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Cross-sectional Study

Optical coherence tomography angiography vessel density parameters in primary open-angle glaucoma

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ABSTRACT

Background: Many studies suggest the existence of an alteration of the retinal hemoperfusion in primary open-angle glaucoma. The OCT-A is a novel technique that allows to provide information on retinal microcirculation in a non-invasive way, thus it represents a possible imaging target for the early diagnosis and follow-up of glaucoma. The aim of our work is to evaluate the contribution of vascular parameters provided by OCT-A and their diagnostic abilities in the different stages of primary open-angle glaucoma.

Method: This is a prospective cross-sectional study involving 200 eyes of control subjects and 250 eyes of glaucomatous subjects divided into early glaucoma, moderate glaucoma and advanced glaucoma subgroups. They were assessed for MD, LV by visual field, RNFL and GCC thickness by SS-OCT papillary and macular vascular densities by SS-OCT A.

Results: OCT-A vessel densities determined in the optic nerve head, in the peripapillary and in the macular regions were significantly lower in glaucomatous eyes. Among the vascular parameters studied the whole image vascular density showed the best diagnostic ability in the discrimination between glaucomatous eyes and healthy eyes with an AUC of 0.949. Nevertheless, the diagnostic ability of vascular parameters remains lower than of the structural parameters RNFL (AUC: 0.981). A significant correlation was found between structural, functional and vascular parameters with $r < 0.05$. The quadratic non-linear model defines better the relationship between structural, vascular and functional damage in glaucoma.

Conclusion: The OCT-A plays an important role in the early diagnosis and follow-up of PAOG. It also contributes to the understanding of some aspects of the vascular role in glaucoma.

1. Introduction

Primary open-angle glaucoma (PAOG) represents the second leading cause of blindness in the world. Early diagnosis and close monitoring of glaucoma are important given the insidious onset of this disease with irreversible nerve damage associated with vision loss [1]. The visual field test remains the gold standard for glaucoma assessment, but there is substantial variability with low reproducibility in some patients [2]. Structural studies of retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) using optical coherence tomography OCT represent an objective measure for glaucoma assessment, but it has limited sensitivity to detect early glaucoma and had a moderate correlation with visual field loss [2]. Glaucomatous optic neuropathy has been shown to be associated with vascular dysfunction [3], suggesting an alternative imaging target for early diagnosis and follow-up of glaucoma. In this context OCT-A has emerged as a promising new technology for the study of ocular perfusion on a microscopic scale and has shown through hundreds of studies its considerable contribution to glaucoma. The OCT-A can provide non-invasive, rapid, detailed, and quantitative information on retinal and choroid micro vascularization of the eye. The technology has already been assimilated into clinical practice in the field of the retina, however, as we will see throughout our study that the role of the OCT-A in the diagnosis and the management of glaucoma is still being elucidated.

The primary goal of our study was to analyze qualitatively and quantitatively the vascular parameters provided by the OCT-A in the papillary retinal microcirculation and in the macular region in the different stages of glaucoma. We also evaluated the diagnostic ability of vascular parameters for discrimination between glaucomatous and healthy eyes. Then we evaluated the correlations between vascular

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parameters, structural parameters (RNFL and GCC) and functional parameters (visual field indices).

2. Method

2.1. Participants

We conducted a prospective cross-sectional monocentric study over a period extending from July 2019 to September 2020 in the ophthalmology department of Farhat Hached hospital in Sousse Tunisia. We recruited all the subjects with glaucoma to represent the glaucoma group and the healthy subjects (non-glaucomatous eyes) represented the control group. Patients' written and oral consent were obtained. All procedures conformed to the guidelines of the Declartion of Helsinki and our study is registered in Research Registry under the number of 6898. https://www.researchregistry.com/registernow#home/registrationdetails/60ca62abcaf311001ede6f00/

The work has been reported in line with the STROCSS criteria [4].

Inclusion criteria for the glaucoma and the control groups included best-corrected visual acuity of 1/20 or better, refractive error between −7.00 and +3.00 diopters, absence of media opacities that could compromise the OCT images quality. We also included subjects with systemic hypertension and diabetes provided they didn't have diabetic or hypertensive retinopathy.

We excluded eyes with coexisting ophthalmologic diseases that are causative of altered vision or visual field. All forms of secondary open-angle glaucoma were also excluded.

All the subjects underwent a complete ophthalmic examination which included visual acuity, refractive error, IOP measured with Goldman applanation tonometer, anterior segment examination by slit-lamp, fundus examination and optic nerve head evaluation and gonioscopy. Automated standard visual field test was performed using the threshold test 24-2 with the help of a field analyzer; the scope of Octopus 101.

PAOG was diagnosed based on characteristic changes in the optical nerve head detected by ophthalmoscopy. The diagnosis was made by an ophthalmologist. These changes included pathological deviation of the neuroretinal margin, extensive papillary excavation, altered vessel path, peripapillary atrophy, defects in the RNFL adjacent to the edge of the optical disc etc. Other diagnostic criteria were a normal anterior segment on the slit lamp and an open angle on gonioscopy. Glaucomatous eyes were divided into 3 groups based on the Hodapp rating scale Parrish-Anderson of the severity of defects in visual field test: early MD < 6 dB, moderate 6 dB $<$ MD < 12 dB and severe MD > 12 dB. The eyes of the control group had a normal IOP < 21 mmHg, normal appearance of the optic nerve head and RNFL and a normal visual filed.

