Diagnostic Accuracy and Relationship Between Optical Coherence Tomography Angiography Vessel Density and Structural/Functional Parameters in Healthy, Preperimetric, and Manifest Glaucoma Eyes

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Abstract

Purpose: To evaluate circumpapillary vessel density (cpVD) in normal subjects, preperimetric glaucoma, and manifest glaucoma, assess the relationship between cpVD and both structural and functional parameters and compare the diagnostic accuracy of the structural and vascular measurements.

Methods: An analytical cross-sectional study of 153 eyes of 83 individuals divided into three groups: Normal subjects, preperimetric glaucoma, and manifest glaucoma. All individuals underwent standard automated perimetry, spectral-domain optical coherence tomography (SD-OCT), and OCT angiography (OCT-A) centered on the optic nerve. We assessed structural (ganglion cell complex [GCC]/retinal nerve fiber layer [RNFL]) and functional parameters (mean deviation [MD]/loss variance [LV]).

Results: Thirty-three normal subjects (66 eyes), 18 patients (30 eyes) with preperimetric glaucoma, and 32 patients (57 eyes) with manifest primary open-angle glaucoma were enrolled. The comparative study of cpVD showed a significant difference comparing glaucomatous subjects versus preperimetric glaucoma (P = 0.025) groups and normal subjects (P < 0.001). The cpVD was strongly correlated with functional parameters, MD, and LV (P < 0.001). Furthermore, cpVD was better correlated with RNFL (P < 0.001) than GCC (P < 0.001). Best regression was observed with mean RNFL (R² = 0.752). The cpVD has a higher diagnostic value than RNFL and GCC, only between preperimetric and manifest glaucoma.

Conclusions: Circumpapillary vessel damages seem to be less prominent, as it was seen only for the manifest glaucoma group. Microvascular changes appear to occur secondary to RNFL and GCC damages. They seem to be well correlated with visual function. Therefore, OCT-A is not as sensitive as SD-OCT in detecting early structural alterations.

Keywords: Optical coherence tomography, Primary open-angle glaucoma, Retinal ganglion cells, Retinal nerve fibers, Vascular density, Visual field

INTRODUCTION

Primary open-angle glaucoma is a chronic progressive optic neuropathy characterized by a progressive loss of retinal ganglion cells and visual field (VF) impairment.1 Spectral-domain optical coherence tomography (SD-OCT) has revolutionized the approach of glaucoma. It allows objective...
OCT angiography (OCT-A) coupled with SD-OCT technology visualizes retinal vascular structures and quantifies circumpapillary vessel density (cpVD) since interest in the vascular component has increased for a better understanding of glaucoma pathogenesis. A reliable clinical method for imaging circumpapillary vascular structure and the comparison between normal subjects, preperimetric, and manifest glaucoma patients would improve our knowledge about the sequential relationship of glaucoma structural damages and their importance in glaucoma assessment. The aim of this study was to compare and assess GCC, RNFL, and cpVD in normal subjects, preperimetric, and manifest glaucoma.

**METHODS**

We conducted a cross-sectional study over 2 years. The study was approved by the Tunisian main military instruction hospital institutional ethical committee. Informed consent was obtained from all the recruited individuals. We performed cpVD, RNFL, and GCC thickness analysis in three groups: healthy (66 eyes), preperimetric glaucoma (30 eyes), and manifest glaucoma (57 eyes), distributed as follows: 19 eyes had mild glaucoma (mean deviation [MD] better than –6 dB), 24 eyes had moderate glaucoma (MD between –6 and –12 dB), and 14 eyes had severe glaucoma (MD worse than –12 dB).

We randomly selected normal subjects from a cohort of nonglaucomatous individuals who met the inclusion criteria: age >40 years old, intraocular pressure (IOP) <21 mmHg, normal papillae on fundus examination, VF, and OCT examination without abnormalities.

The inclusion criteria for the manifest glaucoma group were open iridocorneal angle in the gonioscopic examination, glaucomatous changes of the optic disc (including neuroretinal rim thinning, disc hemorrhage, cupping, and notching), RNFL/GCC defect on SD-OCT, and consistent glaucomatous pattern on VF examinations.

Preperimetric glaucomatous subjects were those stated for the manifest glaucoma group but with normal VF.

