Kaohsiung Journal of Medical Sciences (2015) 31, 420–425

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

# Posterior pole asymmetry analysis and retinal thickness measurements in young relatives of glaucoma patients

**Gökhan Pekel*, Semra Acer, Ramazan Yağcı, Hüseyin Kaya, Fatih Özbakış, Alperen Bahar, Ebru Nevin Çetin**

*Department of Ophthalmology, Pamukkale University, Denizli, Turkey*

Received 30 December 2014; accepted 27 May 2015
Available online 29 June 2015

**KEYWORDS**
Ganglion cell complex;
Posterior pole asymmetry analysis;
Primary open-angle glaucoma;
Retinal arteriolar caliber;
Retinal thickness

**Abstract** The presence of a family history of glaucoma is a known risk factor for primary open-angle glaucoma (POAG) in middle-aged and older individuals. In this study, our aim was to demonstrate possible early glaucomatous alterations in young first- and second-degree relatives of POAG patients by spectral-domain optical coherence tomography. A total of 104 participants (52 relatives of POAG patients and 52 healthy individuals) were recruited in this cross-sectional study. All the participants were between 17 years and 45 years of age. All eyes underwent testing with spectral-domain optical coherence tomography. Peripapillary retinal nerve fiber layer thickness, hemifield macular thickness, macular ganglion cell complex thickness, posterior pole asymmetry analysis, and retinal arteriolar caliber measurements were taken for comparison between the study and control groups. The mean peripapillary retinal nerve fiber layer thickness was 104.9 ± 8.8 μm in the study group and 105.6 ± 7.4 μm in the control group ($p = 0.68$). Although whole macular thickness measurements were higher in the control group when compared with the study group ($p = 0.008$), the macular ganglion cell complex thickness was similar in both groups ($p = 0.87$). The posterior pole asymmetry analysis revealed no statistically significant difference between the groups in the aspect of consecutive black squares ($p = 0.79$). The mean retinal arteriolar caliber was 85.9 ± 4.8 μm in the study group and 86.0 ± 5.0 μm in the control group ($p = 0.90$). In conclusion, young relatives of POAG patients do not show characteristic glaucomatous damage when compared with the controls.


Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Ophthalmology, Pamukkale University, Kınıklı, Denizli 20070, Turkey.
*E-mail address:* gkhanpekel@yahoo.com (G. Pekel).

http://dx.doi.org/10.1016/j.kjms.2015.06.001

## Introduction

Primary open-angle glaucoma (POAG) is the most common type of glaucoma, and is characterized by progressive degeneration of retinal ganglion cells and axons [1]. Risk factors of POAG include increased intraocular pressure (IOP), thinner central corneal thickness (CCT), older age, and a positive family history of POAG [2,3]. There is a 20% risk of glaucoma in both first- and second-generation relatives of those affected compared with controls [4]. As vision loss from POAG is preventable when the disease is managed in its initial stages, early detection is important in high-risk populations such as relatives of POAG patients [5].

Screening and examining for POAG diagnosis mainly includes IOP measurements, evaluation of the optic nerve head, and visual field testing. Although these examinations are very important, they are not always enough to make an early diagnosis. The earliest observable damage in POAG is atrophy of the retinal nerve fiber layer (RNFL) [6]. It was demonstrated that up to 35% of retinal ganglion cells may be lost before a defect occurs in standard visual field analysis [7]. Sometimes, a loss of a lesser percentage of retinal ganglion cells can produce a small but definite visual field defect when it happens to be confined to an entire RNFL axon bundle.

Recently, a new assessment tool—evaluation of asymmetry in hemifield macular thickness—has been introduced for the early diagnosis of glaucoma [8]. Additionally, it was reported that retinal arteriolar narrowing is associated with long-term risk of POAG [9]. The aim of this study was to evaluate the peripapillary RNFL thickness, macular ganglion cell complex (GCC) thickness, posterior pole asymmetry, and retinal arteriolar caliber (RAC) in young relatives of POAG patients. One of our starting points was that it is possible that relatives of glaucoma patients have fewer retinal ganglion cells at the start of their lives and are therefore more likely to display thinner retinal layers. In contrast to previous reports, we included only young adults in order to eliminate age-related glaucoma risk [5,6]. We hypothesized that new early diagnostic techniques may show some defects in the posterior pole retina of young relatives of POAG patients.

