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Effect of methylphenidate treatment on macula and optic disc microvascularity in children with attention-deficit/hyperactivity disorder: A retrospective study

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MAIN POINTS

- This study is among the first to investigate the effects of methylphenidate (MPH) treatment on retinal and optic nerve head microvasculature in children with attention-deficit/hyperactivity disorder (ADHD).
- Significant increases in superficial and deep capillary plexus vessel densities were observed after MPH treatment.
- Radial peripapillary capillary plexus vessel density showed no significant change between pre- and post-treatment measurements.
- These findings suggest that MPH may exert regional and limited effects on retinal microcirculation, and that OCTA could serve as a sensitive tool for monitoring retinal vascular changes in children with ADHD.

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ABSTRACT

Aim: This study aimed to investigate macular and optic nerve head (ONH) microvascularization in children diagnosed with attention deficit hyperactivity disorder (ADHD) before and 6 months after the initiation of methylphenidate (MPH) treatment, and to compare these findings with a healthy control group.

Materials and Methods: This retrospective study included 66 eyes of 66 patients with ADHD and 74 eyes of 74 healthy controls, all aged 6--17 years. Participants were grouped as follows: newly diagnosed treatment-naive ADHD patients, the same patients after 6 months of MPH treatment, and healthy controls. Specular microscopy findings, pupil size (PS), anterior chamber depth (ACD), and lens thickness (LT) values of participants were recorded. Additionally, retinal nerve fiber layer (RNFL) thickness, central macular thickness (CMT), and optic nerve head (ONH) radial peripapillary capillary plexus (RPCP), superficial capillary plexus (SCP), and deep capillary plexus (DCP) vessel density (VD) parameters were measured.

Results: Statistically significant increases in whole-image VD values for SCP and DCP were observed following MPH treatment (both $p<0.001$). Additionally, SCP VD values were significantly lower in treatment-naive children with ADHD compared to healthy controls, while RPCP VD values were higher ($p = 0.006$ and $p = 0.010$, respectively). No statistically significant differences in CMT, RNFL thickness, or anterior segment parameters (PS, ACD, LT) were observed either after MPH treatment within the ADHD group or between the control group and treatment-naive ADHD patients.

Conclusion: In children diagnosed with ADHD, significant increases in SCP and DCP values were observed following MPH treatment. These findings indicate the need for further studies to evaluate the effects and clinical significance of MPH treatment on retinal microvasculature.

Keywords: Attention deficit hyperactivity disorder, Methylphenidate, Optical coherence tomography angiography

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity, resulting from the interaction of genetic and environmental factors [1,2]. Neuroimaging studies have elucidated the neural basis of the disorder by revealing structural differences in the brain [3-7]. Neurotransmitter imbalance in the prefrontal cortex forms the basis of methylphenidate (MPH) treatment [8,9].

Studies indicate that ocular parameters have been investigated to identify biomarkers associated with ADHD. In this context, the macula and optic nerve head (ONH) have become focal points, with ocular findings being evaluated in detail using imaging techniques such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). Based on the vascular theory of neurodevelopmental disorders, it has been suggested that individuals with ADHD may exhibit significant alterations in the vascular structures of the macula and ONH [4-10].

Methylphenidate, commonly used in the treatment of ADHD, is known to alter sympathetic activation in the central nervous system through its effects on neurotransmitter systems. It is thought that this effect could influence the circulation and density of microvascular structures within the retina and ONH. Additionally, considering the potential effects of MPH treatment on anterior segment structures, particularly the corneal endothelium, our study evaluated anterior segment parameters including corneal endothelial cell density (ECD) measured by specular microscopy, anterior chamber depth (ACD), and lens thickness (LT).

This study aimed to evaluate superficial capillary plexus (SCP), deep capillary plexus (DCP), and radial peripapillary capillary plexus (RPCP) vessel density (VD) values in treatment-naive children with ADHD, to determine the changes in these values after six months of MPH treatment, and to investigate the potential effects of MPH on retinal and ONH microvascular structures by comparing these results with healthy controls.

