ORIGINAL ARTICLE

Evaluation of choroidal vascular index in vitamin D deficiency

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ABSTRACT

Purpose: The goal of this study is to investigate the effects of vitamin D deficiency in choroidal vacular index (CVI) and choroidal thickness (CT) of the subfoveal and peripapillary area.

Materials and Methods: All macular and peripapillary images were taken by enhanced depth imaging (EDI) mode of spectral domain optical coherence tomography (SD-OCT). The CT was measured at five different points; at the subfovea and at 500µm intervals away from the optic nerve in the superior, inferior, nasal, and temporal quadrants. Choroid images taken from subfoveal and peripapillary region were divided into luminal and stromal areas determined by image binarization method. CVI was defined as the ratio of LA to total choroid area (TCA).

Results: The mean vitamin D levels were 10.58±3.04 ng/mL in Group 1, and 24.92±3.77 ng/mL in Group 2 ($p < 0.0001$). Subfoveal and peripapillary nasal, superior and inferior CT was found to be statistically significantly thinner in Group 1 ($p < 0.001$, all). CVI in subfoveal region, peripapillary nasal and superior quadrants was statistically significantly lower in Group 1 ($p=0.001$, $p=0.012$, $p=0.011$, respectively). There were positive correlations between vitamin D levels and subfoveal CT, nasal, superior, and inferior peripapillary CT ($p < 0.001$, $p = 0.001$, $p < 0.001$, $p < 0.001$, respectively) and subfoveal CVI, nasal, and superior peripapillary CVI ($p = 0.007$, $p = 0.007$, $p = 0.003$ respectively).

Conclusion: In individuals with vitamin D deficiency, both CT and CVI may be negatively affected in the subfoveal, peripapillary nasal and superior quadrants..

Keywords: Choroidal thickness, choroidal vascular index, luminal area, stromal area, vitamin D.

INTRODUCTION

Vitamin D is a fat-soluble vitamin and is a steroid prehormone that can also be synthesized endogenously.[1] Its most important effect is seen on calcium-phosphorus metabolism and bone mineralization. However, in recent years, it has been shown that vitamin D deficiency is associated with many chronic diseases, including various cancers, cardiovascular diseases, metabolic syndrome, osteoporosis, depression, infectious and autoimmune diseases.[2]

In the body, vitamin D is evaluated by measuring the serum 25 hydroxy vitamin D (25(OH)D3) level. The normal range of 25(OH)D3 is 30-80 ng/mL. (75–200 nmol/L). Values below 20 ng/ml (50 nmol/liter) are defined as vitamin D deficiency.[3]

When investigated from an ophthalmological point of view, the presence of vitamin D receptors and enzymes regulating its metabolism has been demonstrated in such retinal layers as retinal pigment epithelium (RPE), photoreceptors and ganglion cell layer, and in endothelium of vascular structures, pericytes, and choroid.[4] Based on this fact, vitamin D deficiency is thought to play a role in the pathogenesis of ophthalmological diseases such

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as glaucoma, senile macular degeneration, myopia, optic neuritis, and diabetic retinopathy.[5]

The choroid is quite a vascularization-rich one.[6] In particular, vascularization of the prelaminar, laminar, and retrolaminar parts of the optic nerve head, perfusion, nutrition, and thermal regulation of the outer retinal layers are provided by the choroid. Therefore choroidal blood supply is very important for eye health. By measuring choroidal thickness (CT) and choroidal volume, it can be indirectly determined how systemic and ocular diseases affect choroidal blood supply.[7] The Choroidal vascularity index (CVI) is a relatively new parameter used to determine the vascular status of the choroid. Images taken by enhanced depth imaging (EDI) mode of spectral domain optical coherence tomography (SD-OCT) are used for the calculation. Through these images, stromal area (SA), showing the structural part of the choroid and luminal area (LA), showing the vascular part can be measured separately with the binarization method in the ImajeJ program. CVI is the ratio of LA to total choroidal area (TCA).[8, 9]

The aim of this study is to evaluate the effect of vitamin D deficiency on CVI and CT in the subfoveal and peripapillary area.

