



Original Article

Comparison of Choroidal Filling and Optic Nerve Head Perfusion Pattern in Glaucoma Patients with Healthy Controls

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ABSTRACT

Glaucoma is a primary cause of irreversible blindness worldwide, it kills the vision silently, having a financial burden on society regarding therapy expenses and loss of valuable hours of the day.

Objective: To compare the choroidal filling time and grade the status and pattern of optic nerve head (ONH) perfusion by fundus fluorescein angiography (FFA) in glaucoma patients **Methods:** Patients with various types of glaucoma were enrolled and compared them with healthy volunteers with no history and findings of glaucoma. Perfusion status using FFA was studied and analyzed corresponding visual fields (VF) and optical coherence tomography (OCT) findings **Results:** There were 70 participants in the study, including 48 glaucoma patients and 22 healthy controls. Choroidal filling time (CFT) was 9-12, 13-17, 15-22, and 20-33 seconds in healthy individuals and patients with ocular hypertension (OH), primary open-angle glaucoma (POAG), and normal-tension glaucoma (NTG), respectively. In OH, inferonasal and inferotemporal hypofluorescence pattern of ONH perfusion was noted, whereas POAG showed an inferonasal, patchy, and undefined pattern of hypofluorescence. In contrast with the healthy volunteers that showed uniform fluorescence, patients with NTG showed inferonasal hypofluorescence. CFT was significantly delayed in NTG patients ($p < 0.05$). We found a strong correlation between findings of FFA, OCT, and corresponding VF defects in glaucoma patients **Conclusions:** The choroidal filling time is prolonged in patients with various types of glaucoma, especially in cases of normal-tension glaucoma. FFA reveals perfusion defects in the form of areas of hypofluorescence and multiple characteristic optic nerve head perfusion patterns in cases of POAG, NTG, and OH.

INTRODUCTION

Glaucoma is an optic neuropathy that worsens over time and is associated with optic disc cupping and peripheral and central visual field defects, and increased loss of ganglion cells. In the study conducted in 2010, the number of individuals suffering from glaucoma was found to be 60.5 million [1]. The global figure for glaucoma prevalence in 2010 was 1.96% for open-angle glaucoma and 0.69% for angle-closure glaucoma [2]. A national survey of blindness 2002-2004 indicated that 113600 (7.1% of total blind) were blind due to glaucoma. Glaucoma is the fourth foremost cause of vision loss in our country [3]. Intraocular pressure

(IOP) is the only modifiable risk factor in successfully managing glaucoma [4]. Vascular or hematological disorders also play a vital part in glaucomatous optic nerve damage. There is a marked reduction in blood flow volume and velocity parameters in patients with glaucomatous optic neuropathy [5]. In patients with primary open-angle glaucoma (POAG) and ocular hypertension (OH), it was reported that choroidal blood flow was lower as compared to normal [6]. Alterations in the choroidal blood have also been seen in patients with central serous retinopathy, diabetic retinopathy, age-related macular degeneration,

glaucoma, and as well as in smokers [7]. Several methods have been developed to evaluate blood flow in the retina and choroid of the eye, such as radioactively labeled microspheres, laser speckle phenomenon, and color doppler imaging of various large vessels showing blood flow velocity in these vessels [8]. A study showed marked localized narrowing of retinal arterioles in glaucoma patients compared to normal [9]. Angiography is another fundamental method for assessing blood flow by which choroidal circulation has been studied, giving great information about the blood flow in normal individuals, glaucoma patients, and patients with other retinal disorders. Different dyes have been used for angiography, like sodium fluorescein and indocyanine green (ICG) [10]. ICG is an equally good but expensive dye compared to sodium fluorescein dye and is not routinely used in Pakistan. A study showed noticeable optic disc hypoperfusion in patients with ocular hypertension and glaucoma, assessed using fundus fluorescein angiography (FFA) [11]. Glaucoma damages the optic nerve progressively, so if any abrupt change in chorio-retinal blood flow occurs during a follow-up visit, it can be picked easily and the treatment modality adjusted [12]. Choroidal filling and optic nerve head perfusion patterns correlate with visual field defects and optical coherence tomography (OCT) defects. This study was conducted to compare the choroidal filling time and grade the pattern and status of optic nerve head perfusion in patients with normal-tension glaucoma (NTG), OH, and POAG patients and compare the findings with those of healthy individuals. The secondary objective was to correlate the FFA findings with corresponding visual field (VF) and optical coherence tomography(OCT)defects.

