·Clinical Research·

Peripapillary retinal nerve fibre layer thickness measurement with SD-OCT in normal and glaucomatous eyes: distribution and correlation with age

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Abstract

• AIM: To determine peripapillary retinal fiber layer thickness (RNFL) measured with spectral domain optical coherence tomography (SD-OCT) in normal and glaucomatous eyes in a large sample of exclusively white population and compare results with other similarly constructed studies.

• METHODS: Average, maximum, minimum and per quadrant RNFL thickness were measured in normal and glaucomatous Greek patients with a scanning laser ophthalmoscope (SLO)/SD-OCT device. The effect of age in normal RNFL thickness was also determined.

• RESULTS: A total of 278 normal (278 patients) and 67 glaucomatous (67 patients) eyes were included in the study. Average RNFL thickness was 114.8 ±13.3μm in normal and 92.1±18.5μm in glaucomatous eyes(P<0.001). In normal discs, superior quadrant was the thickest, followed by the inferior, nasal and temporal. Decline of normal RNFL thickness with age was statistically significant for average RNFL thickness (1.92μm per decade of life) and for the superior and inferior quadrants of the disc.

• CONCLUSION: SD-OCT peripapillary RNFL measurements can be used to distinguish between normal and glaucomatous eyes and establish normative databases, since normal disc measurements differ between different ethnic groups and between different SD-OCT devices.

• KEYWORDS: SD-OCT; retinal fiber layer thickness optic disc

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INTRODUCTION

Glaucoma is characterized by progressive optic neuropathy due to loss of retinal ganglion cells and retinal nerve fiber layer (RNFL). This can happen despite normal associated visual fields, since 25%-35% of retinal ganglion cell axons may be lost before any diagnostically characteristic defects appear in visual fields examination[1-3]. Therefore, the ability to detect early glaucomatous RNFL damage is very important in early diagnosis and treatment.

Optical coherence tomography (OCT) was first described in 1991 by Huang *et al* [4] and is currently widely used in the management not only of retinal but also of optic nerve diseases, especially glaucoma. OCT imaging has undergone many significant technological advances, the most important being the development of spectral domain OCT (SD-OCT) technology (also known as Fourier domain OCT)[5,6]. Image resolution is five times higher and imaging speed is 60 times faster than in conventional time-domain OCT[7,8].

RNFL thickness measurements generated by SD-OCT machines are interpreted as normal (or abnormal) with the aid of normative databases of RNFL thickness values for age-matched normals, each machine having its own database. For a commonly used SD-OCT (Cirrus, Carl Zeiss Meditech, USA) this database comprises of 284 healthy individuals with an age range of 18-84 years [9]. Normal RNFL measurement values are not interchangeable between different SD-OCT machines[10].

The purpose of our study was to define RNFL thickness values (average, maximum, minimum and per optic nerve head quadrant) in a large population of white individuals of Greek ancestry with SD-OCT and determine the effect of age on these results. We also measured RNFL thickness in a glaucomatous population with the same ethnic characteristics and compared the results with these in the normal population and other studies from the same background.

SUBJECTS AND METHODS

This is a retrospective study of consecutive patients

presenting for examination at the Ophthalmology Department of Athens Medical Center in Athens, Greece, between January 2008 and December 2011. During initial evaluation, all patients underwent a complete slit lamp and dilated fundus examination, together with visual acuity testing, intraocular pressure measurement using Goldmann applanation tonometry and SD-OCT by the same experienced examiner (Kampougeris). Additionally, patients presenting for glaucoma evaluation had corneal pachymetry (ultrasound), gonioscopy, optic nerve photography and visual field testing (Octopus 900, Haag-Streit, Switzerland). Patients were allocated in one of two study groups according to the following criteria: group A (eyes with normal optic discs) had a normal posterior segment examination including normal optic discs (one eye per patient was randomly selected for study inclusion). Group B consisted of eyes with glaucomatous optic discs, which had signs of characteristic optic neuropathy, *i.e.* focal or diffuse neuroretinal rim thinning and/or vertical elongation and also corresponding visual field defects (one eye randomly selected for study inclusion in bilateral cases). In both groups, we excluded all patients with high myopia (>6 diopters), hyperopia >4 diopters and those with significant peripapillary atrophy or with tilted optic discs.

The SD-OCT used in this study incorporates a scanning laser ophthalmoscope (SLO), (Optos, United Kingdom, previously OPKO, Ophthalmic Technologies Inc., Canada). This machine provides a SLO fundus image and a SD-OCT image simultaneously. The SLO image guides repeat or follow-up OCT scanning, so that it is performed at the same location of the initial image. Three continuous RNFL thickness measurements with a scan speed of 32 frames/sec along a circle 3.45mm in diameter centered at the optic disc are obtained and after each measurement is tested for quality (quality test is incorporated in the software and displayed for each image at the OCT screen, not shown in Figure 1), they are averaged to produce single RNFL thickness (Figure 1). For each study eye, we used measurements for average RNFL thickness, minimum and maximum RNFL thickness and RNFL thickness at the four disc quadrants (superior, nasal, inferior and temporal).

