Early Effects of Latanoprostene Bunod on Optical Coherence Tomography and Optical Coherence Tomography Angiography in Glaucoma and Ocular Hypertension

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ABSTRACT

Purpose: To evaluate optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) parameters in open-angle glaucoma (OAG) and ocular hypertension (OHT) patients using latanoprostene bunod (LBN).

Patients and Methods: The study included treatment-naive patients diagnosed with OAG or OHT between June 2023 and May 2024. Intraocular pressure (IOP), OCT and OCTA images were evaluated at baseline, 3 months and 6 months after LBN treatment.

Results: The diagnosis was OHT in 40 eyes (83.3%) and OAG in 8 eyes (16.7%). The mean IOP was 25.4±5.3 mmHg before and 17.3±3.0 and 17.8±3.7 mmHg at months 3 and 6 after LBN treatment, respectively ($p<0.001$ for each visit compared to baseline). No statistically significant difference was observed between baseline and follow-up visits when comparing OCT and OCTA parameters. A moderate positive statistically significant correlation existed between the pre-treatment average ganglion cell layer-inner plexiform layer (GCL-IPL) thickness, minimum GCL-IPL thickness, average retinal nerve fiber layer thickness with the radial peripapillary capillary flux index (RPC-FI) measured at the final examination ($r=0.519$, $p<0.001$; $r=0.543$, $p<0.001$; $r=0.499$, $p<0.001$).

Conclusions: In our study, the decrease in IOP was found to be statistically significant, while the changes in OCT and OCTA parameters were not found to be significant. A statistically significant positive correlation existed between the baseline OCT parameters and the final RPC-FI in OCTA. This result may indicate the importance of the RPC-FI in follow-up.

Key Words: flux index; latanoprostene bunod; ocular hypertension; open-angle glaucoma; optical coherence tomography angiography

INTRODUCTION

Glaucoma is a multifactorial, neurodegenerative disease characterized by the progressive loss of retinal ganglion cells and their axons. [1] It is the leading cause of irreversible vision loss worldwide [2], with an estimated 110 million people worldwide expected to be affected within the next 20 years. [3] Major risk factors include age, intraocular pressure (IOP), and family history, with impaired ocular perfusion playing a significant role in the etiopathogenesis of the disease. [4,5] The only modifiable risk factor is IOP, and lowering IOP has been shown to prevent disease progression. [6,7]

Topical anti-glaucoma eye drops are the most commonly used treatment for glaucoma, with prostaglandin analogs, beta-blockers, alpha-2 agonists and carbonic anhydrase inhibitors commonly used. When topical treatment is inadequate, laser and surgical methods are used. [8-10] Prostaglandin analogs are recommended as first-line therapy for high-tension glaucoma due to their efficacy in lowering IOP, minimal systemic side effects and once-daily dosing. [11,12] Latanoprostene bunod (LBN) 0.024% is a new IOP-lowering eye drop approved by the U.S. Food and Drug Administration in November 2017. LBN

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is a nitric oxide (NO)-donating prostaglandin F2α analog that rapidly metabolizes to latanoprost acid and butanediol mononitrate, an NO donor when applied to the ocular surface. [13,14] Latanoprost acid lowers IOP by increasing uveoscleral outflow, while NO facilitates trabecular outflow by relaxation of the trabecular meshwork and Schlemm's canal. [15] Latanoprostene bunod has been demonstrated to effectively reduce intraocular pressure in several clinical trials, including VOYAGER and LUNAR. [16,17] Moreover, the JUPITER study confirmed that this pressure-lowering effect can be sustained over a long time period. [18]

Several mechanisms have been proposed to explain neural damage observed in glaucoma. One theory suggests that elevated IOP induces mechanical stress at the level of the lamina cribrosa, while another theory suggests that increased IOP leads to reduced ocular blood flow and perfusion, resulting in ischemia. Beyond IOP-related mechanisms, additional hypotheses emphasize the role of impaired vascular autoregulation, oxidative stress, mitochondrial dysfunction, and dysregulation of NO signaling in glaucomatous neurodegeneration. These diverse mechanisms likely interact, contributing to retinal ganglion cell loss and optic nerve head damage through a multifactorial and complex pathophysiological process. [19] In this context, the potential vascular effects of LBN have attracted growing interest. In addition to lowering IOP, LBN may influence ocular blood flow through its NO-donating properties. Nitric oxide is a key regulator of retinal vascular tone, mediating relaxation of vascular smooth muscle cells and thereby facilitating blood flow. Moreover, it plays a crucial role in maintaining IOP homeostasis. [20] Also, there is a significant amount of evidence that indicates NO production is diminished in individuals with primary open-angle glaucoma (POAG) and in preclinical animal models of the disease. [15,21,22]