METHODS

It was a case-control study in which choroidal filling time and optic nerve head perfusion pattern in the eyes of glaucoma patients were compared with normal individuals. The study was conducted at King Edward Medical University and Allama Iqbal Medical College, Lahore, Pakistan, following principles laid down in the declaration of Helsinki. The patients belonging to either gender and above 40 years of age were recruited following non-probability purposive sampling following the below-mentioned selection criteria. Inclusion criteria was open angle glaucoma, Glaucomatous cupping of disc, visual field defects, Retinal nerve fiber layer (RNFL) defects on Optical coherence tomography (OCT), Intraocular pressure (IOP)> 21mmHg, normal-tension glaucoma was diagnosed on the same criteria as for primary open-angle except IOP<21mmHg. Ocular hypertension was considered when there was no glaucomatous cupping, no RNFL defects on

OCT, no visual field defect and IOP> 21mmHg. Exclusion criteria was media opacities (cataract, corneal opacities, vitreous hemorrhage, etc., History of diabetes mellitus, History of ischemic heart disease, Any past glaucoma surgery, History of other variants of glaucoma such as secondary open-angle glaucoma, congenital glaucoma, and primary and secondary angle-closure glaucoma and Individuals having any other ocular pathologies. Fundus angiograms of normal healthy volunteers were taken as controls. These healthy subjects had IOP < 21mmHg and normal findings of anterior and posterior segments on slit-lamp biomicroscopy, visual fields, and OCT of the optic nerve head. Seventy patients were taken out of which 22 were normal healthy individuals, and 48 suffered from ocular hypertension (OH) or glaucoma. The visual fields, OCT of optic nerve head, and gonioscopy were done before FFA. The choroidal and optic nerve head areas were divided into six quadrants so that defects found in VF, OCT, and FFA could be compared anatomically. From OCT retinal nerve fiber layer (RNFL) was taken for comparison. These analyzed quadrants were drawn as follows:

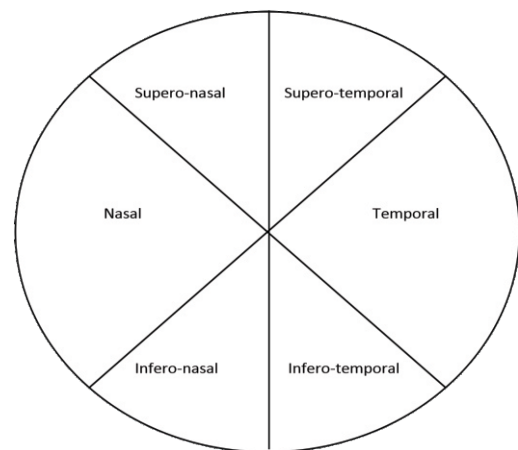


Figure 1: Six Quadrants of Optic Nerve Head for Evaluation

Informed written consent was obtained from all the participants. FFA was performed using the Topcon TRC-50DX FFA machine. As choroidal vessels were filled in seconds, the examination of the fellow eye was missed and was not included in the study. A single eye from each individual was included in the study. Before giving an injection of 25% sodium fluorescein 3ml with a dosage of 250mg/ml into the antecubital vein, baseline colored, and black & white red-free fundus images were taken. A series of black & white images of the chorio-retinal circulation every second for 30-40 seconds and delayed images after 10 and 15 minutes were taken. Pathological changes were recognized by hyper- or hypo-fluorescence of the optic nerve head that exhibited different fluorescence patterns. The collected data was entered and analyzed using statistical software SPSS version 23.0. Quantitative data

are presented as mean ± SD, whereas qualitative variables are presented in frequencies and percentages. Choroidal filling time (CFT) in cases and normal individuals was compared using an independent sample t-test. Choroidal filling patterns and optic nerve head perfusion patterns in cases and normal individuals were compared using a Chi-square test, taking a p-value ≤ 0.05 as statistically significant.

RESULTS

This study included 22(31%) normal individuals and 48(69%) diseased patients. Out of 48 affected individuals, 24 (50.0%) had POAG, 14(29.2%) had NTG, and the rest 10 (20.8%) patients suffered from OH. The age distribution of the study population is shown below (Table 1):

Age Range (years)	Number (%)
40-50	30(43%)
51-60	30(43%)
61-70	8(11%)
71-80	2(3%)

Table 1: Distribution of Patients in Various Age Groups

There were 49% male and 51% female patients in the study. The RNFL loss and the corresponding visual field defects in POAG and NTG patients are presented in Table 3. Most patients (41.7%) showed RNFL loss in the inferonasal quadrant with related VF defects in the supero-temporal quadrant. No patient showed any RNFL loss and visual field defect in the normal healthy population and patients with OH.