2.2. OCT data acquisition

In our study OCT-A imaging was performed using Swept-Source OCT DRI Triton of Topcon with the OCTA-RA algorithm [5].

For papillary OCT-A, 4.5 mm*4.5 mm cubes were used. Vascular density of the papillary region was analyzed in 3 areas. The inside disc vessel density (idVD) in a circle of 1.5 mm diameter centered on the optic disc in the ONH layer. Average and sectoral peripapillary vessel densities (ppVD) were performed at the radial peripapillary capillary (RPC) layer in a diameter of 750 μm (between 2 concentric circles of 1.5 mm and 2.25 mm centered on optic disc). We also analyzed the vessel density in the entire 4.5 mm*4.5 mm disc scan image referred as the whole enface vessel density (wdVD) in the RPC layer.

Swept source-OCT DRI TRITON of TOPCON doesn't have a software that automatically determine the vascular density at the papillary region. So, a specific image processing was carried out manually to binarize the angiograms on the opposite side and to calculate the density of the vessels using the ImageJ software (https://imagej.net/Auto_Threshold). At the end of this image binarization process the ratio of the number of white pixels to the total number of pixels was calculated to obtain the vascular density in percentage. Each image was loaded into the ImageJ software and processed using the "Otsu'' auto selecting algorithm [6].

As for macular region OCT-As 6*6 mm cubes were used. Predefined segmentation was performed to analyze the superficial retinal layer comprising the internal limiting membrane, the RNFL and the GCC. Vascular density of the macular region was analyzed in the superficial capillary plexus at the level of 3 regions: The foveal vascular density (fVD) at the foveal region, the average and sectoral parafoveal vessel densities (pfVD) (defined by a circular ring between two circles centered on the fovea with an internal diameter of 1 mm and an external diameter of 1.5 mm) and the entire 6*6 mm macula scan referred as the whole enface vessel density (wmVD). The SS-OCT DRI TRITON of TOPCON has a software that automatically calculates vascular density at the parafoveal and foveal superficial capillary plexus. For the wmVD the method of calculating vascular density described above was used.

In addition to the vessel density measurement, all subjects underwent circumpapillary RNFL and macular GCC thickness measurement by using SS-OCT DRI TRITON of TOPCON. We analyzed average and four sectoral RNFL thickness; superior, inferior, temporal and nasal and average and sectoral GCC thickness; inferior and superior.

2.3. Statistical analysis

Independent *t*-test was used for the comparison of the demographic and clinical data, OCT angiography vessel density parameters, RNFL thickness, and GCC thickness between the control group and the glaucoma group. One-way analysis of variance with post hoc analysis by using Bonferroni method was performed for multiple comparisons between the groups. Categorical variables were compared using the chi-square test or Fisher's exact test. Spearman's rank correlation test and linear and nonlinear quadratic models with adjusted R2 test were used to investigate the correlation between vessel density parameters and other variables. The diagnostic abilities of the vessel density parameters, RNFL thickness, and GCC thickness for differentiating between control group and glaucoma group (total, early, moderate, and severe subgroups) were evaluated by calculating the area under the receiver operating characteristic curves (AUCs). SPSS v24 was used for data analysis.

The significance level was set at $p < 0.05$.

3. Results

Our study enrolled a total of 200 healthy eyes and 250 of glaucomatous eyes. Table 1 summarizes the characteristics of the participants in the control and glaucoma groups. From 250 glaucomatous eyes, 142 eyes were at the early stage, 65 eyes were at the moderate stage and 43 eyes were at the severe stage.

The mean course of glaucoma ranged from 1 to 20 years with an average of 7.17 years.

Patients received prostaglandine analogues in 80% of cases, beta-blockers in 50% of cases, dorzolamide and brimonidine were used in 10% of cases. Clinical exam found a significative decrease in visual acuity (VA) between the control group and the glaucoma group ($p < 0.05$). The IOP was significantly higher at different stages of glaucoma compared to the control group and the papillary excavation increased significantly with the glaucoma severity. The glaucoma group had also significantly lower visual field indices including the mean deviation (MD) and the low variance (LV). The OCT study of structure found a significant decrease of RNFL and GCC thickness with the severity of glaucoma ($p < 0.05$).

All vessel density parameters of the glaucoma group were significantly lower than those of the control group ($p < 0.05$) except for the fVD ($p = 0.08$). In the subgroup analysis there was a tendency of decreased vessel density with increasing in severity of glaucoma ($p <$

Table 1
Characteristics of the study population.

	Control group (N = 115)	Early glaucoma (N = 81)	Moderate glauccoma (N = 44)	Advanced glaucoma (N = 32)	p
M/F(a)	65/50	38/43	27/17	18/14	0.337
Age(b)	57.36 ± 6.88	56.16 ± 6.77	59.89 ± 6.10	64.52 ± 3.15	0.72
RE/LE(a)	100/100	74/68	32/33	24/19	0.890
Diabetes(a)	18 (15.65%)	12 (14.81%)	5 (13.15%)	8 (25%)	0.475
Systemic hypertension(a)	25 (21.74%)	16 (19.75%)	10 (22.72%)	10 (31.25%)	0.509
Cardio-vascular diseases (a)	7 (8.05%)	5 (6.17%)	3 (6.81%)	3 (9.37%)	0.874
Cataract surgery(a)	17 (14.78%)	12 (14.81%)	5 (3.47%)	7 (21.87%)	0.700
Family history of glaucoma(a)	17 (14.78%)	20 (24.69%)	7 (15.90%)	3 (9.37%)	0.190

N = number of patients, M: male, F: female, RE: right eye, LE: left eye.
Results of the numerical variables are presented as number or mean ± standard deviation.
(a) Statistical significance was tested with the chi-square test.
(b) Statistical significance was tested with the one-way analysis of variance test.