The recent advancements in imaging technologies, such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA), have provided a more detailed understanding of the underlying mechanisms of damage. Mainly, losses in the retinal nerve fiber layer (RNFL) and ganglion cells are significant changes that can be detected with OCT. Furthermore, OCTA allows for detailed optic nerve head vascularity evaluation, providing valuable information on vessel density, flow velocity, and perfusion. Various studies using OCTA have reported that microvascular changes, including vessel density (VD), can be detected in the glaucomatous eye optic nerve and macula. [23-26] Previous studies have shown that certain topical ocular hypotensive drugs affect VD. [27]

The primary objective of this study was to evaluate the effects of LBN on structural and vascular parameters of the optic nerve and retina, as assessed by OCT and OCTA. Specifically, we aimed to investigate changes in RNFL thickness and optic nerve head and macular microvasculature, including vessel density and perfusion, before and after LBN treatment. This study provides a comprehensive assessment of both structural and vascular outcomes, with the goal of investigating the potential dual effects of LBN, beyond IOP reduction, on microvascular regulation. The findings may contribute evidence to inform clinical practice and guide future large-scale, long-term, and controlled studies evaluating the impact of LBN on glaucoma progression.

MATERIALS AND METHODS

The study was conducted in accordance with the tenets of the Declaration of Helsinki and ethical approval was obtained from the Ankara University Faculty of Medicine Human Research Ethics Committee.

This was a retrospective, single-center study, including 24 patients diagnosed with open-angle glaucoma (OAG) (POAG and pseudoexfoliation glaucoma [PEXG]) or ocular hypertension (OHT) who applied to the glaucoma clinic of Ankara University Department of Ophthalmology between June 2023 and May 2024. All patients were Caucasian. Inclusion criteria were having a diagnosis of OHT, POAG or PEXG and not receiving any previous treatment. OHT was defined as, IOP >21 mmHg in at least two measurements and no glaucomatous visual field defect or optic nerve head damage. OAG was defined as, the angle open in all quadrants on gonioscopic examination with the presence of glaucomatous visual field losses and the presence of glaucomatous optic nerve head damage on fundus examination (vertical enlargement of the optic pit and thinning of the neural rim; vertical cup/disc ratio >0.6, cup/disc asymmetry >0.2 between the two eyes). Patients with secondary glaucoma due to causes other than pseudoexfoliation, those who had undergone prior medical, laser, or surgical treatment, patients with angle-closure

glaucoma, significant corneal surface abnormalities, non-glaucomatous optic nerve disease, retinal pathology, ocular infections or inflammations, and media opacities were excluded from the study.

Demographic data, including age, gender, family history, and systemic diseases, were recorded during the initial examination. Afterward, routine ophthalmologic examinations of the patients were performed (best corrected visual acuity, IOP measurement with Goldmann applanation tonometry, anterior segment examination, iridocorneal angle examination, fundus, and optic disc examination). All patients were started on latanoprostene bunod (LBN, Vyzulta, Bausch & Lomb, Inc., USA) as the first treatment. All participants received OCT and OCTA imaging on the same day as Cirrus HD-6000 OCT with AngioPlex (Carl Zeiss Meditec, Dublin, CA, USA). Average RNFL thickness (µm), average and minimum ganglion cell layer-inner plexiform layer (GCL-IPL) thickness (µm) were recorded by OCT. Optic nerve head radial peripapillary capillary flux index (RPC-FI), radial peripapillary capillary perfusion density (RPC-PD)(%), macular vessel density (VD) (mm/mm²) and macular perfusion density (PD) (%) were recorded with OCTA. RNFL thickness was recorded using the Optic Cube 200x200 scanning protocol in OCT, and GCL-IPL thicknesses were recorded using the Macular Cube 512x128 scanning protocol. RPC-FI and RPC-PD were analyzed in the radial peripapillary capillary plexus slabs with ONH Angiography 4.5x4.5 mm scanning protocol (Figure 1A, 1B, 1C) Macular vessel and perfusion densities were recorded in superficial slabs with Angiography 6x6 mm scanning protocol (Figure 1D, 1E, 1F). All tests and measurements were repeated at the third and sixth months after treatment. The measurements did not include scanning images with signal strength below 6/10, artifacts or segmentation errors.

