Investigation of the optic disc and retinal microvasculature by optical coherence tomography angiography in children with asthma

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Abstract:
PURPOSE: To assess the optic disc and retinal microvasculature by optical coherence tomography angiography (OCTA) in asthmatic children.

MATERIALS AND METHODS: Thirty asthmatic children (asthma group) and 30 control age- and sex-matched healthy controls (control group) were included in this cross-sectional study. The asthma group was then divided into two subgroups according to the presence of inhaled steroid use. Demographic findings were noted. Retinal nerve fiber layer (RNFL) thickness and vessel density in different sections of the retina and optic nerve head were analyzed by OCTA.

RESULTS: RNFL thickness for temporal quadrants and flow area for outer retina levels were significantly lower in the asthma group than the control group (72.58 ± 10.99 µm vs 77.73 ± 9.73 µm, \( P = 0.015 \), and 0.60 ± 0.31mm\(^2\) vs. 0.72 ± 0.31mm\(^2\), \( P = 0.047 \), respectively). However, inside disc vascular densities were significantly higher in the asthma group when compared to controls (55.16% ± 3.71% vs. 52.08% ± 3.79%, \( P < 0.001 \)). Inside disc vascular densities were also significantly higher, and RNFL thickness for temporal quadrants was significantly lower in the asthmatic patients without steroid use subgroup when compared to others (\( P < 0.001 \), \( P = 0.012 \), respectively).

CONCLUSION: Lower values of temporal quadrant RNFL, and flow area for outer retina, but higher levels of inside disc vascular density seem to be associated with asthmatic children. OCTA findings in asthmatic children appear to be regardless of inhaled steroid use.

Keywords: Asthma, microvasculature, optic disc, optical coherence tomography angiography, retina, steroid

Introduction

Asthma is a frequent and chronic disorder in the pediatric population, caused by airway inflammation, obstruction, hypoxia and hypercapnia, hyperresponsiveness, and also requires long-term follow-up.\(^{[1-3]}\) Allergen-specific type 2 CD4+ T-helper cells, cytokines, eosinophils, mast cells, macrophages, and epithelial cells, play important roles in the pathogenesis of asthma.\(^{[3]}\)

Optical coherence tomography angiography (OCTA) is a novel and noninvasive tool that delivers picturing of the microvascular construction of the retina, providing the evaluation of the superficial and the deep retinal capillary plexus, the choroid, and the optic nerve head.\(^{[4,5]}\) Related inflammatory cytokines and hypoxia may cause systemic effects of asthma. The effects of obstructive sleep apnea syndrome and chronic obstructive pulmonary disease, chronic respiratory insufficiency on the retina and choroidal microvasculature are already reported in the
literature resulting from chronic hypoxemia, systemic inflammation, vascular dysregulation, and increased sympathetic activity.

Given the role of inflammation and hypoxia in the pathogenesis of asthma, we hypothesized that detection of dysfunction in retinal microvasculature by OCTA may be a useful marker in the follow-up of these patients and moreover may be helpful for the identification of early signs of decompensation stage in asthmatic children population. In addition, early detection, monitoring, and selection of these patients for active treatment have a major importance before severe retinal vascular changes regarding visual impairment occur. In this context, to the best of our knowledge, there is no report regarding the relationship between asthma and retinal microvasculature. Therefore, we aimed to assess the retinal and optic disc microvasculature by OCTA in asthmatic children, and compare it with age- and sex-matched healthy children.

