Ophthalmology Clinics & Research
OCR, 3(2): 139-145
www.scitcentral.com

ISSN: 2638-115X

Original Research Article: Open Access

Peripapilary Microvasculature in Glaucomatous Optic Neuropathy

Amila Chandrasekera*, AG Pramodya Sathsarani* and Dasantha Fonseka

Vision Care Optical Service (Pvt) Ltd., Sri Lanka.

Received November 12, 2019; Accepted December 03, 2019; Published August 15, 2020

ABSTRACT

Objective: The objective of this study is to evaluate the alterations of the optical coherence tomography angiography (OCTA) parameters of peripapilary vascular density and perilously vascular perfusion in patients with glaucomatous optic neuropathy compared to normal.

Methods: Study was conducted with 300 subjects aged 45-65 who were diagnosed with primary open angle glaucoma. In every subject, Retinal nerve fiber layer thickness, peripapillary vascular perfusion and peripapillary vessel density were measured. All were divided in to 4 sub-groups according to the severity of glaucomatous optic neuropathy based on Optical Coherence Tomography based RNFL thickness grading section in Hodapp-Parrish-Anderson criteria for glaucoma.

Results: Peripapillary micro vascular density and peripapillary blood perfusion values were significantly decreased ($p>0.05$) in every glaucomatous subgroup compared to normal. Peripapillary micro vascular density and peripapillary blood perfusion values were directly proportional to the RNFL thickness which indicates a possible reduction of microvasculature of peripapillary region in glaucomatous eyes.

Conclusion: Both peripapilary vessel density and perfusion is proportional to the thickness of Retinal nerve fiber layer and those values correlate with glaucomatous damage in the peripapillary region.

The use of OCT angiography in glaucomatous eyes for evaluation of peripapillary perfusion and vessel density gives access to visualize the defects and quantified the evaluations, with high repeatability and reproducibility.

Keywords: Glaucomatous optic neuropathy, Retinal nerve fiber layer thickness, Peripapillary vessel density, Peripapillary microvascular perfusion

INTRODUCTION

Glaucoma is rated as the second leading cause of blindness in the world and the commonest cause of irreversible blindness affecting almost 60 million people globally [1]. It is characterized by optic neuropathy associated with retinal ganglion cell death, which then leads to retinal nerve fiber layer (RNFL) thinning and optic nerve head (ONH) cupping that leads to a progressive loss of visual field [2,3].

A study conducted in year 2000 at Johns Hopkins University School of Medicine, Baltimore, USA to estimate the prevalence of glaucoma among people worldwide, states that the number of people with primary glaucoma in the world by the year 2000 is estimated nearly 66.8 million, with 6.7 million suffering from bilateral blindness. In developed countries, fewer than 50% of those with glaucoma are aware of their disease [4].

The Glaucoma Service and the Dana Center for Preventive Ophthalmology Baltimore, USA states on a review of published data with use of prevalence models, which was done to estimate the number of people with open angle and angle closure glaucoma in 2010 and 2020 that 60.5 million people with Open Angle Glaucoma (OAG) and Angle Close Glaucoma (ACG) in 2010, increasing to 79.6 million by 2020, and of these, 74% will have OAG. Women will comprise 55% of OAG, 70% of ACG and 59% of all glaucoma in 2010. Asians will represent 47% of those with glaucoma and 87% of those with ACG. Bilateral blindness will be present in 4.5 million people with OAG and 3.9 million people with ACG in 2010, rising to 5.9 and 5.3 million people in 2020, respectively [5].

Corresponding author: Amila Chandrasekera, Diploma in Optometry, Vision Care Optical Services Pvt. Ltd., No 06 Ward Place, Colombo 07, Sri Lanka, Tel: +94777693951; +94112675034; E-mail: emmysampath2@gmail.com

AG Pramodya Sathsarani, Ophthalmic Assistant, Vision Care Optical Services Pvt. Ltd., No 06 Ward Place, Colombo 07, Sri Lanka, Tel: +94712582525; +94112675034; E-mail: pramodya1995@gmail.com

Citation: Chandrasekera A, Sathsarani AGP & Fonseka D. (2020) Peripapilary Microvasculature in Glaucomatous Optic Neuropathy. Ophthalmol Clin Res, 3(2): 139-145.

