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ARTICLE

Ocular haemodynamics in children with vitamin D deficiency

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BACKGROUND: To evaluate the retinal and optic nerve head microvasculature in children with vitamin D deficiency using optical coherence tomography angiography (OCTA).

METHODS: This prospective, cross-sectional study included 74 eyes of 37 children with vitamin D deficiency (Group I) and 64 eyes of 32 healthy children (Group II). All participants underwent OCTA examinations. Foveal retinal thickness (FRT), peripapillary retinal nerve fibre layer (RNFL) thickness, vessel density (VD) in different sections of the retina, and optic disc were analysed and compared between the groups.

RESULTS: The mean ages, gender, mean intraocular pressures, and central corneal thickness levels were similar between the groups. The mean vitamin D levels measured from the venous blood samples of the participants were 11.42 ± 4.94 ng/mL in Group I and 26.03 ± 11.08 ng/mL in Group II, and the difference between these values was statistically significant ($P < 0.001$). There was no significant difference regarding optic disc capillary densities between the groups. However, compared with the Group II, Group I showed significantly higher values of FRT, and lower values of superficial whole, parafoveal and perifoveal VD (287.58 ± 12.43 mm vs 258.21 ± 22.68, $P < 0.001$, 50.85 ± 2.15% vs 51.77 ± 2.30%, $P = 0.01$, 54.05 ± 2.83% vs 55.18 ± 2.40%, $P = 0.01$, 51.27 ± 2.21% vs 52.11 ± 2.27%, $P = 0.03$, respectively). The vitamin D levels showed significantly negative correlation with FRT values in Group I ($r = -0.439$, $P = 0.001$).

CONCLUSIONS: Vitamin D deficiency seems to be associated with higher values of FRT and decreased levels of superficial VD. Retinal microvascular architecture may be affected in paediatric subjects who have vitamin D deficiency.

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INTRODUCTION

Vitamin D deficiency is a significant public health problem in both developed and developing countries with a reported prevalence of 39.8% for children in Turkey [1]. Vitamin D has critical biological importance for the vascular cell function [2–4]. Vitamin D is a potent modulator of inflammatory processes and also responsible of cell protection against oxidative stress [5–10]. Inflammation, endothelial cell dysfunction, and vascular damage due to vitamin D deficiency may also have a particularly deleterious impact on retinal vasculature, blood flow, and vision. The association between vitamin D and different ocular diseases, such as; myopia, age-related macular degeneration, glaucoma, diabetic retinopathy, dry eye syndrome, thyroid eye disease, uveitis, retinoblastoma, cataract were reported in some studies [11, 12].

Optical coherence tomography angiography (OCTA) is a rapid and noninvasive modality for imaging retinal vasculature [13–16]. This property of OCTA makes it a potentially valuable tool for children. Retinal structural alterations with vitamin D deficiency both in children [17], and adult population [18] by optical coherence tomography were shown. There are limited OCTA studies in the literature showing that vitamin D deficiency affects the microvascular structure in adults [14, 15]. However, to the best of our knowledge, there is no OCTA study regarding the association between serum vitamin D levels and retinal microvascular structure in paediatric population. Therefore, we aimed to evaluate the retinal and optic nerve head microvasculature in children with vitamin D deficiency using OCTA.

METHODS

This prospective cross-sectional study was approved by the ethics committee of our institution (approval number: 2022/46) and conducted in accordance with all the relevant tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects. Before the study was conducted, a power analysis was performed to strongly increase the validity of the paper and determine the optimal sample size with G * Power 3.1.9.4 for Windows (Open Source). The optimal sample size was calculated as 69 subjects with alpha value = 0.05 and test power 0.80. Children who have vitamin D deficiency (Group I) were referred consecutively to the ophthalmology outpatient clinic from the department of paediatrics, and age- and sex-matched healthy subjects as controls (Group II) who were also referred consecutively to the ophthalmology outpatient clinic from the department of paediatrics for a routine examination without vitamin D deficiency were included to the study. Patients were newly diagnosed as having vitamin D deficiency (vitamin D level <20 ng/mL) in our paediatric clinic according to the criteria of Endocrine Society guideline [19]. Group I was also separated into subgroups, as group Ia (≤5 ngr/mL vitamin D, severe deficiency), group Ib (≤15 ngr/mL vitamin D, deficiency), and group Ic (<20 ngr/mL vitamin D, insufficiency) [17]. Patients with any systemic disease other than vitamin D deficiency in Group I were excluded. All subjects with refractive error of ≥ ±2.00 dioptres, amblyopia, contact lens wear, previous