Exclusion criteria were as follows: history of eye surgery (other than uncomplicated phacoemulsification cataract surgery, with a minimum postoperative duration of 6 months), presence of ophthalmological or other pathologies responsible for impaired vision or VF (uveitis, maculopathy, diabetic retinopathy, optic neuropathy, dense cataract, venous occlusion, retinitis pigmentosa, etc.), narrow iridocorneal angle in the gonioscopic examination, and all other forms of secondary open-angle glaucoma (posttraumatic, postuveitis, etc.).

We performed standard VF testing using automated standard white-on-white perimetry (Octopus 101 Haag-Streit USA, Inc.; program 24–2).

The test is reliable when fixation losses were <20%. False-positive and false-negative errors were <15%. Each VF defect was confirmed at least in two tests. A software calculated the mean value of VF sensitivity presented as MD and loss variance (LV).

In our study, we considered examination by an OCT-A imaging system (AngioVue; Optovue, Inc., Fremont, CA, USA) with eye-tracking gaze control. The examination was done within 30 days after or before the VF. We obtained the global cpVD and a sectoral analysis including superior-half vessel density (cpVD S–H), inferior-half vessel density (cpVD I–H), superior quadrant (cpVD S), temporal quadrant (cpVD T), inferior quadrant (cpVD I), and nasal quadrant (cpVD N). We measured GCC and RNFL thicknesses by SD-OCT. Optic nerve head mode determined RNFL thickness through data along a 3.45-mm diameter circle around the optic disc.

The GCC scan, centered 1 mm temporal to the fovea, covered a square grid (7 mm × 7 mm) on the central macula. The device measured GCC thickness from the internal limiting membrane to the outer inner plexiform layer boundary. It calculated mean, superior, and inferior GCC thicknesses. We only retained OCT signal strength index >50.

**Statistical analysis**

We tested distribution normality for numerical data by the Kolmogorov–Smirnov test. We calculated descriptive statistics using mean and standard deviation. We compared categorical variables using the Chi-square test. The Student’s t-test compared the means in the case of normal distribution.

Otherwise, we used the Mann–Whitney nonparametric test. To adjust within-subject variation of statistical data that contained both eyes of each individual, generalized estimating equation was used for comparison among the three eye groups.

We adopted the age-adjusted analysis of variance test to compare between groups. We used the Tukey–Kramer honestly significant difference post hoc test to adjust multiple comparisons between groups. Pearson correlation coefficient (r) evaluated correlations between quantitative variables.

Analysis of the relationship of cpVD with structural (RNFL and CCG) and functional (MD and LV) parameters used linear regression to understand the evolutionary profile of the disease. Diagnostic accuracy was tested by receiver operating characteristic (ROC) curves. For the analysis by eye, a between-cluster variance estimator was used to adjust for including both eyes of the same participant in the model. The area under the curves (AUCs) evaluated diagnostic accuracy differentiating between groups. A value of 1 represents perfect discrimination, and an AUC ≤0.5 shows that discrimination is not better than results obtained by chance.

We performed all statistical analyses with SPSS statistical software version 23.0 (SPSS Inc., Chicago, IL, USA) and Excel Microsoft Office. P values less than 0.05 were considered statistically significant.
RESULTS

Demographic, clinical, and ocular characteristics are represented in Table 1. The mean age in the healthy group was significantly lower than in both the manifest and preperimetric glaucoma groups \((P < 0.001)\). Therefore, all comparisons were adjusted for age differences between groups. Compared with preperimetric glaucoma and normal subjects, the manifest glaucoma group had significantly higher IOP \((P = 0.002)\). Central corneal thickness did not show a significant difference between the three groups \((P = 0.73)\). Furthermore, there were no statistically significant differences between family history, myopia, and vasospastic disorder. However, high blood pressure, diabetes, dyslipidemia, and coronary artery disease were statically different between healthy subjects and preperimetric and manifest glaucoma. Evaluation of tomographic and functional parameters (average cup/disc, average RNFL, average GCC, MD, and LV) showed significant differences among groups [Table 1].

Analysis of mean cpVD showed a nonsignificant difference comparing normal subjects and the preperimetric glaucoma group \((P > 0.05\), for all parameters). However, the difference was significant for all parameters between the manifest glaucoma group versus preperimetric glaucoma and normal subject groups [Table 2].