Materials and Methods

This cross-sectional study was performed at the ophthalmology department of the university hospital from February 2020 to December 2020. Thirty asthmatic children aged 6 to 17 years diagnosed according to GINA 2006 guidelines (asthma group) and 30 age- and sex-matched healthy children (control group) who referred from the department of pediatrics to the ophthalmology outpatient clinic, were assessed consecutively. Before the study was conducted, a power analysis was performed to strongly increase the validity of the paper and determine the optimal sample size by using an online program named “Power and Sample Size Calculator” from an address http://www.statisticalsolutions.net/pss_calc.php. The optimal sample size was calculated as 60 subjects with alpha value = 0.05 and test power 0.80. The cohort was divided into two groups, with 60 eyes in the asthma group and 60 eyes in the control group. The asthma group was then divided into two subgroups according to the presence of inhaled steroid use (fluticasone propionate 250 µg/day for at least 1 year). Exclusion criteria were refractive error of ≥±2.00 diopters, amblyopia, history of intraocular surgery or trauma, conjunctivitis, corneal pathologies, glaucoma, uveitis, contact lens use, and topical eye drops use. Children with acute exacerbations of asthma, diabetes mellitus, hypertension, dyslipidemia, any cardiovascular, renal, neurological, thyroid, mental or metabolic disorders, genetic syndromes and other inflammatory diseases except asthma, and systemic steroid use were also excluded from the study. Ocular examination involving best-corrected visual acuity, biomicroscopic anterior segment and fundus examination were done. Intraocular pressure (IOP) and central corneal thickness (CCT) measurements were measured by noncontact tonometer.

The OCTA was taken by the same technician using a spectral-domain OCT system with the AngioVue OCTA software (Avanti RTVue-XR 100, OptovueInc, Fremont, CA). The OCTA provides vascular information of retinal layers as an en face angiogram, a vessel density map and a vessel density percentage (%) calculated as the area covered by flowing blood vessels in the selected region. Volumetric angiograms were semi-automatically segmented into three layers allowing for separate angiograms of the inner retina, outer retina, and choroid. Motion artifacts, including residual axial motion and transverse saccadic motion, were removed by three-dimensional orthogonal registration and by merging the pair of scans using the contained software (ReVue, version 2014.2.0.15; Optovue Inc). Shadow graphic projection artifacts were removed with a slab-subtraction method, reducing inner retinal projection onto the outer retinal angiogram. En-face retinal angiograms were created by projecting the flow signal internal to the retinal pigment epithelium. The OCTA image protocol involved two raster scans covering a 6 mm × 6 mm area centered on the macula and 4.5 mm × 4.5 mm area centered on the optic nerve head. Foveal retinal thickness, retinal nerve fiber layer thickness (RNFL), vessel density in the fovea of superficial and deep capillary plexus, and 300 µm width around the foveal avascular zone (FAZ) were measured. Flow areas of the outer retina and choriocapillaris were also recorded. The densities of radial peripapillary capillary, which includes the whole image, inside disc, and peripapillary capillary plexus, were noted, too. OCTA scans with a quality level <8, and decentered were not used.

Venous blood samples were obtained from the antecubital vein after fasting for at least 8 h for biochemical analysis. The serum hemoglobin, serum total immunoglobulin E (IgE), total eosinophil counts, and C-reactive protein (CRP) levels were noted in asthma subgroups.

The local ethics committee was approved this study (2020/23). The research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all parents.

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 21.0, SPSS, Chicago, IL, USA). All measurements taken from both eyes of each subject were selected for the analysis. The normality of distribution of the continuous variables was determined using the Kolmogorov–Smirnov test,
and nonnormally distributed data were presented as median (interquartile range). The distribution of all variables was found to be normal. Continuous variables were compared by Student’s t-test and expressed as means ± standard deviation. Categorical variables were expressed as numbers and percentages, with differences between groups determined using the Chi-squared test. A one-way ANOVA was used to compare the levels of the OCTA findings among the control group and asthma subgroups according to the presence of steroid use. Subgroup analysis was interpreted with the Bonferroni test. A two-tailed $P < 0.05$ was considered statistically significant.