MATERIALS AND METHODS

This prospective case–control study was conducted between February 2022 and June 2022 and was approved by local ethics committee (date: 23.03.2022, decision no: 2022/51), adhering to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Among the patients who applied to the Internal Medicine Department for a check-up and did not have any additional systemic disease and were referred to the Ophthalmology Department, those with a vitamin D level less than 15 ng/mL were determined as Goup 1, and those with a vitamin D level more than 20 ng/mL were determined as Group 2. Ophthalmological evaluation was performed by the same 2 ophthalmologists (MK, FG). The best corrected visual acuity (BCVA) (logMAR) of the patients was measured. Anterior segment was evaluated with slit lamp biomicroscope and intraocular pressure (IOP) was measured with Goldman applanation tonometry. Fundus examination was performed with a 90D lens following pupil dilation. The axial lengths (AL) of the patients were noted. (IOLMaster 500, Carl Zeiss Meditec, Dublin, CA). Patients with both spherical and cylindrical refractive errors greater than ± 2 diopters (D) and BCVA < 0.0 logMAR, AL <21 mm and >25 mm, IOP > 21 mmHg, previous ocular trauma or any ocular surgery, neurological diseases that may affect the optic nerve and peripapillary retinal nerve fiber layer (pRNFL), ocular diseases such as age-related macular degeneration, glaucoma, pseudoexfoliation syndrome, uveitis, patients younger than 18 years of age and older than 40 years and those receiving treatment for vitamin D deficiency were excluded from the study.

All OCT measurements were performed by the same experienced technician with SD-OCT device following pupil dilation. (SD-OCT, Heidelberg Engineering, Heidelberg, Germany). To exclude the effect of diurnal variations, all images of all participants were taken at the same time interval (between 09:00 and 11:00 a.m). Measurements were performed in EDI mode. Macular OCT images were acquired using horizontal scans centred on the central foveal region. Peripapillary OCT images were obtained using horizontal and vertical scans centred on the optic nerve head. The choroidal thickness was measured at five different points: at the subfovea and at 500μm intervals away from the optic nerve in the superior, inferior, nasal, and temporal quadrants. Choroidal thickness measurements were performed manually from the outer portion of the RPE to the inner surface of the sclera at the subfoveal area. Peripapillary choroidal thickness is a measurement of the distance between Bruch's membrane and the anterior sclera. Only high-quality scans (>25 Q) were evaluated. The obtained raw OCT data (macular and peripapillary) were evaluated with an image processing program for further analysis.

ImageJ software (version 1.53j, National Institutes of Health, Bethesda, MD, USA) was used for the binarization of the EDI-OCT images using the protocol described by Agrawal et al.[8] The total choroidal area (TCA) was measured manually at a 1500 micrometers area, with a margin of 750 micrometers nasal and temporal to the foveal center horizontally and from the RPE to the choroido-scleral border vertically (Figure 1). Binarization was performed using the Niblack auto local threshold method. The selected region was added to the region of interest (ROI) manager and the TCA was calculated. Then, the image type was changed to red-green-blue color, and following this the color threshold was applied to select the dark pixels expressing the LA and saved in the ROI manager. The areas in the ROI manager were selected and merged via an "AND" command, and then LA was calculated. SA, indicated by light-colored pixels was calculated by subtracting LA from the TCA.

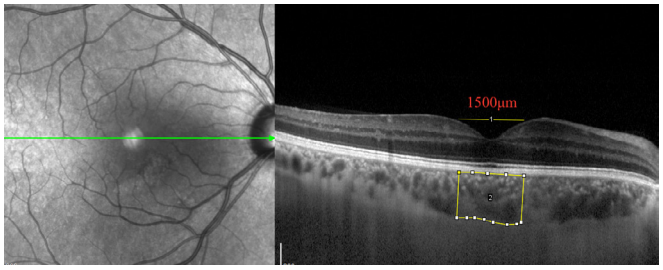

Figure 1: *The technique for measuring the subfoveal choroidal vascularity index* ***A:*** *Enhanced depth imaging mode of spectral domain optical coherence tomography (EDI-OCT). A 1500 µm width reference line (yellow color) was drawn using the line tool.*

Subfoveal CVI was calculated as the ratio of LA to TCA. The optic disk radial EDI-OCT images were evaluated using the previously described method.[10, 11] In these scans, the inferior, superior, nasal, and temporal quadrants (1000 µm width on four sides from the optic disc border) of the peripapillary area were binarized separately (Figure 2). The area between the outermost edge of the RPE and the innermost edge of the choroidoscleral junction was selected using the polygon tool of software, then binarized using Niblack's auto local thresholding method. Peripapillary CVI was calculated as the ratio of LA to TCA. All these measurements were performed separately by three blinded researchers (OA, FG, MK). The average of three measurements was included in the statistical analysis to decrease the measurement errors.

Statistical Analysis

Statistical analysis was performed with SPSS 21.0 program (SPSS Inc., Chicago, IL). The data obtained by taking the average of all measurements were recorded as mean±standard deviation. The distribution of the data within the groups was evaluated with the Kolmogorov-Smirnov test. Independent t-test was used for pairwise comparisons. Relationships between dependent variables were analyzed by Pearson correlation analysis. Chi-square test was used to compare categorical data. A value of $p<0.05$ was considered statistically significant.