Pearson’s correlation study showed a significantly strong correlation between global cpVD and average RNFL and GCC. Sector correlations (cpVD S-H and cpVD I-H) were stronger with RNFL \((cpVD S-H; r = 0.792, P < 0.001)\) \((cpVD I-H; r = 0.838, P < 0.001)\) than GCC \((cpVD S-H; r = 0.578, P < 0.001)\) \((cpVD I-H; r = 0.662, P < 0.001)\). Similarly, global cpVD presented a significant correlation with functional parameters MD \((r = -0.701, P < 0.001)\) and LV \((r = -0.435, P < 0.001)\) [Table 3].

Average RNFL and both global and sector cpVD showed a statistically significant correlation in all groups studied separately. Average GCC significantly correlated with most parameters in the three groups except with cpVD S-H \((P = 0.058)\) in normal subjects and global cpVD \((P = 0.054)\) and cpVD I-H \((P = 0.118)\) in the preperimetric glaucoma groups [Table 4].

We observed the best regression fit with average RNFL \((R^2 = 0.752)\). The regression was moderate for MD \((R^2 = 0.492)\) and average GCC \((R^2 = 0.43)\). However, regression was weak and insignificant for LV \((R^2 = 0.182)\) [Figure 1].

We evaluated the diagnostic value by ROC curves [Figure 2]. The study of normal subjects and preperimetric glaucoma groups showed that the analysis of cpVD is not sufficiently contributory compared to RNFL and GCC. The value of AUC was low \((0.595–0.604) (P > 0.05)\). The comparison between normal subjects and manifest glaucoma groups showed that all parameters presented an acceptable diagnostic value. The diagnostic value of cpVD was relatively better than RNFL and GCC, comparing manifest glaucoma and preperimetric glaucoma groups, AUC \((0.637–0.668) (P < 0.05)\) [Table 5].

DISCUSSION

Liu was the first to demonstrate a significant cpVD reduction in glaucomatous eyes compared to normal eyes. In the current study, cpVD was significantly different, only comparing glaucomatous subjects with preperimetric glaucoma and normal subject groups.

These findings have been confirmed in numerous recent studies, showing a 25% reduction in the perfusion flow index in glaucomatous patients.6–9

Table 1: Characteristics of subjects

| Variables                        | Normal subjects \((n=33)\) | Preperimetric glaucoma \((n=18)\) | Manifest glaucoma \((n=32)\) | \(P\) |
|----------------------------------|----------------------------|-----------------------------------|----------------------------|------|
| Longevity of glaucoma (years)    | 1.38±2.14                  | 1.38±2.14                         | 5.47±4.76                  | <0.001* |
| Age (years)                      | 49.2±14.58                 | 53.2±9.43                         | 61.5±13.8                  | <0.001* |
| Family history (%)               | 21.2                       | 21.2                              | 14                         | 0.484 |
| Myopia (%)                       | 21.2                       | 19.6                              | 33.3                       | 0.294 |
| Diabetes (%)                     | 12.1                       | 27.5                              | 33.3                       | 0.017* |
| IOP (mmHg)                       | 15.2±3.24                  | 16.0±2.26                         | 17±2.71                    | 0.002* |
| High blood pressure (%)          | 21.2                       | 17.6                              | 50.9                       | <0.001* |
| Dyslipidemia (%)                 | 12.1                       | 15.7                              | 29.8                       | 0.007* |
| Coronary artery disease (%)      | 6.1                        | 3.9                               | 24.6                       | 0.002* |
| Vasospastic disorder (%)         | 9.1                        | 7.8                               | 8.8                        | 0.982 |
| Pachymetry (µm)                  | 513.8±19.12                | 515.7±24.03                       | 515.8±32.05                | 0.73  |
| MD (dB)                          | -0.436±0.5                 | -0.663±0.7                        | 9.46±6.91                  | <0.001* |
| LV (dB)                          | 1.77±0.88                  | 2.6±1.54                          | 22.41±19.81                | <0.001* |
| Average cup/disc                 | 0.33±0.13                  | 0.48±0.15                         | 0.525±0.23                 | <0.001* |
| Rim area (mm²)                   | 1.34±0.25                  | 1.2±0.33                          | 0.93±0.46                  | <0.001* |
| Average RNFL (µm)               | 102.26±8.32                | 94.8±7.9                          | 84.6±15.87                 | <0.001* |
| Average GCC (µm)                 | 101.48±9.94                | 94.2±14.41                        | 85.3±16.1                  | <0.001* |