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Table 1. Comparison of demographic and clinical characteristics between the groups.

Characteristics	Group I $n = 74$ eyes	Group II $n = 64$ eyes	*P* value
Number of subjects, *n*	37	32	
Age, years (Mean ± SD)	13.0 ± 3.6	11.7 ± 3.1	0.11
Gender, *n* (%)			
Female	25 (67.5)	17 (53.1)	0.09
Male	12 (32.5)	15 (36.9)	
Body mass index (kg/m^2) (Mean ± SD)	21.6 ± 6.5	20.2 ± 4.4	0.45
Central corneal thickness (μm) (Mean ± SD)	557.3 ± 34.0	557.8 ± 27.1	0.92
Number of eyes with refractive errors (<2.0 Diopter), *n* (%)	6 (8.1%)	3 (4.6%)	0.51
Intraocular pressure (mmHg) (Mean ± SD)	18.0 ± 2.7	17.2 ± 2.7	0.09
Vitamin D levels (ng/mL)	11.4 ± 4.9	26.0 ± 11.0	<0.001
Foveal retinal thickness (μm) (Mean ± SD)	287.5 ± 12.4	258.2 ± 22.6	<0.001

SD standard deviation.

Table 2. The outcomes of retina parameters by OCTA.

	Group I ($n = 74$ eyes)	Group II ($n = 64$ eyes)	*p*
Superficial Vessel Density (%)			
Whole image	50.8 ± 2.1	51.7 ± 2.3	0.01
Fovea	22.0 ± 7.0	23.8 ± 5.6	0.10
Parafovea	54.0 ± 2.8	55.1 ± 2.4	0.01
Perifovea	51.2 ± 2.2	52.1 ± 2.2	0.03
Deep Vessel Density (%)			
Whole image	53.9 ± 5.2	55.4 ± 4.8	0.10
Fovea	38.8 ± 6.9	41.2 ± 6.3	0.03
Parafovea	57.9 ± 3.8	59.1 ± 3.2	0.07
Perifovea	55.4 ± 5.4	56.9 ± 5.1	0.10
FAZ area (mm^2)	0.27 ± 0.0	0.24 ± 0.0	0.15
Flow area for outer retina (mm^2)	0.66 ± 0.3	0.7 ± 0.3	0.48
Flow area for choriocapillaris (mm^2)	2.2 ± 0.1	2.2 ± 0.0	0.19

OCTA optical coherence tomography angiography, *FRT* foveal retinal thickness, *FAZ* area of 300 μm width around the foveal avascular zone, *SD* standard deviation.

ocular surgery, ocular trauma, and other ocular diseases such as uveitis, cataract, or glaucoma, any systemic disease such as diabetes, hypertension, and older than 18 year of age were also excluded. None of the Group I patients were receiving treatment and all measurements of the patients were taken at the same hour of the day (10:00 AM–12:00 PM) in all groups to rule out effect of diurnal variations on OCTA values. Both eyes of all subjects underwent full ophthalmologic exam including best-corrected visual acuity, biomicroscopic anterior segment, and fundus examination. Intraocular pressure (IOP) and central corneal thickness (CCT) measurements were assessed by noncontact tonometer. The ophthalmologist was blinded to the group allocation during the examination of the subjects.