**Results**

The demographic and clinical parameters of the study population are shown in Table 1. The mean ages were 12.57 ± 2.78 years for the asthma group and 12.33 ± 2.98 years for the control group ($P = 0.756$). BMI was 20.37 ± 4.49 kg/m$^2$ in the asthma group, and 19.70 ± 3.26 kg/m$^2$ in the control group ($P = 0.674$). Best-corrected visual acuities were 20/20 in all study patients. Number of eyes with refractive errors ($\leq 1.75$ Diopter) in the asthma group was significantly higher than the control group (20 [33.33%] vs. 4 [6.66%], respectively, $P < 0.001$). Gender rates, CCT values, and intraocular pressures were similar between the groups. RNFL thickness for temporal quadrants and flow area for outer retina levels were significantly lower in the asthma group than the control group (72.58 ± 10.99 µm vs. 77.73 ± 9.73 µm, $P = 0.015$, and 0.60 ± 0.31 mm$^2$ vs. 0.72 ± 0.31 mm$^2$, $P = 0.047$, respectively). However, inside disc vascular densities were significantly higher in the asthma group when compared to controls (55.16 ± 3.71% vs. 52.08% ± 3.79%, $P < 0.001$).

Optic disc OCTA pictures of age- and sex-matched patient from each group are shown in Figure 1. The outcomes of the retina and optic disc parameters by OCTA between groups are shown in Tables 2 and 3, respectively.

There was no statistically significant difference regarding IgE, eosinophil, and CRP values between asthma subgroups according to the presence of steroid use. CCT values were significantly decreased in asthma without steroid use subgroup when compared to with steroid use subgroup and control group ($P = 0.006$). The mean RNFL thickness for temporal quadrants was significantly lower, and flow area for outer retina and peripapillary capillary inside disc densities were significantly higher in patients without steroid use group when compared to with steroid use subgroup and control group ($P = 0.012$, $P = 0.036$, $P < 0.001$, respectively). The outcomes of clinical parameters and macular and optic disc parameters by OCTA among groups are shown in Tables 4 and 5, respectively.

**Table 1: Comparison of demographic and clinical characteristics between the groups**

| Characteristics                      | Asthma group (n=60 eyes) | Control group (n=60 eyes) | $P$  |
|--------------------------------------|--------------------------|---------------------------|------|
| Number of subjects, n                | 30                       | 30                        |      |
| Age (years), mean±SD                 | 12.57±2.78               | 12.33±2.98                | 0.756|
| Gender, n (%)                        |                          |                           |      |
| Female                               | 11 (36.70)               | 15 (50.00)                | 0.297|
| Male                                 | 19 (63.30)               | 15 (50.00)                |      |
| BMI (kg/m$^2$), mean±SD              | 20.37±4.49               | 19.70±3.26                | 0.674|
| CCT (µm), mean±SD                    | 563.81±25.14             | 559.84±25.39              | 0.391|
| IOP (mmHg), mean±SD                  | 16.83±2.34               | 17.78±3.22                | 0.067|
| Number of eyes with refractive errors ($\leq 1.75$ diopter), n (%) | 20 (33.33)               | 4 (6.66)                  | <0.001|
| Duration of asthma (year), mean±SD   | 4.11±3.00                | -                         |      |
| Foveal thickness (µm), mean±SD       | 240.74±14.90             | 242.91±16.67              | 0.457|

SD=Standard deviation, BMI=Body mass index, CCT=Central corneal thickness, IOP=Intraocular pressure

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Figure 1: (a) Optical coherence tomography angiography optic disc vascular density image (radial peripapillary capillary density) of a 14 years old female healthy control subject. (b) Optical coherence tomography angiography optic disc vascular density image (radial peripapillary capillary density) of a 14 year-old female patient with asthma. (c) Optical coherence tomography angiography retinal nerve fiber layer thickness image of a 14 years old female healthy control subject. (d) Optical coherence tomography angiography retinal nerve fiber layer thickness image of a 14 years old female patient with asthma.
To the best of our knowledge, this is the first study that evaluates the relationship between asthma and OCTA findings in the children population. We have found lower values of temporal quadrant RNFL, and flow area for the outer retina but higher levels of inside disc density in asthmatic children when compared with controls. Alterations in ocular blood flow, systemic inflammation, elevation in endothelin-like systemic vasoconstrictor values, and nocturnal hypoxia, leading to axonal damage are possible factors for progressive RNFL loss. This may be a result of chronic hypoxia and systemic inflammation activated by the disease, cytokine release, and changes in the oxidant/antioxidant balance. In our study, significantly lower values of temporal quadrant RNFL, and flow area for outer retina variables were found in the asthma group when compared to controls. Nevertheless, significantly elevated values of inside disc density were seen in asthmatic children than in controls in our study. When inflammation and inadequate delivery of oxygen occurs, blood vessels dilate themselves.\[9\] Therefore, retinal-vascular changes may be the result of these conditions.