The epidemiology of glaucoma by Giangiacomo and Coleman [6] mentioned in 2002, 37 million individuals were blind worldwide, with glaucoma accounting for 12.3% of these individuals. By the year 2020 it is estimated that there will be almost 80 million people in the world with open-angle glaucoma and angle-closure glaucoma. The majority of these individuals will have open-angle glaucoma. Of those with ACG, it is predicted that 70% will be women and 87% will be Asian. Bilateral blindness from glaucoma is projected to affect 8.4 million individuals worldwide by 2010 and greater than 11 million by 2020 [6].

A review of population-based glaucoma prevalence studies in Asians, Cho and Kee [7] states that the glaucoma-related population-based studies from Japan, Mongolia, India, Singapore, Thailand, China, Bangladesh, Myanmar, Sri Lanka and South Korea show a higher glaucoma prevalence in Asian patients, including a higher incidence of primary angle-closure glaucoma, than in white patients, although primary open-angle glaucoma (POAG) is still the most commonly reported [7].

Globally, glaucoma is a significant cause of vision loss that disproportionately affects women and Asians. Risk factors for open-angle glaucoma include increased age, African and Asian ethnicity, family history, increased intraocular pressure, myopia and decreased corneal thickness [3,6,7].

Risk factors for angle closure glaucoma include Inuit and Asian ethnicity, hyperopia, female gender, shallow anterior chamber, short axial length, small corneal diameter, steep corneal curvature, shallow limbal chamber depth and thick, relatively anteriorly positioned lens [6,7].

Elevated intraocular pressure (IOP) is a key risk factor for the development and progression of glaucoma [8,9]. A number of conditions such as congenital, angle-closure and secondary glaucoma clearly show that increased IOP is sufficient to lead to glaucomatous optic neuropathy [10].

Although elevated intraocular pressure (IOP) is the main risk factor for glaucoma, large numbers of patients also develop glaucoma with normal IOP levels [10]. Therefore, other risk factors and in particular vascular risk factors have been implicated in the pathogenesis of glaucoma [3,10].

A study conducted in Pennsylvania, USA in 1999 to find out the effect of systemic hypertension in optic nerve blood flow in glaucoma, found that the optic nerve blood flow is reduced in glaucoma patients. Glaucoma patients without systemic hypertension have lower optic nerve blood flow than those with hypertension [11].

Another study conducted to observe the Optic Nerve Head in Glaucomatous Optic Neuropathy at Washington University School of Medicine, St Louis, Mo in 1997, presents the evidence of specific changes in the extracellular matrix of the lamina cribrosa and the role of astrocytes in glaucomatous optic neuropathy [12]. Hernandez [13] and Roth and Foos [14] have explained the Surface Structure of the Optic Nerve Head in Glaucoma in 1972 and 1973.

It was found that the connective tissue dynamics should directly and indirectly influence astrocyte and glial metabolism as well as axonal transport, glaucomatous damage within the ONH may not necessarily occur at locations with the highest levels of IOP-related connective tissue strain; the study was conducted to observe the mechanical environment of the optic nerve head in glaucoma in Portland, Oregon, USA in 2008 [15].

Another study conducted to evaluate the regional structure-function relationship between visual field sensitivity and retinal nerve fiber layer thickness and optic nerve head measurements using spectral-domain optical coherence tomography in 2014 at University Hospital, CHU Grenoble, Grenoble, France with 142 subjects, states that the structure-function relationship was significantly stronger with Bruch membrane opening minimum rim width than other Optic nerve head SD-OCT parameters [16].

Optical coherence tomography (OCT) angiography is a novel technology that rapidly and conveniently images blood vessels in vivo without the use of exogenous dyes, providing high-resolution and three-dimensional information on the morphology of physiological and pathological blood vessels at different layers of the retina by separating static (tissue) from motion (blood flow) signals [17,18].