0.05) (Tables 2 and 3).

The diagnostic abilities of the OCT angiography vessel density parameters between the control group and glaucoma group calculated by AUCs are presented in Table 4 and Fig. 1.

We found that the AUCs of the OCT-A parameters were comparable in the areas of ppVD (AUC:0.940), wdVD (AUC:0.949), and wmVD (AUC: 0.944). A lower AUC with the idVD (AUC:0.672) and with the pfVD (AUC: 0.748) were noted. We also found that there was a superiority of structural parameters over vessel density parameters in the discrimination between healthy and glaucomatous eyes. In the sectoral ppVD AUCs we found that the upper (AUC: 0.791) and the lower (AUC:0.764) sectors had the best AUCs for the detection of early glaucoma but remained below the discriminatory power of RNFL thickness in the corresponding regions respectively AUC: 0.873 and AUC:0.845.

In this study we have demonstrated the existence of topographic association between the location of vascular damage, structural defects (RNFL and GCC thinning) and functional alteration detected by the VF (Figs. 2 and 3). This association appeared to be more consistent when vascular density analysis was limited to an area with specific structural defect (Fig. 2).

Table 2
Comparison of the vessel density parameters of the papillary region between the glaucoma groups and the control group.

	Control group (A) (N = 200)	Early glaucoma (B) (N = 142)	Moderate glaucoma (C) (N = 65)	Advanced glaucoma (D) (N = 43)	p(a)
wdVD	46.40 ± 2.34	41.41 ± 2.82	36.62 ± 2.69	32.51 ± 2.95	<0.001 A > B > C > D(b)
idVD	40.23 ± 3.63	39.02 ± 3.46	37.21 ± 3.99	34.45 ± 3.37	<0.001 A > B > C > D(b)
ppDV					
Average	48.01 ± 2.08	44.04 ± 2.26	41.82 ± 2.45	35.41 ± 3.90	<0.001 A > B > C > D(b)
Superior	48.59 ± 2.28	45.38 ± 2.94	42.09 ± 4.00	36.74 ± 5.55	<0.001 A > B > C > D(b)
Inferior	49.59 ± 2.29	45.53 ± 3.88	41.90 ± 3.31	36.71 ± 6.55	<0.001 A > B > C > D(b)
Temporal	50.10 ± 2.17	47.81 ± 3.02	46.04 ± 3.34	41.93 ± 5.56	<0.001 A > B > C > D(b)
Nasal	47.24 ± 2.45	44.36 ± 2.85	41.15 ± 3.53	35.90 ± 4.23	<0.001 A > B > C > D(b)

Results of the numerical variables are presented as number or mean ± standard deviation.
(a) Statistical significance was tested with the one-way analysis of variance test.
(b) Post hoc analysis by the Bonferroni method between the normal controls and glaucomatous eyes (“>” means that there is a statistically significant difference between the groups).

Table 3
Comparison of the vessel density parameters of the papillary region between the glaucoma groups and the control group.

	Control group (A) (N = 200)	Early glaucoma (B) (N = 142)	Moderate glaucoma (C) (N = 65)	Advanced glaucoma (D) (N = 43)	p(a)
wmVD	42.37 ± 1.41	39.85 ± 1.21	36.32 ± 0.81	33.11 ± 0.86	<0.001 A > B > C > D(b)
fVD	21.31 ± 1.45	21.62 ± 1.46	20.74 ± 1.34	19.46 ± 1.10	0.08
pfVD					
Average	47.01 ± 2.95	45.79 ± 2.58	42.85 ± 2.67	38.70 ± 1.95	<0.001 A > B > C > D(b)
Superior	49.31 ± 3.12	46.01 ± 3.14	43.15 ± 3.66	40.97 ± 3.13	<0.001 A > B > C > D(b)
Inferior	48.07 ± 3.09	44.94 ± 3.24	41.78 ± 3.73	39.46 ± 2.85	<0.001 A > B > C > D(b)
Temporal	49.52 ± 2.80	46.45 ± 3.19	43.15 ± 2.92	40.73 ± 2.78	<0.001 A > B > C > D(b)
Nasal	48.96 ± 3.09	45.38 ± 3.36	43.62 ± 3.13	41.56 ± 3.25	<0.001 A > B > C > D

Results of the numerical variables are presented as number or mean ± standard deviation.
(a) Statistical significance was tested with the one-way analysis of variance test.
(b) Post hoc analysis by the Bonferroni method between the normal controls and glaucomatous eyes (“>” means that there is a statistically significant difference between the groups).

The correlation study found that vessel density parameters of the papillary and macular regions were significantly correlated with RNFL, GCC thickness and with VF indices in different stages of glaucoma (Table 5). The strength of correlation increases with the severity of glaucoma. Nevertheless, the correlation between vessel density parameters and VF indices was more coherent than the correlation between vascular parameters and the OCT parameters.

