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Effects of the relative positioning between the disc-fovea angle and localized optic disc defects on the 10-2 visual field results in glaucoma

Alexis G Matos, MD, PhD¹, Carlos G De Moraes, MD^{2,*}, Tomas T Pinto, MD¹, Marcelo J L Silva, MD, PhD¹, Jayter S Paula, MD, PhD¹

¹Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil.

²Bernard and Shirlee Brown Glaucoma Research Laboratory, Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University Medical Center, New York, New York, USA.

Abstract

Purpose: To investigate the effects of the foveal position relative to the optic disc on the 10-2 visual field (VF) results of glaucoma patients with localized inferotemporal neuroretinal rim defects (ITD).

Design: Cross-sectional study.

Participants: Fifty-seven eyes of 35 open-angle glaucoma (OAG) patients were included and divided into two groups based upon the presence (18 eyes) or not (39 eyes) of ITD.

Methods: Three different parameters obtained from a spectral domain optic coherence tomography (sdOCT) [disc-fovea angle (DFA), fovea vertical deviation (FVD) from midline, and the angular difference between the ITD border and the DFA (DAD)] were tested for their relationship with four 10-2 VF sectors: superior hemifield, superior edge, nasal edge, and superonasal arcuate. These relationships were tested with regression analyses with linear mixed effects models and random intercepts.

Main Outcome Measures: Influences of DFA, FVD, and DAD on 10-2 VF sectors.

Results: Mean ($\pm$ SD) values of DFA, FVD, and DAD were respectively: $-5.05^\circ \pm 4.40^\circ$, $-1346.6 \text{ um} \pm 1609.0 \text{ um}$, and $43.30^\circ \pm 17.33^\circ$. After adjustment for multiple comparisons, both FVD and DAD, but not DFA, were significantly associated with the severity of defects on the

*Corresponding author. **Address for reprints:** Prof. Jayter Silva Paula. Departamento de Oftalmologia, Otorrinolaringologia e Cirurgia de Cabeça e Pescoço. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Av Bandeirantes, 3900 – Monte Alegre, Ribeirão Preto, São Paulo, Brazil. CEP: 14.049-900.

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predefined VF sectors. Larger DAD values (third tertile: 54°-77°) showed higher coefficient estimate for the nasal edge sector sensitivities.

Conclusions: The vertical foveal location and its position relative to the ITD was associated with loss of sensitivity at 10-2 VF locations in the superior hemifield. This association was significant but weak and was not seen using other conventional parameters that describe foveal position relative to the optic disc on sdOCT.

Manuscript - Précis

In this cross-sectional study, we demonstrated that the anatomical variability of foveal position relative to the optic disc influences the results of the central visual field test in glaucomatous eyes.

INTRODUCTION

Glaucomatous visual field (VF) loss results from damage to the retinal ganglion cells (RGC) and often follow the anatomical arcuate trajectory of the axons in the retinal nerve fiber layer (RNFL).^{1,2} In recent studies, glaucoma at all stages has been associated with damage to the macular RGC complex, with RNFL damage corresponding to this region.³⁻⁶ The investigation of the macular area has gained more attention after advances of imaging technologies that now enable high-resolution, 3-dimensional analysis of the retina layers, particularly after the introduction of spectral-domain optical coherence tomography (sdOCT).⁷

The displacement of the foveal region relative to the optic nerve head is due to a combination of inter-related, variable distances (disc-fovea distance, DFD) and angles (disc-fovea angle, DFA) between the fovea and the optic nerve head among healthy subjects and glaucomatous patients. Inter-individual differences in these parameters could potentially affect the distribution of the RNFL bundles that project from the macula to the optic nerve head. For instance, in myopic eyes the greater the DFD, the greater the DFA.⁸

