

# Central retinal artery resistive index and optical coherence tomography in assessment of glaucoma progression

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## Abstract

• **AIM:** To assess the relation between central retinal artery (CRA) resistive index (RI) and retinal nerve fiber thickness measured by optical coherence tomography (OCT) in assessment of disease progress in cases of open angle glaucoma.

• **METHODS:** Twenty-three patients with diagnosed open angle glaucoma were included in this study. They were examined by colored duplex ultrasonography of CRA with estimation of RI of CRA and ophthalmic artery (OA) with estimation of CRA/OA RI ratio as well as OCT measurement of the average retinal nerve fiber layer (RNFL) thickness in order to assess the disease progress.

• **RESULTS:** There was strong inverse relation between the increased RI in CRA as well as the increased CRA/OA RI ratio and the decrease in average RNFL thickness in cases of open angle glaucoma.

• **CONCLUSION:** Assessment of CRA RI can indirectly assess the vascular changes associated with glaucoma and can assess the degree of retinal atrophy helping in evaluating prognosis thus guiding the choice of treatment.

• **KEYWORDS:** glaucoma; optical coherence tomography; central retinal artery duplex; ophthalmic artery; resistive index

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## INTRODUCTION

World Health Organization (WHO) classified primary open angle glaucoma, as the most frequent cause of preventable irreversible blindness in the world<sup>[1]</sup>. The process involves optic neuropathy with acquired irreversible loss of retinal nerve fibers of the optic nerve. The axonal loss occurs years before detectable defects of the visual field are noticed. Once the alterations occur, visual field loss is irreversible mandating early diagnosis of the disease to prevent progressive visual loss<sup>[2]</sup>.

Glaucomatous injury is very slow and shows no structural abnormalities until advanced disease is already present. Optic nerve head (ONH) perfusion is directly related to retinal vascular circulation that can be examined by color Doppler sonography helping in the evaluation of early changes in vascular flow related to glaucoma. Central retinal artery (CRA) duplex is validated for detecting flow velocity alterations and increased resistive index (RI) in cases of moderate and advanced glaucoma patients in comparison with healthy controls<sup>[3]</sup>.

Pathologic cupping of the optic nerve is usually associated with glaucoma. The cause of cupping in glaucoma is the result of nerve fiber loss in association with disturbed structural integrity of the lamina cribrosa<sup>[4]</sup>. Optical coherence tomography (OCT) is an imaging modality that employs near-infrared light to create cross sectional images of the retina and optic nerve allowing analysis of ONH, macula, and retinal nerve fiber layer (RNFL). It is quick, easy and non-invasive imaging test thus used to evaluate changes of the retinal nerve fiber in glaucoma<sup>[5]</sup>.

OCT has been shown to be accurate in RNFL thickness measures, suggesting it may be a useful tool to monitor disease progression in glaucoma<sup>[6]</sup>. Many studies showed that OCT can be used to evaluate RNFL loss over time and thus correlated with visual dysfunction<sup>[7]</sup>.

The aim of the study is to evaluate the relation between CRA RI and CRA/ophthalmic artery (OA) RI ratio values with the RNFL thickness measured by OCT in known patients with open angle glaucoma.

## SUBJECTS AND METHODS

**Patients Selection** A cross-section study protocol was approved by the ethical committee of Ain Shams University hospitals, and an informed written consent was taken from all

patients according to Declaration of Helsinki. Twenty-three eyes (11 right and 12 left) of 16 patients (7 had bilateral disease), they were 9 males and 7 females with age range from 39-59y (mean  $48 \pm 5.92y$ ) coming to the outpatient ophthalmology clinic with diagnosed open angle glaucoma from the period from April 2013 to December 2013 were included in this study. Patients with systemic disease (diabetes, renal failure or hypertension) that could increase the RI or any optic nerve pathology (multiple sclerosis, optic neuritis, band atrophy or ischemic optic neuropathy) that could decrease the RNFL thickness were excluded.