MATERIALS AND METHODS

This retrospective case-control study was conducted retrospectively following approval by the ethics committee and in accordance with the principles of the Declaration of Helsinki. (Ethics approval code: KAEK/2022.05.153).

Given the retrospective nature of the study, existing patient data were anonymized to ensure confidentiality in accordance with ethical principles.

The study was conducted on patients diagnosed with ADHD between January 2020 and September 2022 at the Child and Adolescent Psychiatry Clinic of our hospital, who were subsequently referred to the Ophthalmology Clinic for routine ocular examinations. Two groups of participants were included in the study. Group 1 included randomly selected 66 eyes from 66 ADHD patients who were treatment-naive before MPH initiation, along with the evaluations performed on the same patients after 6 months of oral MPH treatment. Group 2 included 74 randomly selected eyes from 74 healthy children matched to the ADHD group in terms of age and gender.

All participants were evaluated by child and adolescent psychiatrists using the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version Turkish Form (K-SADS-PL-T) [11,12].

The inclusion criteria were: Best-corrected visual acuity (BCVA) $\geq$20/20, spherical equivalent (SE) (KR-8900, Topcon Corporation, Japan) refractive error within ±3 diopters as assessed by cycloplegic refraction, and intraocular pressure (IOP) $\leq$21 mmHg.

Exclusion criteria included: History of intraocular surgery, presence of any systemic or ocular disease, individuals with inadequate image quality due to media opacity, and participants unable to sufficiently cooperate during ocular examination or imaging procedures. Additionally, individuals with a history of psychiatric disorders, learning or behavioral changes, or medication use were excluded from the study.

During ophthalmological examinations, participants underwent Snellen best-corrected visual acuity (BCVA) measurement, intraocular pressure (IOP) measurement using applanation tonometry, axial length measurement via optical biometry (Tomey Optical Biometry OA-2000 Opt-Meas V.4E) and imaging using swept-source OCT (SS-OCT) and OCT angiography (OCTA). Additionally, to assess the potential effects of MPH treatment on anterior segment structures, corneal ECD was measured using specular microscopy (Tomey EM-4000, Japan), and parameters such as ACD, pupil size (PS) and LT were recorded. The presence of lens opacities was evaluated subjectively via slit-lamp biomicroscopic examination. All measurements were performed by an experienced retina specialist (SE).

Swept-Source OCT imaging protocol

OCT imaging was performed using the Topcon DRI OCT Triton (Topcon Corporation, Tokyo, Japan), which utilizes a laser source with a wavelength of 1050 nm and an A-scan rate of 100,000 scans per second. For macular evaluation, a raster scanning pattern within a 6×6 mm area centered on the macula was employed. Central macular thickness (CMT) was measured using the Early Treatment Diabetic Retinopathy Study grid, specifically within the central 1-mm subfield. Retinal nerve fiber layer (RNFL) assessment was conducted using a 6×6 mm scanning area centered on the optic disc. The device's internal eye-tracking system and artifact removal algorithm were actively utilized to enhance image quality and consistency. A minimum OCT image quality score of 90 was required for acceptance.

Swept-Source OCT angiography imaging protocol

Macular OCTA imaging was performed over a 3×3 mm scanning area centered on the macula. Optic disc OCTA imaging for RPCP was conducted over a 4.5×4.5 mm scanning area centered on the optic disc. Each OCTA scan cube comprised 320 B-scan clusters, with automated segmentation of all vascular plexuses performed using IMAGEnet6 software. Manual segmentation corrections were applied when necessary. RPCP was defined as the vascular structures between the internal limiting membrane and the lower boundary of the RNFL. A minimum image quality score of 70 was required for OCTA images to be included in the analysis.

To ensure measurement reliability and optimal image quality in young patients with ADHD, all examinations were con-

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ducted by the same investigator under conditions designed to optimize patient attention levels. Furthermore, to minimize diurnal variation, all assessments were performed between 09:00 AM and 11:00 AM [13].