Eyes with greater DFA have a difference of more than 20% in the minimum optic nerve rim width between superior and inferior temporal sectors when the centroid of the optic nerve head and fovea are aligned.⁹ Spectral-domain OCT adjustments using the DFA usually result in increased inferotemporal (IT) RNFL and decreased supero-temporal RNFL thickness measurements.¹⁰ More negative DFA (i.e., greater inferior foveal displacement from the horizontal midline) could potentially increase the susceptibility to localized glaucomatous defects due to greater crowding of the RNFL in the IT region, which is a region more susceptible to glaucomatous damage.⁵

Because the fovea is usually located below the horizontal midline, the supero-temporal RNFL bundles project on average closer to the optic disc vertical midline.^{5,10} Both the relative optic disc-fovea positioning and the axial length play a crucial role in the mapping of locations in the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA, USA) 24-2 program.¹¹ Besides, 10-2 VF tests are better at detecting early macular RGC defects,¹² particularly in the upper VF since RNFL bundles in the temporal part of the inferior quadrant have been considered at higher risk of damage, producing arcuate upper VF losses

close to the fixation point.¹³ This region of the circumpapillary retina has been called the “macular vulnerability zone” based upon the work of Hood et al.¹³

Considering that differences in the foveal position are likely to lead to variability of the interpretation of macular structure-function relationships, we investigated the effects of the fovea vertical deviation from horizontal midline on the 10-2 VF results in glaucoma patients with localized IT neuroretinal rim defects.

METHODS

Subjects

Participants were selected from the Glaucoma Services of the Clinical Hospital, Ribeirão Preto Medical School, University of São Paulo, Brazil, and of the Department of Ophthalmology, Columbia University Medical Center, New York, USA. The study protocol was approved by the local Ethic Committees and adhered to the tenets of the Declaration of Helsinki. Informed consents were obtained from all participants.

Patients were divided into two groups. The first group included patients with open-angle glaucoma (OAG), with no other ocular diseases, and whose best-corrected visual acuity was better than 0.2 logMAR OU, spherical equivalent within ± 6 D, VF defects suggestive of glaucoma [mean deviation (MD) better than -12 dB in the 24-2 SITA-Standard strategy of the Humphrey Field Analyzer (HFA), Carl Zeiss Meditec, Dublin, CA, USA), and a well-defined IT defect in the optic nerve neuroretinal (herewith called IT group). Two glaucoma specialists (AGM and MJLS) evaluated all the participants' fundus photos and categorized eyes presenting IT neuroretinal rim defects based upon the Garway-Heath diagram¹⁴, which also had to be confirmed in the same sector with a sdOCT analyzer (Spectralis, Heidelberg Engineering, Heidelberg, Germany), using the circumpapillary RNFL thickness protocol (i.e.: circle scans).

The second group consisted of patients with OAG based upon the same definition of disease and severity, but who differed from the IT group by presenting diffuse RNFL defects, with or without localized superotemporal neuroretinal rim defects (reference group).

Topographical Relationships of optic disc and foveal positions

For all participants, the DFA measures were determined by the default value displayed in the Spectralis report, which is calculated by using the fovea-to-disc alignment function. The DFD was obtained by a manual measurement of the line drawn between the fovea and the center of the optic disc in the RNFL thickness printout, considering the corresponding ratio for calculation in micrometers (Figure 1). The horizontal midline, the DFD, and the fovea vertical deviation (FVD) delimitate a rectangular triangle (Figure 1), in which the FVD could be calculated using basic trigonometry [$FVD = \sin(DFA).DFD$].

Patients in the IT group underwent an additional topographical evaluation, using the angular distance from the IT defect and the fovea-to-disc alignment axis. This variable was named as the defect's angular difference (DAD), and takes in account the angular distance from the upper limit of the IT defect subtracted from the DFA value for each eye (Figure 1). This

upper limit of the IT defect was determined by using the angular value obtained in the x axis of the characteristic double hump TSNIT thickness graph (from the sdOCT printout), where the eye's profile thickness line (black line) crosses the first point of significance for the abnormal population-based mean RNFL thickness area ($P < 1\%$, red area).