The parameters obtained before and after the treatment were statistically tested. Continuous variables were summarized as mean ± standard deviation or median (minimum-maximum), while categorical variables were presented as frequencies (percentages). The Shapiro-Wilk test was used to assess the normality of data distributions. Measurements between pretreatment vs. 3rd month follow-up and pretreatment vs. 6th month follow-up after treatment were compared using the paired t-test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data. Pairwise comparisons for significant results were adjusted using the Bonferroni correction to control for multiple testing. The correlation between baseline IOP and 6th-month follow-up OCTA parameters, including RPC-PD, RPC-FI, macular VD (central, inner, outer, and full), and macular PD (central, inner, outer, and full), was assessed using the Spearman correlation coefficient. The relationship between baseline OCT parameters, including average GCL-IPL thickness, minimum GCL-IPL thickness, average RNFL thickness, and 6th-month follow-up OCTA parameters, was evaluated using the Spearman correlation coefficient, except for the correlations between average RNFL thickness and RPC-PD and RPC-FI, which were normally distributed and were therefore assessed using the Pearson correlation coefficient. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using SPSS version 30.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The study included 48 eyes from 24 patients (15 females [62.5%], nine males [37.5%]). The average age at diagnosis was 59.9 years (range from 18 to 81). The diagnosis was OHT in 40 eyes (83.3%) and OAG in 8 eyes (16.7%) (5 with POAG [10.4%], 3 with PEXG [6.3%]) (Table 1). The tests and measurements were repeated at the 3rd and 6th months after treatment.

The mean pre-treatment IOP was 25.4±5.3 mmHg, which decreased to a mean of 17.3±3.0 mmHg at the third month after LBN treatment($p<0.001$). Comparing the initial with the third-month measurements, the average GCL-IPL thickness on OCT was 78.7 ± 12.8 µm pre-treatment and 79.5±10.0 µm post-treatment ($p=0.926$); minimum GCL-IPL thickness was 75.3±15.3 µm pre-treatment and 73.04±16.9 µm post-treatment ($p=1$); and mean RNFL thickness was 88.7±9.6 µm pre-treatment and 90.4±8.5 µm post-treatment ($p=0.146$). On OCTA, the RPC-PD was 44.5±2.1% pre-treatment and 44.02±1.8% post-treatment ($p=0.310$). The RPC-FI was 0.411±0.05 pre-treatment and 0.414±0.04 post-treatment ($p=1$). The superficial macular VD-central was 5.7±4.1 mm/mm² pre-treatment and 6.2±3.8 mm/mm² post-treatment ($p=1$). The superficial macular VD-inner was 13.2±5.2 mm/mm² pre-treatment and 13.9±4.9 mm/mm² post-treatment ($p=1$). The superficial macular VD-outer was 14.3±4.5 mm/

mm² pre-treatment and 15.0±3.9 mm/mm² post-treatment (p=1). The superficial macular VD-full was 13.9±4.7 mm/mm² pre-treatment and 14.6±4.1 mm/mm² post-treatment (p=1). The superficial macular PD-central was 12.4±9.5% pre-treatment and 13.6±8.9% post-treatment (p=1). The superficial macular PD-inner was 30.8±12.9% pre-treatment and 32.6±11.8% post-treatment (p=0.784). The superficial macular PD-outer was 34.8±11.7% pre-treatment and 36.1±10.2% post-treatment (p=1). The superficial macular PD-full was 33.3±11.7% pre-treatment and 35.0±10.2% post-treatment (p=1). Despite a statistically significant difference in IOP values between the pre-treatment and post-treatment third-month measurements, no significant differences were found in other parameters (Table 2).

Comparing pre-treatment IOP with the sixth months after LBN treatment, the mean pre-treatment IOP was 25.4±5.3 mmHg and 17.8±3.7 mmHg at the final measurement (p<0.001). On OCT, the average GCL-IPL thickness was 78.7±12.8µm pre-treatment and 80.4±8.6 µm post-treatment (p=1); minimum GCL-IPL thickness was 75.3±15.3µm pre-treatment and 74.7±13.3 µm post-treatment (p=1); and mean RNFL thickness was 88.7±9.6 µm pre-treatment and 90.3±9.4 µm post-treatment (p=1). On OCTA, the RPC-PD was 44.5±2.1% pre-treatment and 44.7±1.9% post-treatment (p=1). The RPC-FI was 0.411±0.05 pre-treatment and 0.416±0.04 post-treatment (p=0.360). The superficial macular VD-central was 5.7±4.1 mm/mm² pre-treatment and 7.3±4.8 mm/mm² post-treatment (p=0.076). The superficial macular VD-inner was 13.2±5.2 mm/mm² pre-treatment and 14.5±4.6 mm/mm² post-treatment (p=0.506). The superficial macular VD-outer was 14.3±4.5 mm/mm² pre-treatment and 15.4±4.2 mm/mm² post-treatment (p=0.218). The superficial macular VD-full was 13.9±4.7 mm/mm² pre-treatment and 14.9±4.2 mm/mm² post-treatment (p=0.284). The superficial macular PD-central was 12.4±9.5% pre-treatment and 16.2±11.3% post-treatment (p=0.074). The superficial macular PD-inner was 30.8±12.9% pre-treatment and 34.2±11.5% post-treatment (p=0.432). The superficial macular PD-outer was 34.8±11.7% pre-treatment and 37.7±11.0% post-treatment (p=0.208). The superficial macular PD-full was 33.3±11.7% pre-treatment and 36.3±10.9% at the sixth-month post-treatment measurement (p=0.238). Although there was a statistically significant difference in IOP values between the pre-treatment and post-treatment measurements, no significant difference was found in other parameters (Table 2).

