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Reproducibility of optic nerve head measurements obtained by optical coherence tomography

M. OLMEDO[1], C. CADARSO-SUAREZ[2], F. GOMEZ-ULLA[1,3], C. VAL[1], I. FERNANDEZ[1]

[1]Instituto Tecnológico de Oftalmología, Hospital Nuestra Señora de la Esperanza,
[2]Unit of Biostatistics, Department of Statistics and Operations Research
[3]Department of Ophthalmology, Complejo Hospitalario Universitario de Santiago, University of Santiago de Compostela, Santiago de Compostela - Spain

PURPOSE. To evaluate reproducibility of optic nerve head (ONH) morphometry measurements obtained by optical coherence tomography (the fast optical disk protocol of the Zeiss model 3000 OCT system) in normal and glaucomatous eyes.
METHODS. Prospective instrument-evaluation study. ONH measurements for 20 eyes were obtained in eight scan sessions taken during two visits to an ophthalmology clinic (10 normal patients, 10 glaucoma patients, one eye per subject). At every one of the eight sessions for each eye, estimates of eight ONH morphometry variables (see Main outcome measures) were obtained. The first two sessions were performed by two operators, followed by a 30-minute break. The same operators then completed a third and fourth session. This sequence was duplicated on a second visit. Intrasession, intersession, intervisit, and interoperator reproducibility of the eight variables were calculated by the use of a components variance model. Intraclass correlation coefficients (ICC) were used to assess reliability.
RESULTS. Vertical integrated rim area, horizontal integrated rim area, disk area, cup area, rim area, cup/disk area ratio, cup/disk horizontal ratio, cup/disk vertical ratio. With the exception of the horizontal integrated rim area and rim area in normal subjects, the factor subject was the most important source of variance for all variables. Reliability values as measured by ICC for normal eyes were above 81%, with the exception of measurements of the horizontal integrated rim area (23.1%), rim area (33.3%), and disk area (64.7%). For glaucomatous eyes all values were above 85%, with the exception of the disk area (68.1%).
CONCLUSIONS. ONH measurements obtained using the fast optical disk protocol of the Zeiss 3000 OCT system show good reproducibility, for both normal and glaucomatous eyes.
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KEY WORDS. Optical coherence tomography, Optic nerve head measurements, Reproducibility measurements, Glaucoma diagnosis

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INTRODUCTION

Glaucoma is an optic neuropathy involving a characteristic and progressive pattern of damage to the retinal nerve fiber layer (RNFL) and to the optic nerve head (ONH). One of the key elements in glaucoma diagnosis and follow-up is assessment of the optic disk. ONH measurements are complicated by a very marked variability between individuals in the population. Methods used for ONH measurements include clinical examination and

