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**Peripapillary and optic nerve head vessel density of glaucoma and healthy subjects from Afro-Caribbean and European descent: A pilot study.**

**Densité des vaisseaux péripapillaires et de la tête du nerf optique des sujets avec glaucome et sains d'origine afro-caribéenne et européenne : une étude pilote.**

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## **Abstract**

**Purpose:** To compare the peripapillary and optic nerve head vessel density (PP-ONH VD) between Afro-Caribbean descent (AD) and European descent (ED) healthy and glaucoma subjects (all, early, moderate, and advanced).

**Methods:** It is a cross-sectional study. One eye was evaluated for 90 subjects which included 66 glaucoma patients and 24 healthy subjects who underwent imaging of PP-ONH VD using SPECTRALIS® OpticalCoherence Tomography Angiography (OCT-A). We analysed superficial vascular complex using the AngioTool version 0.6a software. The correlation between the PP-ONH VD and the mean deviation of visual field assessment was evaluated using scatter plot and Rho Spearman.

**Results:** Among healthy subjects, AD had a lower superficial PP-ONH VD [ $43.29 \pm 3.25\%$  (mean  $\pm$  standard deviation)] than ED ( $46.06 \pm 1.75\%$ ) ( $P = 0.016$ ). Overall, superficial PP-ONH VD did not show any significant differences between all AD and ED glaucoma patients and in the subgroup analyses (**early/moderate/advanced**) (AD:  $32.73 \pm 6.70\%$ ,  $37.11 \pm 5.72\%$ ,  $32.48 \pm 5.73\%$ ,  $27.76 \pm 4.74\%$ , respectively; ED:  $33.94 \pm 6.89\%$ ,  $38.52 \pm 3.82\%$ ,  $35.56 \pm 4.18\%$ ;  $27.65 \pm 6.31\%$ , respectively) ( $P > 0.05$  for all). A strong and statistically significant

correlation was established between vessel density and mean deviation among AD and ED glaucoma patients described as ( $r = 0.709$  and  $r = 0.704$ , respectively) ( $p < 0.001$  for both).

**Conclusion:** This pilot study showed that AD healthy subjects had a lower peripapillary and optic nerve head of superficial vessel density than ED healthy subjects, but no significant differences were found between AD and ED glaucoma groups (all, **early**, moderate, and advanced).

**Keywords:** Peripapillary vessel density, Optical Coherence Tomography Angiography (OCT-A), Afro-Caribbean and European descent, Glaucoma.

## Résumé

**Objectif:** Comparer la densité des vaisseaux péripapillaires et de la tête du nerf optique (PP-ONH VD) **chez les sujets sains et glaucomateux (tous, débutant, modérés et avancés) d'ascendance afro-caribéenne (AD) et d'ascendance européenne (ED).**

**Méthodes:** Il s'agit d'une étude transversale. Un œil est évalué pour 90 sujets, dont 66 patients atteints de glaucome et 24 sujets sains à ceux qui ont une photo de PP-ONH VD avec l'aide de l'angiographie par tomographie par cohérence optique SPECTRALIS® (OCT-A). Nous avons analysé le complexe vasculaire superficiel avec l'aide du logiciel AngioTool version 0.6a. La corrélation entre PP-ONH VD et l'écart moyen (DM) du champ visuel a été évaluée par nuage de points et Rho Spearman.

**Résultats:** Parmi les sujets sains, la AD avait une PP-ONH VD superficielle inférieure [ $43,29 \pm 3,25\%$  (moyenne  $\pm$  écart-type)] que la ED ( $46,06 \pm 1,75\%$ ) ( $P = 0,016$ ). Dans l'ensemble, la PP-ONH VD superficielle n'a pas montré de différences significatives entre tous les patients atteints de glaucome AD et ED et dans l'analyse en sous-groupe (léger / modéré / avancé) (AD:  $32,73 \pm 6,70\%$ ,  $37,11 \pm 5,72\%$ ,  $32,48 \pm 5,73\%$ ,  $27,76 \pm 4,74\%$ , respectivement; ED:  $33,94 \pm 6,89\%$ ,  $38,52 \pm 3,82\%$ ,  $35,56 \pm 4,18\%$ ;  $27,65 \pm 6,31\%$ , respectivement) ( $P > 0,05$  pour tous).