There were no statistically significant correlations between pretreatment IOP and RPC-PD (ρ=0.113, p=0.449), RPC-FI (ρ=-0.262, p=0.075), superficial macular VD (central [ρ=0.177, p=0.235], inner [ρ=0.143, p=0.337], outer [ρ=0.060, p=0.689], full [ρ=0.085, p=0.570]), and PD (central [ρ=0.190, p=0.201], inner [ρ=0.140, p=0.347], outer [ρ=0.066, p=0.659], full [ρ=0.086, p=0.567] measured at the final examination) (Table 3).

A moderate positive statistically significant correlation existed between the pre-treatment average GCL-IPL thickness and the RPC-FI measured at the final examination (ρ=0.519, p<0.001). There was no correlation between the pre-treatment average GCL-IPL thickness and the RPC-PD (ρ=-0.127, p=0.412), superficial macular VD (central [ρ=-0.018, p=0.910], inner [ρ=0.080, p=0.605], outer [ρ=0.228, p=0.137], full [ρ=0.192, p=0.211]), and PD (central [ρ=-0.034, p=0.828], inner [ρ=0.057, p=0.712], outer [ρ=0.216, p=0.159], full [ρ=0.176, p=0.254]) measured at the final examination (Table 3 and Figure 2A).

A moderate positive statistically significant correlation was found between the pre-treatment minimum GCL-IPL thickness and the RPC-FI measured at the final examination (ρ=0.543, p<0.001). No correlation was found between the pre-treatment minimum GCL-IPL thickness and the RPC-PD (ρ=-0.088, p=0.570), superficial macular VD (central [ρ=0.072, p=0.643], inner [ρ=0.147, p=0.343], outer [ρ=0.280, p=0.066], full [ρ=0.243, p=0.112]), and PD (central [ρ=0.054, p=0.729], inner [ρ=0.122, p=0.431], outer [ρ=0.270, p=0.076], full [ρ=0.229, p=0.134]) measured at the final examination (Table 3 and Figure 2B).

A moderate positive statistically significant correlation existed between the pre-treatment average RNFL thickness and the RPC-FI measured at the final examination (Pearson r=0.499, p<0.001). No correlation was found between the pre-treatment average RNFL thickness and the RPC-PD (Pearson r=0.101, p=0.499), superficial macular VD (central [ρ=-0.167, p=0.261], inner [ρ=-0.089, p=0.553], outer [ρ=0.053, p=0.723], full [ρ=0.017, p=0.908]), and PD (central [ρ=-0.183, p=0.219], inner [ρ=-0.096, p=0.521], outer [ρ=0.042, p=0.778], full [ρ=0.006, p=0.970]) (Table 3 and Figure 2C).

Table 1. *Evaluation of demographic and clinical characteristics*		
Variable		
Age (years)	**Mean±SD**	59.92±15.65
	Median (Min – Max)	63.00 (18.00 – 81.00)
Gender, n(%)	Female	15 (62.5)
	Male	9 (37.5)
Diagnosis, n(%)	OHT	40 (83.3)
	OAG	8(16.7)
	§ POAG	5 (10.4)
	§ PEXG	3 (6.3)
OHT: Ocular Hypertension; PEXG: Pseudoexfoliation glaucoma; OAG: Open Angle Glaucoma; POAG: Primary open-angle glaucoma		