The OCTA images were obtained by a single technician using a spectral-domain OCT system with the AngioVue OCTA software (Avanti RTVue-XR 100, Optovue Inc, 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 3 layers allowing for separate angiograms of the inner retina, outer retina, and choroid. The OCTA image protocol involved scans covering a 6*6-mm area centred on macula and 4.5* 4.5-mm area centred in optic nerve head.

Statistical analysis

Statistical analyses were performed with IBM SPSS for Windows Version 21.0 software. Numerical variables were expressed as mean ± SD. Categorical variables were summarized as numbers and percentages. The normality of distribution of continuous variables was evaluated with the aid of the Kolmogorov–Smirnov test. Independent samples *t* test was used to determine the difference between 2 groups. Comparison of means among subgroups of Group I was conducted by using one-way ANOVA. Pearson correlation coefficient was used for the correlations between variables, and *P* value < 0.05 was considered to reflect statistical significance.

RESULTS

The mean ages, gender, mean IOP, and CCT levels, and body mass index levels were similar between the groups. Best-corrected visual acuities were 20/20 in all participants. The mean vitamin D levels measured from the venous blood samples of the participants were 11.42 ± 4.94 ng/mL in Group I, and 26.03 ± 11.08 ng/mL in Group II, and the difference between these values was statistically significant ($P < 0.001$). The demographic and clinical findings were shown in Table 1. There was no significant difference regarding optic disc capillary densities between the groups (Table 2). However, compared with the Group II, Group I showed significantly higher values of FRT, and lower values of superficial whole, parafoveal and perifoveal VD (287.58 ± 12.43 mm vs 258.21 ± 22.68, $P < 0.001$, 50.85 ± 2.15% vs 51.77 ± 2.30%, $P = 0.01$, 54.05 ± 2.83% vs 55.18 ± 2.40%, $P = 0.01$, 51.27 ± 2.21% vs 52.11 ± 2.27%, $P = 0.03$, respectively). The outcomes of retinal OCTA of study groups were shown in Table 3. OCTA retinal images of a subject from Group I and II were presented in Figs. 1 and 2, respectively. Deep foveal VD levels, and temporal quadrant of RNFL thicknesses in Group I were significantly lower than in Group II (38.86 ± 6.94% vs 41.29 ± 6.38%, $P = 0.03$, 73.56 ± 9.20 vs 76.93 ± 9.62%, $P = 0.03$, respectively). The vitamin D levels showed significantly negative correlation with FRT values in Group I ($r = -0.439$, $P = 0.001$). We have also compared the OCTA results among subgroups of Group I. There were 5 patients in Group Ia, 18 patients in Group Ib, and 14 patients in Group Ic. However, no significant difference was found for all OCTA parameters among subgroups ($p > 0.05$ for all).

DISCUSSION

This OCTA study showed that compared with the Group II, the Group I had significantly higher values of FRT, and lower values of superficial whole, parafoveal, perifoveal, deep foveal VD. Significant decreased temporal quadrant of RNFL thicknesses were

Table 3. The outcomes of optic disc parameters by OCTA.

	Group I $n = 74$ eyes	Group II $n = 64$ eyes	p
RNFL thickness (μm) (Mean ± SD)	116.4 ± 11.8	117.2 ± 22.6	0.78
Inferior quadrant (μm)	153.2 ± 18.4	146.0 ± 30.5	0.08
Superior quadrant (μm)	138.6 ± 14.7	144.5 ± 28.3	0.12
Temporal quadrant (μm)	73.5 ± 9.2	76.9 ± 9.6	0.03
Nasal quadrant (μm)	103.8 ± 16.7	105.5 ± 28.9	0.67
RPC density (%) (Mean ± SD)			
Whole image	49.1 ± 1.9	49.1 ± 2.4	0.98
Inside disc	52.2 ± 4.1	51.7 ± 4.3	0.49
Peripapillary	50.6 ± 2.6	50.5 ± 2.9	0.79

OCTA optical coherence tomography angiography, *RNFL* retinal nerve fibre layer, *RPC* radial peripapillary capillary, *SD* standard deviation.

also found in Group I. However, there was no significant difference for optic disc capillary densities between the groups.