## Materials and methods

In this cross-sectional and comparative study, a total of 104 participants were recruited (52 participants in the "relatives of POAG patients" group and 52 healthy young adults in the control group). This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Pamukkale University Ethics Committee.

### Study population

The eligibility criteria for the study group include the following: (1) being between 17 years and 45 years of age; (2) having visual acuity of at least 20/20; (3) having normal anterior and posterior segments by clinical examination; (4) having at least one POAG relative (1$^{st}$ or 2$^{nd}$ degree); and (5) being able to perform high-quality optical coherence tomography (OCT) examinations. Individuals with pre-existing systemic medical conditions, pre-existing ocular disorders, any history of ocular surgery, a refractive error of $>$2.0 D, or abnormal keratometry readings (i.e., $>$46 D or $<$42 D), or those using ocular or systemic medications were excluded from the study. There were no relationships between the participants in the study group. In the present study, the participants' first- and second-degree relatives who had POAG consisted of parents ($n = 38$), grandparents ($n = 8$), and aunts and uncles ($n = 6$). The inclusion and exclusion criteria for the age-matched healthy controls were the same, except for having a POAG relative. Participants who were not sure about their family history for glaucoma were also excluded. Additionally, we checked the medical records of the patients in order to confirm the POAG diagnosis. In some cases, we invited the patients' relatives to perform the ophthalmological examination. Despite our efforts to reveal the exact family history of the participants, it is not always possible to have the complete glaucoma history of every member of the family tree.

### Ocular examination techniques

One of the eyes of each participant was selected randomly for the study. There were 28 right eyes and 24 left eyes in the study group, and there was 32 right eyes and 20 left eyes in the control group. All the participants underwent ocular examinations, including a visual acuity assessment (Snellen chart), an automatic refractometer measurement, biomicroscopy, gonioscopy, IOP measurement, stereo-examination of the optic nerve head and macula, pachymetry, and OCT. The OCT measurements were taken with spectral-domain (SD) OCT (Spectralis software version 5.8, Heidelberg Engineering, Heidelberg, Germany). Posterior pole asymmetry analysis (PPAA), macular hemifield thickness, peripapillary RNFL thickness, macular GCC thickness, and RAC measurements were performed with the SD-OCT.

In the PPAA technique, a macular thickness map is divided into 64 squares (an 8 $\times$ 8 square grid) centered on the foveola (Figure 1). PPAA provides the data derived from the square-to-square comparison between corresponding squares across the hemisphere within each eye. In this study, we compared the mean superior hemisphere thickness and mean inferior hemisphere thickness, in addition to the square-to-square comparison. Hemisphere asymmetry was calculated by comparing each cell in the inferior hemisphere with the corresponding cell in the superior hemisphere, and displayed as an asymmetry map. For a square-to-square comparison between superior and inferior hemispheres, at least two consecutive black squares were taken into consideration. A black square indicates that the difference between two corresponding superior—inferior retinal square thicknesses is $>$ 30 $\mu$m. Squares that cut through a blood vessel were not included for analysis, as the retinal thickness in these squares is measured to be thicker. The PPAA screen also shows the average thickness values of superior and inferior macular hemifields. For peripapillary RNFL analysis, the thicknesses of all the quadrants (superior, inferior, temporal, and nasal) were recorded separately.