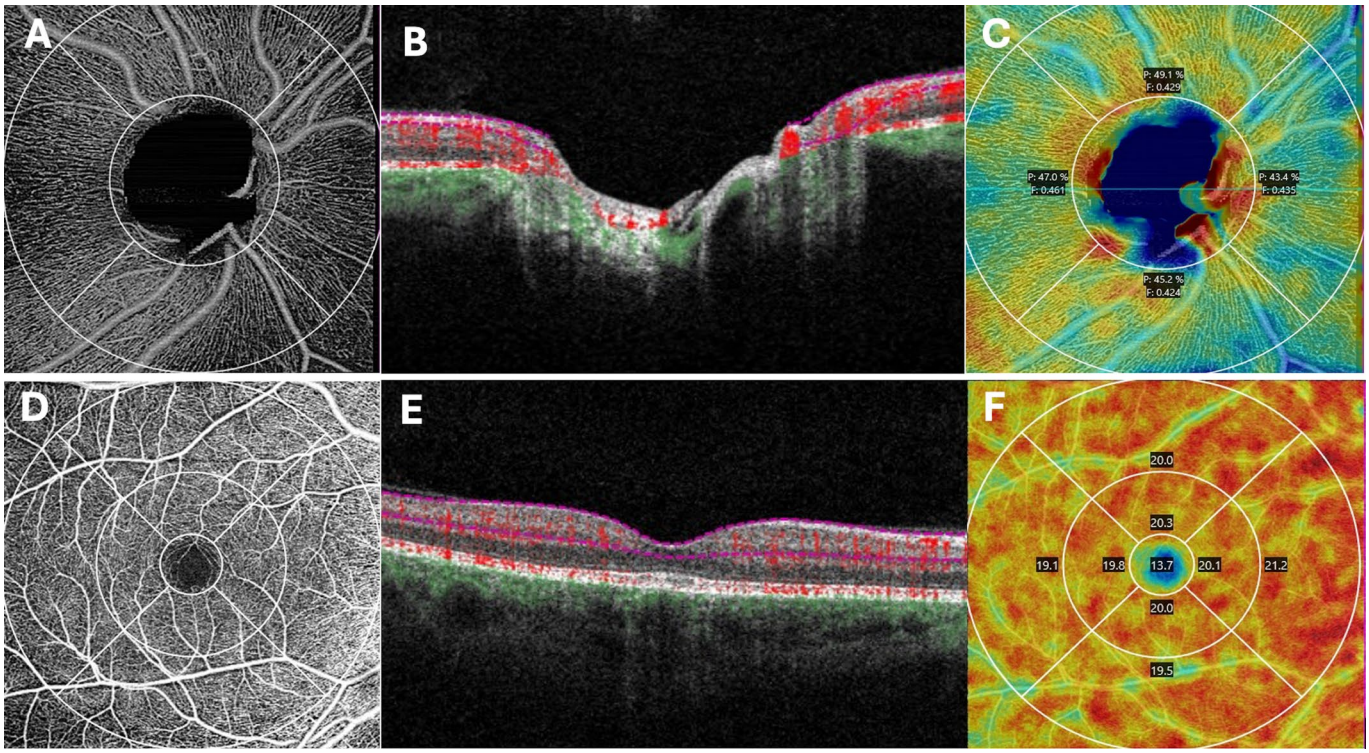


Figure 1. *Optical coherence tomography angiography image of the optic nerve head and macula of a representative case with ocular hypertension.*

A: En face images of the radial peripapillary capillaries of the optic nerve head; B: Corresponding B-scan segmentation of the optic nerve head; C: Vascular density map of radial peripapillary capillaries of the optic nerve head; D: En face image of the macular superficial capillary plexus; E: Corresponding B-scan segmentation of the macula; F: Vascular density map of the macular superficial capillary plexus

Table 2. *Baseline, first and second follow-up optical coherence tomography and optical coherence tomograpy angiography measurements*