Sectorial analysis of the 10-2 VF tests

The analysis of 10-2 VF results was based upon the total deviation plots from the HFA SITA-Standard 10-2 program. Visual field results with fixation losses of $> 20\%$ or false positive response rates of $> 15\%$ were classified as "low reliability", and excluded from the analysis. Because we aimed to evaluate the sensitivity of test locations that matched RGC damage that projected to the IT defects, we only analyzed the entire superior hemifield 10-2 VF tests as one of the dependent variable. Moreover, we arbitrarily defined three 10-2 VF sectors in the superior hemifield area, as other dependent variable: a) the superior edge (delimited by the upper 8 test points), b) the nasal edge (delimited by the 4 nasal-most test points adjacent to the horizontal midline), and c) the supero-nasal arch (defined as combination of all superior edge and nasal edge points in addition the point at the location n5s5 (5 degrees nasal and 5 degrees superior) (Figure 1). The mean of the sensitivity values and the number of points significantly abnormal ($P < 0.1\%$) of these pre-defined sectors were considered for the analyses.

Statistical Analyses

Data were analyzed using descriptive and inferential statistics. Continuous variables are presented as means and standard deviation. The VF total deviation sensitivity and number of abnormal points in the superior hemifield, superior edge, nasal edge, and supero-nasal arch sectors were normalized with the MD and with the total number of abnormal points ($P < 1\%$) in the total deviation plot, respectively. These VF parameters were then tested as dependent variables. Univariable regressions with mixed effects linear models and random intercepts were used to verify the individual effects of DFA, FVD, and DAD on each dependent variable. The Benjamini-Hochberg method was used to address multiple comparisons based upon a false discovery rate of 25%. A *post-hoc* correlation analysis was also performed using mixed effects to evaluate which peripheral 10-2 VF sectors were more affected by different DAD values divided in tertiles. Computerized statistical analyses were performed with Stata version 14.2 (StataCorp LLC, College Station, TX, USA) and significance was defined at $P < 0.05\%$.

RESULTS

Fifty-seven eyes of 35 OAG patients [mean ($\pm$ SD) age: 59.7 ± 23.3 years] were included and divided into the IT group (18 eyes/16 patients) and the reference group (39 eyes/26 patients). Twenty participants (57.1%) were women, and the OD/OS proportion was 28/29. Mean values of DFA, DFD and FVD were respectively: $-5.05^\circ \pm 4.40^\circ$, $3976.7 \text{ um} \pm 366.0 \text{ um}$, and $-1346.6 \text{ um} \pm 1609.0 \text{ um}$. Demographic characteristics, including results from the pre-defined 10-2 VF parameters and sdOCT topographic parameters of both groups are presented in Table 1. Of note, mean RNFL thickness measurements were not significantly different between groups ($p = 0.92$). DAD values from the reference group (patients without

IT defects) were neither measured nor considered for analysis since there was no abnormality in their TSNIT profile.

Although DFA was not significantly associated with any of the VF sectors designed in the 10-2 superior hemifield, univariable regression models showed significant relationships between both FVD and DAD and the VF parameters in patients with localized IT defects (Table 2). Although normalized supero-nasal arch sensitivity correlated with FVD in patients without localized IT defects ($p=0.006$), no other significant correlation was observed in those patients.

After adjustment for multiple comparisons, there was a weak but significant relationship between all 10-2 VF parameters and FVD and DAD (R-squared range: 0.0016 – 0.1229; P-value range: 0.027 – 0.0001) in patients with IT defects (Figure 2 and Table 3). Patients with no localized IT defects had a significant relationship only between supero-nasal arch sensitivity and FVD ($p=0.006$; Table 3). Besides, larger DAD (delimited in the third tertile: 54° - 77°) showed higher coefficient estimates for the nasal edge sector sensitivities (Figure 3).