Vitamin D is very important for children's health and ocular structures. Anterior segment of eye can also be affected in children with vitamin D deficiency [20].

Several studies have demonstrated the inverse association between vitamin D and inflammation [5–7]. Oxidative stress also affects the retinal pigment epithelium leading to development of vascular eye diseases [21, 22]. Vitamin D is a known modulator of oxidative stress and angiogenesis. Vitamin D can protect the retina and retinal pigment epithelium from oxidative damage and inflammation [21, 22]. Based on the evidence indicates that vitamin D may improve vascular function, Gayrard et al. [23] evaluated microvascular reactivity in obese adolescents, and reported that vitamin D supplementation attenuated microvascular dysfunction.

Vitamin D receptor expression has been reported in retinal vascular endothelial cells [3]. Vitamin D receptor plays a fundamental role in maintaining the angiogenic and inflammatory status of retinal endothelial cells. Vitamin D enhances barrier function, and provides a protective mission in ocular health.

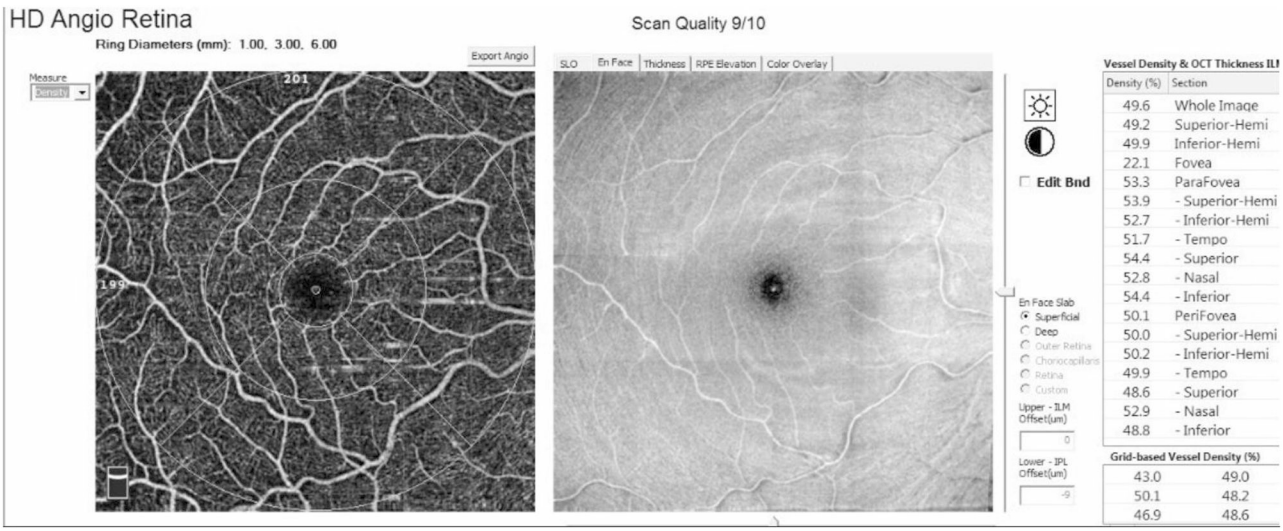


Fig. 1 OCTA image (superficial vessel density) of a 15-year-old female subject from Group I. OCTA indicates optical coherence tomography angiography.