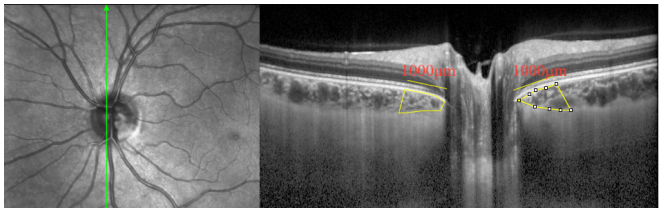

Figure 2: *Illustration of inferior and superior peripapillary choroidal vascularity index measurement* ***A:*** *Vertical scan centered on the optic nerve head using enhanced depth imaging optical coherence tomography (EDI-OCT). A 1000 µm width reference line (yellow color) was drawn using the line tool.*

RESULTS

The study included 38 eyes of 38 patients with 25(OH)D_3 deficiency (Group I) and 34 eyes of 34 healthy controls (Group II). The mean ages of participants in Groups 1 and Group 2 were 27.23 ± 4.94 (range: 19-37) and 28.44 ± 5.76 (range: 19-39), respectively ($p = 0.348$), and the female to male ratios were 23/15 and 20/14, respectively ($p = 0,883$).

The mean 25(OH)D_3 levels were 10.58 ± 3.04 ng/mL (3.00-14.94) in Group 1 and 24.92 ± 3.77 ng/mL (20.67-34.23) in Group 2 ($p <0.0001$). The mean AL measurements were 23.01 ± 0.81 mm (range 21.45- 24.72) in Group 1 and 23.32 ± 0.97 mm (range 21.23-24.90) in Group 2. There was no statistically significant difference between the groups ($p = 0.151$). The mean refractive error measurements were -0.46 ± 0.8 diopters (D) (range:-2.50 - +1.12) in Group 1 and -0.35 ± 1.03 D (range: -2.37 - +1.50) in Group 2 ($p = 0.615$). The mean BCVA in both groups was logMAR 0.0. The groups were similar in terms of the average IOP ($p = 0.488$).

Subfoveal and peripapillary nasal, superior and inferior CT was found to be statistically significantly thinner in Group 1 ($p <0.001$, all) (Table 1). There was no significant difference between the groups in terms of CT in the temporal quadrant ($p = 0.155$). CT measurements are shown in Table 1.

CVI in subfoveal region, peripapillary nasal and superior quadrants was statistically significantly lower in Group 1 ($p=0.001$, $p=0.012$, $p=0.011$, respectively). There was no significant difference in the peripapillary temporal and inferior quadrants ($p = 0.914$, $p = 0.393$, respectively). CVI measurements are shown in Table 2.

In addition, there were positive correlations between vitamin D levels and subfoveal CT, nasal, superior, and inferior peripapillary CT ($p <0.001$, $p = 0.001$, $p <0.001$, $p <0.001$, respectively) and subfoveal CVI, nasal, and superior peripapillary CVI ($p = 0.007$, $p = 0.007$, $p = 0.003$, respectively) in all patients (Table 3).

DISCUSSION

Vitamin D deficiency is a common public health problem affecting about half of the world's population.[12] Although

Table 1: *Comparison of choroidal thickness between the vitamin D deficiency and control groups.*

	Group 1	Group 2	p value
	Mean ± SD	Mean ± SD	
Subfoveal CT (µm)	323.63 ± 47.79	364.79 ± 35.62	**0.001**
Peripapiller CT (µm)			
Nasal	172.97 ± 47.56	211.7 ± 46.84	**0.001**
Temporal	189.15 ± 39.9	203.7 ± 45.3	0.152
Superior	174.57 ± 39.93	209.3 ± 37.89	**0.001**
Inferior	148.68 ± 37.22	186.91 ± 38.48	**0.001**

CT: Choroidal thickness SD: Standart Deviation,
$p < 0.005$ was considered statistically significant between Groups 1 and 2

Table 2: *Comparison of choroidal vascular index values between the vitamin D deficiency and control groups.*