Quadrants	RNFL Loss (n %)		Visual Field Defect (n %)	
	POAG, (N=24)	NTG, (N=14)	POAG, (N=24)	NTG, (N=14)
Inferonasal	10 (41.7)	6 (42.9)	3 (12.5)	0 (0.0)
Inferotemporal	6 (25.0)	4 (28.6)	3 (12.5)	2 (14.3)
Superonasal	3 (12.5)	2 (14.3)	5 (20.8)	4 (28.6)
Nasal	2 (8.3)	1 (7.1)	1 (4.2)	1 (7.1)
Superotemporal	2 (8.3)	0 (0.0)	10 (41.7)	6 (42.9)
Temporal	1 (4.2)	1 (7.1)	2 (8.2)	1 (7.1)

POAG: Primary open angle glaucoma
NTG: Normal tension glaucoma

Table 2: RNFL Loss and Corresponding Visual Field Defect in Various Types of Glaucoma

We performed FFA in our patients and studied choroidal filling time and optic nerve head perfusion pattern (ONHPP). The results of choroidal filling time in various conditions are listed below (Table 3):

Diagnosis	Choroidal Filling Time (seconds)
Ocular hypertension (OH)	13 to 17
Primary Open Angle Glaucoma (POAG)	15 to 22
Normal-Tension Glaucoma	20 to 33
Normal Individuals	09 to 12

Table 3: Choroidal Filling Time in Ocular Hypertension, Primary Open Angle Glaucoma, Normal-Tension Glaucoma, and Normal

Individuals

Analysis of the ONH perfusion pattern showed that in patients with ocular hypertension, 2 (20.0%) showed inferonasal, 1 (10.0%) each showed inferotemporal, extensive, patchy hypofluorescence, and 4(40.0%) showed normal fluorescence. In POAG, 6(25.0%) showed extensive, 5 (20.8%) patchy, 4 (16.7%) inferonasal, 4 (16.7%) inferotemporal, 3 (12.5%) normal, 1 (4.3%) each nasal, superonasal and superotemporal. In NTG, 4 (28.6%) individuals showed inferonasal hypofluorescence, 3 (21.4%) patchy hypofluorescence, 2 (14.3%) each superonasal, inferotemporal, extensive, and 1 (7.1%) showed nasal hypofluorescence. Normal Individuals showed normal fluorescence in all quadrants.

DISCUSSION

The study's primary objectives to compare the choroidal filling time and optic nerve head perfusion patterns in glaucoma patients with healthy individuals were successfully met. In OH, FFA showed vascular disturbance, but no defects were present in VFs and OCT, which implied that the areas highlighted in FFA could become the actual defects, and these cases could become glaucomatous in old ages. The choroidal filling time was delayed in both NTG and POAG, showing that this parameter could potentially indicate optic nerve head perfusion in glaucoma patients. Characteristically, glaucomatous damage causes RNFL and retinal ganglion cell loss that occurs focally and diffusely. OCT, a non-contact, non-invasive technology, yields high-resolution cross-sectional in vivo imaging of retinal layers. While structural abnormalities might pave the way for functional anomalies, it may be expected that an OCT abnormality would be observed clearly when no glaucomatous VF loss is present. We observed corresponding areas of visual field defect in glaucoma patients, which correlated with the areas of OCT structural damage. In a study by Weinreb and Robert et al., blood flow was measured in peripapillary choroidal tissue and optic nerve head area using indocyanine green (ICG) dye. It was found that choroidal filling time was significantly delayed in glaucoma patients. Hypofluorescence of ONH was also noted [13]. Similar results were seen in the current study using fluorescein as the study dye. Our findings authenticate the effectiveness of sodium fluorescein in diagnosing different abnormalities in glaucoma patients. The study participants' responses showed that sodium fluorescein was easy to apply, less expensive, and had tolerable side effects. Clinically, the primary purpose of FFA is to examine blood circulation within chorioretinal tissue to understand glaucoma better [14]. A systematic understanding of the circulation appearance and phases of the dye in an individual with a normal eye is necessary for