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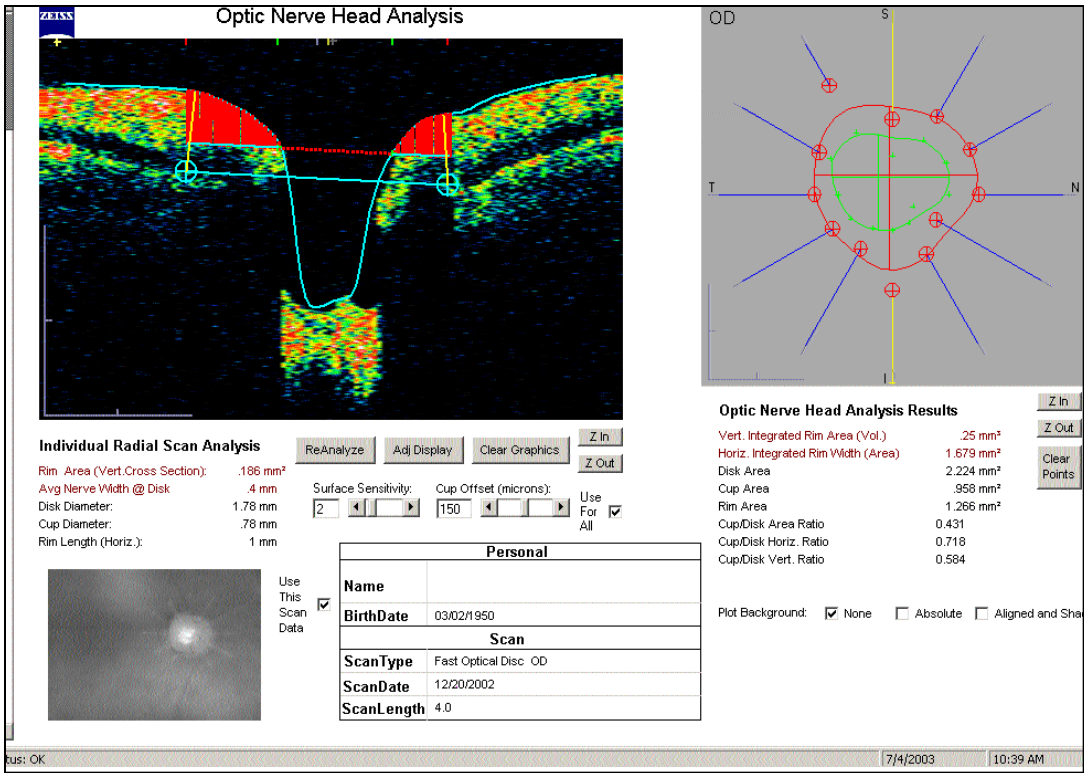

Fig. 1 - Example of an optic nerve head (ONH) scan output screen obtained with the fast optical disk protocol of the Zeiss 3000 OCT system. To the left is one of the six false-color-enhanced cross-sections of the ONH; to the right is a map of the ONH, showing the eight calculated ONH morphometry variables considered in the present study.

stereoscopic photography, as well as more objective methods such as Heidelberg retina tomography and optical coherence tomography (1).

Stereoscopic photographs clearly require interpretation by an experienced ophthalmologist who is able to detect the characteristic effects of glaucoma, such as excavation and notching (2). Heidelberg retina tomography offers the possibility of semiautomated analysis, but requires an experienced operator to delimit the disk margin (3-5).

Optical coherence tomography (OCT) is an imaging technique for the study of retinal tissues in vivo (6, 7). Its usefulness for RNFL evaluation has been extensively documented (8-11).

It is a noninvasive noncontact method (8-10). Recently developed software for the Zeiss 3000 system evaluated in the present study generates detailed OHN images on the basis of a series of radial scans.

Here we report an analysis of reproducibility of ONH measurements obtained using the Zeiss 3000 OCT system in normal and glaucomatous eyes. This aspect has not been investigated previously, though it is clearly relevant if our aim is to use automated OCT measurements of the ONH in following up glaucomatous patients.

METHODS

Subjects

We examined one randomly selected eye from each of 20 subjects, 10 with glaucoma and 10 healthy (i.e., no glaucoma or other known retinal disorder). All subjects gave informed consent to participation. Patients were selected in order of arrival at the clinic and by their eligibility. Mean age (± standard deviation) was 33±17 years in the normal group and 62±14 years in the glaucomatous group. After anamnesis of personal and family history, all subjects underwent complete ophthalmologic examination, including determination of visual acuity testing with refraction, intraocular pressure, standard achromatic perimetry (Octopus 1-2-3; Interzeag AG, Switzerland), slit-lamp biomicroscopy, and dilated ONH biomicroscopy. Criteria for inclusion in both groups were visual acuity of 20/40 or higher, no systemic pathology potentially affecting the visual field (VF) and/or the appearance of the optic disk, and no history of retinal pathology, surgery, or laser surgery. Additional inclusion criteria for the normal subject group were normal anterior segment, normal VF, normal