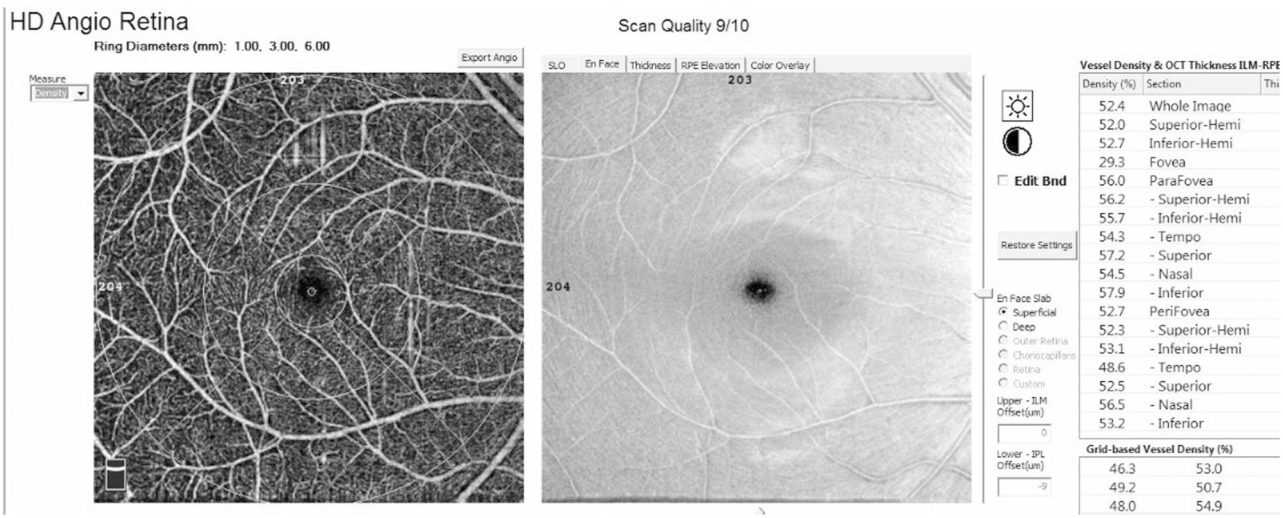


Fig. 2 OCTA image (superficial vessel density) of a 15-year-old female subject from Group II. OCTA indicates optical coherence tomography angiography.

Vitamin D deficiency is a risk factor for poor endothelial function. The fovea, and especially superficial capillaries may be more sensitive to blood circulation alterations in vitamin D deficiency, and might have an early structural damage before irreversible progression of optic disc damage. The vitamin D levels showed significantly negative correlation with FRT values in Group I. We predicted that the elevated FRT levels in Group I was for auto-regulation and compensation mechanism. The lack of significant effect on the optic nerve head may be explained by its resistance to inflammation or different vascular supply. Additionally, the duration of the disease may also be an effective factor. Possible changes can be seen within the prolongation of the vitamin D deficiency period. The small number of patients may be another possible reason for the unaffected optic disc.

Significant decreased temporal quadrant of RNFL thicknesses were found in Group I. It is known that the layer with the highest density of retinal ganglion cells is the temporal retina and the temporal quadrant is already thinner than the other quadrants [24]. Therefore, temporal RNFL may be more prone to be affected by inflammation due to vitamin D deficiency and less likely to have residual parts.

Although the clinical and functional importance of these significant results are not clear, we thought that vascular dysregulation caused by vitamin D deficiency may affect microvascular circulation and ocular blood flow which can cause visual problems. Given the role of inflammation and oxidative stress in vitamin D deficiency, significantly lower values of superficial VD and decreased temporal quadrant of RNFL thicknesses may cause potential eye diseases such as retinal vascular occlusions [25], glaucoma [26], and finally, visual impairment can occur.

Our study has some limitations. First, the number of participants in the groups was relatively small. Second, we could not measure the axial lengths of patients, which could affect the retinal VD results. Additionally, longer axial lengths in myopic eyes can cause significant ocular magnification in OCTA images. However, all subjects with refractive error of $\geq \pm 2.00$ dioptres were excluded from the study. Therefore, we predict that axial lengths may not be long in study population. Third, the lack of a significant difference among subgroups in terms of the severity of vitamin D deficiency may be related to the small number of patients in subgroups. Finally, patients who were receiving treatment were excluded from the study. The patients in Group I were newly diagnosed ones. Outcomes could also be compared in the follow-up after treatment. This can be the subject of another study.