A study conducted at Doheny Eye Institute, Los Angeles, California, USA to measure the Repeatability of automated vessel density measurements using optical coherence tomography angiography found that automated vessel density measurements using OCT-A showed excellent repeatability in healthy individuals. Although repeatability will also need to be established in the setting of disease, the level of reproducibility should be useful for assessing the significance of differences in capillary density over time or under different conditions [19].

Study conducted in Bangalore, India to evaluate the diagnostic ability of peripapillary vessel density measurements of optical coherence tomography angiography (OCTA) in primary open-angle (POAG) and primary angle-closure glaucoma (PACG) states that the Diagnostic ability of peripapillary vessel density parameters of OCTA, especially the inferio-temporal sector measurement, was good in POAG and PACG. Diagnostic abilities of vessel density measurements were comparable to RNFL measurements in both POAG and PACG [17].

A pilot study conducted at Portland, USA in 2012 to obtain Quantitative measurements of OCT angiography of optic nerve head blood flow, indicates that the OCT angiography can detect the abnormalities of optic nerve head perfusion and has the potential to reveal the Optic nerve head blood flow mechanism related to glaucoma [20].

Also, a study done to observe the optical coherence tomography angiography of optic disc perfusion in Glaucoma in Oregon Health & Science University, Portland suggest that the optical coherence tomography angiography, repeatedly measures optic disc perfusion and may be useful in the evaluation of glaucoma and glaucoma progression [21].

Optical coherence tomography angiography vessel density had similar diagnostic accuracy to RNFL thickness measurements for differentiating between healthy and glaucoma eyes. A study done in California United States in 2016, with 164 eyes suggests that OCT-A measurements reflect damage to tissues relevant to the pathophysiology of OAG [22].

Vessel Density is defined as the total length of perfused vasculature per unit area in a region of measurement. It is measured in units of inverse millimeters. Vessel density can be thought of as Untangling all the vasculature in a region of tissue. Vascular density was defined as the percentage of the sample area occupied by vessel lumens following binary reconstruction of images. Vascular density equals to the Proration of the flowing vessel divided by total scan area [23].

Perfusion density is defined as the total area of perfused vasculature per unit area in a region of measurement. This metric is calculated by summing up the number of pixels which contain perfused vasculature and dividing the sum by the total number of pixels in the considered region [23].

Optical coherence tomography has become an essential tool for evaluation of Retinal nerve fiber layer. The Cirrus HD-OCT (Carl Zeiss Meditec, Inc. Dublin, CA) is a spectral-domain OCT that provides visualization of the distribution pattern and measurement of RNFL abnormalities in a 200 × 200 μ area. Analysis of the RNFL thickness deviation maps—a color-coded map displaying areas of RNFL abnormalities—detects glaucoma with high sensitivity and specificity.

OBJECTIVE

The objective of this study is to evaluate the alterations of the optical coherence tomography angiography (OCTA) parameters of peripapillary vascular density and peripapillary vascular perfusion in patients with glaucomatous optic neuropathy compared to normal.

There are many studies that have been investigated in microvasculature of the peripapillary area in glaucomatous optic neuropathy on different types of ethnic groups [15,16,20,21].

Each study was found relations as well as differences in the peripapillary microvasculature in glaucomatous eyes.

There is no any research or studies have been found in the literature regarding a Sri Lankan sample and very few with south Asian samples regarding this topic.

METHODS

Participants

A retrospective cross sectional study according to convenience sampling was carried out at Vision Care Optical Services Pvt. Ltd., No 6 ward place Colombo 7, form 2017 March to 2019 April. Participants were 150 Sri Lankan adults (300 eyes), 150 males and 150 females' age range from 45 to 65 years who were diagnosed with Primary Open Angle Glaucoma (POAG). Subjects who presented with any type of secondary glaucoma, angle closed glaucoma, any other ocular pathology and those who presented with systemic vascular disorders were excluded from the study. All participants were given a full explanation of investigation procedures with the option to withdraw from the study at any time.