	Baseline		3rd Month		6th Month		p value†	p value‡
	Mean±SD	Median (Min – Max)	Mean±SD	Median (Min – Max)	Mean±SD	Median (Min – Max)		
IOP	25.44±5.34	24.00 (15.00 – 42.00)	17.27±3.02	18.00 (10.00 – 22.00)	17.81±3.68	18.00 (10.00 – 34.00)	<0.001[a]	<0.001[a]
Average GCL-IPL Thickness	78.73 ± 12.76	82.00 (35.00 – 96.00)	79.49 ± 9.99	81.00 (42.00 – 98.00)	80.39 ± 8.63	82.00 (55.00 – 96.00)	0.926[b]	1.000[b]
Minimum GCL-IPL Thickness	75.27 ± 15.25	80.00 (23.00 – 94.00)	73.04 ± 16.93	77.00 (13.00 – 95.00)	74.70 ± 13.33	76.50 (31.00 – 94.00)	1.000[b]	1.000[b]
Average RNFL Thickness	88.71 ± 9.55	88.00 (67.00 – 108.00)	90.41 ± 8.54	90.00 (68.00 – 104.00)	90.34 ± 9.44	91.00 (63.00 – 106.00)	0.146[a]	1.000[b]
RPC-PD	44.52 ± 2.07	44.10 (41.70 – 52.40)	44.02 ± 1.82	44.10 (38.80 – 48.30)	44.71 ± 1.90	44.60 (39.80 – 49.20)	0.310[b]	1.000[b]
RPC-FI	0.41 ± 0.05	0.42 (0.30 – 0.48)	0.41 ± 0.04	0.42 (0.31 – 0.51)	0.42 ± 0.04	0.43 (0.31 – 0.48)	1.000[a]	0.360[b]
Macula VD Central	5.70 ± 4.10	5.85 (0.00 – 13.40)	6.23 ± 3.75	6.25 (0.10 – 17.50)	7.28 ± 4.79	6.40 (0.10 – 17.10)	1.000[b]	0.076[b]
Macula VD Inner	13.15 ± 5.23	14.10 (2.40 – 19.30)	13.94 ± 4.89	15.30 (1.20 – 20.80)	14.46 ± 4.56	15.40 (3.10 – 20.10)	1.000[b]	0.506[b]
Macula VD Outer	14.29 ± 4.51	15.50 (3.30 – 19.70)	14.98 ± 3.94	16.30 (2.70 – 19.50)	15.36 ± 4.20	16.20 (4.60 – 20.50)	1.000[b]	0.218[b]
Macula VD Full	13.90 ± 4.66	15.25 (3.40 – 19.30)	14.57 ± 4.07	15.95 (2.40 – 19.70)	14.91 ± 4.20	15.70 (4.50 – 20.20)	1.000[b]	0.284[b]
Macula PD Central	12.41 ± 9.45	12.60 (0.00 – 31.10)	13.64 ± 8.88	13.70 (0.10 – 42.60)	16.18 ± 11.32	13.60 (0.30 – 40.80)	1.000[b]	0.074[a]
Macula PD Inner	30.83 ± 12.86	33.30 (5.00 – 46.70)	32.57 ± 11.84	36.05 (2.40 – 46.70)	34.23 ± 11.52	35.80 (6.50 – 48.30)	0.784[a]	0.432[b]
Macula PD Outer	34.75 ± 11.65	38.45 (7.10 – 49.20)	36.07 ± 10.15	39.70 (6.20 – 48.30)	37.72 ± 11.00	40.40 (10.50 – 50.10)	1.000[b]	0.208[b]
Macula PD Full	33.29 ± 11.74	37.50 (7.20 – 48.00)	34.95 ± 10.23	37.80 (5.50 – 47.40)	36.31 ± 10.89	38.30 (10.10 – 48.90)	1.000[b]	0.238[b]

IOP: intraocular pressure; GCL-IPL: ganglion cell complex-inner plexiform layer; RNFL: retinal nerve fiber layer; RPC-PD: radial peripapillary capillary perfusion density; RPC-FI: radial peripapillary capillary flux index; VD: vascular density; PD: perfusion density
†: baseline vs. post-treatment third-month, ‡: baseline vs. post-treatment sixth-month, a: Paired t-test, b: Wilcoxon signed-rank test

Table 3. *Intraocular pressure (baseline), optical coherence tomography (baseline) and optical coherence tomography angiography (post-treatment 6th month) correlations*

	IOP		Average GCL-IPL Thickness		Minimum GCL-IPL Thickness		Average RNFL Thickness	
	r	p	r	p	r	p	r/ρ	p
RPC-PD	0.113	0.449	-0.127	0.412	-0.088	0.570	0.101†	0.499
RPC-FI	-0.262	0.075	0.519	<0.001	0.543	<0.001	0.499†	<0.001
Macula VD Central	0.177	0.235	-0.018	0.910	0.072	0.643	-0.167	0.261
Macula VD Inner	0.143	0.337	0.080	0.605	0.147	0.343	-0.089	0.553
Macula VD Outer	0.060	0.689	0.228	0.137	0.280	0.066	0.053	0.723
Macula VD Full	0.085	0.570	0.192	0.211	0.243	0.112	0.017	0.908
Macula PD Central	0.190	0.201	-0.034	0.828	0.054	0.729	-0.183	0.219
Macula PD Inner	0.140	0.347	0.057	0.712	0.122	0.431	-0.096	0.521
Macula PD Outer	0.066	0.659	0.216	0.159	0.270	0.076	0.042	0.778
Macula PD Full	0.086	0.567	0.176	0.254	0.229	0.134	0.006	0.970

IOP: intraocular pressure (pretreatment visits); GCC-IPL: ganglion cell complex-inner plexiform layer; RNFL: retinal nerve fiber layer; RPC-PD: radial peripapillary capillary perfusion density; RPC-FI: radial peripapillary capillary flux index; VD: vascular density; PD: perfusion density

† Pearson correlation was used for comparisons involving Average RNFL Thickness with ONH Perfusion and ONH Flux Index. Spearman correlation was used for all other comparisons.