The study had Institutional Review Board approval and all patients had given informed consent for the scientific use of their data. All values are expressed as mean ±standard deviation (SD). Statistical evaluation was conducted with commercial statistical software (SPSS 12.0.1, Professional Statistics Release, Chicago, USA). The *t*-test for independent samples was used in all cases. Linear regression analysis was performed to establish any relation between RNFL thickness and age or sex in normal discs (group A).

RESULTS

The study included 278 patients in group A (278 eyes classified as having normal optic discs) and 67 patients in group B (67 eyes classified as having glaucomatous optic discs). Group A consisted of 132 male and 146 female patients, whereas group B consisted of 39 male and 28 female patients. In group A, there were 137 right and 141 left eyes and in group B 35 right and 32 left eyes. Mean age for group A was 58.03±15.62 years and for group B 62.57±14.5 years. Measurements for average, maximum, minimum and four quadrants RNFL thickness for groups A and B are shown in Table 1. Table 1 also shows comparison between the two groups for all RNFL measurements. As shown in Table 1, *P* value reached statistical significance ($P<0.05$) in all cases except for the minimum RNFL thickness between the two groups. There was no significant association between sex and average RNFL thickness for group A ($P=0.82$). A statistically significant association between RNFL thickness decline and age was found for average, superior quadrant and inferior quadrant RNFL thickness (Table 2). Table 2 also shows RNFL loss per decade of age, based on linear regression analysis.

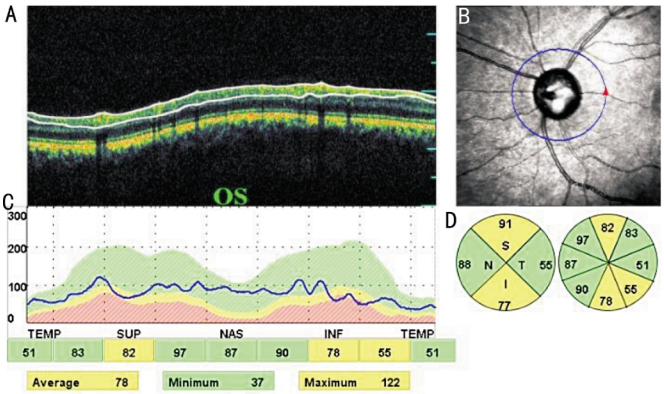

Figure 1 RNFL scan typical appearance in a glaucomatous patient with the SLO/SD-OCT used in the study A: RNFL depiction; B: Simultaneous SLO image; C: Blue line represents distribution of RNFL thickness in microns in the four quadrants. Average, minimum and maximum RNFL thickness values are also depicted; D: RNFL thickness in 4 and 8 sectors of the disc.

DISCUSSION

Normal RNFL thickness values have been studied with time domain OCT technology (TD-OCT) for more than a decade[11]. With the advent of SD-OCT technology, most researchers and clinicians adopted its use due to superior analysis and less time required per examination. It has been shown that TD-OCT and SD-OCT measurements are not interchangeable and the same applies to different SD-OCTs as already mentioned[10,12,13]. As shown in a previous study, the SD-OCT used in our population has very good short- and long-term reproducibility in measuring RNFL [14], which matches our own experience during the last six years.

RNFL thickness in our normal study population followed a bell curve distribution (Figure 2) and average RNFL thickness value was 114.8±13.3μm. This is higher than other

Table 1 RNFL thickness (in μm±SD) for normal (*n*=278) and glaucomatous (*n*=67) optic discs (*P*<0.05 was considered statistically significant)

	Group A (normal)	Group B (glaucoma)	*P*	95% Confidence Interval of the Difference (equal variances not assumed)
Average	114.8±13.3	92.1±18.5	<0.001	17.9 to 27.4
Max	184.9±21.5	145.1±31.2	<0.001	31.8 to 47.8
Min	53.1±9.7	49.6±20.4	0.17	-1.6 to 8.6
Superior	136.7±18	105±25.1	<0.001	25.3 to 38.2
Nasal	107.2±17.8	92.3±19.2	<0.001	9.8 to 20
Inferior	134.5±18.1	102.9±24.8	<0.001	25.2 to 38
Temporal	79.5±15.3	68.8±16.5	<0.001	6.3 to 15.1

Table 2 Effect of age in average and per quadrant RNFL thickness decline in the normal population of this study (*P*<0.05 is considered statistically significant, N/A: not applicable)