appearance of the optic disk, and an intraocular pressure of 21 mmHg or less. Glaucomatous subjects also had to meet all the following criteria: intraocular pressure greater than 21 mmHg in at least two measurements prior to treatment; abnormal VF, defined as the detection in at least two campimetric evaluations of a) corrected pattern standard deviation less than 5% of normal limits or b) a cluster of three or more contiguous points with p<0.5%, including at least one of these with p<0.1% in the pattern deviation plot (12); characteristic morphologic alterations of the optic disk, such as excavation, notching, focal or diffuse atrophy of neuroretinal rim area, vertical cup/disk ratio >0.6, cup/disk asymmetry between fellow eyes >0.2, disk hemorrhage, baring of circumlinear blood vessels (13). The stability of the disease in glaucomatous patients was determined by absence of any deterioration in the visual field over the preceding 6 months.

OCT instrumentation

OCT assesses the ultrastructure of retinal tissues on the basis of the delay in back-scattering of light, using low-coherence interferometry (6, 7). It is thus rather similar to ultrasonography, but using light rather than sound, and giving a resolution about 10-fold better: in the Zeiss Model 3000 Optical Coherence Tomography system used in the present study (Carl Zeiss Jena GmbH, Germany), axial resolution is 8 to 10 µm (1). Fast optical disk is a scan acquisition protocol based on six diametral sections obtained at 30° intervals, each 4 mm and 128 points in length, centered on the disk and requiring 1.92 seconds. For each radial scan in the group, the ONH analysis protocol detects the anterior surface of RNFL and the retinal pigmented epithelium on the basis of its characteristic reflectivity. The algorithm detects the disk reference points, where the retinal pigment epithelium ends on each side of the disk. Based on these anatomic markers it locates and measures the disk diameter as a line between the two disk reference points and the cup diameter on a line parallel to the disk line and offset anteriorly by 150 µm (by default – cup offset is adjustable). In the output display, placement of the disk reference points can be adjusted. For the rim lateral boundaries it uses lines extending from the disk reference points up to the anterior surface of the disk. For each individual radial scan the program gives several measurements: rim area, average nerve width at disk, disk diameter, cup diameter, and rim length.

ONH analysis then combines the analysis and measurements of each individual scan into a composite image with the following measurements:

1) Vertical integrated rim area (volume), calculated as the average of rim areas multiplied by the perimeter, representing the volume of tissue in the neuroretinal ring
2) Horizontal integrated rim width (area), calculated as the average of rim length multiplied by the perimeter
3) Disk area, i.e., area bounded by disk perimeter
4) Cup area, i.e., area bounded by the cup perimeter
5) Rim area (i.e., disk area–cup area).
6) Cup/disk area ratio
7) Cup/disk horizontal ratio
8) Cup/disk vertical ratio.

TABLE I - MEAN VALUES (together with standard deviations (SD) and 95% confidence intervals (CI)) OF THE EIGHT OPTIC NERVE HEAD MORPHOMETRY VARIABLES IN THE NORMAL AND GLAUCOMA GROUPS

	Mean	SD	95% CI
Normal eyes			
HIRW	0.465	0.213	0.442-0.489
VIRA	1.811	0.155	1.794-1.828
Disk area	2.562	0.392	2.519-2.606
Cup area	0.790	0.465	0.739-0.841
Rim area	1.764	0.306	1.731-1.798
C/D area	0.293	0.147	0.278-0.310
C/D horiz.	0.545	0.152	0.529-0.562
C/D vertic.	0.499	0.152	0.483-0.516
Glaucomatous eyes			
HIRW	0.327	0.279	0.297-0.358
VIRA	1.489	0.440	1.441-1.538
Disk area	2.514	0.489	2.460-2.568
Cup area	1.212	0.705	1.134-1.289
Rim area	1.299	0.638	1.229-1.369
C/D area	0.476	0.223	0.451-0.500
C/D horiz.	0.698	0.185	0.678-0.718
C/D vertic.	0.642	0.158	0.624-0.659

HIRW = Horizontal integrated rim width; VIRA = Vertical integrated rim area; C/D = Cup to disk ratio

OCT procedure

Each subject underwent eight OCT sessions, in two visits separated by 6 to 8 weeks. In each session a total of four scans were obtained (total 32 scans).