### Table 2: The outcomes of retina parameters by optical coherence tomography angiography

|                      | Asthma group (n=60 eyes) | Control group (n=60 eyes) | P    |
|----------------------|--------------------------|---------------------------|------|
| **Superficial vessel density (%)** |                        |                           |      |
| Whole image          | 51.30±2.42               | 51.74±2.33                | 0.321|
| Fovea                | 22.06±6.25               | 22.81±6.96                | 0.540|
| Parafovea            | 54.60±3.18               | 54.97±2.37                | 0.471|
| Perifovea            | 51.81±2.44               | 52.21±2.28                | 0.364|
| **Deep vessel density (%)** |                        |                           |      |
| Whole image          | 56.75±5.04               | 55.80±5.59                | 0.288|
| Fovea                | 39.15±6.65               | 39.33±6.60                | 0.902|
| Parafovea            | 59.84±3.45               | 59.28±3.19                | 0.363|
| Perifovea            | 58.24±5.51               | 57.36±4.83                | 0.358|
| **FAZ area (mm²)**   | 0.28±0.09                | 0.27±0.142                | 0.795|
| **FAZ, FD (%)**      | 56.42±3.81               | 56.68±3.36                | 0.689|
| **Flow area for outer retina (mm²)** | 0.60±0.31               | 0.72±0.31                 | 0.047|
| **Flow area for choriocapillaris (mm²)** | 2.24±0.88               | 2.22±0.10                 | 0.133|

FAZ=Area of 300 µm width around the foveal avascular zone, FD=Fractal dimension

### Table 3: The outcomes of optic disc parameters by optical coherence tomography angiography

|                      | Asthma group (n=60 eyes) | Control group (n=60 eyes) | P    |
|----------------------|--------------------------|---------------------------|------|
| **RNFL thickness (µm)** |                        |                           |      |
| Whole image          | 110.96±25.81             | 117.80±26.59              | 0.192|
| Inferior quadrant    | 146.85±21.77             | 145.52±35.78              | 0.817|
| Superior quadrant    | 137.01±22.17             | 146.15±32.23              | 0.094|
| Temporal quadrant    | 72.58±10.99              | 77.73±9.73                | 0.015|
| Nasal quadrant       | 104.82±21.95             | 105.95±33.71              | 0.838|
| **RPC density (%)**  |                          |                           |      |
| Whole image          | 49.76±1.91               | 49.03±2.72                | 0.111|
| Inside disc          | 55.16±3.71               | 52.08±3.79                | <0.001|
| Peripapillary        | 50.90±2.70               | 50.37±3.10                | 0.359|

RNFL=Retinal nerve fiber layer, RPC=Radial peripapillary capillary, SD=Standard deviation

### Table 4: The outcomes of clinical parameters among subgroups

|                      | Asthma subgroup (mean±SD) | Control group (n=60 eyes) | P    |
|----------------------|---------------------------|---------------------------|------|
| **CCT (µm)**         | 555.08±25.08*             | 575.23±20.58*             | 0.006|
| **IOP (mmHg)**       | 16.46±1.94                | 17.30±2.75                | 0.098|
| **Foveal thickness (µm)** | 240.11±12.47            | 241.62±18.04              | 0.713|
| **RNFL thickness (µm)** | 109.67±31.06             | 112.95±14.92              | 0.387|
| **Flow area for outer retina (mm²)** | 0.60±0.31               | 0.72±0.31                 | 0.047|
| **Flow area for choriocapillaris (mm²)** | 2.24±0.88               | 2.22±0.10                 | 0.133|

\[P<0.006, \ast P<0.024, \ast\ast P<0.01, \text{RNFL=}\text{Retinal nerve fiber layer, SD=}\text{Standard deviation, CCT=}\text{Central corneal thickness, IOP=}\text{Intraocular pressure}\]

**Discussion**

To the best of our knowledge, this is the first study that evaluates the relationship between asthma and OCTA findings in the children population. We have found lower values of temporal quadrant RNFL, and flow area for the outer retina but higher levels of inside disc density in asthmatic children when compared with controls.

