Comparison of Macular and Peripapillary Measurements for the Detection of Glaucoma

An Optical Coherence Tomography Study

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Objective: To evaluate macular nerve fiber layer (NFL) thickness in glaucomatous damage by optical coherence tomography (OCT) and to compare its discriminating power for glaucoma and glaucoma suspects with that of total macular thickness and peripapillary NFL thickness.

Design: Cross-sectional, case–control, comparative study.

Participants: A total of 133 eyes from 133 subjects including 46 normal eyes, 48 glaucoma-suspect eyes, and 39 glaucoma eyes were enrolled.

Methods: Macular NFL thickness, total macular thickness, and peripapillary NFL thickness were measured by Stratus OCT in each diagnostic group.

Main Outcome Measures: The patterns and measurements of macular NFL, total macular, and peripapillary NFL thickness in total mean, 4 quadrants, and 12 clock hours. The discriminating power of each parameter for detection of glaucoma suspects and glaucoma was evaluated by areas under the receiver operating characteristic curve (AROC). Correspondence with visual field function was studied by linear regression analysis.

Results: The macular NFL profile exhibited a double-hump pattern with peaks over superonasal and inferonasal sectors. A significant difference in macular NFL thickness between normal and glaucoma-suspect groups was found at the 6-o'clock position, whereas a difference was found in all except the temporal clock hours between normal and glaucoma subjects. No significant difference in AROCs for detection of glaucoma suspects or glaucoma was found when macular NFL thickness and total macular thickness measurements were compared. However, mean macular NFL thickness demonstrated a stronger correlation with visual function than mean macular thickness ($r = 0.39/R^2 = 0.15$ vs. $r = 0.23/R^2 = 0.05$, $P = 0.042$). Among all the findings, inferior peripapillary NFL thickness had the best performance in discriminating glaucoma (AROC, 0.91) and glaucoma suspects (AROC, 0.67). It also had the strongest correlation with visual function ($r = 0.60/R^2 = 0.36$, $P < 0.001$).

Conclusions: Macular NFL thickness was significantly reduced in glaucoma. It had a similar discriminating power for glaucoma detection but a stronger correlation with visual function than total macular thickness. Peripapillary NFL thickness, however, outperformed both total macular and macular NFL thickness in terms of glaucoma detection and visual function correlation. Peripapillary NFL thickness, as a total measurement of both macular and peripheral NFL, is still the best surrogate marker in glaucoma assessment. *Ophthalmology 2005; 112:391–400 © 2005 by the American Academy of Ophthalmology.*

The concept of measuring retinal thickness at the macular region in evaluating glaucomatous damage has received increasing attention since it was hypothesized by Zeimer et al.[1] The anatomic macula measuring approximately 6 mm is recognized histologically by the presence of xanthophyll pigment and multilayered ganglion cells. There are up to 7 layers of ganglion cell bodies in the central retina or macula and as few as 1 cell layer in the peripheral retina. Therefore, it is conceivable that loss of retinal ganglion cells, the primary pathology of glaucoma, can be more readily de-

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tected over the macular region than the peripheral retina. This assumption was supported by the observable facts from experimental primate models of glaucoma in which foveal ganglion cells seemed to be vulnerable to glaucoma injury and the loss took place even in mild glaucomatous changes.[2]

It has not yet been possible to measure the retinal ganglion cell layer precisely in human subjects in vivo. Because retinal ganglion cells and retinal nerve fiber layer (NFL) over the macula constitute 30% to 35% of the thickness of the retina,[3] it was proposed that loss of retinal ganglion cells and NFL can be reflected by a reduction in central retinal thickness. In a pilot study, Zeimer et al[1] first demonstrated quantitatively in vivo that there is a loss of total macular thickness in glaucoma. It was also suggested by other studies that total macular thickness may provide a potential objective and quantitative parameter for evaluation of glaucoma.[4–6]

Theoretically, the retinal NFL thickness is more specific than the total retinal thickness in representing the proportional loss of retinal ganglion cells. Previous studies focused mostly on the peripapillary region,[7–10] which is the core area for evaluation of retinal NFL, and little is known about the role of macular NFL in glaucoma. As retinal nerve fiber bundles arising from individual retinal ganglion cells converge toward the optic disc, retinal NFL over the macula is much thinner than that around the peripapillary region, thus rendering this layer difficult to delineate and to quantify.