Between sessions subject position and focus were randomly disrupted, so that all alignment parameters had to

be newly adjusted at the start of each session.

Two experienced operators performed two consecutive sessions. At the completion of the second session the patient rested for about 30 minutes.

The third and fourth sessions were performed in a similar fashion during the same visit.

The operator selection during the first and second and again during the third and fourth sessions was randomly determined.

This procedure was repeated in the second visit for the fifth to eighth sessions. All scans were obtained without pupil dilatation, with occlusion of the fellow eye and internal fixation. No manual correction has been applied to the OCT output.

Statistical analysis

All data were analyzed with the aid of the statistical package SPSS version 11.0 for Windows (SPSS Inc., Chicago, IL). For variance components analysis, a random-effect analysis of variance model was used to investigate the influence of subject, operator, visit (nested within subject), and session (nested within visit). The analysis also estimated the subject x operator interaction (this refers to operator linked variation in measurements of a given patient), and residual variability. For each variable and group, using a simplified model with subject as the only factor, we also calculated root mean squared error (RMSE; i.e., a measure of overall variability not attributable to subject), and intersubject coefficients of variation (CV = 100 x RMSE/group mean). Intraclass correlation coefficients (ICC) were calculated as a measure of reliability, as the ratio of intersubject variance to total variance.

RESULTS

Figure 1 shows an example of a scan screen obtained with the Zeiss 3000 OCT system. OCT was well tolerated by all subjects at all visits. Variances were homogeneous in the two groups only for the variables disk area and cup/disk vertical ratio. Table I shows basic descriptive statistics for the two groups. Variance components analysis indicated that for all variables the factors operator, session, and visit had zero or near-zero effect (Tab. II). In glaucomatous patient group, there is a significant difference ($p < 0.001$) in the patient component for all eight variables. In the normal subject group this was the case for

TABLE II - TOTAL VARIANCE AND PERCENTAGES OF VARIANCE EXPLAINED BY EACH CANDIDATE SOURCE, FOR EACH VARIABLE IN EACH GROUP

Total variance	% Subject (ICC)	% Operator	% Subject by operator	% Visit	% Session	% Residual	%
Normal eyes							
HIRW	0.0493	81.3*	0.0	3.7	0.0	0.0	14.8
VIRA	0.0247	23.1	0.0	12.2*	1.2	0.0	63.6
Disk area	0.1648	64.7*	0.0	1.8	3.5	0.4	29.9
Cup area	0.2380	89.1*	0.3	3.2	0.1	0.0	7.3
Rim area	0.0973	33.3	0.0	10.1*	3.8	0.2	52.6
C/D area	0.0238	89.1*	0.0	3.8	0.0	0.0	7.1
C/D horiz.	0.0253	89.7*	0.4	2.4	0.0	0.0	7.1
C/D vertic.	0.0252	89.3*	0.0	2.8	0.0	0.0	7.9
Glaucomatous eyes							
HIRW	0.0854	85.4*	0.0	0.5	0.4	0.6	13.4
VIRA	0.2126	90.6*	0.0	0.8	0.1	0.2	8.3
Disk area	0.2586	68.1*	1.2	2.3	0.0	0.0	28.4
Cup area	0.5473	93.8*	0.1	1.4	0.1	0.1	4.6
Rim area	0.4448	87.1*	0.0	1.2	0.0	0.0	11.7
C/D area	0.0546	92.3*	0.0	0.6	0.0	0.0	7.1
C/D horiz.	0.0378	95.2*	0.0	0.0	0.0	0.3	4.2
C/D vertic.	0.0273	89.7*	0.0	1.5	0.0	0.0	8.8