*Statistically significant. \(P\): Degree of significance, IOP: Intraocular pressure, RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, MD: Mean deviation, LV: Loss variance.
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Table 2: Means and standard deviations of circumpapillary vessel density measurements in different groups

|                      | Normal subjects | Preperimetric glaucoma | Manifest glaucoma | cpVD comparison between groups (P) |
|----------------------|-----------------|------------------------|-------------------|-----------------------------------|
| Global cpVD          | 54.281±4.902    | 51.330±6.030           | 45.45±10.84       | 0.105†                             |
|                      |                 |                        |                   | <0.001‡                           |
|                      |                 |                        |                   | 0.04§                             |
| cpVD superior-half   | 54.255±3.366    | 52.073±6.129           | 46.99±10.62       | 0.129†                             |
|                      |                 |                        |                   | <0.001‡                           |
|                      |                 |                        |                   | 0.036‡                             |
| cpVD inferior-half   | 53.048±3.773    | 50.496±6.713           | 44.63±10.74       | 0.136†                             |
|                      |                 |                        |                   | <0.001‡                           |
|                      |                 |                        |                   | 0.11§                             |
| cpVD superior quadrant| 53.672±4.780   | 51.230±6.613           | 45.6±11.01        | 0.060†                             |
|                      |                 |                        |                   | <0.001‡                           |
| cpVD temporal quadrant| 55.733±3.258   | 52.933±7.531           | 45.8±11.11        | 0.345†                             |
|                      |                 |                        |                   | <0.001‡                           |
|                      |                 |                        |                   | 0.025‡                             |
| cpVD inferior quadrant| 53.790±4.992   | 51.355±8.599           | 43.66±10.66       | 0.479†                             |
|                      |                 |                        |                   | <0.001‡                           |
|                      |                 |                        |                   | <0.001‡                           |
| cpVD nasal quadrant  | 50.636±4.231    | 50.244±6.049           | 42.21±10.5        | 0.972†                             |
|                      |                 |                        |                   | <0.001‡                           |

†Difference between the group of normal subjects and preperimetric glaucoma, ‡Difference between the group of normal subjects and proven glaucoma, §Difference between the group of preperimetric glaucoma and proven glaucoma. cpVD: Circumpapillary vessel density, SD: Standard deviation

Table 3: Correlation between circumpapillary vessel density, structural, and functional parameters, in the total group

|                      | RNFL (r, P)   | GCC (r, P)   | MD (r, P)    | LV (r, P)    |
|----------------------|---------------|--------------|--------------|--------------|
| Global cpVD          | 0.867, <0.001 | 0.662, <0.001| −0.754, <0.001| −0.458, <0.001|
| cpVD superior-half   | 0.792, <0.001 | 0.578, <0.001| −0.758, <0.001| −0.443, <0.001|
| cpVD inferior-half   | 0.838, <0.001 | 0.662, <0.001| −0.774, <0.001| −0.452, <0.001|

cpVD: Circumpapillary vessel density, RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, MD: Mean deviation, LV: Loss variance, P: Degree of significance, r: Correlation coefficient

However, in later studies,5-9 there is no explanation for the sequential relationship between cpVD and retinal neuron degeneration. Based on our results, the cpVD comparative study revealed an absence of difference between normal subjects and preperimetric glaucoma patients. This allows us to suggest that the reduction of cpVD could occur after RNFL damage.

A correlation study showed that cpVD was better correlated with RNFL than GCC. Therefore, cpVD is more closely related to RNFL than ganglion cells. In addition, it strongly correlated with functional parameters. Thereby, vessel density seems to be also related to visual function.

Our results were consistent with the study by Wang that showed a significant correlation between cpVD and disease severity.8 These observations were corroborated by other studies.9,10

Our findings suggest that vascular density is more correlated with RNFL thickness than with visual function.