Optical coherence tomography (OCT) is one of the imaging technologies commercially available for measuring total retinal thickness and retinal NFL thickness. The design is based on the principle of low-coherence interferometry, and measurement is determined by the time-of-flight delay from backscattering signals of the retina, analogous to an ultrasound B scan.[11] In the earlier models of OCT, transverse resolution is limited by having only 100 scan points and axial resolution of 10 to 20 μm. The latest model of OCT (Stratus OCT; Carl Zeiss Meditec Inc., Dublin, CA) allows cross-sectional imaging of the retina, achieving an axial resolution of <10 μm, and the number of scan points reaches 512 for transverse resolution. With a higher resolving power, measurement of NFL over the macula is made possible.

In this study, we attempt to investigate the clinical significance of macular NFL thickness in glaucoma. Second, we try to identify the most favorable surrogate marker for glaucomatous damage among all the measurements of macular NFL thickness, total macular thickness, and peripapillary NFL thickness.

Materials and Methods

Subjects

One hundred thirty-three Hong Kong Chinese including 46 normal subjects, 48 glaucoma suspects, and 39 glaucoma patients examined during the period from October 2003 to February 2004 in the Department of Ophthalmology, Caritas Medical Center, who met the inclusion criteria of the study, were included. Caritas Medical Centre is the ophthalmic referral center in the Hong Kong Hospital Authority Kowloon West Cluster, serving a population size of approximately 1.2 million. The study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Hong Kong Hospital Authority Kowloon West Cluster. Informed consent was obtained from the study individuals.

All subjects underwent a full ophthalmic examination, including visual acuity, refraction, intraocular pressure measurement with Goldmann tonometry, and dilated fundus examination with stereoscopic biomicroscopy of optic nerve head under slit-lamp and indirect ophthalmoscopy. The inclusion criteria included best-corrected visual acuity of at least 20/40, with spherical refractive error between $+3.00$ and -6.00 diopters. Patients with any kind of retinal pathology, retinal laser procedure, retinal surgery, neurologic diseases, or a history of diabetes were excluded. Standard visual field testing was obtained with static automated white-on-white threshold perimetry (Program central 30-2, Humphrey Field Analyzer II, Humphrey Instruments, Dublin, CA). A visual field was defined as reliable when fixation losses were $<20\%$, and false-positive and false-negative rates were $<25\%$. Subjects would not be included in the study if they could not complete a reliable visual field test within 3 attempts.

Normal subjects consisted of healthy individuals with no history of intraocular pressure >21 mmHg, normal optic nerve head appearance on the basis of stereoscopic examination under slit lamp, and normal Humphrey visual field result. Normal optic nerve head appearance was defined as symmetric cup-to-disc ratio of <0.5 with uniform neuroretinal rim. A normal visual field was one with less than 3 nonedge contiguous points identified as significant ($P<0.05$) on the same side of the horizontal meridian in the pattern deviation plot and was graded as within normal limits in the glaucoma hemifield test.

Glaucoma suspects consisted of individuals with ocular hypertension and/or preperimetric glaucoma. Subjects belonged to the subgroup of ocular hypertension when they had intraocular pressure >21 mmHg but not more than 30 mmHg measured in at least 3 separate visits and had normal optic nerve head appearance. Patients were diagnosed to have preperimetric glaucoma when they had an asymmetric cup-to-disc ratio of >0.2 and showed early glaucomatous optic disc changes, including thinning of neuroretinal rim and notching. However, all subjects belonging to the glaucoma suspect group had normal visual field results as defined in the normal group.

Glaucomatous neuropathy was defined as having loss or thinning of neuroretinal rim, notching, or excavation with an associated visual field defect in the corresponding location. A glaucomatous visual field defect had 3 or more significant ($P<0.05$) nonedge contiguous points with at least 1 at the $P<0.01$ level on the same side of the horizontal meridian in the pattern deviation plot and graded outside normal limits in the glaucoma hemifield test. All patients with abnormal visual field results had undergone visual field testing at least twice to confirm the visual field defect.

Optical Coherence Tomography Measurements

Optical Coherence Tomography was performed with OCT version 3 (STRATUS OCT, Carl Zeiss Meditec Inc., Dublin, CA). The optical principles and applications of OCT have been recently reviewed by Jaffe and Caprioli.[12] Before the scan, the pupil size of each subject was determined. If the pupil size is <4 mm under ambient conditions, the pupil would then be dilated with 0.5% tropicamide and 0.5% phenylephrine. Subjects underwent 3 scanning protocols, including (1) fast retinal NFL thickness scan with 3 sequential circular scans of 3.4-mm diameter over the macula, (2) fast retinal NFL thickness scan with 3 sequential circular scans of 3.4-mm diameter over the optic nerve head, and (3) fast macular thickness scan with 6 linear scans spaced 30° with each other over