**Clinical Assessment** Participants underwent a full ophthalmologic assessment that included clinical history, slit lamp evaluation, assessment of the intraocular pressure (IOP) was measured in a sitting position using Goldmann applanation tonometry, visual acuity testing, dilated fundus examination, and visual field testing. Clinical assessment of the glaucomatous changes of the ONH was performed after mydriasis (0.5% tropicamide; Alcon Laboratories Inc., Fort Worth, TX, USA) by obtaining stereophotographs of the optic disc using (Canon CF-60UV fundus camera; Canon Inc., Tokyo, Japan). Glaucomatous optic disc changes were defined as diffuse neuroretinal rim narrowing with concentric enlargement of the optic cup, localized notching, or both (Figure 1A).

**Optical Coherence Tomography Examination** All patients underwent imaging by Cirrus high definition OCT (HD-OCT) spectral domain technology (Carl Zeiss Meditec, Inc.) in both eyes, with results analyzed using software version 5.1.1.6. Two OCT scan protocols were performed on both eyes of each patient: RNFL thickness, and ONH mode. The software creates a RNFL thickness map using the 3-dimensional cube data set and centers the disc. Then, it extracts a circumpapillary circle whose radius is 1.73 mm for RNFL thickness measurements. The OCT machine scans this area and reports the average RNFL thickness values ( $\mu\text{m}$ ) in 12 clock hours and 4 quadrants (superior, inferior, nasal, and temporal; Figure 1B), as well as an average RNFL thickness for the entire circumference. The amount of neuroretinal tissue in the optic nerve is used to sure the rim width around the circumference of the optic disc edge (Figure 1C). The ONH mode is a 3-dimensional dataset obtained from 200 A-scans that are derived from 200 B-scans and analyzes a 6 mm<sup>2</sup> area centered on the optic disc. The software allows the measurement of ONH parameters, such as rim area, disc area, average cup/disc ratio, vertical cup/disc ratio and cup volume (Figure 1D). Only well-centered scans were included. We excluded all poor-quality scans analyzed at printouts. All images were acquired with dilated pupils by a single, well-trained ophthalmologist, masked for the diagnosis.

**Duplex Examination** All the US examinations were performed with (ALPINION E-CUBE 9, Seoul, Korea) ultrasound machine with a 7.5 MHz linear phased array transducer. The same radiologist performed all the studies where the patients were examined in the supine position with the probe gently placed on the closed upper eyelid avoiding any globe pressure using a coupling gel. The ultrasound study began with a B-mode morphologic evaluation of the ocular structures in order to locate, in the conal region, the hypoechoic central band corresponding to optic nerve, the reference place for the Doppler study of the retinal vessels. Later, hemodynamic measurements of the CRA and OA RI (Figure 1E, 1F), CRA was identified next to central retinal vein as two parallel vascular structures with opposite flow sense included in the hypoechoic central band of the conal region. Correction of the insonation angle was performed when the axis of the studied vessel was not enough aligned with the ultrasound beam. The parameters evaluated included arterial peak systolic velocity (PSV), end-diastolic velocity (EDV), RI [ $RI = (PSV - EDV) / PSV$ ].