Nous établissons une corrélation forte et statistiquement significative entre le VD et l'écart moyen chez les patients atteints de glaucome AD et ED décrits comme ( $r = 0,709$  et  $r = 0,704$ , respectivement) ( $p < 0,001$  pour les deux).

**Conclusion:** Cette étude pilote a montré que les sujets sains AD avaient une tête de nerf péripapillaire et optique inférieure de densité de vaisseaux superficiels que les sujets sains ED, mais aucune différence significative n'a été trouvée entre les groupes de glaucome AD et ED (tous, **débutant**, modérés et avancés).

**Mots clés:** Densité des vaisseaux péripapillaires, angiographie par tomographie par cohérence optique (OCT-A), descendance afro-caribéenne et européenne, glaucoma.

## **Introduction**

Glaucoma is the leading cause of irreversible blindness in the world and the management of glaucoma is more challenging in patients of African descent (AD). AD patients show a higher frequency of open-angle glaucoma (OAG) likewise faster progression, greater severity and earlier onset than patients of European descent (ED).[1,2] Another important difference between the two groups is that AD patients have more systemic vascular diseases (arterial hypertension, cardiovascular disease, stroke, diabetes mellitus), but the cause remains unknown.[3] Some of the ocular structural abnormalities in the AD glaucoma patients are explained by the larger optic disc areas, larger cup-to-disc ratios, thinner corneas, deeper maximum cup depth and lower retrobulbar blood flow,[4] but no differences have been found in aqueous humour dynamics.[5]

The vascular factor plays a role in the onset and progression of OAG, characterized by ocular blood flow deficiencies in retinal, choroidal and retrobulbar circulation, decreased ocular perfusion pressure (OPP)[6], and reduced peripapillary and macular vessel density.[7–9]

However, recent controversy publications **show** peripapillary vascular differences between AD and ED glaucoma and healthy subjects.[10,11] This pilot study was designed to compare the peripapillary (PP) and optic nerve head (ONH) vessel density (VD) among two ethnicity AD and ED glaucoma subjects in one hand and in the other hand between AD and ED healthy subjects.

## **Materials and methods**

### ***Participants***

It is a pilot study and cross-sectional study where we selected a total of 90 subjects by consecutive sampling, which consisted of 66 glaucoma patients and 24 healthy subjects from the glaucoma service at St Thomas' Hospital (London, UK) and Clinico San Carlos Hospital (Madrid, Spain) from July 2018 to September 2019. One eye of every subject was included. This study was approved by the London Fulham Research Ethics Committee, the R&D Department of Guy's and St Thomas' NHS Foundation Trust and the Ethical Committee on Clinical Research of the Hospital Clinico San Carlos of Madrid. Informed consent was carried out following the tenets of the Declaration of Helsinki and was obtained from all participants. The inclusion criteria for glaucoma patients were age >18 years and diagnosis of primary open-angle glaucoma. The inclusion criteria for control subjects were age >18 years with no history of glaucoma, ocular hypertension or other ocular pathology, trauma or surgery and normal optic nerve. The exclusion criteria for all participants consisted of large refractive errors ( $> \pm 4D$  sphere or  $> 2D$  cylinder), concomitant ocular disease (excluding early cataract), severe dry eye, ocular arterial or venous obstruction (branch or central occlusion), chronic autoimmune diseases, Parkinson disease, Alzheimer disease or dementia. Demographic data on ethnicity, sex and age were also collected for this purpose.

### ***Clinical examination***

All subjects with glaucoma underwent a comprehensive ophthalmologic examination, including best corrected visual acuity, slit-lamp biomicroscopy, pachymetry, Goldmann applanation tonometry, and funduscopy. Optic disc was also evaluated for the healthy subjects.