After examining the correlations between the different parameters, we investigated the type of relationship between structure, vascularization and function using linear and nonlinear quadratic regression analysis with the adjusted R2 test (Table 6).

The structure-function relationship was best explained by quadratic nonlinear regression model assessing MD and RNFL. The evaluation of the nature of the relationship between ppVD and RNFL, ppVD and MD, pfVD and MD showed that the quadratic models best described the nature of the studied relationships (Fig. 4).

Table 4
Diagnostic abilities of the optical coherence tomography angiography vessel density parameters for differentiation between the control and glaucoma groups.

	Groupe glaucome (N = 250)	Glaucome précoce (N = 142)	Glaucome modéré (N = 65)	Glaucome avancé (N = 43)
DVipe	0.949 (0.932–0.966)	0.911 (0.882–0.940)	0.998 (0.995–0.991)	1.000 (1.000–1.000)
DVp	0.672 (0.623–0.722)	0.597 (0.537–0.658)	0.712 (0.634–0.790)	0.861 (0.810–0.911)
DVpp	0.940 (0.920–0.959)	0.907 (0.877–0.936)	0.972 (0.954–0.991)	1.000 (1.000–1.000)
DVime	0.944 (0.926–0.962)	0.902 (0.872–0.932)	1.000 (1.000–1.000)	1.000 (1.000–1.000)
DVpf	0.748 (0.703–0.792)	0.640 (0.581–0.700)	0.823 (0.768–0.878)	0.991 (0.977–1.000)
RNFL	0.981 (0.971–0.991)	0.966 (0.949–0.983)	1.000 (1.000–1.000)	1.000 (1.000–1.000)
GCC	0.923 (0.901–0.946)	0.889 (0.856–0.923)	0.947 (0.921–0.973)	1.000 (1.000–1.000)

Variables are presented as the areas under the receiver operating characteristics curves with 95% confidence interval values in the parentheses.

4. Discussion

In our study, vascular density was assessed at the at the optic nerve head, at the global and sectoral peripapillary and in the whole disc scan. In accordance with the literature those vascular parameters tend to decrease in glaucomatous eyes with worsening glaucoma compared to controls. Concerning the vascular density of the optic disc the data in the literature are discordant and both significant [7,8] and non-significant [9,10] decrease were found. This may be related to the physiological variations generally observed in the optic nerve head in terms of size, shape, inclination, and the position of retinal central vessels etc.

The data concerning the peripapillary vessel density are more concordant and a significant decrease was found by almost all the authors who studied this parameter Yarmohammadi and al. [11], Mantalas and al [12]. and Chen and al [13]. Thus, measurements of the ppVD appear to provide useful diagnostic information and have become the main focus of research in this field. Similarly to our study Chung and al [14] and Kumar and al [15]. found that wdVD was significantly lower in all glaucomatous eyes regardless the degree of glaucoma. Kumar and al. showed that this decrease was also observed in the group of pre-perimetric glaucoma. This finding also involved eyes suspected of