DISCUSSION

We investigated the effects of the fovea vertical deviation from horizontal midline with the 10-2 VF results in glaucoma patients with localized IT neuroretinal rim defects. We found that a new parameter – defined as the angular distance from the IT defect and the fovea-to-disc alignment axis – was significantly associated with more asymmetrical loss in the superior relative to the inferior hemifield. Despite its statistical significance, the effect was modest. Of note, conventional parameters used to describe the disc-to-fovea relationships on sdOCT (i.e.: DFA and FVD) were not significant.

Patients with glaucoma at any stage may present thinning of the RNFL thickness measurements within the macular region.⁵ Recent studies have shown that the relationship between the central VF and the macular RNFL should consider taking into account topographical parameters related to inter-subject variability of the disc-fovea axis.^{3,4,8}

Despite differences in the location and orientation of the temporal raphe,³ RNFL bundles emerging from the macula tend to converge to the supero- and inferotemporal sectors of optic nerve.³ This anatomical assortment of bundles along with the relative vertical position of the fovea influences the topographical relationship between optic nerve rim thinning and central VF damage in glaucoma.^{3-6,8}

As a result of this vertical asymmetry of the temporal rim, eyes with a more negative DFA, i.e. eyes in which the center of the fovea is located more inferiorly, might display more frequently losses in the superior hemifield of the 10-2 VF.^{8,14}

By evaluating patients with localized glaucomatous IT defects in the optic nerve rim with different DFA, we demonstrated that damage in the superior hemifield, as well as peripheral superior and nasal locations of the 10-2 VF (superior edge, nasal edge, and supero-nasal arch), are affected by the relative topographical position between the fovea and the optic

nerve head. Even though DFA measurements did not correlate significantly with any of the VF sectors studied, our findings demonstrated the effects of the FVD and DAD values on the results of all the sectors arbitrarily defined in the superior 10-2 VF.

Choi et al. have shown correlations between the DFA and differences in the temporal portion of the peripapillary RNFL thickness, which might be affected by the disc-fovea distance.^{5,8} Since DFA and the disc-fovea distance may be correlated, in the present study we proposed a new parameter, the FVD, as one that was shown to be able to predict damage to the 10-2 superior hemifield. In fact, larger FVD values were significantly associated with the worse normalized mean sensitivity and the number of abnormal points in all the peripheral 10-2 VF sectors studied, except for the total superior hemifield sensitivity. This could be explained based upon the model of structure-function relationships in the macula described by Hood et al.¹³ Defects seen in the macular vulnerability zone correspond to areas of damage in the nasal-most part of the superior hemifield of the 10-2, and not the totality of test locations in that hemifield.

Because we included eyes with localized defects in the IT region (most of which within the MVZ), it is therefore plausible that the average sensitivity of the superior hemifield (which includes normal areas) would not hold a significant relationship with the FVD.

Since the influence of the anatomical position of the fovea (FVD) on the 10-2 superior hemifield could depend on the relative distance between the fovea (as the center of the VF) and the beginning of the localized IT defect (as a landmark for macular RGC damage), we proposed the DAD as an alternative parameter to test for relationships with damage in the 10-2 VF. Smaller DAD values were significantly correlated with all the VF sectors' variables studied, except for the normalized mean nasal edge sensitivity in the IT group. We believe that lack of a significant relationship between DAD and superior hemifield may also be due to the afore-described explanation for the lack of significant relationship between FVD and 10-2 superior hemifield. With regard to nasal edge sensitivities; however, it is possible that inter-subject variability in the relationship between macular RGC thickness maps and the 10-2 test locations – particular edge test locations – may help explain the lack of a significant relationship. For instance, Raza and Hood¹⁵ showed how the displacement between RGC and photoreceptors can affect the structure-function relationships in the macula, as edge VF locations tend to be pushed more peripherally. Moreover, Turpin et al.¹⁶ proposed that individualizing macular displacement measurements based on OCT data for an individual can result in large spatial shifts in the retinal area corresponding to 10-2 locations, which may be important for clinical structure-function analysis when performed on a local, spatial scale. Mavrommatis et al. examined the structure-function relationship in glaucoma between deep defects seen on 10-2 VF and deep losses in the circumpapillary retinal nerve fiber layer on optical sDOCT circle scans and found that the individual DFA adjustment improved agreement in only 1 of 32 eyes with an extreme angle.¹⁷ Their results agree with our observation of lack of significant influence of DFA on most of 10-2 VF peripheral defects. Furthermore, larger distances between the fovea and limits of the IT defect (DAD) have influenced only very peripheral 10-2 points in the nasal edge (Figure 3).