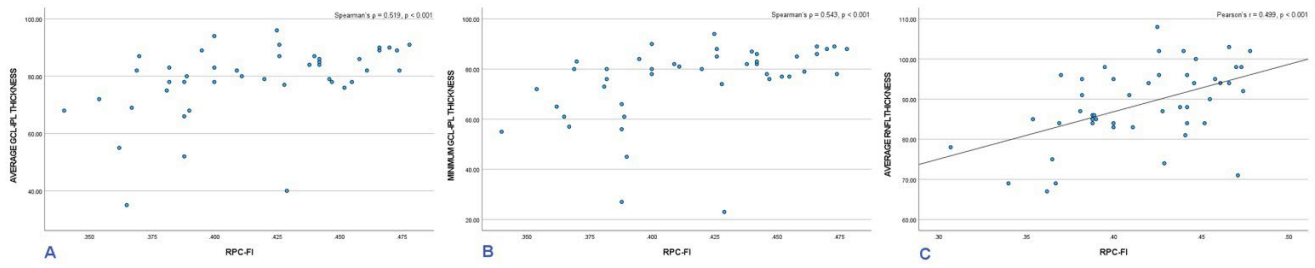


Figure 2. *Scatter plot analysis of the positive correlations of the radial peripapillary capillary plexus-flux index (RPC-FI) with structural optical coherence tomography (OCT) parameters. A: Correlations of the RPC-FI with average ganglion cell layer-inner plexiform layer (GCL-IPL) thickness; B: Correlations of the RPC-FI with minimum GCL-IPL thickness; C: Correlations of the RPC-FI with average retinal nerve fiber layer (RNFL) thickness. Correlation coefficients for panels A and B (GCL-IPL) were calculated using Spearman's rank correlation, whereas the coefficient for panel C (RNFL) was calculated using Pearson correlation.*

DISCUSSION

In this study, treatment with LBN resulted in a significant reduction in IOP among treatment-naive patients with OHT and OAG. However, no significant changes were observed in OCT or OCTA parameters over a six-month period. Moderate correlations were identified between baseline structural OCT parameters and the OCTA outcomes at the six-month visit; however, these findings should be interpreted cautiously due to the exploratory nature of the analysis.

This study demonstrated that the significant IOP-lowering effect of LBN is consistent with previous clinical trials. The VOYAGER study demonstrated that LBN provided superior IOP reduction compared to latanoprost. [16] Similarly, the LUNAR trial confirmed the effectiveness of LBN over timolol across various patient populations. [17] Additionally, the long-term JUPITER study reported sustained IOP reduction over a 12-month period in Japanese patients.[18] Together, these findings support the strong hypotensive efficacy of LBN, which was also observed in our study.

Many studies have shown that optic nerve head blood flow is significantly decreased in patients with glaucoma [28-30], and that ocular perfusion can increase after lowering IOP through medical or surgical intervention. [31-34] Earlier studies have examined ocular perfusion using fluorescein angiography or color Doppler imaging, techniques limited by low repeatability, invasiveness, and low resolution. OCTA is a non-invasive imaging modality that allows qualitative and quantitative assessment of microvascular structures at different levels in the macula, optic disc, and peripapillary area. [35] Although OCTA has recently been introduced in glaucoma, its use is less widespread than OCT. [36,37] The decrease in macular VD on OCTA in patients with glaucoma has been reported by many authors. [38-40] In the study by El-Nimri et al., it was shown that macular VD, especially in the superficial capillary plexus, was decreased in glaucoma patients and those suspected of glaucoma compared to healthy individuals. Furthermore, it was observed that the superficial capillary plexus VD was lower than that of the deep capillary plexus in glaucomatous eyes. [41] This is an expected finding due to the perfusion of the damaged GCL and RNFL from the superficial capillary plexus in glaucomatous eyes. [42,43]

Importantly, some studies have also demonstrated increases in ocular microvascular density after significant IOP reduction. Hollo et al. reported an increase in RPC-PD measured by OCTA in six eyes (with OHT and glaucoma) that were medically treated with IOP lowering of more than 50% [44], and Liu et al. found that latanoprost treatment was associated with increased optic nerve head and RPC vessel density. [45]

As the use of OCTA in glaucoma is a relatively recent development, only a limited number of studies have examined microvascular changes and ocular perfusion following LBN treatment. In a randomized, single-center clinical study by El-Nimri et al. on 50 eyes of 50 patients (10 healthy, 26 with OHT, and 14 with POAG) the authors compared retinal VD after topical treatment with LBN 0.024% and timolol maleate 0.5% (TM). OCTA imaging was performed with the Optovue Avanti-Angiovue Device (OptoVue Inc.; software version 2017.1.0.151). A significant increase in macular VD was observed in patients with OHT and OAG treated with LBN, with a trend toward an increase in peripapillary VD. No change was observed in the group treated with TM in macular VD, while a decrease in peripapillary VD was noted. No alterations in the healthy control group were noted in peripapillary or macular VD (n = 10). [27] In a recent prospective single-center study, Özer et al. evaluated 66 patients with newly diagnosed OAG, which included both POAG and PEXG. They compared these patients to 32 healthy controls. After one month of treatment with LBN 0.024%, the authors observed a mean IOP reduction of 7.7 mmHg, which corresponds to approximately 30% from baseline. The reductions in IOP were similar for both groups, with a decrease of 29.9% in the POAG group and 31.8% in the PEXG group. OCTA analysis revealed that in the choriocapillaris slab, vessel density in the superior quadrant significantly improved after treatment in both groups. [46]