### ***Optical Coherence Tomography Angiography (OCT-A) evaluation***

All the participants underwent SPECTRALIS®OCT Angiography (OCT-A) Module (Heidelberg Engineering, Heidelberg, Germany), which used an active eye-tracking system (TruTrack™). This provided a resolution of 5.7 microns per pixel transversally in both direction for the visualisation of capillaries, and an axial resolution of 3.9 microns per pixel which enables precise multilayer segmentation. The image size was 10 degrees x 10 degrees[12] that included the optic nerve head (ONH) and peripapillary (PP) area. Superficial vascular complex (SVC), constituted by nerve fibre layer and superficial vascular plexus, and deep vascular complexes (DVC), compounded by intermediate and deep capillary plexuses, were also examined by this device.[13]

### ***Image processing***

No dilation was required for the OCTA scans. The subjects were asked to focus on the external fixation target to scan the optic nerve. Only images with acceptable quality without artefacts, such as motion, blurry, vitreous floaters or peripapillary atrophy, were selected by the researcher and included in this study. Due to the many artefacts of DVC, only the SVC images were selected and analysed them using the software AngioToolSetup64.exe (version 0.6a [64 bits], October 2014). SVC (Superficial vascular complexes) were included from internal limiting membrane (ILM), Retinal nerve fibre layer (RNFL), Ganglion cell layer (CGL), to superficial Inner plexiform layer (IPL).[13] Vessel density (VD) was the proportion of flowing

vessel area over the total evaluated area and were measured in percentages of VD (Figure 1).[14]

### ***Visual Field (VF) Testing***

VF tests to determine the mean deviation (MD) were performed with the help of Humphrey Field Analyzer II (Carl Zeiss Meditec, Inc., Dublin, CA, USA) using 24-2 threshold test and standard SITA algorithm. Glaucoma severity was classified as **early** ( $MD > -6$  dB), moderate ( $MD \leq -6$  to  $\geq -12$  dB) or advanced ( $MD < -12$  dB).[15]

### ***Statistical analyses***

Data was shown in mean and standard deviation (SD). Shapiro-Wilk test or Kolmogorov-Smirnov-Lilliefors was used to find normality data distribution. Chi-square test or Fisher test was used in order to compare proportions of categorical variables, and Student's t-test or Mann-Whitney U test was applied to analyze means of quantitative and categorical variables. Correlations between PP-ONH VD and MD were evaluated using a scatter plot and Rho Spearman. Subsequently, Kruskal Wallis test was used to compare mean values among subgroups of glaucoma severity (**early**, moderate and advanced). All analyses were performed with statistical software IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Statistical significance was set at  $P < 0.05$ . Statistically significant differences with P values lower than 0.001 was expressed as  $P < 0.001$ .

## **Results**

### ***Patient baseline characteristics***

Analysis were performed on 90 eyes subjects which included 66 eyes glaucoma patients (divided into 33 AD and 33 ED) and 24 eyes healthy subjects (distributed in 12 AD and 12 ED).

Glaucoma subjects were subdivided based on its severity depending on Hodapp-Parrish classification.[15] Thus, each AD and ED glaucoma group included 14 **early** glaucoma, 7 moderate glaucoma and 12 advanced glaucoma eye cases.

Baseline characteristics in AD and ED of all glaucoma and healthy subjects showed that AD and ED glaucoma group had no statistically significant differences in terms of age, gender, number of glaucoma medications and surgeries, visual acuity, VF mean deviation (MD), central corneal thickness (CCT), cup-to-disc ratio (C/D) and mean IOP. Otherwise, AD and ED glaucoma group had significant differences for treatment with prostaglandin analogues (PGs) ( $P = 0.046$ ), carbonic anhydrase inhibitors (CAIs) ( $P=0.006$ ) and trabeculectomy surgery ( $P = 0.001$ ) for ED. The AD and ED healthy group was similar in age and gender (Table I).

Baseline characteristics of AD and ED glaucoma subgroups (**early**, moderate and advanced) showed significant differences in CAIs ( $P = 0.025$ ) as well as in selective laser trabeculoplasty (SLT) procedure ( $P = 0.005$ ) for advanced glaucoma but no significant differences were found in the rest of data (Table II).

### ***Peripapillary and ONH Vessel Density of AD and ED glaucoma and healthy subjects***

Vessel density analysis showed that AD healthy subjects had significantly lower mean superficial PP-ONH VD than ED healthy subjects ( $43.29 \pm 3.25\%$ ;  $46.08 \pm 1.75\%$ ,  $P < 0.016$ ) (Figure 2, Table I).