Some limitations could be considered in this study as follows: the relatively small sample of eyes with IT defects, the manual measurement of sdOCT images for calculation of the disc-fovea distance and DAD values, and the potential influence of head tilt on the measurements during OCT and VF examination. However, all measurements were made by an experienced examiner (AGM), using high quality and magnified images and a caliper. Although angle measurements are usually minimally affected in routine examinations¹⁸, we were careful in stabilizing head's position, keeping a very horizontal line between patients' pupils. Both the width and depth of inferotemporal RNFL quadrant, in and out the IT rim defect, could also affect losses of sensitivity on the superior hemifield tests unlikely. Considering the similar mean RNFL thickness between groups and by testing DAD, we attempted to contemplate most of the potential OCT influences on the 10-2 VF analyses, regarding the depth and width of the RNFL thickness respectively.

Based on Hood's models for the structural-function relationship, RNFL thickness' defects in the inferotemporal quadrant yield arcuate VF defects in the superior locations of the central VF (particularly in the "macula vulnerability zone").^{8,14} Considering the effects of defects in the vulnerability zones on central VFs, as well as the observation of a moderate proportion of patients presenting losses in the 10-2 VF before changes in the regular 24-2 VF¹², our study contributes for further adjusting between OCT and VF analyses in patients with localized IT rim defects, particularly those under risk of losses close to the fixation or with still non compromised 10-2 VF. Thus, a better understanding of the topographical variation of the fovea positioning will help clinicians to be aware of the different presentation of central VF losses in glaucoma patients with localized IT defects. Further studies with a larger sample size will permit testing the diagnostic prediction of the proposed parameters in several clinical scenarios.

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Figure 1.

Determination of parameters used for evaluating the relative disc-fovea positioning (*left*) and delimitation of proposed sectors (shadow areas) in the superior 10-2 hemifield (*right*). *Left*: DFA - Disc-fovea angle; DAD - Defect's angular difference; DFD - Disc-fovea distance; FVD - Fovea vertical deviation. *Right*: SE – superior edge; SH – (entire) superior hemifield; NE – nasal edge; SN – Supero-nasal arch.

Figure 2.

Examples of patients with comparable disc-fovea angle (DFA) and localized inferotemporal rim defects presenting different patterns of losses in the superior edge (SE) sector of the 10-2 visual field (uppermost 8 point-locations in the total deviation plot). Note that the right eye of the second patient shows worst SE losses and both large fovea vertical deviation (FVD) and small defect's angular difference (DAD).

Figure 3. Mixed effects model coefficient estimates of sensitivity decreases in the 10-2 VF sectors using DAD tertiles. Note that larger DAD values (third tertile: 54°-77°) showed higher coefficient estimate for the nasal edge sector sensitivities.

Table 1.

Demographic and clinical characteristics of participants described by presence or not of localized defects in the inferotemporal optic nerve rim.