Note that percentage of variance explained by subject is often referred to as the intraclass correlation coefficient (ICC). * $p<0.001$.
HIRW = Horizontal integrated rim width; VIRA = Vertical integrated rim area; C/D = Cup to disk ratio

the variables of volume, disk area, cup area, C/D area, C/D horizontal, and C/D. Another significant source of variance was the subject x operator interaction for the variables area and rim area, and in both cases residual error was also high. In the glaucomatous group the percentage of variance due to subject (i.e., the ICC) was higher than 85% for all the parameters, except disk area (68%), and higher than 81% for five variables in the nonglaucomatous group. ICC for disk area in this group is 64.7% and the values for area and rim area are low (23.1 and 33.3%, respectively). Mean intersubject CV are shown in Table III. The figures range from 7.3 to 19.6 for the normal group and from 5.9 to 18 in the glaucomatous group, with a value of 33.6 in the parameter volume, which diverges from the range of our other results.

DISCUSSION

OCT is increasingly used for a variety of purposes. In the present study we have used the fast optical disk acquisition protocol and the optic disk analysis protocol for the Zeiss 3000 OCT system, introduced in 2002. This is particularly attractive for clinical use because it rapidly obtains information on the optic disk. As a first step, we have evaluated the repeatability of ONH measurements obtained with this protocol, although we will carry out further studies to evaluate optical disk acquisition protocols with a greater number of sections.

As explained in OCT instrumentation, the protocol enables the reference points to be repositioned. In this present study we have attempted to evaluate the practicality of the technique when the participation of the ophthalmologist is reduced to a minimum.

Schuman et al (1) concluded that automated determination of the disk margin performed as well as subjective assessment and could be used in clinical practice. Moreover, it must be noted that Zeiss 3000 OCT system does not strictly connect each measured reference point but rather interpolates among the 12 measured points to create a best fit curve defining margin.

Due to our randomized system of patient selection there is a wide age difference between groups. While this may be a significant limiting factor in tests requiring a greater degree of patient collaboration, we believe that in our case this is not so. Patients with possible age-related problems such as significant media opacity were excluded from the study. Given that it was never our intention to establish a comparison between both groups, demographic factors have not been taken into consideration. However, this aspect is being dealt with in a current work in progress.

Regarding the evaluation of the results, the age difference clearly urges caution because of its possible influence on certain measurements affecting repeatability. However, we found that while most publications on the influence of age on OHN morphometry reported no such relationship (14-16), some (17) found a slight increase in some parameters (disk area, cup area, cup to disk area ratio), and still others (18) reported a decrease (disk area).

Variance component analysis indicates that in glaucomatous subjects, and for all variables, most measurement variability (at least 65%) was explained by the subject, and little or no variability was attributable to operator, vis-

TABLE III - ROOT MEAN SQUARED ERROR (RMSE) FOR THE ONE-FACTOR MODEL AND CORRESPONDING INTERSUBJECT COEFFICIENTS OF VARIATION (CV), FOR EACH VARIABLE IN EACH GROUP

	RMSE		Intersubject CV (%)	
	Normal eyes	Glaucomatous eyes	Normal eyes	Glaucomatous eyes
HIRW	0.0909	0.1099	19.6	33.6
VIRA	0.1319	0.1374	7.3	9.2
Disk area	0.2217	0.2709	8.6	11.1
Cup area	0.1477	0.1728	18.7	14.3
Rim area	0.2415	0.2338	13.7	18.0
C/D area	0.0463	0.0481	15.7	9.7
C/D horiz.	0.0470	0.0414	8.6	5.9
C/D vertic.	0.0487	0.0506	9.7	7.9

In the one-factor model, the only factor considered is subject, and thus RMSE is a measure of all variance not explained by this factor.
HIRW = Horizontal integrated rim width; VIRA = Vertical integrated rim area; C/D = Cup to disk ratio

it, or session. Only residual (unexplained) variability is rather high (a value of 28.4) for disk area. These results indicate good within-subject scan-to-scan repeatability, and good interoperator concordance.