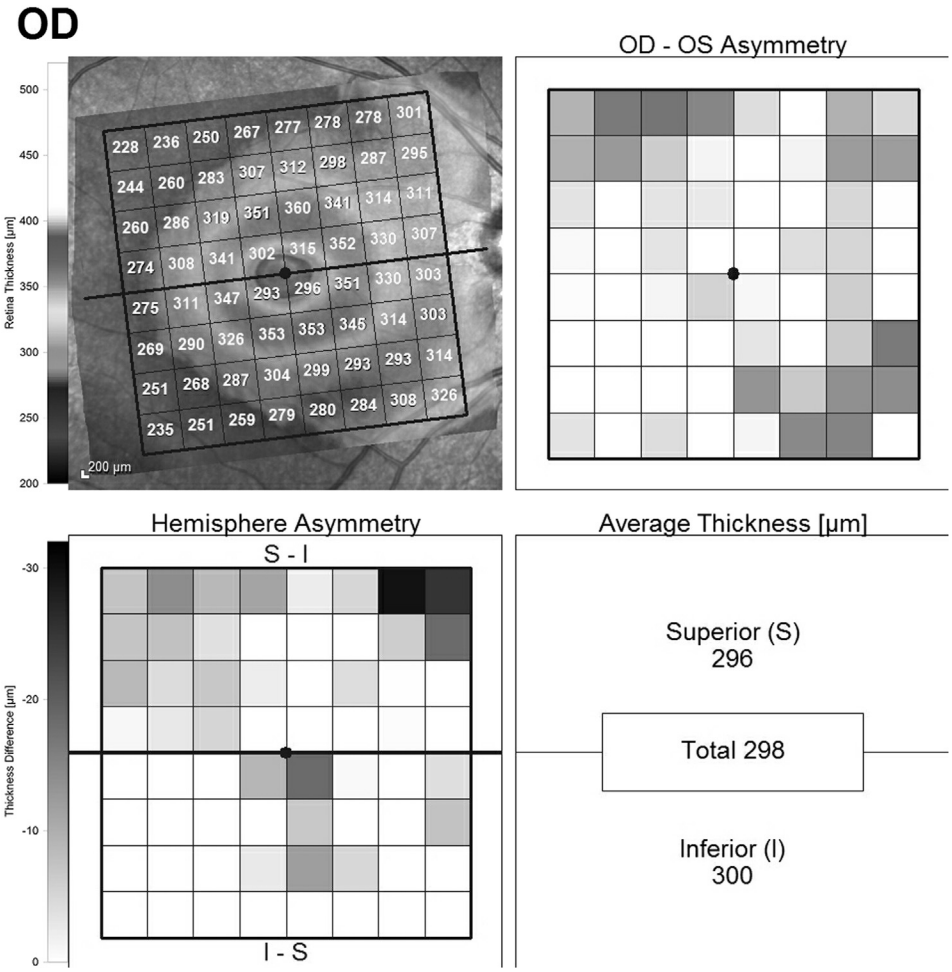


**Figure 1.** Posterior pole thickness asymmetry analysis screen of Spectralis OCT. OCT = optical coherence tomography.

The GCC consists of the three innermost retinal layers: the RNFL, the ganglion cell layer, and the inner plexiform layer. For GCC analysis, the PPAA macular screen was chosen. We measured the thickness of GCC using manual caliber tools provided by Spectralis software (Heidelberg Engineering, Heidelberg, Germany). In order to achieve standardization, the horizontal placement 3 mm temporal to the center of the fovea was chosen arbitrarily to measure GCC thickness in all eyes (Figure 2).

For RAC analysis, the three largest retinal arterioles passing through an area of one-disc diameter from the optic disc margin were measured (Figure 3). RAC measurements were taken with the manual caliber provided by the Spectralis software (Heidelberg Engineering, Heidelberg, Germany) on the peripapillary RNFL analysis screen. A magnification of approximately 250% was used to detect borders of arterioles more accurately. The mean thickness values of retinal arterioles were calculated for each participant and recorded for analysis. The CCT was measured by a contact ultrasound pachymeter (UP-1000; Nidek, Gamagori, Japan). IOP was measured by noncontact pneumotonometry (Tonoref II; Nidek). Visual field testing was performed only on the participants who raised the suspicion of having glaucoma in the clinical examination and OCT measurements.