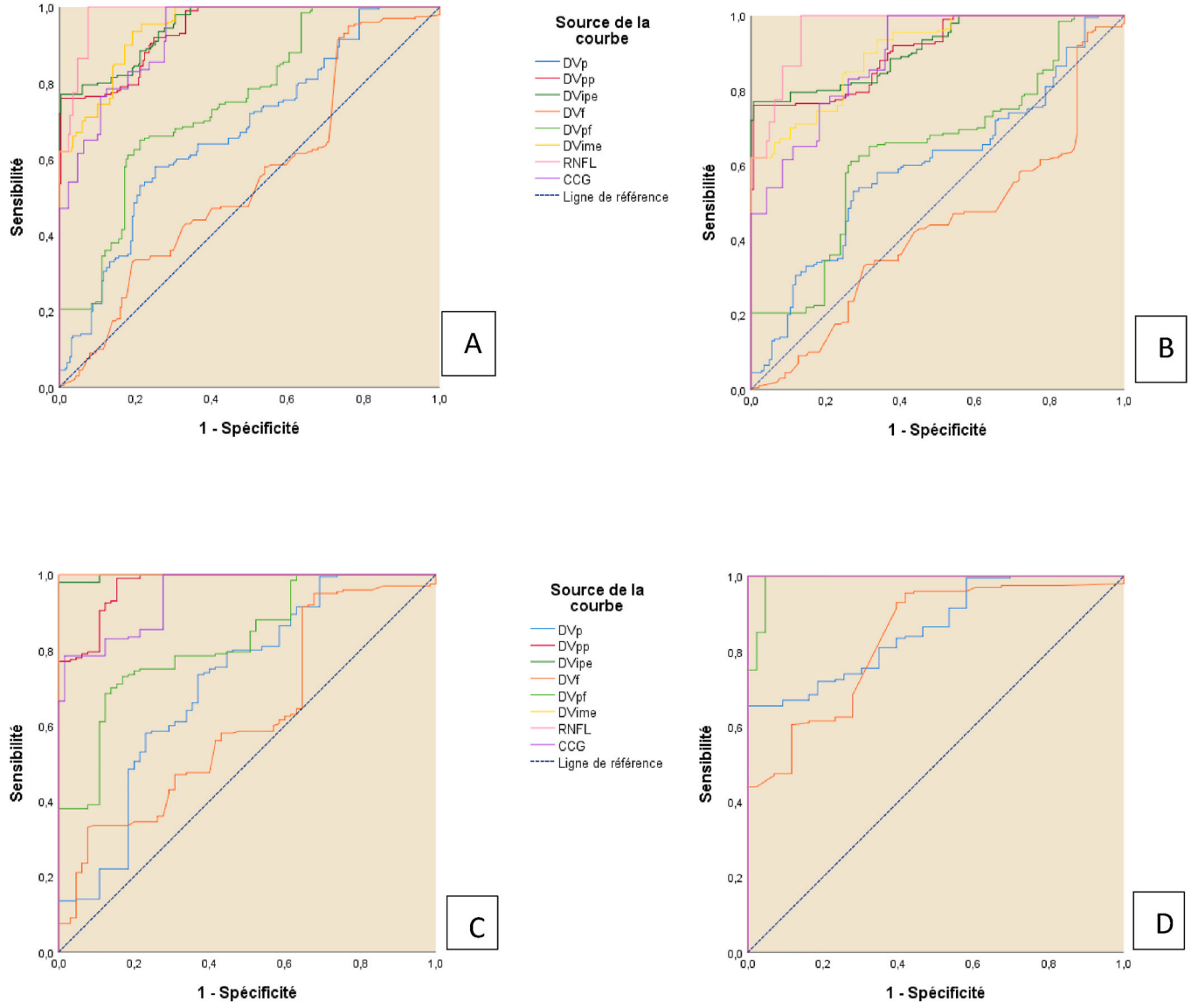

Fig. 1. Area under the receiver operating characteristic curves of the OCT-A vessel density parameters, RNFL and GCC for glaucoma diagnosis in the total glaucoma group (A), early stage glaucoma group (B), moderate stage glaucoma group.

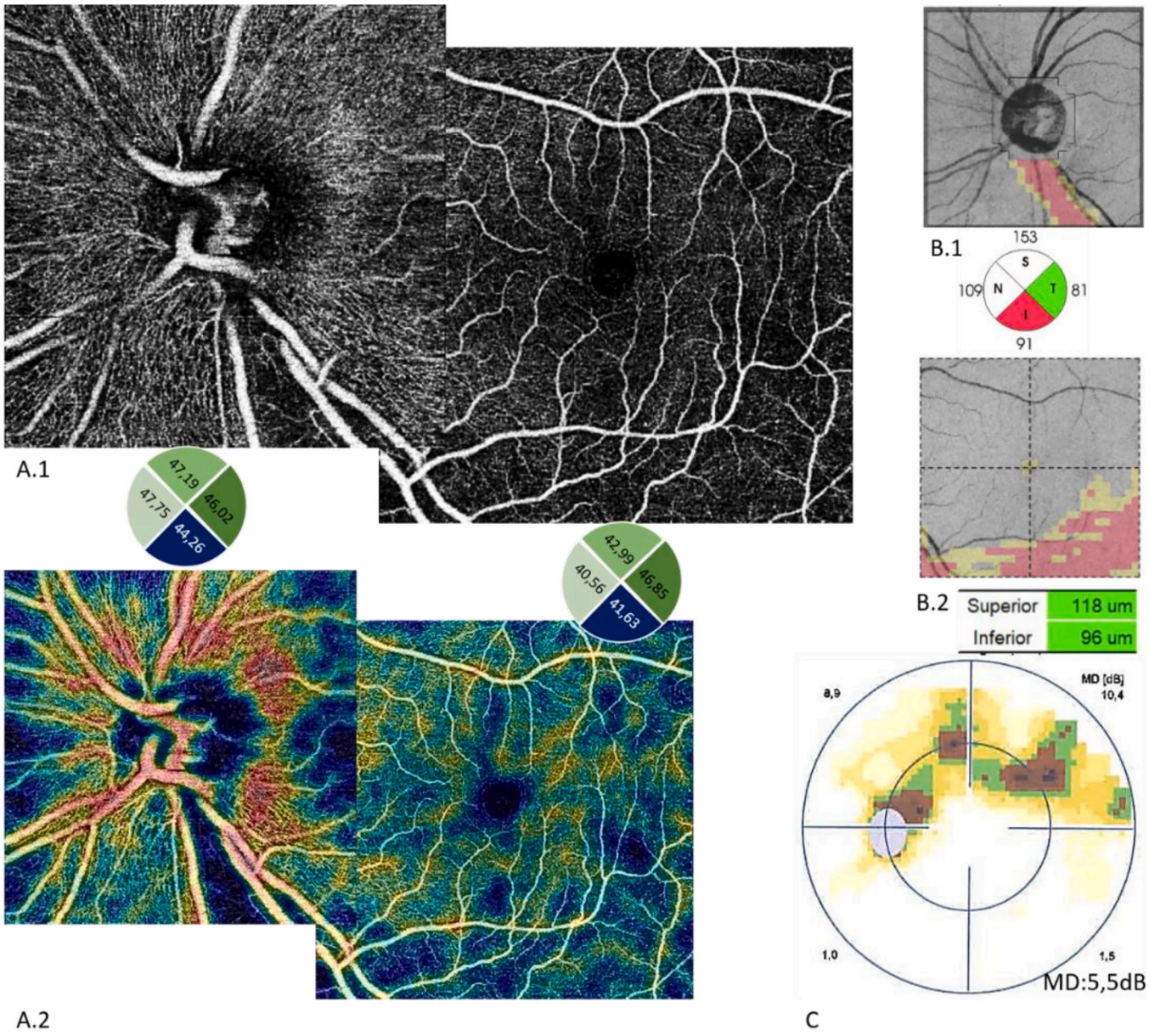

Fig. 2. Association of vascular defect (A), RNFL (B1), GCC (B2) thinning, visual field damage (C) in early glaucoma.

glaucoma as demonstrated by Yarmohamadi and al [11]. which could mean that wdVD is as important as the other papillary vascular parameters.