Statistical analysis

In this study, continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as numbers and percentages. The normality distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. To compare individuals with ADHD and the control group, an independent samples t-test was utilized for variables with normal distribution, whereas the Mann-Whitney U test was used for those not normally distributed. For variables analyzed using non-parametric tests, descriptive statistics were presented as median (interquartile range) or median (minimum–maximum), in accordance with best statistical practices. Pre- and post-treatment values of patients with ADHD were compared using the paired samples t-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables. Associations between categorical variables were evaluated using the Chi-square test. The 95% confidence intervals (CI) for differences between groups were calculated and reported as footnotes beneath the respective tables. Statistical analyses were conducted using IBM SPSS Statistics, Version 28.0 (Armonk, NY: IBM Corp.), with a significance level set at $p<0.05$. The minimum required sample size was calculated using G*Power software (version 3.1.9.7, Heinrich Heine University, Düsseldorf, Germany). A priori power analysis was performed for a two-tailed paired-samples t-test with an alpha level of 0.05, statistical power (1−β) of 0.80, and a medium effect size of 0.50, as defined by Cohen. The analysis revealed that a minimum of 34 participants would be necessary to detect a significant within-subject difference. Given that our study included 66 treatment-naive ADHD patients, the statistical power was deemed sufficient.

RESULTS

A total of 140 eyes from 140 participants were included in this study. No significant differences were observed between groups regarding demographic and clinical characteristics, including age, sex distribution, cycloplegic SE values, IOP, ECD, axial length, ACD, PS, LT, CMT, RNFL thickness, and rim volume. These findings indicate that the study groups were comparable, sharing similar baseline ocular characteristics. Additionally, among the ADHD patients, no statistically significant changes were observed in the previously mentioned parameters at the 6-month evaluation after MPH treatment compared to baseline ($p>0.05$ for all parameters). At the 6-month follow-up, no participants developed lens opacity.

IOP; intraocular pressure, ECD; endothelial cell density, ACD; anterior chamber depth, PS: pupil size, LT; lens thickness, CMT; central Macular thickness, RNFL; retinal nerve fiber layer

Values are expressed as mean ± standard deviation. The 95% confidence intervals (CI) for differences between groups are as follows: age (-1.60; 0.20), IOP (-0.90; 0.50), ECD (-27.50; 160.50), axial length (-0.85; 0.05), ACD (-0.25; 0.05), PS (-0.01; 0.81), LT (-0.06; 0.04), CMT (-4.20; 14.40), RNFL (-7.30; 10.30), and rim volume (-0.07; 0.07).

In the treatment-naive ADHD group (Group 1a), the mean whole-image SCP VD was significantly lower compared to healthy controls (Group 2) ($p = .006$). Post-treatment (Group 1b), a significant increase was observed in the whole-image SCP ($p < .001$). Although SCP values in the superior quadrant were numerically higher in treatment-naive ADHD patients compared to healthy controls, this difference was not statistically significant ($p = .177$). Following MPH treatment, there was a significant increase in the superior quadrant ($p < .001$); however, no statistically significant changes were observed in temporal, inferior, and nasal quadrants compared to pre-treatment values. These findings suggest that MPH treatment may exert region-specific effects on SCP.

Regarding DCP VD, pre-treatment values in the ADHD group (Group 1a) showed no statistically significant differences compared to healthy controls. Following MPH treatment, DCP values significantly increased in the whole image, temporal, and nasal quadrants ($p < .001$, $p < 0.001$, and $p = .025$, respectively), while a statistically significant but small decrease was observed in the superior and inferior quadrants ($p = .037$ and $p = .049$). These findings suggest that MPH treatment may exert region-specific effects on deep retinal microvascular density. Detailed results are presented in Table 2.