	Localized IT defects	No localized IT defects	P value
<i>Number of eyes (subjects)</i>	18 (16)	39 (26)	--
<i>OD/OS</i>	10/8	18/21	0.58 *
<i>10-2 VF Mean Deviation, dB</i>	-5.4 ± 6.3	-4.9 ± 5.1	0.79 **
<i>Average RNFL, μm</i>	74.9 ± 11.2	74.5 ± 19.7	0.92 **
<i>DFA, degrees</i>	-5.7 ± 4.5	-4.9 ± 4.5	0.68 **
<i>FVD, μm</i>	-1501.1 ± 1154.9	-1275.4 ± 1809.3	0.89 **
<i>DAD, degrees</i>	43.3 ± 17.3	***	***

IT: Inferotemporal. VF: Visual field. RNFL: Retinal nerve fiber layer. DFA: Disc Fovea Angle. FVD: Fovea Vertical Deviation. Continuous variables are presented as mean ± standard deviation (SD).

* : Fisher's exact test.

** Mann-Whitney U test.

*** Not calculated.

Table 2.

Univariate correlation results between topographical factors and normalized losses in selected superior sectors of the 10-2 visual field in patients with or without localized defects in the inferotemporal optic nerve rim.

Factor	Normalized Dependent Variable	No localized IT defect (P value)	Localized IT defect (P value)
DFA	<i>SE sensitivity</i>	0.933	0.124
	<i>SE points</i>	0.672	0.438
	<i>NE sensitivity</i>	0.509	0.126
	<i>NE points</i>	0.511	0.876
	<i>SH sensitivity</i>	0.770	0.434
	<i>SH points</i>	0.264	0.076
	<i>SN sensitivity</i>	0.743	0.948
	<i>SN points</i>	0.508	0.067
FVD	<i>SE sensitivity</i>	0.090	0.559
	<i>SE points</i>	0.293	0.114
	<i>NE sensitivity</i>	0.435	<0.001
	<i>NE points</i>	0.387	0.004
	<i>SH sensitivity</i>	0.349	0.528
	<i>SH points</i>	0.971	0.019
	<i>SN sensitivity</i>	0.006	0.027
	<i>SN points</i>	0.522	0.002
DAD	<i>SE sensitivity</i>	*	<0.001
	<i>SE points</i>	*	<0.001
	<i>NE sensitivity</i>	*	0.468
	<i>NE points</i>	*	0.001
	<i>SH sensitivity</i>	*	<0.001
	<i>SH points</i>	*	0.002
	<i>SN sensitivity</i>	*	0.027
	<i>SN points</i>	*	0.012

IT: Inferotemporal. NE: Nasal edge; SE: Superior edge; SH: Superior hemifield; SN: Supero-nasal arch.

DFA: Disc Fovea Angle. FVD: Fovea Vertical Deviation. DAD: Defect's angular difference.

Table 3.

Significant multiple comparisons' results of topographical factors influencing normalized losses in selected superior sectors of the 10-2 visual field in patients with or without localized defects in the inferotemporal optic nerve rim.

Normalized Dependent Variables	Factor	IT defect	P value	Rank	R-squared
<i>NE sensitivity</i>	FVD	yes	0.0001	1	0.0892
<i>SE sensitivity</i>	DAD	yes	0.0001	2	0.0283
<i>SE points</i>	DAD	yes	0.0001	3	0.0062
<i>SH sensitivity</i>	DAD	yes	0.0001	4	0.1178
<i>NE points</i>	DAD	yes	0.001	5	0.1229
<i>SN points</i>	FVD	yes	0.002	6	0.0172
<i>SH points</i>	DAD	yes	0.002	7	0.0016
<i>NE points</i>	FVD	yes	0.004	8	0.0139
<i>SN sensitivity</i>	FVD	no	0.006	9	0.0681
<i>SN points</i>	DAD	yes	0.012	10	0.0408
<i>SH points</i>	FVD	yes	0.019	11	0.006
<i>SN sensitivity</i>	FVD	yes	0.027	12	0.1055
<i>SN sensitivity</i>	DAD	yes	0.027	13	0.0317

IT: Inferotemporal. NE: Nasal edge; SE: Superior edge; SH: Superior hemifield; SN: Supero-nasal arch. FVD: Fovea Vertical Deviation. DAD: Defect's angular difference.