In the normal subject group, variance component analysis shows similar results for the factors of volume, cup area, C/D area, C/D horizontal, and C/D vertical. Once more, there was a greater residual variance for disk area, but this variable, for both groups, is only statistically significant for the effect of the subject component.

Greater attention should be paid to the factors of area and rim area in normal subjects. Both refer to the same concept, but through a different mathematical approach. In both cases the subject x operator interaction is more than 10% and its effect on measurement variability is significant for both variables. During scans we have observed that, in optic disks with very small cups, a very slight error in centering may lead to significant inaccuracies in measurement. In three cases (in two subjects) the image-analysis program failed entirely to recognize the cup, and interpreted the disk margin as the cup margin. Although these two patients were excluded from the study, other less dramatic incidents of this kind might be the cause of the problematic results obtained for area and rim area.

We also found a high residual variance, greater than 50% for these variables. This fact may be explained by the very low general variability (all values were very similar), which leaves little room for the influence of operator, visit, or other variable and gives more scope to other unidentified factors.

The relatively small amount of intervisit, intersession, and interoperator variance may have favorable clinical implications for comparison of OHN measurements taken for the same patient over a period of time.

ICC is commonly used as a measure of reliability. If the figure is high the variability of measurements is for the most part the result of interindividual differences. In the glaucomatous group the values of ICC are all greater than 0.7, which indicates a high level of reliability. For the normal subject group, ICC was also high for all variables except area (0.23) and disk area (0.33), which correlates with the previously mentioned high residual variability values.

Apart from these, the values for other variables are near to those considered in the literature as demonstrating good reliability for reproducibility as reported by Shields et al (19) (0.67 to 0.94), Schuman et al (8) (figures from 0.43 to 0.92 for mean values), and Carpineto et al (11) (0.49 to 0.54).

CV values (Tab. III) were low for all variables in both groups, again indicating high within-subject repeatability. The exception is the variable volume, for which CV was markedly higher in glaucomatous eyes (33.6%). However, RMSE for the variable volume is similar in both groups, which suggests that the figure of CV might be inflated due to the fact that in the glaucomatous subjects included in this study the mean for this variable is low (Tabs. I and III). With all due caution, we do not believe that this lower mean is connected to the greater age of this group, given that, as mentioned above, existing studies on OHN morphometry report no significant effect of age on this measurement (volume) (14-18).

Given the absence of any comparable study, we have been unable to compare our results with others on OHN analysis by OCT, but CV values published for topographic measurements using optic nerve analyzer are similar to ours: 6.1 to 24.2% (19) and 1.9 to 18.6% (20). Also, studies on OHN analysis by laser scanning tomography report findings similar to ours: Mikelberg et al (3) (3.4 to 30.6), Kruse et al (21) (3.85 to 18.20%), and Rohrschneider et al (22), with values ranging from 0.3 to 25%.

In conclusion, the results of the present study show that OCT using the fast optical disk protocol of the Zeiss 3000 system displays good intersession, intervisit, and interoperator reproducibility for most ONH morphometry variables in glaucomatous patients. The good reproducibility on a given eye holds promise for a longitudinal study of change. Further studies area necessary to assess reproducibility in normal subjects.

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Reprint requests to:
Francisco Gomez-Ulla, MD
Instituto Tecnológico de Oftalmología
Hospital N. S. de la Esperanza
Avda. de las Burgas, 2
15705 Santiago de Compostela, Spain
ciulla@usc.es