In contrast, our study did not find significant changes in OCTA parameters over the six-month follow-up period. Several factors may explain this discrepancy: first, most participants had OHT, which may indicate that vascular alterations detectable by OCTA may not yet have developed. Second, the sample size was relatively small, limiting the statistical power. Third, the six-month follow-up period may have been insufficient to detect subtle

vascular changes. However, our findings are aligned with those of Hsueh et al., who reported no significant short-term OCT and OCTA changes in patients treated with LBN, suggesting that vascular and structural improvements may not be expected during early treatment. [47]

Other studies have indicated that different agents can lead to varying vascular responses. Nutterova et al. observed a significant increase in radial peripapillary capillary plexus VD in the third month following treatment in 46 patients treated with carteolol and 52 patients treated with latanoprost for high-pressure glaucoma. However, no statistically significant difference was identified in RNFL thickness between the two groups. [48] In the study by Lestak et al., statistically significant changes were observed in RNFL in patients with high-pressure glaucoma treated with beta-blockers, compared to the group treated with latanoprost and the group receiving combined glaucoma therapy. [49]

Latanoprostene bunod is a prostaglandin analog similar to latanoprost, with NO-donating moiety. Both latanoprost acid and NO reduce IOP in humans. [50-54] Endogenously, endothelial NO (eNOS) is synthesized in the trabecular meshwork, ciliary muscle, and Schlemm's canal. [55] While latanoprost acid lowers IOP by increasing uveoscleral outflow, NO facilitates trabecular outflow by relaxing the trabecular meshwork and Schlemm's canal. [15] In the study by Samaha et al. investigating the effects of LBN and latanoprost on optic nerve head oxygen saturation and optic nerve head blood volume in 21 healthy volunteers, it was demonstrated that LBN resulted in a significant 4% increase in optic nerve head oxygen saturation in comparison to latanoprost. Furthermore, it was demonstrated that LBN resulted in a more than twofold increase in optic nerve head blood volume, with a higher optic nerve head blood volume compared to latanoprost. [56] Although these findings indicate a biological basis for vascular effects related to the nitric oxide donor component, our clinical data did not reveal measurable changes in OCTA within a six-month period.

A moderate positive statistically significant correlation was found between the OCT parameters (average GCL-IPL thickness, minimum GCL-IPL thickness, and average RNFL thickness) and RPC-FI at the final measurement (Spearman $r=0.519$, $p<0.001$; Spearman $r=0.543$, $p<0.001$; Pearson $r=0.499$, $p<0.001$). These findings indicate a significant association between retinal structural integrity and peripapillary microvascular perfusion in patients with glaucoma or ocular hypertension. The observed positive correlation suggests that greater thickness of the GCL-IPL and RNFL is associated with higher RPC-FI values, indicative of enhanced peripapillary blood flow. Clinically, this relationship suggests that RPC-FI may provide complementary information regarding retinal structural status. These findings support the potential value of combining OCT and OCTA assessments to provide a more comprehensive evaluation of disease status and progression in glaucoma management.

This study has several limitations. First, the sample size was relatively small. Second, the follow-up period was short, and the retrospective design lacked a control group. Third, as a limitation, both eyes of each patient were included in the analysis, while the potential correlation between fellow eyes was not explicitly accounted for in the statistical models. This should be considered when interpreting the statistical estimates. Additionally, as most participants had OHT, the ocular blood flow may not yet have been compromised, which could have influenced the results. This might explain the absence of difference in the OCTA parameters before and after LBN treatment.

This study differs from other studies in that OCT and OCTA findings were evaluated together in cases treated with LBN. To our knowledge, no study has been found in the literature examining the correlation between OCT and OCTA parameters in glaucoma cases treated with LBN. The exploratory analysis of correlations between structural and vascular parameters represents strengths and provides new insights.

In conclusion, LBN effectively lowered IOP in treatment-naive patients with OHT and OAG. However, we did not observe any measurable early changes in optical OCT or OCTA parameters. While our findings are limited, they suggest that the vascular and structural effects of LBN may not be apparent in the short term. Therefore, there is a need for long-term, controlled studies involving a larger number of cases to better understand the impact of LBN on ocular perfusion.

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Conflict of Interest

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