In the treatment-naive ADHD group (Group 1a), the RPCP VD of the ONH was significantly higher in the whole-image and superior quadrant averages compared to healthy controls (Group 2). Following MPH treatment, no significant differences in RPCP vessel density were observed when comparing pre-treatment (Group 1a) and post-treatment (Group 1b) measurements of the same patients. A comparison between the post-treatment patient group (Group 1b) and healthy controls (Group 2) was not performed. These findings suggest that MPH treatment does not have a pronounced effect on RPCP vessel density. Detailed results of the RPCP vessel density analysis are summarized in Table 3.

DISCUSSION

Attention deficit hyperactivity disorder is a complex and multifactorial neurodevelopmental disorder investigated through various ocular structures and parameters [1,4,10]. As extensions of the central nervous system, the retina and ONH can provide important insights into the pathophysiology of ADHD. Recent advances in OCT technology have enabled the identification of alterations in ONH and macular parameters, highlighting retinal manifestations of neuropsychiatric disorders [4,14-19]. Grönlund et al. reported significant morphological changes in the SCP, DCP, and ONH in children

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Table 1. Demographic and clinic characteristics of the study participants.

	Group 1 (a) (treatment naive)	Group 1 (b) (post-treatment)	Group 2 (control)	p 1(a) &1(b)	1(a) & 2
Age (years)	9 (8-10.5)	-	10.5 (9-13)	-	0.122[a]
Sex (female/male)	30/36	-	36/38	-	0.874[b]
Spherical equivalent (D)	0.00±0.60	0.05±0.40	--0.08±0.45	0.574[c]	0.388[c]
IOP (mmHg)	14.2±1.7	14.3±1.5	14.4±3.0	0.721[c]	0.924[c]
ECD (cells/mm^2)	3022.3±222.5	3020.1±212.6	2955.8±323.7	0.954[c]	0.164[c]
Axial length (mm)	23.0±0.5	23.1±0.5	23.4±1.3	0.936[c]	0.089[c]
ACD (mm)	3.78 (3.67--3.93)	3.78 (3.67--3.93)	3.71 (3.19--4.41)	1.0[a]	0.075[a]
PS (mm)	7.3 (6.73--8.08)	6.99 (6.36--7.84)	6.86 (6.05--7.95)	0.103[a]	0.054[a]
LT (mm)	3.49 (3.43--3.57)	3.49 (3.43--3.57)	3.48 (3.37--3.63)	1.0[a]	0.200[a]
CMT (µm)	278.1 (259.70--302.90)	277.71 (270.29--287.71)	274.13 (262.23--290.17)	0.589[a]	0.105[a]
RNFL (µm)	79.69 (61.23--104.57)	80.34 (63.32--103.28)	80.05 (72.29--90.51)	0.941[a]	0.634[a]
Rim volume(mm^3)	0.38 (0.29--0.49)	0.37 (0.28--0.50)	0.37 (0.26--0.52)	1.0[a]	0.630[a]

[a] Mann–Whitney U test, [b] Chi-square test, [c] Independent-samples t-test, [d] Paired-samples t-test. Values are expressed as median (interquartile range) for variables analyzed using non-parametric tests (Mann–Whitney U test), and as mean ± standard deviation for variables analyzed using parametric tests (independent- or paired-samples t-test). Categorical variables are presented as counts and percentages. *p < 0.05. Bold values represent the variables which show statistical significance.

Table 2. Vessel density values of the superficial and deep capillary plexus in the study participants.