Alterations in ocular blood flow, systemic inflammation, elevation in endothelin-like systemic vasoconstrictor values, and nocturnal hypoxia, leading to axonal damage are possible factors for progressive RNFL loss. This may be a result of chronic hypoxia and systemic inflammation activated by the disease, cytokine release, and changes in the oxidant/antioxidant balance. In our study, significantly lower values of temporal quadrant RNFL, and flow area for outer retina variables were found in the asthma group when compared to controls. Nevertheless, significantly elevated values of inside disc density were seen in asthmatic children than in controls in our study. When inflammation and inadequate delivery of oxygen occurs, blood vessels dilate themselves.\[9\] Therefore, retinal-vascular changes may be the result of these conditions.
Macular microvascular findings in healthy children using OCTA were mentioned previously.\cite{12} Previous researches showed that age, sex, and amblyopia could influence the density of retinal and choroidal capillary plexuses.\cite{12,13} In diabetic children without diabetic retinopathy, enlargement of the FAZ area was found by OCTA.\cite{14} In another study, significant changes regarding OCTA findings were not found in type 1 diabetic children when compared to healthy ones.\cite{14,15} Veronese et al.\cite{16} mentioned that pediatric choroidal vascular patterns can be shown by OCTA. The OCTA also allows to see the progressive damage of the retinal vascular perfusion in children with acute problems like retinal artery occlusion and may be an alternative to the standard fluorescein angiography.\cite{17}

It is known that there may be changes in the retinal and optic disc vascular structure in many ocular and systemic diseases, such as choroidal neovascularization, diabetes, and retinopathy of prematurity, in which inflammation plays a role in the etiology.\cite{14,16,18} Decreased retinal microvascular patterns in children with diabetes,\cite{14} and retinopathy of prematurity\cite{19} was reported. In our study, the lack of influence on superficial or deep vessel densities may be explained by the compensation mechanism against hypoxia. In possible case, the duration of the disease may also be an effective factor. Possible changes can be seen within the prolongation of the asthma period.

Despite the current treatment and management guidelines, asthma continues to be a significant morbidity in the pediatric population. There are several clinical reports regarding ophthalmological findings in patients with asthma.\cite{20,21,22,23,24,25,26} Most of them were about intranasal or inhaled corticosteroid use in asthmatic children, and the results were controversial. In a study, lower RNFL levels were found under steroid use. In contrast to this study, Dereci et al.\cite{26} mentioned that asthmatic children with inhaled fluticasone propionate have similar peripapillary RNFL measurements compared to controls. Jhonson et al.\cite{27} did not find a significant effect on CCT and IOP by using inhaled fluticasone at the regular dose used over a short period (6–24 months) in asthmatic children. In our study, significantly lower values of temporal quadrant RNFL, and elevated CCT levels were found in asthmatic children without inhaled steroid use when compared with asthmatic children with steroid use and controls. However, IOP were not significant among the groups. This means that the reduction in RNFL and higher levels of CCT are not due to inhaled steroids but to hypoxia and inflammation in the pathogenesis of asthma. It is also known that retinal ganglion cells are denser in the temporal retina and the temporal quadrant is already thinner than the other quadrants.\cite{22} Therefore, temporal RNFL may be more prone to be affected by hypoxia and less likely to have residual parts. Arjamaa et al.\cite{28} reported that hypoxia in human retinal pigment epithelial cells leads to the release of vascular endothelial growth factor followed by a strong inflammatory reaction by the secretions of IL-6 and IL-8. Vascular alterations in asthma arise from elevated angiogenesis mostly triggered by vascular endothelial growth factors.\cite{29,30,31} Flow areas for choriocapillaris in asthmatic children with