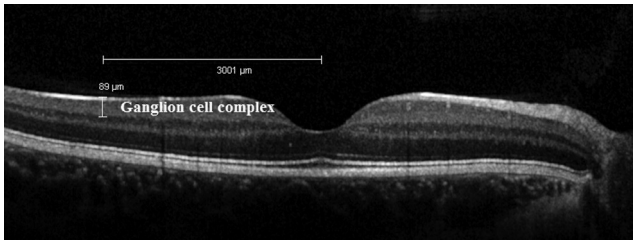


**Figure 2.** Measurement technique of macular ganglion cell complex thickness.

## Statistical analysis

For statistical analysis, SPSS version 17.0 software for Windows (SPSS Inc., Chicago, IL, USA) was used to analyze the outcomes. A $p$ value $<0.05$ was considered statistically significant. All data are expressed as the mean $\pm$ standard error of the mean. Independent sample $t$ test was used for comparison of macular hemifield thickness, peripapillary RNFL thickness, GCC thickness, RAC, CCT, and IOP measurements between the study and control groups. A Chi-square test was used for comparison of consecutive black cells (PPAA) between the groups. The Pearson correlation test was used to detect the association between RAC, IOP, and RNFL thicknesses.

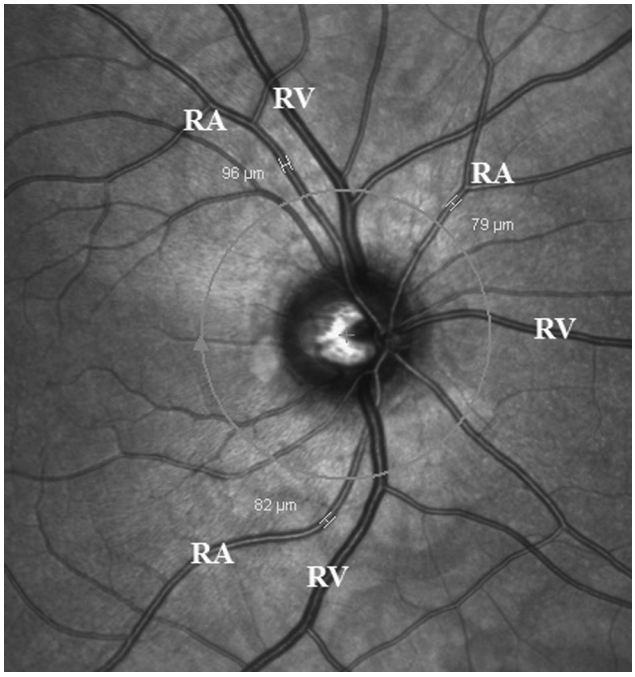


**Figure 3.** Retinal arteriolar caliber measurement screen. RA = retinal arteriole; RV = retinal venule.

## Results

The mean age, sex distribution, refractive error, IOP, CCT, and vertical cup-to-disc ratio of the participants are shown in Table 1. Age and sex distributions were similar in both groups. Although the mean IOP value of the study group was slightly higher than that of the control group, the difference was not statistically significant. The mean CCT and vertical cup-to-disc ratio values were similar in both groups. We did not diagnose glaucoma in any of the participants by clinical examination and diagnostic tests.

The mean peripapillary RNFL thickness was 104.9 ± 8.8 μm in the study group and 105.6 ± 7.4 μm in the control group ($p = 0.68$). Segmental peripapillary RNFL thickness (inferior, superior, nasal, and temporal) measurements are shown in Table 2. There were no statistically significant differences in thickness of the quadrants between the study and control groups.

**Table 1** Mean age, sex distribution, refractive error, intraocular pressure, central corneal thickness, and vertical cup-to-disc ratio of the participants.

| | POAG relatives | Control group | *p* |
|---|---|---|---|
| Age (y) | 27.8 ± 7.9 | 27.4 ± 8.3 | 0.83 |
| Sex | 25 M, 27 F | 26 M, 26 F | 0.84 |
| Refractive error (SE) | −0.42 ± 0.85 | −0.32 ± 0.57 | 0.54 |
| IOP (mmHg) | 15.0 ± 3.0 | 14.4 ± 2.8 | 0.25 |
| CCT (μm) | 545.7 ± 32.5 | 545.5 ± 25.3 | 0.98 |
| Vertical c/d ratio | 0.29 ± 0.16 | 0.27 ± 0.13 | 0.60 |

Data are presented as mean ± SD.
CCT = central corneal thickness; c/d ratio = cup-to-disc ratio; F = female; IOP = intraocular pressure; M = male; POAG = primary open-angle glaucoma; SE = spherical equivalent.