Materials

Data were recorded in each subject by carrying out a questionnaire. Questionnaire was divided into three parts; first part is for social demographic data which include age, gender, marital status and area of residence. Second part is for personal health and medical status which include level of blood sugar, blood pressure levels, body mass index, cholesterol levels, family history of ocular or other diseases, past ocular/systemic medical and surgical history, current ocular/systemic medications, history of habits- alcohol consumption/smoking, etc. Third part is for optical coherence tomography assessment which includes retinal nerve fiber layer thickness, peripapillary vessel density and peripapillary perfusion.

Retinal nerve fiber layer thickness, peripapillary vessel density and peripapillary perfusion was measured by the Cirrus 5000 spectral domain Optical Coherence Tomography by Carl Zeiss Meditec with acquired 200 × 200 Optic disc cube scans for RNFL thickness measurements and 6 × 6 angioplex scanning strategy on the Optic nerve head for the measurements of peripapillary vessel density and peripapillary perfusion and all the acquired images were analyzed by Cirrus 5000 software version 5000.10.1 and 5000.10.1 angioplex matrix. Reports with signal strength less than 6 were excluded.

Procedure

Grading of the subjects was done according to the basis of RNFL thickness of each subject. The Optical Coherence Tomography based RNFL thickness grading section in Hodapp-Parrish-Anderson criteria for Glaucoma was used for grading of Glaucoma stages.

All subjects were divided in to 3 stages of glaucoma and in to an age matched normal group. Stage 3 includes the subjects with average RNFL thickness of 37 ± 8.77, Stage 2 includes the average RNFL thickness of 47 ± 8.77 µ, Stage 1 includes the average RNFL thickness of 67 ± 8.77 µ while the controlled group indicate average RNFL thickness more than 83.77 µ.

The changes in peripapillary vessel density and peripapillary perfusion in the disease groups was analyzed using one-way ANOVA.

All statistical analyses were performed using the Statistical Package for the Social Sciences by IBM Company, Chicago, IL.

RESULTS

In the study population peripapillary perfusion and vessel density was studied in 50 normal eyes and 200 glaucomatous eyes. Glaucomatous eyes were divided in to 3 stages based on and each group contends 50 subjects which were randomly selected and the rest was excluded. The mean age of the study group was 56.6 ± 7.53 years of age. Each group contained 50 subjects. The Average RNFL thickness in controlled group was 94.6+2.6 µ, in stage 1 glaucoma group 76.3+3.1 µ, Stage 2 glaucoma groups 46.8+2.7 µ and in stage 3 glaucoma group 38.5+1.8 µ. One way ANOVA Statistical test was performed in analysis of data. In controlled group the average PVD was 17.44 ± 0.53 and average PMP was 66.4 ± 3.12. In glaucoma stage 1 group the average PVD was 16.33 ± 0.16 and average PMP was 55.43 ± 4.71. In glaucoma stage 2 group the average PVD was 15.20 ± 0.23 and average PMP was 44.77 ± 4.82 and in glaucoma stage 3 group the average PVD was 14.06 ± 0.17 and average PMP was 37.33 ± 6.61.

Test of homogeneity of variances in vessel density levene statistics based on mean was 11.049, based on median was 10.320, based on median and with adjusted df was 10.320 and based on trimmed mean was 10.966, P=0.0001. One way ANOVA test shows 382.563 F Value and P=0.001. Test of homogeneity of variances in peripapillary perfusion levene statistics based on mean was 0.896, based on median was 0.826, based on median and with adjusted df was 0.826 and based on trimmed mean was 0.854, P=0.044. One way ANOVA test shows 1669.107 F value and P=0.001.

In vessel density comparisons TUKEY HSD analysis shows a mean deference between groups 1 and 2=1.10 (P=0.001) between 1 and 3=2.23 (P=0.001) between 1 and controlled=3.37 (P=0.001); mean deference between groups 2 and 3=1.13 (P=0.001) 2 and controlled=2.27 (P=0.001) and mean difference between groups 3 and controlled=1.14 (P=0.001). In every group mean deference is significant at the 0.05 level.