RNFL thickness (average and per 4 quadrants)	*P* (correlation of RNFL thickness decline with age)	RNFL thinning (in μm) per decade of age
Average	0.001	1.92
Superior quadrant	0.001	2.51
Nasal quadrant	0.2	N/A
Inferior quadrant	0.001	3.47
Temporal quadrant	0.16	N/A

reported average RNFL values for white European populations, where another SD-OCT was used (Spectralis, Heidelberg Engineering, Heidelberg, Germany) [15]. The average RNFL thickness values in the Bendschneider *et al* [15] study were 97.2±9.7μm. This is supportive of the fact that different machines produce different results in similar ethnic groups, possibly due to differences in scanning algorithms and equipment between them. Most of RNFL studies in normal populations are conducted in the USA, Asia or the UK, where populations recruited have not the homogeneity of our population. It is possible therefore that in the future, investigators will try to define the various RNFL thickness values between different populations and incorporate their findings in large normative databases for different ethnic groups for each machine, as was one of the scopes of our study.

Traditionally, the ISNT rule is applied to normal human optic discs, where the thickest to thinnest neuroretinal rim is: inferior, superior, nasal and temporal[16]. The neuroretinal rim is the distance between the border of the disc (scleral rim) and the bending of the blood vessels and although it's related to the amount of nerve fibers present in any area of the disc, it is not necessarily coinciding with RNFL thickness in any given disc quadrant. In our study, superior quadrant RNFL was thickest (136.7±18), followed by inferior (134.5±18.1), nasal (107.2±17.8) and temporal (79.5±15.3). Difference between superior and inferior quadrants was small but statistically significant (*P*<0.01). Other studies with similar methodology have shown some discrepancy from the ISNT rule in normal discs [17]. This could be attributed to the variation that normal optic discs show in the distribution of

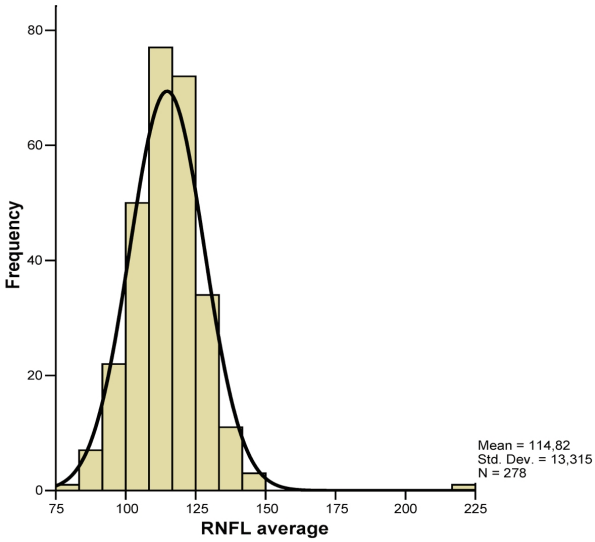

Figure 2 Distribution of RNFL thickness in the normal population in this study (bars, bell curve drown for comparison). The outermost value to the right is an outlier.

the retinal ganglion cell axons as they enter the disc, so that discs should not be considered abnormal if their RNFL thickness does not follow the ISNT rule in OCT measurements.

Our study has shown a steady decline of the average RNFL thickness with age, which was statistically significant (Table 2). The same applied to the RNFL thickness in the superior and inferior quadrants but not to the nasal and temporal quadrants. This is in close agreement with previous studies [17-20] and is possibly related to the location of the main retinal blood vessels in the corresponding areas of the disc, as hypothesised by Hood *et al* [19,20]. The rate of average RNFL loss per decade of life in our study (1.92μm) correlates well

with Alasil *et al*[17], who reported a rate of 1.6-μm loss per decade in white people with Spectralis. In agreement with previously published studies, sex was not related to RNFL thickness in our study[15,17,21,22].

Normal RNFL measurements had a strong statistically significant difference when compared with these of glaucomatous eyes (Table 1). Only the minimum RNFL thickness comparison did not reach statistical significance between groups A and B. Since this can reflect a greater overlapping of normal/thinner to abnormal minimum RNFL measurements, especially among older individuals (who have thinner RNFL values and increased glaucoma prevalence), we recommend that the minimum RNFL thickness should not be used as a means of discriminating between normal and glaucomatous eyes.

A limitation of this study could be the way of recruiting normal patients (consecutive patients presenting at a private Hospital) and the relatively small number of glaucomatous patients. Regarding the normal sample, we admit that it is difficult for such a practice to recruit random normal patients of all ages for SD-OCT measurements. On the other hand, we excluded all patients with significant retinal pathology that might have affected peripapillary RNFL thickness and we examined clinically all optic discs for any sign of pathology before allocating patients to the normal group.

In summary, our study evaluated the average and per quadrant RNFL thickness values for normal and glaucomatous optic discs in a large homogenous population and provided data about their distribution with age. To our knowledge, this is the first SD-OCT study with this design conducted in our country and one of the few with such a large sample of normal data. Our results also agree with the literature on the ability of SD-OCT measurements to provide important data on the diagnosis of glaucomatous optic neuropathy.

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