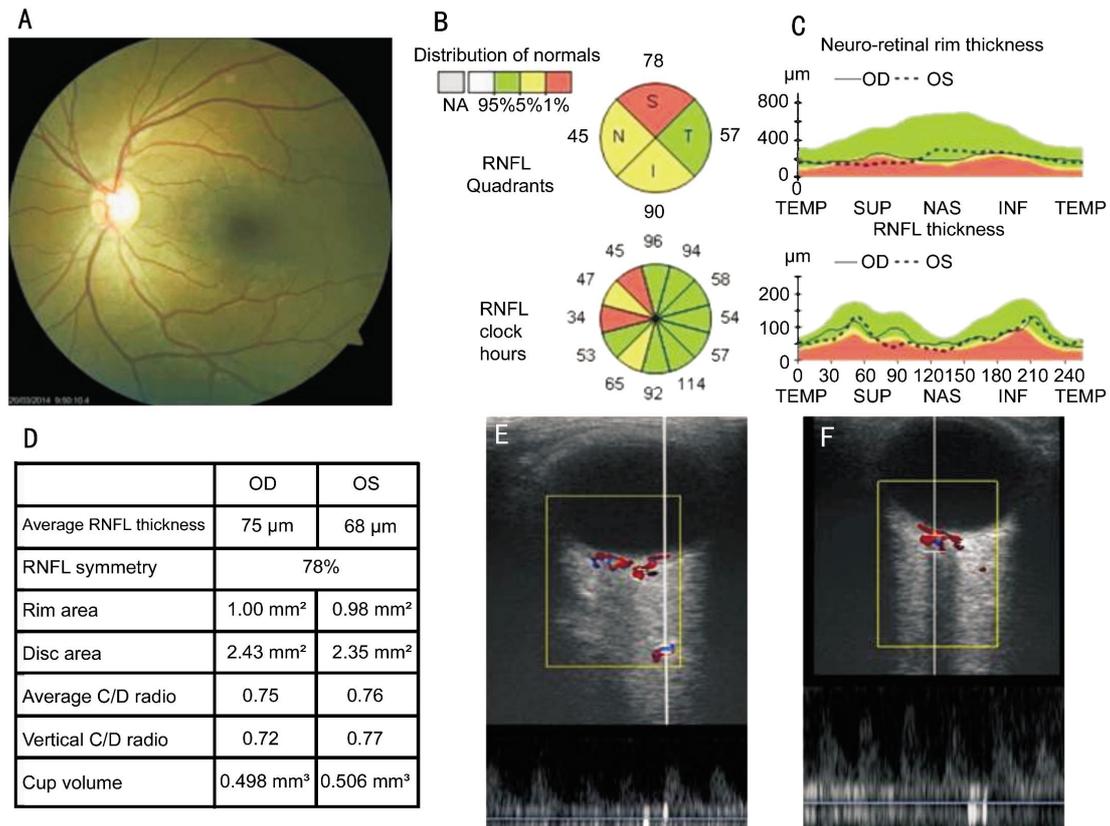
**Statistical Analysis** Statistical analysis was done using SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA). Independent Student's *t*-test was performed for the comparison between the CRA/OA RI ratio and average RNFL thickness included in our study. The result was regarded as statistically significant if  $P < 0.05$ .

## RESULTS

Twenty-three eyes: 11 right (47.83%) and 12 left sided (52.17%) of 16 patients with mean age of  $48 \pm 5.92y$  (range 39-59y) with diagnosed open angle glaucoma were included in this study. The mean IOP was  $28.87 \pm 3.47$  mm Hg (range 24-34 mm Hg). The OCT showed that the average RNFL thickness was lower than normal values with RNFL thickness range from 65-104  $\mu\text{m}$  and mean thickness of 85  $\mu\text{m}$ , while there was increased CRA RI values (range 0.64-0.86) compared to OA RI values (range 0.61-0.8) in all patients with mean CRA RI of 0.791 compared to mean OA RI of 0.707 with increased CRA/OA RI ratio in all patients (range 1-1.197) with mean ratio of 1.116 (Table 1), there was an highly significant relation between the increased CRA/OA RI ratio and the decreased RNFL thickness with unpaired Student's *t*-test  $P < 0.0001$ .

## DISCUSSION

Since screening for open angle glaucoma is very difficult, the diagnosis of asymptomatic glaucoma is very rare. Patients with early disease remain undiagnosed, the fact that half of the cases can be missed even among patients who perform routine ophthalmological examination is really unacceptable<sup>[8]</sup>.