No statistically significant differences were found on PP-ONH VD between AD glaucoma groups (all glaucoma  $32.73 \pm 6.70\%$ , **early**  $37.11 \pm 5.72\%$ , moderate  $32.48 \pm 5.73\%$  and advanced  $27.76 \pm 4.74\%$ ) and ED glaucoma groups (all glaucoma  $33.94 \pm 6.89\%$ , **early**  $38.52 \pm 3.82\%$ , moderate  $35.56 \pm 4.18\%$  and advanced  $27.65 \pm 6.31\%$ ) ( $P = 0.471, 0.450, 0.277, 0.963$ , respectively) (Tables I, II).

AD and ED glaucoma showed lower value in the advanced glaucoma subgroup ( $27.70 \pm 5.46\%$ ) as compared to the moderate glaucoma ( $34.02 \pm 5.07\%$ ) and **early** glaucoma ( $37.82 \pm 4.83\%$ ) subgroups ( $P < 0.001$ , for both AD and ED) (Figure 2).

### *Correlation between disc vascular density and severity of glaucoma*

A strong and statistically significant linear correlation was found between superficial PP-ONH VD and VF MD in all AD ( $r = 0.709$ ,  $P < 0.001$ ) and ED ( $r = 0.704$ ,  $P < 0.001$ ) glaucoma patients (Figures 3, 4).

## **Discussion**

Our results showed lower superficial PP-ONH VD in AD healthy subjects compare to ED healthy subjects ( $P = 0.016$ ), but among AD and ED glaucoma groups (all, **early**, moderate and advanced), we did not find statistically differences ( $P = 0.27-0.96$  range). These contradictory results could be explained by the influence of others factors such as age,[16,17] vascular disease,[18,19] hypotensive drops,[20,21] autoregulation mechanism,[22] and small sample as part of a pilot study.

Recently and similar to our study, Taylor et al did not found significant differences in peripapillary and macula microcirculation blood flow metrics between AD and ED glaucoma patients,[10] but Moghimi et al reported lower peripapillary vessel density in European glaucoma patients as compared to African descent.[11] Siesky et al showed significantly lower peak systolic velocity in retrobulbar blood vessels in AD compared with ED **early** OAG patients, which probably highlights for localized vascular deficits, faulty vascular regulation, or systemic vascular disease in the AD population. The authors also found higher OPP in AD glaucoma but no differences in pourcelot vascular resistive index.[4]

Similarly for healthy groups, Kaskan et al found that retrobulbar blood flow is lower in healthy eyes of AD compared with ED people.[23] Chun et al studied macular differences between black and white subjects, and found that black subjects had a lower foveal VD in the superficial capillary plexus, lower parafoveal VD in deep capillary plexus, and decreased choriocapillaris blood flow area.[24]

Decreased vessel density as age increases has been reported by several studies.[16,17] Although, our study did not show statistical differences in age between AD and ED healthy and glaucoma groups, a younger age trend was recorded in ED healthy subjects but opposite of that, AD healthy subjects registered lower PP-ONH VD. These results showed that others factors could be involved in vascular supply like cardiovascular disease. Cao et al showed that diabetic patients with no signs of diabetic retinopathy also had a reduction in ONH vascular density.[18] Systemic hypertension was also associated with decreased macular perfusion density[25] but no differences were observed in peripapillary perfusion density.[26]

Hypotensive topical medication can affect vascular parameters. Fuchsjäger-Mayrlet al reported an increased blood flow in the ONH after treatment with dorzolamide, but not with timolol drops.[20] Kuryshvahas demonstrated increased OPP but decreased vessel density in the ONH of **early** glaucoma group after the use of PGs, which they explained by an autoregulation mechanism in the early stages of glaucoma but this does not apply to other stages of glaucoma.[21] In our study, the use of PGs and CAIs was greater in all glaucoma AD but it is difficult to assess the positive or negative influence of topical medications on vessel density since there are not enough studies to support it.

Another contributing factor in glaucoma is autoregulation in the ONH, thus ONH blood flow will be regulated by OPP, capillary vascular bed, and other mechanisms.[22] A recent study showed that ONH parameters were associated with vascular density but not OPP. It would be

interesting to perform more studies in this field since the information available between VD and OPP is limited.