REFERENCES

1. Schuman JS, Wollstein G, Farra T, et al. Comparison of optic nerve head measurements obtained by optical coherence tomography and confocal scanning laser ophthalmoscopy. Am J Ophthalmol 2003; 135: 504-12.
2. Wollstein G, Garway-Heath DF, Fontana, Hitchings RA. Identifying early glaucomatous changes. Comparison between expert clinical assessment of optic disc photographs and confocal scanning ophthalmoscopy. Ophthalmology 2000; 107: 2272-7.
3. Mikelberg FS, Wijsman K, Schulzer M. Reproducibility of topographic parameters obtained with Heidelberg Retina Tomograph. Glaucoma 1993; 2: 101-3.
4. Zangwill L, Shakiba S, Caprioli J, Weinreb RN. Agreement between clinicians and a confocal scanning laser ophthalmoscope in estimating cup/disk ratios. Am J Ophthalmol 1995; 119: 415-21.
5. Dreher AW, Tso PC, Wenreb RN. Reproducibility of topographic measurements of the normal and glaucomatous optic nerve head with the laser tomographic scanner. Am J Ophthalmol 1991; 111: 221-9.
6. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. Science 1991; 254: 1178-81.
7. Hee MR, Izatt JA, Swanson EA, et al. Optical coherence tomography of the human retina. Arch Ophthalmol 1995; 113: 325-32.
8. Schuman JS, Hee MR, Puliafito CA, et al. Quantification of nerve fiver layer thickness in normal and glaucomatous eyes using optical coherence tomography. Arch Ophthalmol 1995; 113: 586-96.
9. Blumenthal EZ, Williams JM, Weinreb RN, et al. Reproducibility of nerve fiber layer thickness measurements by use of optical coherence tomography. Ophthalmology 2000; 107: 2278-82.
10. Bowd C, Weinreb RN, Williams JM, Zangwill LM. The retinal nerve fiver layer thickness in ocular hypertensive, normal and glaucomatous eyes with optical coherence tomography. Arch Ophthalmol 2000; 118: 22-6.
11. Carpineto P, Ciancaglini M, Zuppardi E, et al. Reliability of nerve fiber layer thickness measurements using optical coherence tomography in normal and glaucomatous eyes. Ophthalmology 2003; 110: 190-5.
12. Hodapp E, Parrish RK, Anderson DR. Clinical decisions in glaucoma. St. Louis: CV Mosby; 1993: 52-61.
13. Pederson JE, Anderson DR. The mode of progressive disc cupping in ocular hypertension and glaucoma. Arch Ophthalmol 1980; 98: 490-5.
14. Saruhan A, Orgul S, Kokak I, et al. Descriptive information of topographic parameters computed at the optic nerve head with the Heidelberg retina tomograph. J Glaucoma 1998; 7: 420-9.
15. Agarwal HC, Gulati V, Sihota R. The normal optic nerve head on Heidelberg Retina Tomograph II. Ind J Ophthalmol 2003; 51: 25-33.
16. Jonas JB, Thomas R, George R, et al. Optic disk morphology in south India: the Vellore Eye Study. Br J Ophthalmol 2003; 87: 189-96.
17. Durukan AH, Yucel I, Akar Y, et al. Assessment of optic nerve head topographic parameters with confocal scanning laser ophthalmoscope. Clin Exp Ophthalmol 2004; 32: 259-64.
18. Hermann MM, Theofylaktopoulos I, Bangard N, et al. Optic nerve head morphometry in healthy adults using confocal laser scanning tomography. Br J Ophthalmol 2004; 88: 761-5.
19. Shields MB, Martone JF, Shelton AR, et al. Reproducibility of topographic measurements with the optic nerve head analyzer. Am J Ophthalmol 1987; 104: 581-6.
20. Mikelberg FS, Douglas GR, Schulzer M, et al. Reliability of optic disk topographic measurements recorded with a video-ophthalmograph. Am J Ophthalmol 1984; 98: 98-102.
21. Kruse FE, Burk ROW, Völcker HE, et al. Reproducibility of topographic measurements of the optic nerve head with laser tomographic scanning. Ophthalmology 1989; 96: 1320-4.
22. Rohrschneider K, Burk ROW, Kruse FE, Völker HE. Reproducibility of the optic nerve head topography with a new laser topographic scanning device. Ophthalmology 1994; 101: 1044-9