**Table 2** Segmental peripapillary RNFL thickness (inferior, superior, nasal, and temporal) values in the study and control groups.

| | POAG relatives | Control group | *p* |
|---|---|---|---|
| Inferior quadrant (μm) | 138.2 ± 14.3 | 139.3 ± 13.7 | 0.69 |
| Superior quadrant (μm) | 130.1 ± 13.9 | 129.3 ± 14.1 | 0.78 |
| Nasal quadrant (μm) | 78.0 ± 15.4 | 78.9 ± 12.3 | 0.75 |
| Temporal quadrant (μm) | 73.4 ± 12.2 | 74.8 ± 9.4 | 0.52 |

Data are presented as mean ± SD.
POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer.

The total, superior, and inferior hemifield macular thickness measurements are shown in Table 3. All the full-thickness macular measurements were slightly higher in the control group than in the study group. PPAA revealed no statistically significant difference between the groups in the aspect of consecutive black squares ($p = 0.79$). The mean thickness of GCC was 83.4 ± 5.9 μm in the relatives of POAG patients, while it was 83.6 ± 5.9 μm in the healthy controls ($p = 0.87$).

The mean RAC was 85.9 ± 4.8 μm in the study group and 86.0 ± 5.0 μm in the control group ($p = 0.90$). A slightly negative correlation was observed between RAC and IOP when all the participants were analyzed ($r = -0.11$, $p = 0.28$). A statistically significant moderate correlation existed between RAC and the mean peripapillary RNFL thickness ($r = 0.39$, $p < 0.001$).

There were no significant differences between the first- and second-degree relatives of POAG patients with respect to the mean RAC, RNFL, GCC, CCT, and PPAA ($p > 0.05$). Moreover, visual field analysis did not show any glaucomatous damage in participants who performed the tests.

## Discussion

This study shows that characteristic glaucomatous damage indicators—including peripapillary RNFL thickness, GCC

**Table 3** Mean macular thickness measurements of whole, superior, and inferior hemifields.

| | POAG relatives | Control group | *p* |
|---|---|---|---|
| Whole macula (μm) | 298.4 ± 11.4 | 304.3 ± 10.0 | 0.008 |
| Superior hemifield (μm) | 298.0 ± 11.7 | 304.3 ± 9.8 | 0.006 |
| Inferior hemifield (μm) | 298.7 ± 11.6 | 304.2 ± 10.7 | 0.019 |

Data are presented as mean ± SD.
POAG = primary open-angle glaucoma.

thickness, IOP, CCT, RAC, and PPAA—were similar in young relatives of POAG patients and healthy controls. Since age is an important determinant in the occurrence of POAG, we included only young adults in order to eliminate the age-related risk of glaucoma. With the development of SD-OCT and new software programs, it is now easier to detect glaucoma in individuals at early ages.

Macular thickness measurements have been investigated for an early diagnosis of glaucomatous damage. Several studies have shown that early glaucoma diagnostic capability of macular thickness measurements was generally lower than that of peripapillary RNFL thickness measurements [10—12]. The most possible reason is that the measurements of macular thickness include thicknesses of outer retinal layers that are not affected in glaucoma, which may influence the sensitivity of the test; by contrast, peripapillary RNFL can estimate early glaucomatous changes because it contains only retinal ganglion cell axons [13]. In our study, total and hemifield macular thickness measurements were lower in the study group, while peripapillary RNFL thickness values were similar in both groups. Although this result is worthy of attention, it does not indicate the superiority of macular thickness analysis over peripapillary RNFL thickness analysis in early diagnosis of glaucoma, since there was no evidence of glaucoma in any of the participants.

In the presence of practically identical RNFL measurements, the smaller total macular thickness value in the study group compared to that in the control group may be an incidental finding. The approximately 5-μm difference in retinal thickness is statistically significant, but it may be clinically irrelevant. In addition, the likely false positive rate of such a diagnostic test (i.e., macular full-thickness analysis) might be high. The measurement of perifoveal GCC thickness has emerged as a new early diagnostic parameter of glaucoma in recent years [14]. It has been reported that glaucoma preferentially affects GCC rather than all macular layers [15]. Therefore, we measured the thickness of GCC in addition to total macular thickness. Although the mean total macular thickness was thinner in the study group, the GCC thickness was similar in both groups. Apart from our results, Rolle et al [16] reported that the eyes of individuals with a positive family history for POAG have significantly thinner RNFL and GCC than normal eyes. That difference seems to be a result of the younger age of our participants and the different measurement techniques; we made the GCC measurements manually using the caliber tools of the OCT software. In addition, different OCT devices may give different measurement outcomes, since they differ in terms of scan time, tissue resolution, frame rate, and software.