In conclusion, given the role of inflammation, endothelial cell dysfunction, and vascular damage in vitamin D deficiency, destructive effects on retinal vasculature, blood flow, and vision may occur. This analysis showed that OCTA may be a useful tool in early detection of retinal microvascular damage in children vitamin D deficiency. Therefore, paediatricians should pay more attention to children with vitamin D deficiency for also ocular microvascular impacts. Additionally, continuing vitamin D deficiency in childhood may be an independent risk factor for retinal degeneration in adulthood. Future studies should be needed to confirm the mechanisms of this process.

SUMMARY

Vitamin D is very important for children's health and ocular structures. Given the role of inflammation, endothelial cell dysfunction, and vascular damage in vitamin D deficiency, destructive effects on retinal vasculature, blood flow, and vision may occur. This analysis showed that OCTA may be a useful tool in early detection of retinal microvascular damage in children vitamin D deficiency. Therefore, paediatricians should pay more attention to children with vitamin D deficiency for also ocular microvascular impacts. Future studies should be needed to confirm the mechanisms of this process.

What is known about this topic

- Vitamin D is very important for children's health and ocular structures.
- Given the role of inflammation, endothelial cell dysfunction, and vascular damage in vitamin D deficiency, destructive effects on retinal vasculature, blood flow, and vision may occur.

What this study adds

- This analysis showed that OCTA may be a useful tool in early detection of retinal microvascular damage in children vitamin D deficiency.
- Paediatricians should pay more attention to children with vitamin D deficiency for also ocular microvascular impacts.
- Future studies should be needed to confirm the mechanisms of this process.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author, upon reasonable request.

REFERENCES

1. Alpdemir M, Alpdemir MF. Vitamin D deficiency status in Turkey: a meta-analysis. Int J Med Biochem. 2019;2:118–31.
2. Jamali N, Sorenson CM, Sheibani N. Vitamin D and regulation of vascular cell function. Am J Physiol Heart Circ Physiol. 2018;314:H753–65.
3. Jamali N, Wang S, Darjatmoko SR, Sorenson CM, Sheibani N. Vitamin D receptor expression is essential during retinal vascular development and attenuation of neovascularization by 1, 25(OH)2D3. PLoS ONE. 2017;12:e0190131.
4. Alsalem JA, Patel D, Susarla R, Coca-Prados M, Bland R, Walker EA, et al. Characterization of vitamin D production by human ocular barrier cells. Invest Ophthalmol Vis Sci. 2014;55:2140–7.
5. Song YS, Jamali N, Sorenson CM, Sheibani N. Vitamin D receptor expression limits the angiogenic and inflammatory properties of retinal endothelial cells. Cells. 2023;12:335.
6. Cunningham ET Jr, Sobrin L, Hall AJ, Zierhut M. Vitamin D and ocular inflammation. Ocul Immunol Inflamm. 2020;28:337–40.
7. Lee V, Rekhi E, Hoh Kam J, Jeffery G. Vitamin D rejuvenates aging eyes by reducing inflammation, clearing amyloid beta and improving visual function. Neurobiol Aging. 2012;33:2382–9.
8. Tohari AM, Zhou X, Shu X. Protection against oxidative stress by vitamin D in cone cells. Cell Biochem Funct. 2016;34:82–94.
9. Hernandez M, Recalde S, González-Zamora J, Bilbao-Malavé V, Sáenz de Viteri M, Bezunartea J, et al. Anti-inflammatory and anti-oxidative synergistic effect of vitamin D and nutritional complex on retinal pigment epithelial and endothelial cell lines against age-related macular degeneration. Nutrients. 2021;13:1423.
10. Fernandez-Robredo P, González-Zamora J, Recalde S, Bilbao-Malavé V, Bezunartea J, Hernandez M, et al. Vitamin D protects against oxidative stress and inflammation in human retinal cells. Antioxid. 2020;9:838.
11. Chan HN, Zhang XJ, Ling XT, Bui CH, Wang YM, Ip P, et al. Vitamin D and ocular diseases: a systematic review. Int J Mol Sci. 2022;23:4226.
12. Skowron K, Pawlicka I, Gil K. The role of vitamin D in the pathogenesis of ocular diseases. Folia Med Cracov. 2018;58:103–18.
13. Ponugoti A, Baumal CR, Vajzovic L. Optical coherence tomography angiography in pediatric retinal disorders. J Vitreoretin Dis. 2022;6:221–8.
14. Icel E, Ucak T, Ugurlu A, Erdol H. Changes in optical coherence tomography angiography in patients with vitamin D deficiency. Eur J Ophthalmol. 2022;32:3514–21.
15. Karabulut M, Karabulut S, Canbek TD, Sül S, Karalezli A. The effect of vitamin D deficiency on the retinal microvasculature: an observational case-control study. Arq Bras Oftalmol. 2022;85:584–9.