**Figure 1** Forty–nine years old female with progressive deterioration of the visual acuity in the left eye diagnosed clinically as primary open angle glaucoma, her investigations before receiving any treatment revealed A: Fundus photography showing neuro-retinal rim narrowing with concentric enlargement of the optic cup and localized notching; B: OCT showed decreased RNFL thickness of the superior and nasal portions of the optic disc; C: OCT maps of the neuro retinal rim and RNTL thickness by OD and OS modes showed global decrease in neuro retinal rim as well as the RNTL thickness; D: OCT values showed average RNFL thickness=75  $\mu\text{m}$ ; E: Colored duplex measurement of OA RI=0.75; F: Colored duplex measurement of the CRA RI=0.82 with CRA/OA RI ratio of 1.09.

**Table 1** CRA RI, OA RI as well as the corresponding RNFL of each of our patients patient with estimation of CRA/OA RI ratio

Case no.	OA RI	CRA RI	RNFL ( $\mu\text{m}$ )	CRA/OA RI ratio
1	0.66	0.79	104	1.18
2	0.66	0.77	99	1.16
3	0.66	0.75	95	1.13
4	0.63	0.64	98	1.01
5	0.70	0.78	85	1.11
6	0.69	0.79	89	1.14
7	0.68	0.80	94	1.17
8	0.64	0.79	87	1.19
9	0.67	0.75	92	1.19
10	0.68	0.81	85	1.19
11	0.73	0.83	82	1.13
12	0.78	0.85	69	1.08
13	0.80	0.85	65	1.06
14	0.75	0.81	77	1.08
15	0.78	0.84	92	1.07
16	0.69	0.69	100	1.00
17	0.79	0.86	68	1.08
18	0.74	0.79	72	1.06
19	0.75	0.82	75	1.09
20	0.71	0.79	81	1.11
21	0.68	0.81	82	1.19
22	0.69	0.78	79	1.13
23	0.71	0.81	85	1.14

Glaucoma is a multi-factorial optic neuropathy characterized by a loss of retinal ganglion cells with resulting visual impairment. Unfortunately, early detection of glaucoma remains a challenge. No symptoms appear until there is advanced retinal ganglion cell death and visual field loss. Estimates of undiagnosed glaucoma range from 40% to 90%, with higher percentages found in underdeveloped nations<sup>[9]</sup>. OCT generates cross-sectional and three-dimensional (3D) images of retinal structures by detecting coherent (non-scattered) light echoes with an interferometer. The most important glaucoma application of the device is the measurement of RNFL thickness. Thinning of the RNFL has been well correlated with the fundamental pathophysiology of glaucoma namely the destruction of the ganglion cell layer of the retina<sup>[10]</sup>.

Different techniques are employed to assess vascular dysfunction in the eye. Fluorescein angiography and colour Doppler imaging (CDI) are established techniques used for evaluation of circulatory ocular disorders, particularly in glaucoma. Defects in the microcirculation of the optic disc in glaucoma patients are significantly correlated with the loss of visual field and reduction of the RNFL. Various studies have

compared the vascular parameters in primary open angle glaucoma and normal tension glaucoma with those of normal control subjects. The results of these studies emphasize the important role of ocular haemodynamics in glaucomatous optic neuropathy<sup>[11]</sup>.

The changes in retinal blood flow dynamics are well recognized in glaucoma. Many studies have shown that vascular effects play an important role in glaucoma pathogenesis due to autoregulation failure<sup>[12]</sup>. Moreover, although elevated IOP is a major risk factor for glaucoma, there are numerous patients in whom glaucoma progressed despite IOP therapeutic reduction<sup>[13]</sup>. Combined decrease in CRA flow velocities and increase in resistive indices was documented in progressing glaucoma eyes compared to the stable eyes. These results suggest that assessment of orbital hemodynamics by CDI are helpful to discriminate glaucoma patients with higher risk for progression. Therefore Doppler US may institute a more aggressive management in cases with high progression risk<sup>[14]</sup>.