		Group 1 (a) (treatment naive)	Group 1 (b) (post-treatment)	Group 2 (control)	p 1(a) &1(b)	1(a) & 2
SCP VD (%)	Whole Image	43.07 (39.45--47.95)	44.34 (41.70--47.90)	45.18 (42.19--49.21)	**<0.001*,b**	**0.006*,a**
	Superior	46.42 (44.81--48.59)	47.26 (45.88--49.12)	44.89 (42.53--48.07)	**<0.001*,b**	0.177[a]
	Temporal	44.65 (43.21--46.59)	44.57 (43.25--46.35)	44.30 (42.00--47.40)	0.368[b]	0.086[a]
	Inferior	46.32 (44.71--48.49)	45.88 (44.62--47.59)	44.41 (41.59--48.21)	0.060[b]	0.397[a]
	Nasale	44.88 (43.04--47.36)	44.91 (43.24--47.16)	44.92 (42.73--47.86)	0.276[b]	0.071[a]
DCP VD (%)	Whole Image	45.53 (41.68--50.72)	48.01 (44.62--52.58)	46.09 (41.43--52.37)	**<0.001*,b**	0.142[a]
	Superior	48.36 (46.41--51.00)	47.83 (46.28--49.92)	46.66 (44.70--49.30)	**0.037*,b**	0.101[a]
	Temporal	48.61 (46.37--51.63)	49.63 (48.08--51.72)	48.64 (46.57--51.43)	**<0.001*,b**	0.351[a]
	Inferior	48.04 (46.54--50.05)	47.87 (46.55--49.65)	45.69 (43.33--48.87)	**0.049*,b**	0.231[a]
	Nasale	49.15 (46.56--52.64)	50.25 (48.81--52.19)	48.41 (46.17--51.43)	**0.025*,b**	0.391[a]

[a] Mann–Whitney U test, [b] Wilcoxon signed-rank test. Values are expressed as median (interquartile range) for all parameters, as they were analyzed using non-parametric tests. *p < 0.05. Bold values represent the variables which show statistical significance.SCP: Superficial Capillary Plexus, DCP: Deep Capillary Plexus VD: Vessel Density.Values are expressed as mean ± standard deviation. The 95% CI for differences between groups are as follows: For comparison between Group 1(a) and Group 1(b): SCP whole image (-1.72; -0.48), superior quadrant (-1.26; -0.34), temporal quadrant (-0.43; 0.63), inferior quadrant (-0.02; 1.02), nasal quadrant (-0.56; 0.56); DCP whole image (-3.48; -1.32), superior quadrant (0.04; 1.16), temporal quadrant (-1.42; -0.38), inferior quadrant (0.00; 0.40), nasal quadrant (-1.68; -0.12).For comparison between Group 1(a) and Group 2: SCP whole image (-3.41; -0.59), superior quadrant (-0.48; 3.28), temporal quadrant (-0.11; 0.51), inferior quadrant (-1.10; 2.40), nasal quadrant (-0.09; 0.29); DCP whole image (-1.63; 0.23), superior quadrant (-0.33; 1.73), temporal quadrant (-0.44; 0.44), inferior quadrant (-0.18; 2.58), nasal quadrant (-0.81; 2.41).

Table 3. Optic nerve head radial peripapillary capillary plexus vessel density of the study participants.

		Group 1 (a) (treatment naive)	Group 1 (b) (post-treatment)	Group 2 (control)	p 1(a) &1(b)	1(a) & 2
RPCP VD (%)	Whole Image	55.39 (53.61--57.79)	55.47 (53.57--58.03)	53.80 (51.50--56.90)	0.313[b]	**0.010*,a**
	Superior	57.76 (56.38--59.62)	57.62 (56.01--59.79)	55.94 (53.87--58.73)	0.594[b]	**0.035*,a**
	Temporal	54.20 ± 2.20	54.30 ± 2.00	54.20 ± 3.40	0.185[c]	0.066[a]
	Inferior	57.67 (56.35--59.45)	57.75 (56.31--59.69)	56.55 (54.54--59.26)	0.313[b]	0.100[a]
	Nasale	57.10 ± 2.70	57.20 ± 2.80	56.30 ± 3.70	0.219[d]	0.730[a]