The macula vessel density parameters are less studied in literature. Similarly, to our study the pfVD and wmVD are found to decrease in the glaucoma proportionally to its severity like shown by Peng Lu and al [17]. and Takusagawa and al [18]. However, we did not find any significant difference in the foveal vascular density between the control group and glaucoma groups at any stage. This may be explained by the presence of the foveal avascular area which occupies most of the surface area in the calculation of fVD.

In the present study we have shown that the ppVD and wdVD have a strong ability to differentiate between glaucomatous and healthy eyes. Our results are consistent with many published studies. Rao and al [18]. found that ppVD and wdVD 4.5*4.5 mm had high diagnostic ability with AUCs of 0.93 and 0.85 respectively. The same applies to the study of Yarmohammadi and al [11]. who found an excellent discriminating ability of those parameters with AUCs of 0.94 and 0.83 respectively.

WmVD was also found to have a high diagnostic ability with an AUC of 0.94 in our study. Rao and al. [9], being the first to study the diagnostic accuracy of macular circulation in 2016, reported a low AUC value of 0.69. Their study differs from ours in the size of the macular area of interest (3*3 mm versus 6.6 mm in our study), so their smaller scan size may have missed peripheral ganglion cell involvement. Indeed, the macular areas most vulnerable to glaucoma are the temporal and inferotemporal ones located mainly outside the 3.3 mm core area but within the 6.6 mm area [19,20].

In this study when a sectoral analysis of AUCs for early glaucoma was performed, the upper and lower 2 sectors were found to have the highest AUCs. Most studies have also shown that the lower (AUC = 0.83 ± 0.03) and upper (AUC = 0.87 ± 0.1) sectors are the most promising for discriminating early glaucoma. Even though OCT-A may be useful in the diagnosis of early glaucoma it's not superior to structural OCT with AUCs that are either comparable [16–21] or significantly lower [14–22]. This finding may suggest that there are smaller or relatively delayed changes in vascular density compared to the damage of the RNFL in early glaucoma.