developing a better understanding of these abnormalities [15]. To correlate the FFA findings with defects in VFs & OCT anatomically, we divided the peri-papillary choroidal area and ONH into six quadrants/sections (nasal, temporal, superonasal, superotemporal, inferonasal, and inferotemporal). We observed a strong correlation between these three parameters, with defects in VFs and OCT corresponding with each other. Numerous studies have reported that the prevalence of glaucomatous changes in patients with OH without defects in the visual field or ONH changes with age over 40 years varies between 4 - 10% [16]. The OH patients that progress to overt glaucoma in untreated individuals is about 2% per year, and about 1% per year in individuals on anti-glaucoma treatment [17]. In our study, patients with OH showed that 61.1% of individuals had an abnormality in the choroidal filling and ONH perfusion pattern in the absence of visual fields and RNFL loss. It showed that these individuals are at risk of developing open-angle glaucoma later in their lives. The current study showed that 44% of individuals of POAG had defects in corresponding regions of FFA, VFs, and RNFL, and 48% showed patchy and undefined generalized filling defects along with quadrant/sectoral defects. Another study reported that the raised IOP in POAG caused generalized compression on choroidal vasculature and ONH, resulting in a generalized type of defects compared to specific defects in a particular quadrant [18]. In NTG, 71% of individuals showed defects in the corresponding RNFL quadrant with reciprocal VF changes. We propose that raised IOP was well documented in POAG, which caused a generalized effect on all the choroidal and ONH vasculature resulting in generalized filling defects. However, patients with NTG showed quadrant-wise defects as a specific quadrant was primarily involved in these patients [19-23].

CONCLUSIONS

The choroidal filling time is delayed in patients with various types of glaucoma. FFA revealed perfusion defects in the form of hypofluorescence and multiple patterns of optic nerve head perfusion in cases POAG, NTG, and OH. FFA revealed corresponding vascular flow disturbances in the quadrants that showed changes in RNFL loss with reciprocal VF changes in POAG and NTG patients. In the case of OH, FFA would help individuals be screened before defects are detected on VFs and OCT.

REFERENCES

- [1] Butt NH, Ayub MH, Ali MH. Challenges in the management of glaucoma in developing countries. *Taiwan journal of ophthalmology*. 2016 Sep 1;6(3):119-22. doi: 10.1016/j.tjo.2016.01.004.
- [2] Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262-7. dx.doi.org/10.1136/bjo.2005.081224
- [3] Dineen B, Bourne RR, Jadoon Z, Shah SP, Khan MA, Foster A, et al. Causes of blindness and visual impairment in Pakistan. The Pakistan national blindness and visual impairment survey. *Br J Ophthalmol*. 2007;91(8):1005-10. doi: 10.1136/bjo.2006.108035.
- [4] Mamikonian VR, Galoian NS, Sheremet NL, Kazarian EE, Kharlap SI, Shmeleva-Demir OA et al. Peculiarities of ocular blood flow in ischemic optic neuropathy and normal tension glaucoma. *Vestnik Oftalmologii*. 2013 Jul 1;129(4):3-8.
- [5] Javaid U, Ali MH, Jamal S, Butt NH. Pathophysiology, diagnosis, and management of glaucoma associated with Sturge-Weber syndrome. *International Ophthalmology*. 2018 Feb;38(1):409-16. doi: 10.1007/s10792-016-0412-3.
- [6] Portmann N, Gugleta K, Kochkorov A, Polunina A, Flammer J, Orgul S. Choroidal blood flow response to isometric exercise in glaucoma patients and patients with ocular hypertension. *Invest Ophthalmol Vis Sci*. 2011;52(10):7068-73. doi: 10.1167/iovs.11-7758.
- [7] Duijm HF, van den Berg TJ, Greve EL. Choroidal haemodynamics in glaucoma. *Br J Ophthalmol*. 1997;81(9):735-42. doi: 10.1136/bjo.81.9.735.
- [8] Aquino MV. Suggested Formula for Setting Target Intraocular Pressure. *Asian J Ophthalmol*. 2004;6(1):2-6
- [9] Zhong Y, Wang J, Luo X. Integrins in trabecular meshwork and optic nerve head: possible association with the pathogenesis of glaucoma. *BioMed Research International*. 2013 Jan 1;2013. doi: 10.1155/2013/202905.
- [10] Harris A, Kagemann L, Chung HS, Ciulla TA. The use of dye dilution curve analysis in the quantification of Indocyanine green angiograms of the human choroid. *Ophthalmol Clin. North Am*. 1998;11(3):331-337. doi.org/10.1016/S0896-1549(05)70060-2.
- [11] Schmidl D, Boltz A, Kaya S, Werkmeister R, Dragostinoff N, Lasta M, et al. Comparison of choroidal and optic nerve head blood flow regulation during changes in ocular perfusion pressure. *Invest Ophthalmol Vis Sci*. 2012;53(8):4337-46. doi: 10.1167/iovs.11-9055.
- [12] Yoneya S. A new approach for studying the retinal and choroidal circulation. *Nippon Ganka Gakkai Zasshi*. 2004 Dec 1;108(12):836-61.
- [13] Weinreb RN, Bartsch DU, Freeman WR. Angiography of the glaucomatous optic nerve head. *J Glaucoma*. 1994 Jul 1;3:S55-60.
- [14] Yasuzumi K, Ohno-Matsui K, Yoshida T, Kojima A,