Previous studies have shown that glaucoma patients present a reduced vessel density and blood flow in the ONH, peripapillary and macula area compared with a healthy control group[7–9] and reduction in vascular density at greater severity of glaucoma.[7,14] Our results have shown that AD and ED groups indicate an incremental decrease in PP-ONH VD from **early**, moderate and advanced glaucoma cases (37%, 34%, 27%,  $P < 0.001$ , respectively). Several factors like age[16,17] and others mentioned above could influence our results. Other authors have reported a PP VD from 58% to 81% for **early** glaucoma and 41%-72% for moderate and severe glaucoma, this wide range of VD is due to the use of different OCT-A devices and different segmentation or programs for image and data analyses.[14,27]

SVC (Superficial vascular complexes) was analysed including from ILM to IPL and also includes large vessels in the main vasculature present on the central retina ONH. Akil et al and Bojikian et al found reduced vessels density in glaucoma patients even though they use different segmentation and included large vessels as we did.[8,9] Akil *et al* used SS-OCT from ILM to RPE of ONH, peripapillary and papillary.[8] Bojikian *et al* used Cirrus HD-OCT from IML to the anterior surface of the lamina cribrosa (LC) of the ONH.[9]

We also found a strong linear correlation between VD and the severity of visual field in AD and ED glaucoma patients. Our results are similar to those of other authors who demonstrated a significant correlation between VD measurements and visual field loss.[14,27] Yarmohammadi *et al* applied OCT-A AngioVue assessment and found reduced peripapillary vascular density from ILM to RNFL in OAG eyes and an association due to severity of visual field loss.[14]

Several limitations are present in our study. Firstly, we had a small sample size as part of a pilot study and this can affect the statistical power results among AD and ED groups. We also

omitted collecting data of papillary size, diabetes or systemic medications. We understand that this may partially affect our results.

Similar to other authors, we believe that it is important to standardize the methodology for analysing OCT-A images of the ONH for future research purposes and for clinical applications in glaucoma. Being able to ascertain the differences between different racial groups are also important as patients of African descent represents a high-risk group with rapid disease progression and worse prognosis[8,10,28], probably secondary to multiple factors like poor response to treatment, cicatrization, or vascular condition. Vascular factor could be used to monitor the high-risk patients of African descent for early detection, appropriate treatment, and follow-up thereby reducing the impact of sight loss and blindness. We believe that low vessel density could be a cause or consequence of the RNFL decrease, on the one hand some subjects with reduced ocular perfusion could cause RNFL damage and on the other hand, chronic damage of the RNFL could lead to a secondary reduction in ocular perfusion.

In conclusion, our pilot study showed a significantly lower superficial PP-ONH VD in AD as compared to ED in healthy subjects, although the sample size is small. No statistically significant differences were found between AD and ED glaucoma patients (all, early, moderate and advanced glaucoma). Other studies have shown a variety of results. [4,8,10,11] It is thus not clear at the moment and more studies are needed with a larger number of subjects comparing both populations and including a deep layer study. To ascertain if AD healthy subjects have a poor prognosis of glaucoma, a prospective study will be necessary.

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Overall responsibility: Salazar, Deantonioramirez, Guzman, Yu-Wai-Man, Sheng, García

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### Figure legends

Figure 1. Pictures from OCT-A spectralis are shown in black and white, their corresponding vessel density analysis are shown in colour images. (A) AD glaucoma patient; (B) ED glaucoma patient; (C) AD healthy subject; (D) ED healthy subject.

Figure 2. Superficial peripapillary and ONH vessel density between AD and ED of all normal, all glaucoma, **early**, moderate, and advanced glaucoma patients ( $P < 0.001$ ,  $P = 0.800$ ,  $0.744$ ,  $0.353$ ,  $0.624$ , respectively).

Figure 3. Correlation between superficial peripapillary and ONH vessel density and visual field mean deviation in AD glaucoma patients ( $r = 0.709$ ,  $P < 0.001$ ).

Figure 4. Correlation between superficial peripapillary and ONH vessel density and visual field mean deviation in ED glaucoma patients ( $r = 0.704$ ,  $P < 0.001$ ).