Nakatani et al [17] found that macular parameters in SD-OCT had high discriminating power for early glaucoma, comparable with peripapillary RNFL parameters. Um et al [8] reported that macular hemifield thickness asymmetry has a better performance than average peripapillary RNFL thickness measurements with respect to diagnostic sensitivity, especially in eyes with early-stage glaucoma. PPAA demonstrates more localized macular thickness differences when compared with the total or hemifield macular thickness measurements [18]. PPAA detects localized retinal nerve fiber defects with high sensitivity and specificity [18]. Asrani et al [19] suggested that early recognition of glaucoma might be easier by combining the diagnostic potential of peripapillary RNFL thickness with PPAA. In this study, PPAA showed similar values in relatives of POAG patients and in healthy controls.

In population-screening studies, the ratio of glaucoma diagnosis is generally high in relatives of POAG patients [20—22]. In the present study, we could not make a glaucoma diagnosis in any of the participants, neither in relatives nor in controls. The reason may be that our patients were younger than 45 years. The participants in both groups had similar IOP and CCT measurements. The normal peripapillary RNFL characteristics, in which segmental thickness decreases in the order inferior > superior > nasal > temporal, were observed in both groups.

Kawasaki et al [9] reported that early retinal vessel alterations are involved in the pathogenesis of open-angle glaucoma, and they suggest that measurements of RAC might be useful for identifying people with an increased risk of developing glaucoma. In this study, we performed RAC measurements in a high-risk glaucoma population (i.e., relatives of POAG patients) and found no significant difference between young relatives of POAG patients and healthy controls in terms of RAC. Similar to previous reports [23,24], we found that RAC is associated with peripapillary RNFL thickness.

Our study has its limitations. First, we measured the thickness of GCC at a single point rather than at multiple points because of the relatively old software version. Second, RAC examinations generally have some limitations of their own, such as obtaining measurements from only one retinal image and also the fact that measurements do not reflect the exact three-dimensional structure of the vessels. Last, it would be valuable to have some additional functional parameters such as a pattern electroretinogram, which reflects retinal ganglion cell damage.

In conclusion, we did not detect any early glaucomatous damage in young relatives of POAG patients after measuring peripapillary RNFL thickness, GCC thickness, RAC, and PPAA. Additionally, CCT, IOP, and cup-to-disc ratios were similar in both groups, except for macular full-thickness measurements. As expected, age seems to be the main determinant in the occurrence of glaucomatous damage in relatives of POAG patients. Further prospective studies that would determine the changes in retinal thickness measurements with time are required.

## References

[1] Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet 2004;363:1711—20.
[2] Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. Arch Ophthalmol 1994;112:69—73.
[3] Janssen SF, Gorgels TG, Ramdas WD, Klaver CC, van Duijn CM, Jansonius NM, et al. The vast complexity of primary open angle glaucoma: disease genes, risks, molecular mechanisms and pathobiology. Prog Retin Eye Res 2013;37:31—67.
[4] Wang X, Harmon J, Zabrieskie N, Chen Y, Grob S, Williams B, et al. Using the Utah Population Database to assess familial risk of primary open angle glaucoma. Vision Res 2010;50:2391—5.