In peripapillary perfusion multiple comparisons TUKEY HSD analysis shows a mean deference between groups 1 and 2=10.97 (P=0.001), between 1 and 3=21.63 (P=0.001), between 1 and controlled=29.07 (P=0.001); mean deference between groups 2 and 3=10.66 (P=0.001), 2 and control=18.10 (P=0.001) and mean deference between group 3 and control=7.43 (P=0.001). In every group mean deference is significant at the 0.05 level.

According to the results of our study it was noted in every group, peripapillary microvascular perfusion and peripapillary vessel density significantly decreased when the severity of glaucomatous optic neuropathy increased **(Figures 1 and 2)**.

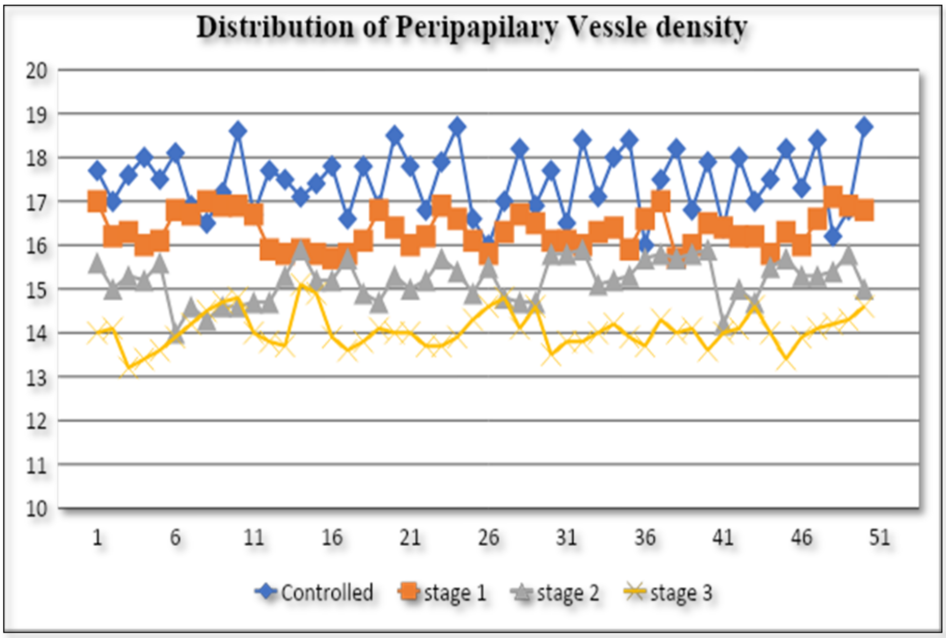

Figure 1. Distribution of peripapillary vessel density in the study group.

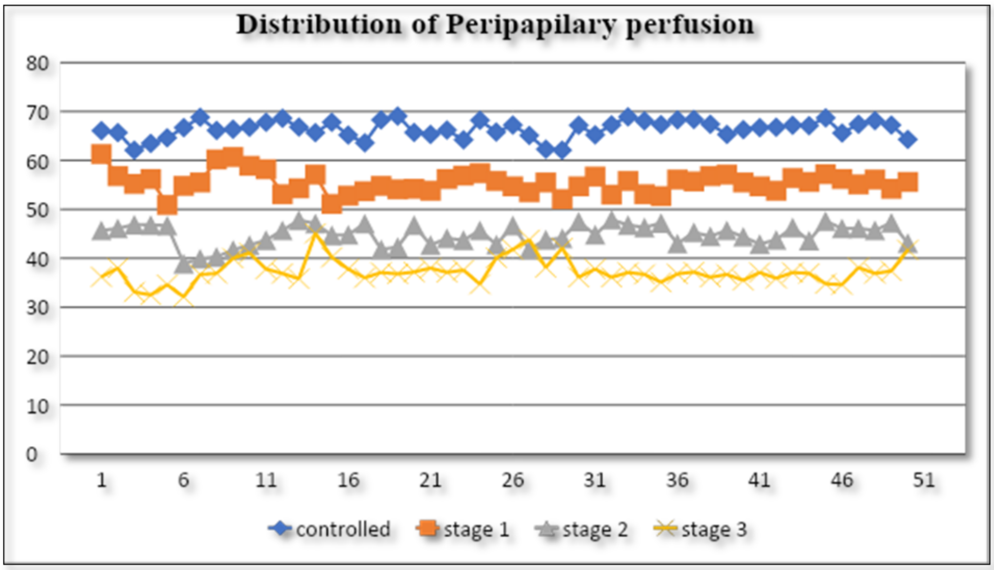

Figure 2. Distribution of peripapillary perfusion in the study group.