16. Korkmaz MF, Can ME, Kazancı EG. Effects of iron deficiency anemia on peripapillary and macular vessel density determined using optical coherence tomography angiography on children. Graefes Arch Clin Exp Ophthalmol. 2020;258:2059–68.
17. Aydemir E, Ilhan C, Aksoy Aydemir G, Bayat AH, Bolu S, Asik A. Evaluation of retinal structure in pediatric subjects with vitamin D deficiency. Am J Ophthalmol. 2022;233:30–37.
18. Vural E, Hazar L, Çağlayan M, Şeker Ö, Çelebi ARC. Peripapillary choroidal thickness in patients with vitamin D deficiency. Eur J Ophthalmol. 2021;31:578–83.
19. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:1911–30.
20. Aksoy Aydemir G, Ilhan C, Pehlıvanoglu B, Aydemir E, Kiziltoprak H, Bolu S. Conjunctival histopathological changes in children with vitamin D deficiency. Eye Contact Lens. 2022;48:289–94.
21. Murugeswari P, Firoz A, Murali S, Vinekar A, Krishna L, Anandula VR, et al. Vitamin-D3 (α-1, 25(OH) 2D3) protects retinal pigment epithelium from hyperoxic insults. Invest Ophthalmol Vis Sci. 2020;61:4.
22. Tohari AM, Almarhoun M, Alhasani RH, Biswas L, Zhou X, Reilly J, et al. Protection by vitamin D against high-glucose-induced damage in retinal pigment epithelial cells. Exp Cell Res. 2020;392:112023.
23. Gayrard S, Carrere M, Landrier JF, Amiot MJ. Effect of vitamin D supplementation on microvascular reactivity in obese adolescents: a randomized controlled trial. Nutr Metab Cardiovasc Dis. 2021;31:2474–83.
24. Dichtl A, Jonas JB, Naumann GO. Retinal nerve fiber layer thickness in human eyes. Graefes Arch Clin Exp Ophthalmol. 1999;237:474–9.
25. Bhanot R, Kumar A, Shankar S, Singh A, Ambiya V, Srujana D. Serum vitamin D level alterations in retinal vascular occlusions. Photodiagn. Photodyn Ther. 2024;45:103855.
26. Yoo TK, Oh E, Hong S. Is vitamin D status associated with open-angle glaucoma? A cross-sectional study from South Korea. Public Health Nutr. 2014;17:833–43.

AUTHOR CONTRIBUTIONS

Conception and design: BE Kurtul, C Sipal, C El; Acquisition of data: BE Kurtul, C Sipal, C El; Analysis and interpretation of data: BE Kurtul; Drafting the manuscript: BE Kurtul; Revising the manuscript for intellectual content: BE Kurtul; Final approval of the completed manuscript: BE Kurtul, C Sipal, C El.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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