relevant controlled clinical studies yet have clearly and undoubtedly reported that one single imaging device outperforms the others in diagnostic ability and accuracy. Nowadays, most imaging technologies have comparable diagnostic accuracies, but each of them has its own objective limitations. Progression detection software is still relatively new, and long-term prospective data on progression analysis are limited. There is still missing definition of imaging obtained structural change as gold standard in glaucoma. Also, the artefacts due to eye movements scan quality, ocular media transparency and some other pathologic conditions of the optic disc and macula could significantly influence diagnostic accuracy. The normative database in each imaging device is different; resulting in outcome as "outside of normal limits" message that could lead to false diagnosis. Taking all these facts into account, one has to conclude that imaging methods are undoubtedly extremely useful in providing quantitative information regarding structural damage as early phenomenon in glaucoma. But, for real, relevant assessment of each glaucoma patients it is necessary to obtain and interpret comprehensive data of thorough clinical examination, functional investigation and imaging devices. The outcome should result in individually tailored therapeutic approach for every glaucoma patient.

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