	Group 1	Group 2	p value
	Mean ± S	Mean ± SD	
Subfoveal			
TCA (mm^2)	0.503 ± 0.071	0.540 ± 0.050	**0.013**
LA (mm^2)	0.317 ± 0.049	0.356 ± 0.041	**0.001**
SA (mm^2)	0.185 ± 0.035	0.184 ± 0.022	0.814
CVI (%)	63.02 ± 3.58	65.91 ± 3.12	**0.001**
Peripapiller			
Nasal			
TCA (mm^2)	0.168 ± 0.046	0.209 ± 0.046	**0.001**
LA (mm^2)	0.102 ± 0.033	0.132 ± 0.033	**0.001**
SA (mm^2)	0.066 ± 0.016	0.077 ± 0.018	**0.012**
CVI (%)	60.71 ± 4.32	63.14 ± 3.59	**0.012**
Temporal			
TCA (mm^2)	0.183 ± 0.044	0.206 ± 0.049	**0.049**
LA (mm^2)	0.115 ± 0.031	0.129 ± 0.036	0.076
SA (mm^2)	0.067 ± 0.017	0.0.76 ± 0.015	**0.036**
CVI (%)	62.93 ± 3.28	62.82 ± 4.69	0.916
Superior			
TCA (mm^2)	0.176 ± 0.040	0.208 ± 0.037	**0.001**
LA (mm^2)	0.106 ± 0.028	0.131 ± 0.027	**0.001**
SA (mm^2)	0.069 ± 0.017	0.076 ± 0.013	0.063
CVI (%)	60.23 ± 4.77	62.89 ± 3.74	**0.011**
Inferior			
TCA (mm^2)	0.150 ± 0.036	0.187 ± 0.037	**0.001**
LA (mm^2)	0.092 ± 0.027	0.113 ± 0.028	**0.003**
SA (mm^2)	0.057 ± 0.012	0.074 ± 0.053	**0.001**
CVI (%)	61.32 ± 4.66	60.34 ± 5.0	0.395

SD: Standart Deviation, CVI: Choroidal vascularity index, TCA: Total choroidal area, LA: Luminal area SA: Stromal area
$p < 0.005$ was considered statistically significant between Groups 1 and 2

Table 3: *Correlation analysis between vitamin D level and CT and CVI.*

	CT		CVI	
	r	P	r	P
Subfoveal	0.418	**< 0.001**	0.315	**0.007**
Peripapillary nasal	0.388	**0.001**	0.318	**0.007**
Peripapillary superior	0.425	**< 0.001**	0.343	**0.003**
Peripapillary temporal	0.146	0.223	-0.004	0.974
Peripapillary inferior	0.462	**< 0.001**	-0.055	0.648

The p value columns show the statistical difference between the groups., p value <0,05 is considered as significant. CT: Choroidal thickness CVI: Choridal vascularity index

a small part of vitamin D can be obtained from the diet, the main source is derived from the part synthesized out of cholesterol in the skin under the influence of ultraviolet B. Vitamin D, a prohormone, is converted to its active form by two-step hydroxylation in the liver and kidney. It regulates many genes related to cell differentiation and proliferation by binding to the intracellular nuclear vitamin D receptor (VDR). The presence of VDR has been demonstrated in immune cells, osteoblasts, myocytes, vascular endothelial cells, vascular smooth muscle cells, pericytes, neurons, adipose tissue cells and retinal cells. In addition to its effects on calcium-phosphorus metabolism and bone mineralization, it also has a role in the prevention of many cancer types, autoimmune, allergic, cardiovascular and infectious diseases as a result of its anti-inflammatory, anti-neovascular, immunomodulatory properties as well as its effects on cytokine levels.[3]

Vitamin D has important functions in maintaining a healthy vascular structure. It has been shown that pericytes, the perivascular support cells located outside the vascular structures and playing a major role in angiogenesis and vascular development, contain more VDR than vascular endothelial cells. Vitamin D suppresses their proliferation and migration.[13] It is a potent inhibitor of endothelial cell proliferation induced by vascular endothelial growth factor.[14] It also suppresses the replication of vascular smooth muscle cells and the vascular mitogenic response triggered by some stimuli.[15] As a result of the decrease in these antineovascular effects in vitamin D deficiency, diseases with neovascularization such as age-related macular degeneration (AMD) and diabetic retinopathy (DRP) may progress more severely.[16, 17] Again, vitamin D increases vascular endothelial cell-dependent vasodilation by affecting the renin-angiotensin system, so hypertension can be observed in case of any deficiency.[18,19] In addition, with its anti-inflammatory effect, it prevents the vascular endothelium from being damaged by metabolic damages or oxidative stress.[19] Further, there are studies revealing the association between its deficiency and cardiac dysfunction, and also there are studies shoowing that this deficiency is seen as an independent risk factor for atherosclerosis, and is associated with increased vascular calcification and increased platelet aggregation.[20]

Considering all these, vascular changes due to vitamin D deficiency may reduce ocular blood flow. Considering that 85% of the ocular blood flow comes to the choroid, the choroid will be affected first. Evaluation of the vascular portion of the choroid, consisting of a dense vascular network and stromal tissue elements, will better reflect these effects. Quantitative values have been intensively studied in order to determine and follow the effects of ocular or systemic diseases on the choroid, the most famous of these is CT by which the vascular part can indirectly be evaluated. CT can be affected by factors such as age, gender, refractive error, AL, IOP, and measurement time. There are studies showing a negative correlation between age and CT, whereas a positive correlation between refractive changes and CT.[21] In our study, there was no difference between the groups in terms of the factors mentioned.