Peripapillary capillaries come from the precapillary arterioles of the posterior pole. They are intimately associated with the RNFs, of which they represent the main nourishing source. They have a longer and straighter path with few anastomoses as well as a parallel disposition to the RNF.

These findings were consistent with Akagi study that showed the concordance between perimeter alteration and impairment of the corresponding cpVD. However, RNFL decrease has been observed even outside the functional areas.11 Therefore, glaucoma appears to be responsible for a synchronous Wallerian-type degeneration, independent of apoptosis. It would explain axonal rarefaction and secondarily lead to somatic atrophy and neuronal death.12

Therefore, we could hypothesize that affected retinal ganglion cells might have reduced perfusion before apoptosis actually occurs, explaining the strong correlation with VF measurements. Thus, this allows the clinician to detect the affected ganglion cells and therefore initiate effective treatment as quickly as possible to lower IOP.

In the present study, the best regression fit was obtained when cpVD was plotted against RNFL. The association was less...
when plotted with MD and GCC. These results were consistent with other publications.\textsuperscript{8,10,13}

In the same perspective, the study of Yarmohammadi showed a good association between cpVD and MD. Thus, each 1% decrease in cpVD was associated with a loss of 0.64 dB in MD.\textsuperscript{14}

The histological analysis of Henkind explained the predictive nature of cpVD for structural (RNFL) and functional (MD) damage. He demonstrated that radial peripapillary capillaries (RPC) are limited in their distribution to the posterior pole, intimately associated with superficial nerve fibers. RPCs probably nourish the inner part of the nerve fiber layer around the disc, and this is where the nerve fibers are the thickest.

According to Wolff and Penman, the innermost nerve fibers near the disc derive from the posterior pole ganglion cells. The latter represents the nerve fibers supplemented by the RPC layer.\textsuperscript{15}

CpVD presented a better diagnostic value only between the preperimetric and manifest glaucoma groups. For other comparisons, it has a moderate diagnostic value compared to the RNFL and the GCC. Other publications reported similar results.\textsuperscript{8-10,13,16,17} These studies have also shown that the diagnostic value of cpVD increases with the severity of glaucoma.\textsuperscript{17}

These findings indicate that cpVD appears to have limited discriminatory capacity compared to SD-OCT in the diagnosis of early-stage glaucoma, thus suggesting that the vascular

| Table 4: Correlation between circumpapillary vessel density and, average retinal nerve fiber layer, ganglion cell complex, mean deviation, and loss variance in the three groups |
|---------------------------------------------------------------|
| Normal subjects (r, P) | Preperimetric glaucoma (r, P) | Manifest glaucoma (r, P) |
|-------------------------|-----------------------------|-------------------------|
| **Global cpVD**         |                             |                         |
| RNFL                    | 0.644, <0.001               | 0.865, <0.001           | 0.888, <0.001           |
| GCC                     | 0.346, 0.004                | 0.356, 0.054            | 0.731, <0.001           |
| MD                      | 0.216, 0.334                | −0.023, 0.903           | −0.756, <0.001          |
| LV                      | 0.111, 0.621                | 0.097, 0.611            | −0.269, 0.043           |
| **cpVD superior-half**  |                             |                         |
| RNFL                    | 0.381, 0.002                | 0.782, <0.001           | 0.829, <0.001           |
| GCC                     | 0.234, 0.058                | 0.373, 0.042            | 0.651, <0.001           |
| MD                      | 0.199, 0.374                | −0.009, 0.962           | −0.757, <0.001          |
| LV                      | 0.140, 0.534                | 0.083, 0.663            | −0.266, 0.046           |
| **cpVD inferior-half**  |                             |                         |
| RNFL                    | 0.619, <0.001               | 0.777, <0.001           | 0.870, <0.001           |
| GCC                     | 0.258, 0.038                | 0.291, 0.118            | 0.749, <0.001           |
| MD                      | 0.209, 0.352                | −0.041, 0.830           | −0.763, <0.001          |
| LV                      | 0.054, 0.812                | 0.116, 0.542            | −0.248, 0.062           |

RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, MD: Mean deviation, LV: Loss variance, cpVD: Circumpapillary vessel density, P: Degree of significance, r: Correlation coefficient