In the study of the relation structure-vascularization-function we

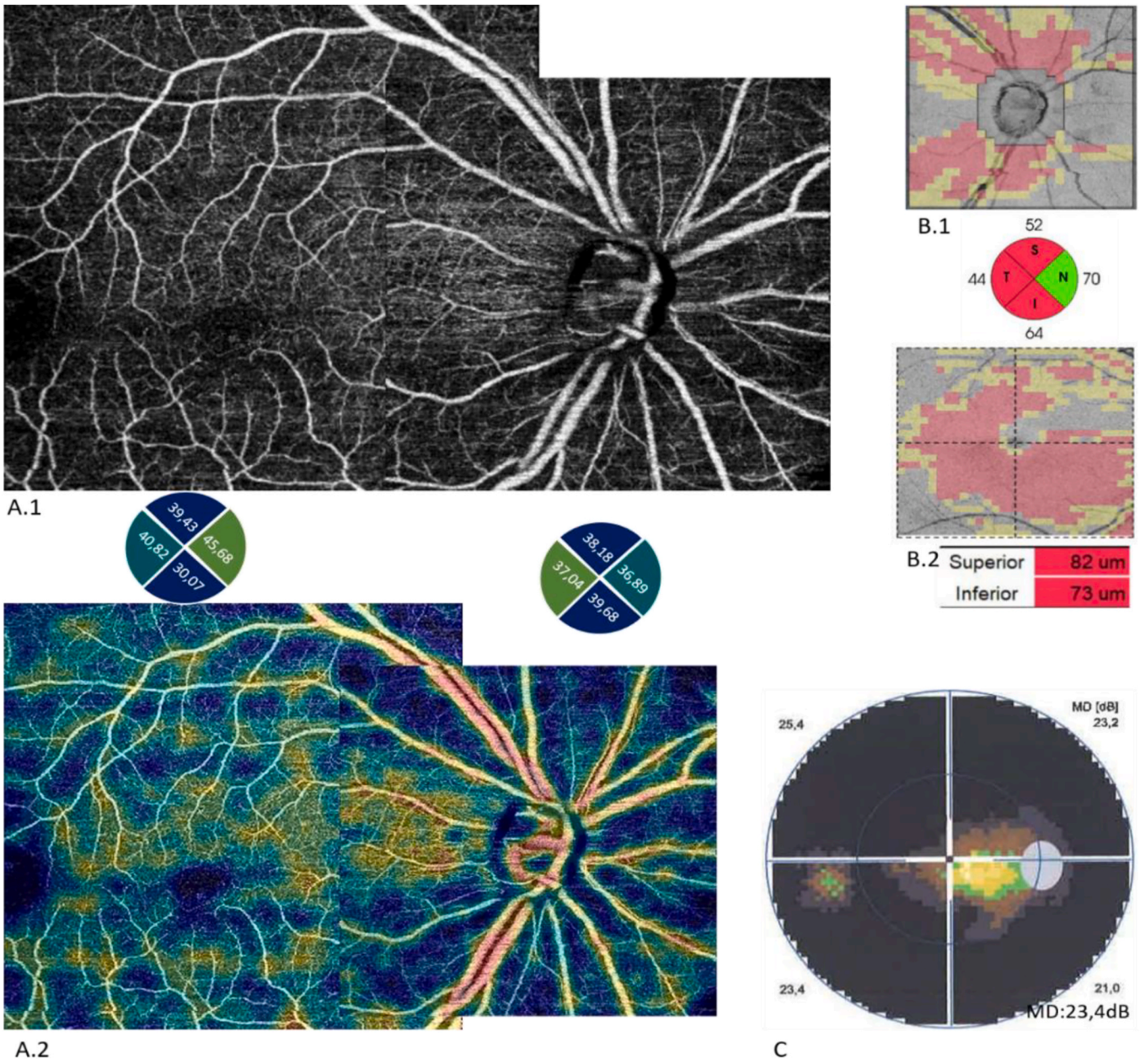

Fig. 3. Association of vascular defect (A), RNFL (B1), GCC (B2) thinning, visual field damage (C) in early glaucoma.

Table 5
Correlation between the optical coherence tomography angiography vessel density parameters and other parameters in the glaucomatous eyes.

	DVipe	DVp	DVpp	DVime	DVpf
MD	0.826 (<0.001)	0.464 (<0.001)	0.875 (<0.001)	0.824 (<0.001)	0.756 (<0.001)
LV	0,748 (<0,001)	0,413 (<0,001)	0,742 (<0,001)	0,796 (<0,040)	0,727 (<0,001)
RNFL	0.814 (<0.001)	0.424 (<0.001)	0.852 (<0.001)	0.728 (<0.001)	0.757 (<0.001)
CCG	0.690 (<0.001)	0.453 (<0.001)	0.801 (<0.001)	0.583 (<0.001)	0.762 (<0.001)

Variables are presented as the Spearman's rank correlation coefficient (r) with P values in the parentheses.

Table 6
Comparison of linear model and quadratic model for the evaluation of the association between function, structure, and vascularization.

	Model		Linear	Model		Quadratic
	R2	p	Adjusted R2	R2	p	Adjusted R2
RNFL vs MD	0.740	<0.001	0.739	0.776	<0.001	0.774
DVpp vs RNFL	0.739	<0.001	0.738	0.765	<0.001	0.763
DVpp vs MD	0.810	<0.001	0.809	0.835	<0.001	0.833
DVpf vs MD	0.656	<0.001	0.655	0.661	<0.001	0.658

have demonstrated the existence of a topographic association between the location of vascular damage, structural defects and functional deficits detected by visual field. Quantitatively, significant correlations, similarly to the literature, were found between these different parameters with a more consistent correlation between the OCT-A parameters and visual field indices than with the structural parameters [23–25]. It