- Shimada N, Futagami S, Tokoro T, Mochizuki M. Peripapillary crescent enlargement in highly myopic eyes evaluated by fluorescein and indocyanine green angiography. *Br J Ophthalmol*. 2003 Sep 1;87(9):1088-90. doi: 10.1136/bjo.87.9.1088.
- [15] Zakir R, Iqbal K, Tarar AA, Azhar Z, Ali MH, Hashmani N, Zakir M. The role of ocular coherence tomography angiography in the diagnosis of diabetic retinopathy and a comparison with the current gold standard fundus fluorescein angiography. *Journal of Fatima Jinnah Medical University*. 2021;15(4):184-8. doi.org/10.37018/100X6573
- [16] Akagi T, Zangwill LM, Shoji T, Suh MH, Saunders LJ, Yarmohammadi A, Manalastas PI, Penteado RC, Weinreb RN. Optic disc microvasculature dropout in primary open-angle glaucoma measured with optical coherence tomography angiography. *PLoS One*. 2018 Aug 7;13(8):e0201729. doi: 10.1371/journal.pone.0201729.
- [17] Ali MH, Shah SR, Butt AN, Jamal S, Hamza U, Butt NH. Efficacy And Surgical Outcome of Trabeculectomy with Mitomycin-C In Congenital Glaucoma with Hazy Cornea: Outcome of Trabeculectomy with Mitomycon-C in Congenital Glaucoma. *Pakistan BioMedical Journal*. 2022 May 31:272-5. doi.org/10.54393/pbmj.v5i5.458
- [18] Hitching RA, Spaeth GL. Fluorescein angiography in chronic simple and low tension glaucoma. *Br J Ophthalmol*. 1977; 61: 126-32. doi: 10.1136/bjo.61.2.126.
- [19] Usman M, Iqbal K, Ali MH, Nafees K. Features and diagnostic accuracy of optical coherence tomography angiography in neovascular age-related macular degeneration. *Cureus*. 2019 Dec 28;11(12):e6485. doi:10.7759/cureus.6485.
- [20] Ayub A, Akhtar FM, Saleem N, Ali MH, Ayub MH, Butt NH. Frequency and risk factors of dry eye disease in Pakistani population, a hospital based study. *Pakistan Journal of Ophthalmology*. 2017 Dec 1;33(4). doi.org/10.36351/pjo.v33i4.26
- [21] Jamal S, Ali MH, Ayub MH, Butt NH. Frequency and grading of diabetic retinopathy in diabetic end stage renal disease patients. *Pakistan Journal of Ophthalmology*. 2016 Jun 30;32(2). doi.org/10.36351/pjo.v32i2.100.
- [22] Ali MH, Javaid M, Jamal S, Butt NH. Femtosecond laser assisted cataract surgery, beginning of a new era in cataract surgery. *Oman journal of ophthalmology*. 2015 Sep;8(3):141. doi: 10.4103/0974-620X.169892.
- [23] Zakir R, Iqbal K, Ali MH, Mirza UT, Mahmood K, Riaz S, Hashmani N. The outcomes and usefulness of Intraoperative Optical Coherence Tomography in vitreoretinal surgery and its impact on surgical decision making. *Romanian Journal of Ophthalmology*. 2022 Jan;66(1):55-60. doi: 10.22336/rjo.2022.12.