In the literature, there are two studies examining the effect of vitamin D deficiency on CT draw attention. In their study examining subfoveal and peripapillary 4-quadrant CT values, Vural et al. showed that the subfoveal and peripapillary nasal and inferior CT were thinner in the vitamin D deficient group than in normal healthy individuals.[22] They also reported a positive correlation between vitamin D levels and CT. In addition, Öncül et al. observed that the CT measurements they made in 5 regions at a distance of 500 µm and 1500 µm from the fovea center in the subfoveal, nasal and temporal regions were thinner in all quadrants in the vitamin D deficient group than in the

control group. Also, they treated the patients with vitamin D deficiency appropriately and assessing the CT again 3 months later, they reported that there was significant thickening in all quadrants compared to the pre-treatment CT. Based on this finding, they concluded that endothelial dysfunction and choroidal blood flow changes due to vitamin D deficiency are reversible. They also stated that there is a significant correlation between CT and vitamin D levels.[23] Consistent with the studies mentioned in our study, CT in the subfoveal and peripapillary nasal, inferior and superior quadrants was significantly thinner in the vitamin D deficient group than in the control group. In addition, there was a positive correlation between vitamin D levels and CT in these quadrants.

CVI is a relatively new parameter by which the vascular part of the choroid can be evaluated in more detail.[8,9] The luminal and stromal parts of the choroid tissue of the desired width are evaluated separately and the CVI is calculatedn through this technique using the binarization method. It is less affected by diurnal variations than CT. In addition, it has been stated that when CT takes measurements from a single point, it gives more accurate results as CVI is calculated as a percentage of a certain area.[7] In our study, CVI in the subfoveal and peripapillary nasal and superior quadrants were found to be lower in the vitamin D deficiency group than in the control group. In addition, there was a positive correlation between vitamin D levels and CVI in these quadrants.

It was observed in the study that both CVI and CT values in the subfoveal, peripapillary nasal and superior quadrants were significantly lower in the vitamin D deficient group than in the control group. In the inferior quadrant, a significant difference was found between the groups in terms of CT, yet no significant difference was observed in terms of CVI. It is known that the CT in the inferior quadrant is also thinner in the healthy population than in the other quadrants.[24] Although the reason for this condition is not known exactly, it is thought to be caused by a difference in the developmental period of the eye. It is stated that it may be due to the location of the optic fissure in the inferior of the optic cup during eye development and that this is the last closure area.[25] The thin choroid in this region may increase vascular resistance and decrease blood flow in the choriocapillary. Vascular changes, which we think are due to vitamin D deficiency, may not be observed clearly in the already-reduced blood flow.

Changes in choroidal blood flow can affect both the structural and functional state of the retina. It has been shown that vitamin D deficiency also causes a decrease in retinal blood flow and decreases macular perfusion.[26] Due to the importance of the peripapillary choroid in the blood supply of the optic nerve head, the decrease in CVI in this region may increase the progression of diseases such as glaucoma and pathological myopia. It has also been shown to be lower in glaucoma patients.[27] In addition, it is known that subfoveal CVI is decreased in both DRP and AMD patients compared to the normal population (28, 29). It has even been suggested that CVI can be used as a biomarker for dry type AMD progression.[30]

This study has some limitations. Although the groups were similar with respect to age, sex, AL, refractive error, BCVA, and IOP, the number of eyes studied was relatively small. The duration of vitamin D deficiency was unknown; moreover, we did not consider the effect of vitamin D supplementation on CVI and CT.

In conclusion, to the best of our knowledge, this is the first study to compare CVI between those with vitamin D deficiency and those within the normal range of vitamin D. This study indicated that CVI and CT decreased both in the subfoveal area and in the peripapillary nasal and superior quadrants in those with vitamin D deficiency. In addition, there were a positive correlation between vitamin D level and CT and CVI in these regions. Further research is needed to demonstrate the effects of vitamin D on the choroidal vascular structure.

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