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Table 5: The outcomes of macular and optic disc parameters among groups by optical coherence tomography angiography

| Asthma subgroup (mean±SD) | Control group (n=60 eyes) | P |
|---------------------------|--------------------------|---|
| **Superficial vessel density (%)** | | |
| Whole image | 51.62±2.54 | 50.85±2.22 | 51.74±2.33 | 0.294 |
| Fovea | 22.47±6.07 | 21.49±6.59 | 22.81±6.96 | 0.711 |
| Parafovea | 54.63±3.64 | 54.54±2.46 | 54.97±2.37 | 0.766 |
| Perifovea | 52.12±2.55 | 51.38±2.27 | 52.21±2.28 | 0.337 |
| **Deep vessel density (%)** | | |
| Whole image | 56.67±5.58 | 56.85±4.28 | 55.80±4.59 | 0.565 |
| Fovea | 38.88±5.93 | 39.53±7.67 | 39.33±8.60 | 0.945 |
| Parafovea | 59.83±3.81 | 59.85±2.94 | 59.28±3.19 | 0.662 |
| Perifovea | 58.06±6.16 | 58.50±4.56 | 57.36±4.83 | 0.626 |
| FAZ area (mm$^2$) | 0.27±0.07 | 0.28±0.11 | 0.27±0.14 | 0.957 |
| FAZ, FD (%) | 56.22±3.93 | 56.70±3.70 | 56.68±3.36 | 0.816 |
| Flow area for outer retina (mm$^2$) | 0.63±0.37 | 0.56±0.20 | 0.72±0.31 | 0.104 |
| Flow area for choriocapillaris (mm$^2$) | 2.23±0.12 | 2.28±0.07* | 2.22±0.10* | 0.036 |
| **RPC density (%)** | | |
| Whole image | 50.02±1.73 | 49.38±2.13 | 49.03±2.72 | 0.171 |
| Inside disc | 54.94±4.19* | 55.51±2.87* | 52.08±3.79* | <0.001 |
| Peripapillary | 51.31±2.23 | 50.28±3.27 | 50.37±3.10 | 0.283 |

*P<0.037, ▲P<0.002, ▲▲P<0.003. FAZ=Area of 300 µm width around the foveal avascular zone, FD=Fractal dimension, RPC=Radial peripapillary capillary, SD=Standard deviation
steroid use and controls were similarly low. It may be due to the anti-inflammatory properties of steroids, such as reducing mediator release and inhibiting the angiogenesis effect of them.\cite{11,12}

There are some study limitations. First, the study has a relatively small number of patients. Second, we could not measure the axial lengths of patients, which could affect the results, but in the children population, it is hard to apply such ocular examinations by various ophthalmic devices. Third, number of eyes with refractive errors in the asthma group were significantly higher than the control group, but these refraction errors were ≤±1.75 Diopter. Therefore, we thought that it would not affect the outcomes. Finally, the data were collected and analyzed from both eyes of the same individuals, which may cause potential bias.

Airway inflammation, obstruction, and hypoxia may be responsible for the changes in retinal OCTA parameters. A decrease in vascular densities in the macula and optic nerve head may influence the visual capability of these children. It is necessary to follow-up on these patients and to provide effective treatment for stable visual functions. Therefore, children who are defined as asthmatic children in pediatric clinics should have eye examinations before severe retinal alterations develop. In light of our study, children with asthma should be evaluated in more detail for accompanying retinal microvascular problems that may arise from systemic inflammation and hypoxemia.

**Conclusion**

Lower values of temporal quadrant RNFL and flow area for outer retina, but higher levels of inside disc density by OCTA can be seen in children with asthma. These results may shed light on the understanding of how asthma could affect retinal microvasculature. Therefore, pediatricians and ophthalmologists should keep in mind the impact of asthma on retinal microvasculature while examining these children. To verify our outcomes, randomized- and larger-sized controlled further investigations regarding the association of asthma with OCTA measurements; and the effects of the chronic inflammation and hypoxic status of asthmatic patients on ocular tissues should be carried on in the future.

**Data availability statement**
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**Conflicts of interest**
There are no conflicts of interests.

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