[a] Mann–Whitney U test, [b] Wilcoxon signed-rank test, [c] Paired-samples t-test, [d] Independent-samples t-test. Values are presented as median (interquartile range) for variables analyzed using non-parametric tests (Wilcoxon signed-rank test), and as mean ± standard deviation for those analyzed using parametric tests (paired-samples t-test), specifically in the temporal and nasal quadrants. *p < 0.05. Bold values indicate statistically significant differences. RPCP: Radial peripapillary capillary plexus, VD: Vessel Density. Values are expressed as mean ± standard deviation. The 95% confidence intervals (CI) for differences between groups were as follows:For comparison between Group 1(a) and Group 1(b): RPCP whole image (-0.40; 0.80), superior quadrant (-0.29; 0.49), temporal quadrant (-0.74; 0.14), inferior quadrant (-0.29; 0.49), nasal quadrant (-0.51; 0.31). For comparison between Group 1(a) and Group 2: RPCP whole image (0.61; 4.39), superior quadrant (0.12; 3.68), temporal quadrant (-0.62; 0.02), inferior quadrant (-0.22; 2.42), nasal quadrant (-1.12; 3.32).

with ADHD, suggesting that these findings may reflect early developmental impairments in neural and vascular tissues of the brain [14]. In the present study, we investigated alterations in macular and ONH microvasculature, as well as the potential effects of MPH treatment on these structures.

In our study, no differences were detected among the groups regarding global RNFL thickness, which is consistent with previous studies [1,4,20]. This finding supports the idea

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that ADHD is a neurodevelopmental disorder rather than a neurodegenerative one. Additionally, no significant differences were observed in quadrant analyses of RNFL thickness. Similarly, CMT did not differ significantly among the three groups, aligning well with existing literature [4,21,22]. Nevertheless, conflicting findings have also been reported in other studies [23,24]. These discrepancies may arise from technical differences among OCT devices (e.g., variations in resolution and segmentation algorithms). Although such technical differences would affect all participants similarly within a given study, inconsistencies between different studies may result from the utilization of various OCT devices. Furthermore, demographic characteristics (e.g., age, gender distribution, ethnicity) and clinical conditions (e.g., refractive errors, concurrent systemic diseases, medication usage) of study populations could represent confounding factors affecting OCT measurements. Thus, it is crucial to consider these potential confounders when interpreting results across different studies.

Literature regarding microvascular parameters of the macular region is limited. To date, only one previous study has compared OCTA values of the macula in individuals diagnosed with ADHD who were treated with MPH versus those who were not. Tarakcioglu et al. conducted a cross-sectional analysis of 80 treatment-naive children with ADHD and 106 children with ADHD treated with MPH, finding differences in choriocapillaris flow between the groups [10]. However, no significant differences were observed between the groups in SCP and DCP analyses. Researchers suggested that MPH may have only a limited effect on retinal blood flow. In contrast, our study compared OCTA values within the same individuals before and after MPH treatment. By using this within-subject comparative method, heterogeneity caused by inter-individual variability was minimized, leading to potentially more reliable and consistent results. Using this approach, we observed significant increases in SCP measurements in the whole image and superior quadrants. Regarding DCP, MPH treatment led to significant increases in the whole image, temporal, and nasal quadrants, but small yet statistically significant decreases in the superior and inferior quadrants, suggesting region-specific vascular responses. These findings suggest that MPH treatment may cause regional variations in retinal microvasculature. MPH inhibits the reuptake of dopamine and norepinephrine, thereby increasing levels of these neurotransmitters in the synaptic cleft. It has been hypothesized that this increase may lead to vasodilation of cerebral and retinal microvascular structures, enhancing blood flow [25]. This mechanism could explain the observed regional increases in retinal microvascular parameters following MPH treatment in our study. Additionally, these results support the idea that MPH might have quadrant-specific effects on retinal microvascular structures, further highlighting OCTA as a sensitive tool for assessing retinal blood flow in ADHD patients. Our study is the first to compare macular OCTA parameters before and after treatment within the same subjects, which reduces potential confounding effects arising from inter-individual variability.