[5] Vistamehr S, Shelsta HN, Palmisano PC, Filardo G, Bashford K, Chaudhri K, et al. Glaucoma screening in a high-risk population. J Glaucoma 2006;15:534—40.
[6] Li G, Fansi AK, Boivin JF, Joseph L, Harasymowycz P. Screening for glaucoma in high-risk populations using optical coherence tomography. Ophthalmology 2010;117:453—61.
[7] Kerrigan-Baumrind LA, Quigley HA, Pease ME, Kerrigan DF, Mitchell RS. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. Invest Ophthalmol Vis Sci 2000;41:741—8.
[8] Um TW, Sung KR, Wollstein G, Yun SC, Na JH, Schuman JS. Asymmetry in hemifield macular thickness as an early indicator of glaucomatous change. Invest Ophthalmol Vis Sci 2012;53: 1139—44.
[9] Kawasaki R, Wang JJ, Rochtchina E, Lee AJ, Wong TY, Mitchell P. Retinal vessel caliber is associated with the 10-year incidence of glaucoma. Ophthalmology 2013;120:84—90.
[10] Medeiros FA, Zangwill LM, Alencar LM, Bowd C, Sample PA, Susanna Jr R, et al. Detection of glaucoma progression with stratus OCT retinal nerve fiber layer, optic nerve head, and macular thickness measurements. Invest Ophthalmol Vis Sci 2009;50:5741—8.
[11] Parikh RS, Parikh SR, Thomas R. Diagnostic capability of macular parameters of Stratus OCT 3 in detection of early glaucoma. Br J Ophthalmol 2010;94:197—201.
[12] Wollstein G, Ishikawa H, Wang J, Beaton SA, Schuman JS. Comparison of three optical coherence tomography scanning areas for detection of glaucomatous damage. Am J Ophthalmol 2005;139:39—43.
[13] Na JH, Sung KR, Baek S, Sun JH, Lee Y. Macular and retinal nerve fiber layer thickness: which is more helpful in the diagnosis of glaucoma? Invest Ophthalmol Vis Sci 2011;52: 8094—101.
[14] Moreno PA, Konno B, Lima VC, Castro DP, Castro LC, Leite MT, et al. Spectral-domain optical coherence tomography for early glaucoma assessment: analysis of macular ganglion cell complex versus peripapillary retinal nerve fiber layer. Can J Ophthalmol 2011;46:543—7.
[15] Tan O, Chopra V, Lu AT, Schuman JS, Ishikawa H, Wollstein G, et al. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Ophthalmology 2009;116:2305—14.
[16] Rolle T, Dallorto L, Briamonte C, Penna RR. Retinal nerve fibre layer and macular thickness analysis with Fourier domain optical coherence tomography in subjects with a positive family history for primary open angle glaucoma. Br J Ophthalmol 2014;98:1240—4.
[17] Nakatani Y, Higashide T, Ohkubo S, Takeda H, Sugiyama K. Evaluation of macular thickness and peripapillary retinal nerve fiber layer thickness for detection of early glaucoma using spectral domain optical coherence tomography. J Glaucoma 2011;20:252—9.
[18] Seo JH, Kim TW, Weinreb RN, Park KH, Kim SH, Kim DM. Detection of localized retinal nerve fiber layer defects with posterior pole asymmetry analysis of spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 2012;53: 4347—53.
[19] Asrani S, Rosdahl JA, Allingham RR. Novel software strategy for glaucoma diagnosis: asymmetry analysis of retinal thickness. Arch Ophthalmol 2011;129:1205—11.
[20] Vegini F, Figueiroa Filho N, Lenci RF, Garcia Neto D, Susanna Junior R. Prevalence of open angle glaucoma in accompanying first degree relatives of patients with glaucoma. Clinics (Sao Paulo) 2008;63:329—32.
[21] Green CM, Kearns LS, Wu J, Barbour JM, Wilkinson RM, Ring MA, et al. How significant is a family history of glaucoma? Experience from the Glaucoma Inheritance Study in Tasmania. Clin Exp Ophthalmol 2007;35:793—9.
[22] Kong X, Zhu W, Chen X, Chen Y, Sun X. Familial aggregation of primary open angle glaucoma in Shanghai, China. Mol Vis 2013;19:1859—65.
[23] Samarawickrama C, Huynh SC, Wang JJ, Pai A, Joachim N, Burlutsky G, et al. Relationship between retinal structures and retinal vessel caliber in normal adolescents. Invest Ophthalmol Vis Sci 2009;50:5619—24.
[24] Zheng Y, Cheung N, Aung T, Mitchell P, He M, Wong TY. Relationship of retinal vascular caliber with retinal nerve fiber layer thickness: the Singapore Malay Eye Study. Invest Ophthalmol Vis Sci 2009;50:4091—6.