DISCUSSION

We found that the peripapillary vessel density and perfusion was lower in glaucomatous eyes when compared with aged-matched normal eyes and the vessel density progressively decreased with the severity of glaucoma stage. The correlation between the reduction in RNFL thickness and vessel density and perfusion was proportional and this was significant in every group.

A study to compare optic disc perfusion between normal subjects and subjects with glaucoma using optical coherence tomography angiography and to detect optic disc perfusion changes in glaucoma with 24 normal subjects and 11 patients with glaucoma was conducted in Oregon Health & Science University, Portland, Oregon. It shows that the disc flow index was reduced by 25% in the glaucoma group; In our study we have found that the vessel density was reduced in 13.2% in stage 1 glaucoma group, 14% in stage 2 glaucoma group and 15.7% in stage 3 glaucoma group, while the peripapillary perfusion reduced in 32.1% in stage 1 glaucoma group, 38.9 % in stage 2 glaucoma group and 50.9% in stage 3 glaucoma group.

A study on diagnostic agreement with Heidelberg Retinal Tomography Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography done at Hong Kong, China in 2010 with 79 glaucoma and 76 normal subjects states that the optics disc blood flow was significantly decreased in glaucomatous patients compared to age matched normal group [21]. Even though we have used the Cirrus 5000 Optical coherence tomography for measurements of ONH microvasculature every glaucoma group showed a reduction of the density and the perfusion values in peripapillary microvasculature.

Microvascular density in glaucomatous eyes with hemifield visual field defects was evaluated in a study conducted in Kyoto, Japan in 2016 with 60 eyes with primary open angle glaucoma, 41 with superior and 19 with inferior hemifield visual field defect. They have found that the microvascular reduction was associated with VF defects in a region-specific manner. Even though we have not measured any functional aspects in the study group, we suggest that the functional evaluation with structural changes happens in peripaillary area deserves further study [24].

The sample that we used was selected on Sri Lankan population and subjects of any other ethnicity were not included in the study. Studies that carried out to evaluate the Peripapillary microvasculature based on the population samples in United States of America, Africa, China, Japan and other parts of the world indicates that there is a co-relation between the reductions of peripapillary microvascular parameters in development of glaucoma [25-29].

However, a prospective study conducted for a 2 year time period in Budapest, Hungar with individuals who use anti-glaucoma eye drops states that the peripapillary vessel density measurement did not support the detection of glaucomatous progression. But in our study the behavior of vessel density measurements strongly agreed for understanding the changes in the peripapillary area in the development of glaucoma [30].

CONCLUSION

According to our study peripaillary vessels density and peripapillary vessel perfusion shows decreased values in glaucomatous optic neuropathy in the observation of patients with primary open angle glaucoma.

Both peripapillary vessel density and perfusion is proportional to the thickness of retinal nerve fiber layer and those values correlates with glaucomatous damage in the peripapillary region.

Using OCT angiography in glaucomatous eyes for evaluation of peripapillary perfusion and vessel density will give access to visualize the defects and quantified the evaluations, with high repeatability and reproducibility. Quantitative OCT angiography measurements may have a value in future studies to determine its potential usefulness in glaucoma evaluation.

LIMITATIONS

There could be a potential effect of anti0glaucoma drugs on microvasculature of the peripapillary area [31,32]. 143 eyes that were included in the study which was categorized into any of glaucoma stages had been receiving different anti-glaucoma eye drops for different time period. Some studies states that there is no decrease in blood circulation found with anti-glaucoma eye drops [33]. Nevertheless, the effect of anti-glaucoma eye drops on perfusion and vessel density require further investigations.

However, the focal nature of the eyes with decreased vessel density and perfusion correlates with glaucomatous damage which indicates with an RNFL defects.

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