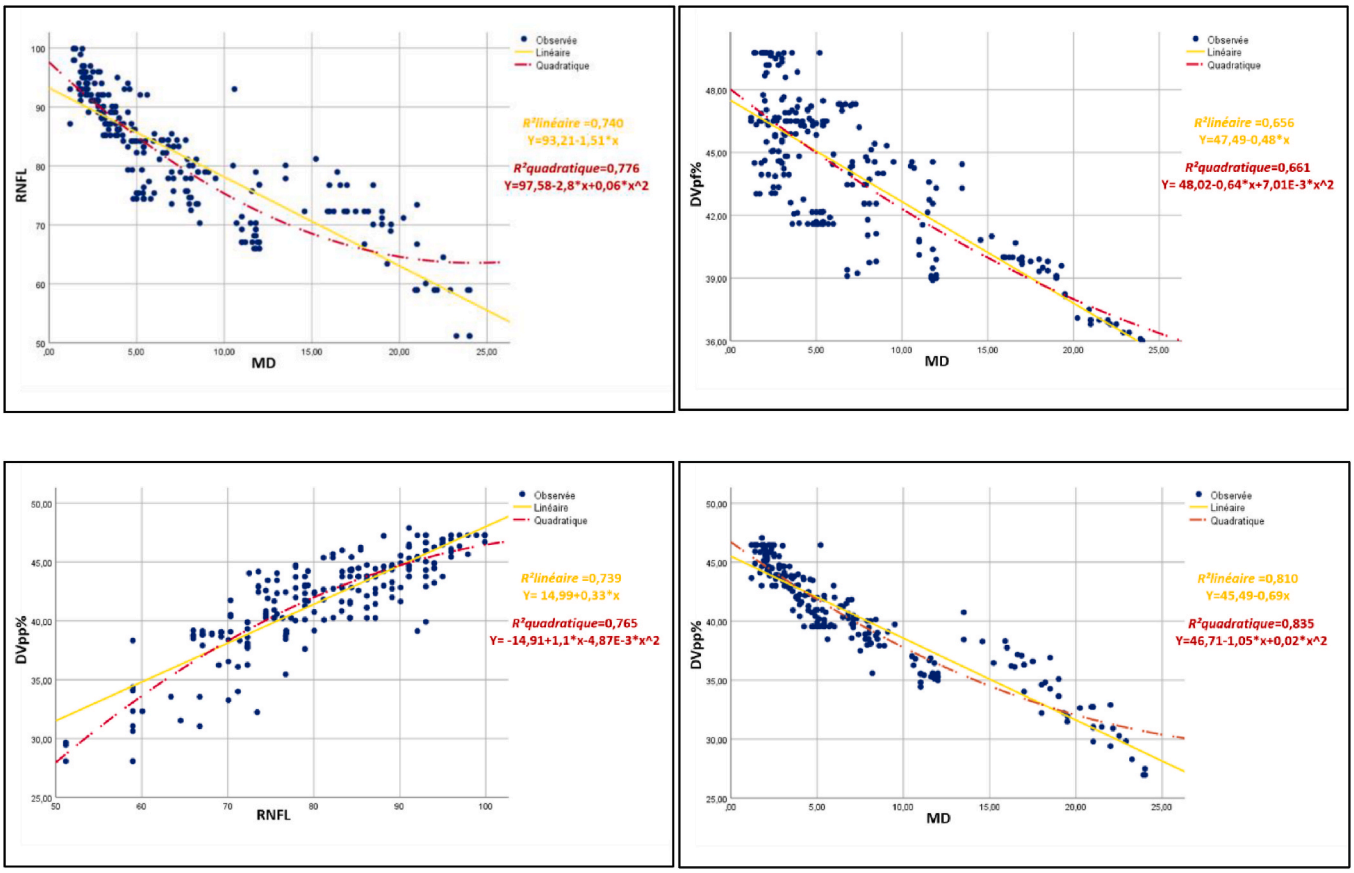

Fig. 4. Point cloud illustrating the linear and curvilinear correlation between structural, functional and vascular parameters.

was also found that the nature of the relationship between these three parameters is curvilinear rather than linear.

There is little in the literature on the nature of this relationship. Yarmohamadi et al. [24] in their study found that the quadratic model provides a better fit for the relationship between vessel density, RNFL thickness and MD than the linear model.

Rao and al. [26] used the fractional polynomial model instead of the quadratic model. They found that this model better and significantly described the structure-vascularization, vascularization-function and structure function relationships.

Analysis of the point clouds of the structure-vascularization and vascularization function relationships has shown a different behavior through the stages of severity of glaucoma. In our study the relationship between ppVD with MD was more linear in early glaucoma than with RNFL when MD was less then 6 dB. A similar finding was reported by song et al. [27] who used a nonlinear statistical broken-stick model and showed that the relationship between the ppVD and MD is more linear in the early stage of glaucoma and stronger with MD than with RNFL thickness. This suggests that in early glaucoma ppVD may have a potential role in monitoring visual function in eyes with onset glaucoma especially for those who can not perform a good quality visual field. In our study in advanced glaucoma, changes in ppVD and RNFL become slower than changes in MD and are indistinguishable from 20 dB for ppVD and 17 dB for RNFL. We also noted that from 20 dB the decrease in pfVD is almost linear with glaucoma severity.

Rao an al. [26] showed that the ppVD reached a measurement floor at a MD about 15 dB while RNFL reached this level with a loss of visual sensitivity of 10–15 dB. Moghimi and al. [28] found values of measurement floor at 19.5 dB for ppVD and 14 dB for RNFL. These researchers demonstrated that the density of pfVD was the least likely parameter to reach a measurement floor compared to ppVD and RNFL. Although the measurement floor values differ from one study to another because of the severity of glaucoma at this stage, this means that the RNFL thickness reaches its baseline level or floor effect before ppVD and pfVD. It can be concluded that even in advanced glaucoma both ppVD and pfVD allow a better monitoring of the visual function than RNFL or GCC thickness.

There are some limitations in this study. We didn't exclude patients with systemic vascular disease which could affect the retinal blood flow. Most participants in glaucoma groups were using topical IOP-lowering medications at the time of OCT angiography imaging. When interpreting the OCT angiography parameters, the effect of IOP lowering medication should be considered. We didn't include suspects of glaucoma in our study. This could have demonstrated more the role of OCT-A in detecting glaucoma. Another limitation is that the manual procedure for calculating vascular density is a time-consuming, impractical and could be misleading and a source of bias.

However, the strength of our study consists in the large sample studied, the high resolution of the Swept-Source Oct angiography. Also, our study represents the first study that validates the automatic OTSU screening method for calculating vascular density.

5. Conclusion

The OCT-A vascular parameters provide important information for clinical management of the PAOG, they may be included in the routine of monitoring of glaucoma along with structural OCT and visual field test. The OCT-A also helped as understand some aspects of the vascular damage found in PAOG. However, we have not been able to determine the causal link between the structural, vascular, and functional parameters. Longitudinal studies are therefore needed to determine how retinal vascularization is involved in the physiopathology of glaucoma.

Declaration of competing interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Sources of funding

No sponsors involvement.

Ethical approval

Approval has been given.

Consent

Oral informed consent was obtained from the subjects to participate in this study.

Author contribution

Oumaima Khayrallah: study conception, data collection, writing the paper. Ahmed Mahjoub: data analysis, writing the paper. Nadia Ben Abdesslam: data collection and analysis. Anis Mahjoub: data collection. Mohamed Ghorbel: data interpretation. Leila Knani: writing the paper. Fathi Krifa: study design. Hachmi Mahjoub: study design.

Registration of research studies

1. Name of the registry: Research registry
2. Unique Identifying number or registration ID: researchregistry6898
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Dr Oumaima Khayrallah.

Provenance and peer review

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102671.

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