Optic nerve assessment by clinical examination is limited by subjectivity and wide variation in the optic nerve structure of normal subjects. Some studies support the claim that early RNFL and optic disk abnormalities are associated with the development of glaucoma changes in ocular hypertensive and glaucoma suspect eyes. These results reinforce the importance of optic disk and RNFL examination and monitoring in glaucoma suspect eyes<sup>[15]</sup>.

Validation of measuring retinal thickness using OCT was reported. OCT showed progressive linear reduction in RNFL thickness in eyes with increased IOP compared with control ones that show no detectable changes with correlation range within 10  $\mu\text{m}$ . The measured thickness decrease with increasing age or distance from the optic disc. Measured RNFL thickness in glaucomatous eyes are significantly less than normal eyes, and good correlation was noted between the measured RNFL thickness and visual function<sup>[16]</sup>.

The discriminating powers of OCT, for detection of early glaucoma (average visual field mean defect 4.0 dB) were compared. The areas under the receiver operating characteristic (ROC) curves for OCT was in the 0.85 to 0.90 range and sensitivities, at a fixed specificity 90%, were in the 70% to 80% range for the best parameters<sup>[16]</sup>.

RNFL loss in non glaucomatous optic cupping is not in the superior and inferior quadrants, as seen in glaucoma, that shows more RNFL loss in the superior and inferior quadrants that are consistent with the typical visual field defects noted in glaucoma<sup>[17]</sup>.

Topical carbonic anhydrase inhibitors (CAIs) have been recognized by The 2009 World Glaucoma Association consensus group to enhance blood flow regulation and increase ocular blood flow not depending on their

hypotensive effects. Several studies have shown similar IOP reductions with both topical CAI and a non-CAI hypotensive treatment, with only the CAI increasing ocular blood flow<sup>[18]</sup>. Stankiewicz *et al*<sup>[19]</sup> showed that the addition of dorzolamide to timolol monotherapy decreases IOP and increases retinal blood flow in glaucomatous patients following 8mo of treatment, the increased retinal blood flow may increase oxygen delivery to the retina. Adjunctive dorzolamide therapy to morning-dosed bimatoprost 0.03% reduced diurnal IOP and vascular resistance in the OA but did not alter retinal circulation<sup>[20]</sup>.

All the above data shows the importance of combining detecting the vascular flow disturbances in open angle glaucoma patients using an easy and accurate method like color duplex sonography with measuring RNFL thickness using OCT as done in our study as this would affect the type and dose of the given topical medicine.

Aikimbaev *et al*<sup>[21]</sup> as well as Sharma and Bangiya<sup>[22]</sup> showed that OA RI is higher than CRA RI in normal controls while Niwa *et al*<sup>[23]</sup> and Huber *et al*<sup>[11]</sup> showed increased CRA RI compared to OA RI in glaucomatous patients, these results are similar to our results that showed increased CRA RI than OA RI with increased CRA/OA RI ratio in glaucomatous patients. Our study showed good correlation between the decrease in RNFL thickness with the increase in CRA RI as well as the CRA/OA RI ratio with  $P < 0.0001$ , these results are similar to those obtained by Cellini *et al*<sup>[24]</sup>. Popa and Stanila<sup>[25]</sup> stated that the power to identify normal tension glaucoma using colour duplex imaging reaches 48% sensitivity at 90% specificity.

The limitations of this study are the low number of patients, absence of controls, young age range of patients that will affect the assessment of vascular changes as well as the lack of follow up or the response to different types of treatment.

In conclusion, our results demonstrate that thinner baseline OCT RNFL measurements, when used with estimation of CRA RI can be prognostic parameters of the degree of retinal damage by glaucoma. Larger prospective studies with control groups are recommended.

### ACKNOWLEDGEMENTS

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