Recent studies have demonstrated that OCTA is effective for assessing ONH microvascularization [26-29]. Wang et al. [27] reported decreased ONH VD in neurodegenerative diseases such as multiple sclerosis, while Asanad et al. found reduced temporal peripapillary VD in patients with schizophrenia [28]. In our study, treatment-naive ADHD patients exhibited significantly higher RPCP VD values, especially in the superior quadrant and whole-image areas, compared to healthy controls. While neuronal cell loss in neurodegenerative diseases typically leads to reduced retinal and optic nerve head vessel densities, neurodevelopmental disorders may exhibit increased microvascular density due to heightened sympathetic activation and differences in autoregulatory mechanisms [27,28]. This variation could be associated with increased vascular reactivity observed in cerebral and retinal vascular structures in ADHD.

RPCP VD did not show a significant change after MPH treatment compared to pretreatment values. This suggests that MPH may have a limited effect on potential increases in vascular reactivity. However, the absence of a post-treatment comparison with healthy controls limits definitive conclusions. Therefore, further prospective comparative studies involving healthy controls are needed, particularly to evaluate post-treatment changes.

MPH, commonly used in the treatment of ADHD, is an α1-sympathomimetic amine with adrenergic and anticholinergic properties, potentially causing ocular side effects such as mydriasis, accommodation disturbances, and transient visual disturbances [10,14,30-33]. In our study, a minimal but statistically insignificant increase in pupil diameter was observed after MPH treatment. Although previous reports indicate that MPH may transiently elevate IOP our findings suggest that MPH treatment is not associated with clinically significant changes in IOP [30,31,33]. Despite earlier reports proposing that MPH could significantly decrease ACD after cycloplegia and thereby increase glaucoma risk, no significant differences were found regarding this parameter in our study [31]. Additionally, despite the suggestion that long-term MPH use may induce lens opacities, we did not detect any lens opacity during the 6-month follow-up period [27]. These findings suggest that ocular side effects related to MPH may vary based on duration and dosage. A previous study reported that MPH does not exhibit significant toxic effects on ECD [34]. Our study also supports this, demonstrating no significant change in corneal endothelial cell density associated with MPH treatment. However, due to the retrospective design of our study, our results indicate associations rather than causality and should therefore be interpreted with caution. Prospective longitudinal studies are needed to clarify these causal relationships.

One of the significant strengths of our study is the compar-

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ison of pre- and post-treatment data within the same individuals, enhancing methodological consistency and homogeneity of data. However, our study has several limitations. Firstly, the retrospective design of the study itself constitutes a primary limitation. Additionally, our sample size was relatively small. MPH doses were standardized, and thus, the dose-response relationship was not investigated. The relatively short duration of the study limits the evaluation of long-term effects. Furthermore, the absence of 6-month follow-up data for the healthy control group restricts our ability to differentiate whether microvascular changes observed in the ADHD group were directly related to MPH treatment or resulted from natural developmental processes. Future prospective studies with larger sample sizes, inclusion of healthy controls, and extended follow-up periods are necessary to better understand the long-term effects of MPH on retinal microvascular structures. Furthermore, although the study was initially labeled as cross-sectional, its retrospective nature—characterized by reliance on previously recorded data and the inclusion of both within-subject (pre- and post-treatment) and between-group (ADHD vs. control) comparisons—more accurately reflects a retrospective study design. This clarification has been implemented throughout the manuscript to enhance methodological accuracy.

CONCLUSION

In conclusion, this study demonstrates that MPH treatment in children with ADHD significantly increases SCP and DCP vessel density in certain regions of the macula but does not lead to a significant change in RPCP vessel density. These findings suggest that MPH may exert specific and regional effects on retinal microvascular circulation, whereas its impact on optic disc perfusion appears to be limited. We propose that OCTA may serve as a clinical monitoring tool for assessing retinal vascular effects associated with MPH treatment in individuals diagnosed with ADHD. Further comprehensive studies are needed to better elucidate potential microvascular changes related to MPH therapy.

Ethics Committee Approval: Ethical approval for this study was received from Başakşehir Çam ve Sakura City Hospital Clinical Research Ethics Committee (Date: 20.09.2022, Decision no: KAEK/2022.05.153).

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