Figure 1: Regression study between circumpapillary vessel density (cpVD) and structural retinal nerve fiber layer (RNFL), ganglion cell complex (GCC)/functional mean deviation (MD), loss variance (LV) parameters, (a) Regression between global cpVD and RNFL, (b) Regression between global cpVD and MD, (c) Regression between global cpVD and GCC, (d) Regression between global cpVD and LV.
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Table 5: Assessment of the diagnostic value of circumpapillary vessel density compared to retinal nerve fiber layer, ganglion cell complex, mean deviation, and loss variance

|                          | Normal subjects versus preperimetric glaucoma | Normal subjects versus manifest glaucoma | Manifest glaucoma versus preperimetric glaucoma |
|--------------------------|-----------------------------------------------|----------------------------------------|-------------------------------------------------|
| **AUC**                  | **P**                                         | **AUC**                                 | **AUC**                                         |
| Global cpVD              | 0.608                                         | 0.090                                  | 0.668                                           |
| cpVD superior-half       | 0.604                                         | 0.106                                  | 0.637                                           |
| cpVD inferior-half       | 0.599                                         | 0.121                                  | 0.666                                           |
| Average RNFL             | 0.822                                         | <0.001                                 | 0.618                                           |
| RNFL superior-half       | 0.761                                         | <0.001                                 | 0.654                                           |
| RNFL inferior-half       | 0.825                                         | <0.001                                 | 0.609                                           |
| Average GCC              | 0.815                                         | <0.001                                 | 0.587                                           |
| GCC superior-half        | 0.816                                         | <0.001                                 | 0.561                                           |
| GCC inferior-half        | 0.818                                         | <0.001                                 | 0.592                                           |
| MD                       | 0.589                                         | 0.100                                  | 1                                               |
| LV                       | 0.306                                         | <0.001                                 | 0.948                                           |

RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, MD: Mean deviation, LV: Loss variance, cpVD: Circumpapillary vessel density, P: Degree of significance, AUC: Area under the curve

...system is not likely the primary target for glaucomatous disease and that the loss of RNF is independent of vascular alterations.

In this regard, one can hypothesize that this mismatch of structure/vascular density indicates that neurodegeneration occurs before vascular damage. Therefore, vessel damage may be secondary to loss of RNF, confirming the results observed previously.

Another explanation is that OCT-A might not be as sensitive as SD-OCT in detecting early changes and thus might miss a subtle depletion of vascular capillaries. Additional longitudinal studies are essential to answer this question.13

It is important to note that our study has certain limitations. First, we did not exclude subjects based on their systemic pathologies or the nature of their treatments. In fact, the antiglaucoma eye drops effects require 1–4 weeks to wash out. Thus, for ethical and medical reasons, the glaucomatous patients in the present study did not stop using antiglaucoma treatments at the time of the examination. Therefore, the glaucomatous eyes in the current study should be better defined as medically treated glaucomatous eyes. We should consider their effect on interpreting parameters of OCT-A.17

Furthermore, we did not investigate the balance of blood pressure and the intake of antihypertensive drugs. Thus, we
cannot exclude the effect of blood pressure and systemic medication on the peripapillary vascular density.

Furthermore, patients with manifest glaucoma were significantly older than normal and preperimetric glaucoma subjects, which can explain differences observed when analyzing glaucoma systemic factors. Although we accounted for this difference during statistical analysis, it would have been ideal to match the groups during recruitment.

Last, bias might exist in patient selection. In fact, owing to the difficulty, we encountered in recruiting normal subjects during the COVID-19 pandemic, the sample size was smaller than we had originally planned. Thereby imposing sometimes, the recruitment of normal subjects from relatives accompanying glaucomatous patients could explain the overestimation of the frequency of glaucoma family history.

In summary, circumpapillary vessel damages seem to be less prominent, as it was seen only for the manifest glaucoma group. Microvascular changes appear to occur secondary to RNFL and GCC damages. Therefore, OCT-A is not as sensitive as SD-OCT in detecting early structural alterations but presents an incontestable contribution for follow-up and detection of glaucoma progression.

However, further studies excluding the effects of systemic factors and glaucoma medications are needed to investigate the relationship between circumpapillary vessel changes and glaucomatous damages.

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Conflicts of interest
There are no conflicts of interest.

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